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IMPACT ON LIFE AFTER INTRACRANIAL ANEURYSM RUPTURE

Health-related quality of life and epidemiologic outcomes

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Stockholm 2012

Published by Karolinska Institutet. Printed by Universitetsservice, US-AB
Box 700 14, SE-100 44 Stockholm, Sweden

ISBN 978-91-7457-927-7

ABSTRACT

The overall aim of this thesis was to describe impact on life up to ten years after intracranial aneurysm rupture in terms of health-related quality of life, changes in everyday life and descriptive epidemiology with the intention to contribute to an increased understanding of the long-term perceived consequences of that impact.

Study I aimed to describe changes and transitions in everyday life during the first two years following an intracranial aneurysm rupture. A consecutive sample of 88 patients was followed-up at three time points. A majority of respondents perceived changes in their everyday life during the first two years following aneurysm rupture. Transitions were revealed within changes in personality, changed social roles and relationships, and changed abilities and behavior.

In **Study II** epidemiology in relation to gender differences and treatment modalities ten years after aneurysm rupture was investigated. Ten years after the onset, 63.9% of the 468 admitted patients were still alive. The incidence in women was higher than that of men; they were older at onset and were diagnosed with more aneurysms. There were no significant differences in survival times between patients treated with different active aneurysm treatments, or between men and women.

In **Study III** survivors from study II (n=217) were followed-up with questionnaires and telephone interviews, aiming to describe psychological, physical and cognitive functions ten years after intracranial aneurysm rupture. Compared to reference groups, the aneurysm respondents scored higher levels of anxiety and depression. Respondents with ruptured aneurysms in the posterior circulation of the brain scored significantly more symptoms of anxiety and depression. A small proportion, 2.8%, scored for severe physical disability and 21.7% scored below the cut-off value, indicating cognitive impairments.

Study IV used the same sample as study III (n=217), and a general population sample (n=434) from the Stockholm Public Health Survey, matched by age and sex. The aim was to measure health-related quality of life (HRQoL), and to explore factors affecting HRQoL, ten years after intracranial aneurysm rupture. Compared to general population, the aneurysm sample reported significantly more problems with mobility, self-care, usual activities and anxiety/depression and had significantly lower overall HRQoL values. HRQoL in the aneurysm sample was most affected in respondents with worse neurological outcome, respondents with comorbidities, and respondents with low perceived recovery.

In conclusion, intracranial aneurysm ruptures impacts upon life in several ways for an extensive period of time after the onset. The results indicate a need for follow-up and support, and to identify subgroups of aneurysm patients who might benefit from support: patients with ruptured aneurysms in the posterior circulation of the brain; patients with worse neurological outcome at hospital discharge; patients with comorbidities; and patients with low perceived recovery.

Ten years after the onset of aneurysm rupture the majority of patients were still alive. Differences between men and women were apparent in incidence and clinical presentation at the onset of aneurysm rupture, not in survival times. Survival time was equal between patients within active treatment modalities.

LIST OF PUBLICATIONS

This doctoral thesis is based on the following papers, referred in the text by their Roman numerals:

I. **von Vogelsang A-C**, Wengström Y, Svensson M, Forsberg C.
Transitional experiences of patients following intracranial aneurysm rupture
Submitted

II. **von Vogelsang A-C**, Wengström Y, Svensson M, Forsberg C.
Descriptive epidemiology in relation to gender differences and treatment modalities 10 years after intracranial aneurysm rupture in the Stockholm cohort 1996-1999
Accepted for publication, World Neurosurgery

III. **von Vogelsang A-C**, Svensson M, Wengström Y, Forsberg C.
Cognitive, physical, and psychological status after intracranial aneurysm rupture: a cross-sectional study of a Stockholm case series 1996 to 1999
Accepted for publication, World Neurosurgery

IV. **von Vogelsang A-C**, Burström K, Wengström Y, Svensson M, Forsberg C.
Health-related quality of life ten years after intracranial aneurysm rupture: a retrospective cohort study using EQ-5D
Submitted

CONTENTS

LIST OF ABBREVIATIONS

ACA	Anterior cerebral artery
ACoA	Anterior communicating artery
ADL	Activities of daily living
BI	Barthel Index
CI	Confidence Interval
EQ-5D	EuroQol instrument
GCS	Glasgow Coma Scale
GOS	Glasgow Outcome Scale
HADS	Hospital Anxiety and Depression Scale
HADS-A	HADS subscale Anxiety
HADS-D	HADS subscale Depression
HC	Hydrocephalus
H&H	Hunt and Hess classification of subarachnoid hemorrhages
HRQoL	Health-Related Quality of Life
ICA	Internal carotid artery
ICD-9	International Classification of Diseases, 9th revision (1987-1996)
ICD-10	International Classification of Diseases, 10th revision (from 1997)
IQR	Inter Quartile Range
ISAT	International Subarachnoid Aneurysm Trial
ISUIA	International Study of Unruptured Intracranial Aneurysms
MCA	Middle cerebral artery
QoL	Quality of Life
SAH	Subarachnoid hemorrhage
SCDR	The Swedish Cause of Death Register
SCP	Survivorship care plan
SPSS	Statistical Package for Social Science
STAI	State Trait Anxiety Inventory
SWD	Sleep-wake disorders
TICS	Telephone Interview for Cognitive Status
VAS	Visual Analogue Scale
WHO	World Health Organization

1 INTRODUCTION

My clinical experience of patients suffering from ruptured intracranial aneurysms is both as an operating room nurse, and as a center coordinator in a multicenter study (International Study of Unruptured Intracranial Aneurysms, ISUIA) during a period of seven years, with yearly follow-up with questionnaires and telephone interviews. Over four years I also conducted telephone follow-ups one year after rupture, of all patients treated for ruptured intracranial aneurysms at the clinic. Some patients described that they had returned to their former life, while others described that life was 'upside-down' despite having a good neurological outcome at hospital discharge. During the follow-up calls it became evident that they needed someone to talk to about their experiences, and more information about the expectations around their condition. A large proportion described suffering from increased anxiety. Some of the patients expressed a need for support, and were dissatisfied with the fact that their caregivers in primary health care lacked knowledge and understanding of the specific problems they had experienced in the aftermath of intracranial aneurysm rupture.

The literature provides several descriptions of how aneurysm ruptures impact upon different aspects of health and life, but information on the perceived long-term consequences, beyond the first 18 months after the rupture, is insufficient.

This doctoral thesis is an attempt to contribute to an increased understanding of the long-term perceived consequences from which patients suffer after intracranial aneurysm rupture.

2 BACKGROUND

2.1 HEALTH, HEALTH STATUS AND HEALTH STATE

Health is an essential core component in the nursing discipline, but is also central to other disciplines, such as in medicine and public health.[1] In 1946, the World Health Organization (WHO) formulated a definition of health that is commonly used within different disciplines: "a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity".[2 (p.2)]

In the literature, health has been conceptualized in different ways: in a classical scientific perspective described by the medical and molecular indications of the presence or absence of illness; or in a psychological perspective where health and illness are expressions of deeper meanings and personality is related to behavioral approaches of stress reduction. Other views of health in the literature are: the preventive/promotional perspective, where risk assessments, self-care and individual choices play an important role; the social/political perspective that addresses the role of the environment; and the metaphorical perspective where the meanings of health are found in intuition and symbolism.[1] In nursing, the territory for theoretical development that unifies these different views of health are: human responses to health and illness situations, the subjective world of ill or healthy clients, self-care behaviors in health and illness, therapeutic actions that enhance recovery and well-being, client-nurse interactions, client-environment interactions, and coping styles. [1]

Health may be described in the context of health status or health state. Health status has been defined by WHO[3] to be a description of and/or a measurement of the health of an individual or a population at a specified time point, and against identifiable standards or health indicators.

A health state can include different dimensions of health status, which allows creating health profiles and overall measures of health in one single number. In health-related quality of life research there are two types of health states; the self-state of the respondent during a given period of time, and hypothetical health states that the respondent may, or may not have experienced.[4]

2.2 QUALITY OF LIFE AND HEALTH-RELATED QUALITY OF LIFE

In order to understand the perceived consequences of an illness, and to compare different treatments or to improve care, quality of life measures can be used.[5] WHO have defined quality of life (QoL) as "individuals' perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns".[6 (p. 1405)] QoL is a broad-ranging concept that includes both positive and negative aspects of life.[6] Fayers & Machin[5] describe QoL as a latent construct; it is a hypothetical concept that is assumed to exist, but is not possible to directly measure or observe, since QoL means different things to different people.

QoL aspects that directly relate to an individual's health are referred to as health-related quality of life (HRQoL).[7] There is a general agreement that QoL and HRQoL are subjective parameters that can only be assessed by the patient (or person) self, and proxy assessments are only used if the person is unable to make a coherent response. For that reason, outcomes in HRQoL studies are also referred to as PRO (patient-reported outcomes, or person-reported outcomes, as participants in all studies are not always patients).[5] Another important conceptual issue to bear in mind is that QoL and HRQoL fluctuate and vary over time.[8]

It is generally agreed that HRQoL is a multidimensional concept and that a number of aspects should be included in its measurement. A minimum of four aspects (physical functioning, emotional and psychological functioning, social functioning and disease/treatment-related symptoms) plus a global measure of health status have been suggested to be sufficient to cover for multifactoriality.[8,9] Dimensions that are relevant to include may vary between studies, and depend on which aspects are affected by disease or treatment for disease. Also, indirect consequences of disease, such as unemployment or financial difficulties, may be included.[5]

In this thesis a description of HRQoL after stroke by de Haan et al.[10,11] has been used, including the following dimensions: psychological, physical, functional and social health. The psychological dimension comprises cognitive function, emotional status and general perceptions of health. Physical health refers to disease-related and treatment-related symptoms, and functional health has to do with self-care, mobility and physical activity level. The social dimension refers to social contacts and interactions. The results related to HRQoL in this thesis are presented within all of these dimensions.

2.2.1 HRQoL measurements

HRQoL measures are classified into three types; generic health indices and profiles, specific measures (such as disease, population) and preference measures.[4] Generic instruments are intended for general use and are often also applicable to healthy people, while specific measures focus on the particular concerns to a specific population or patients with a specific disease.[5]

Preference is an expression of which option of action a person might prefer in a situation after informed deliberation of the risks and benefits.[4,12,13] There are some important differences between health state preferences and generic or specific HRQoL measures; generic and specific measures focus on identifying presence/absence, frequency, severity, duration of specific symptoms, or disabilities or impairments, whereas preference measures assesses individuals' preferences for health states or outcomes. Preferences measures provide an overall measure of HRQoL in which the respondent response combines the positive and negative dimensions of a specific health state into a single number that reflects the net effect of positive and negative aspects as perceived by the respondent. Contrary to specific HRQoL measures, preference measures provide a common unit of analysis that allows comparisons between different programs on the same scale.[4]

Measured preferences may be ordinal or cardinal; ordinal preferences are simply rank ordered from most to least preferred. Cardinal (or fundamental) preferences have a number on an interval scale that represents the strength of the preference of the outcome, relative to other preferences.[13] Cardinal preferences are typically measured on a scale between 1 and 0, where 1 represents perfect health, and 0 is death, [4,13,14] but since some health states may be regarded as worse than death, negative values should be allowed.[15]

2.3 ANEURYSM ETIOLOGY, PREVALENCE AND INCIDENCE

An intracranial aneurysm is an abnormal dilatation of the vascular lumen of a cerebral artery and occurs most frequently in arterial bifurcations.[16] The exact etiology is still unclear.[17] It has been hypothesized that a congenital defect, a weak spot, in the muscle layer of the arterial wall allows the inner layers to bulge out and form an aneurysm. But since defect muscle layers in cerebral arteries also occur in people without aneurysms, it is believed that the pathogenesis include both congenital and acquired factors, such as hemodynamics, altered structures in cerebral arteries, genetics, trauma, infections and inflammation.[16,17] In up to 30% of all patients with intracranial aneurysms, more than

one aneurysm is present,[18] a state which is defined as 'multiple aneurysms'. Within the subgroup of patients with multiple aneurysms about one-third has mirror aneurysms (two different aneurysms located bilaterally on corresponding arteries).[19]

The prevalence of harboring an intracranial aneurysm varies between autopsy studies and angiography studies,[20] with estimates ranging from 0.2% to 9.9% with a mean of approximately 5%.[21]

Intracranial aneurysms are most commonly asymptomatic before they rupture and cause a subarachnoid hemorrhage (SAH), which is also known as a hemorrhagic stroke, and accounts for up to 7.0% of all strokes.[22]

The ISUIA investigated the risk of rupture in patients harboring an intracranial aneurysm. In patients with no previous history of SAH, the risk of rupture depends on aneurysm size and aneurysm location. The cumulative rupture rate in patients with aneurysms less than 10mm in diameter was about 0.05% per year, and in patients with aneurysms a diameter of ≥ 10mm the rupture rate was 20 times higher.[21] The relative risk for rupture in aneurysms < 10mm in diameter is 11.6 times lower than in aneurysms 10-24 mm in diameter, and 59.0 times lower than giant aneurysms (≥ 25mm in diameter). The relative risk for rupture was highest for aneurysms located at the basilar tip (13.8), and aneurysms in the vertebrobasilar arteries or posterior cerebral artery (13.6), when compared with other locations.[21]

SAH incidence varies widely round the world, depending on geographical region, [23,24] gender, [25,26] and ethnicity.[27-29] Overall, the SAH incidence is higher in women, but differs between ages; men are predominant in the first three decades of life, then the incidence is equal by the fifth decade, and thereafter women predominate the incidence.[16] A 2.1 times higher SAH incidence has been found in black people compared to whites.[30] In a meta-analysis by de Rooij et al.[23], an overall SAH incidence of 9.1/100 000 person-years was calculated. A large multinational study including populations from Europe and China found a ten-fold variation of the annual incidence of SAH between countries; from 2.0/100 000 in China to 22.5/100 000 in Finland.[24] In Japan the incidence of SAH is one of the highest in the world, 23.0/100 000.[31] Since Swedish SAH patients not are included in the Swedish stroke register, Riks-Stroke, [32] previous epidemiological studies on Swedish samples are regional; covering northern Sweden, [24,33] southern Sweden[34,35] and Örebro. [36] To our knowledge only one study has investigated national incidence variations in Sweden and found an overall incidence of

12.4/100 000 person-years, increasing by latitude from 11.4 in the south to 15.2 in the north, and incidence was higher for women (14.4/100 000) than for men (10.3/100 000).[37] In the aforementioned Swedish studies, all diagnoses of SAH were included. However, SAHs could have causes other than ruptured aneurysms as the percentage of SAHs originating from ruptured aneurysms varies between >75% to >90% among SAH studies.[38] A specified aneurysmal SAH incidence of 5.5/100 000 person years has been reported in Uppsala, a catchment area north of Stockholm.[39]

2.4 RISK FACTORS FOR DEVELOPING ANEURYSMS AND SAH

Familial aneurysms

Several studies have reported that relatives of intracranial aneurysm patients have an increased risk in the development, growth and rupture of aneurysms, a phenomenon which is called 'familial aneurysms'. [38,40-43] A two-to-four times higher prevalence of intracranial aneurysms have been found in symptom-free first-degree relatives compared to the general population, [41] and the risk strongly increases in cases where there are two or more affected first-degree relatives.[42,43]

Hormonal factors

The predominance of aneurysmal SAH in women starts at age 55 and increases thereafter,[23] leading to suggestions that female sex hormones may play a role in the pathogenesis of intracranial aneurysms.[44] Female sex hormones and their relation to SAH have been studied as both endogenous and exogenous factors, but the results are ambiguous; Johnston et al.[45] reported that high-estrogen oral contraceptives produced a small increased risk for SAH, but, in contrast, other studies have found that oral contraceptives do not affect the risk of SAH.[46-48] The use of postmenopausal hormone replacement therapy have been reported to reduce the risk of SAH.[46,47,49] Pregnancies have been reported to have a protective effect on the risk of SAH[47,50] and others have found that the risk of SAH mortality decreases in women who have experienced more than one pregnancy.[51] Mhurchu et al.[47] reported a declined risk of SAH with older maternal age at first birth, but conversely, Yang et al.[51] found an increased risk of 8% for SAH mortality for each year of the mother's age at first birth.

Hypertension, smoking and alcohol

The most important risk factors for SAH are smoking, hypertension, [52,53] and excessive alcohol consumption.[46,48] Feigin et al.[46] found that hypertension increased the risk of

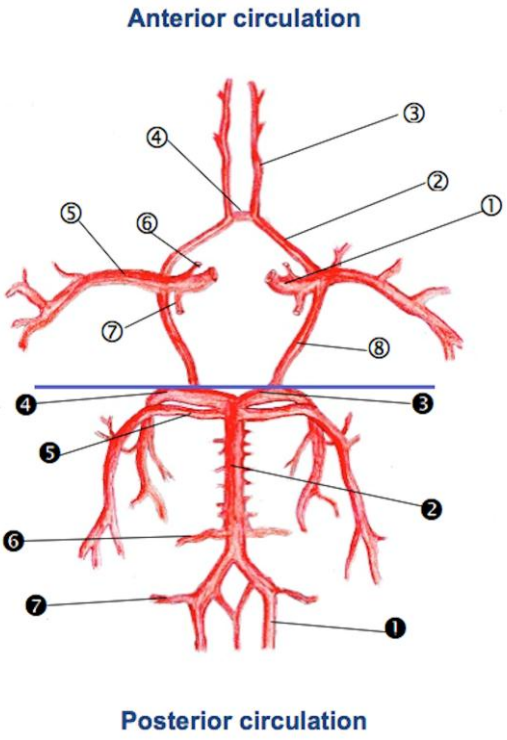
SAH by 2.5 times. Smoking women had a two-fold risk of SAH compared to smoking men, and excessive alcohol consumption had a more hazardous effect in women.

2.5 FEATURES OF ANEURYSM RUPTURE

SAH occurs at a younger age than ischemic strokes,[54] as a large multinational study demonstrated, where a total target population of more than 3.8 million people showed an average age of 49.0 (±10.0) years at onset of SAH.[24] The mean age at onset of stroke for other stroke types in Sweden is above 70 years.[55]

The circumstances surrounding intracranial aneurysm ruptures have been studied and results showed that aneurysms ruptured during stressful events (physical exertion or emotional strain) in 42.8% of cases. On the other hand, in 34.4% of cases, aneurysms ruptured during non-stressful activities, and for 11.8% of cases, during sleep.[56] Significant differences in the diurnal variation of onset aneurysm ruptures have been found, with an initial peak of incidence between 8:00 and 10:00 a.m., and a second peak between 6:00 and 10.00 p.m. Ruptures are less likely to occur between 10.00 p.m. and 6:00 a.m. No significant seasonal variation has been found.[31]

The three most common aneurysm locations are within in the anterior circulation of the circle of Willis: 30% in the region of the anterior communicating artery (ACoA), 25% in the region of the posterior communicating artery (PCoA) and 14% in the region of the middle cerebral artery (MCA).[16] Only 5-15 % of aneurysms are located in the posterior circulation (vertebral and basilar arteries).[16,57] Figure 1 shows a schematic overview of the arteries in the circle of Willis.



Anterior circulation

① Internal Carotid Artery (ICA)
② Anterior Cerebral Artery (ACA) segment A1
③ Anterior Cerebral Artery (ACA) segment A2 (Pericallosa)
④ Anterior Communicating Artery (ACoA)
⑤ Middle Cerebral Artery (MCA)
⑥ Ophthalmic Artery (OA)
⑦ Anterior Choroid Artery (AChA)
⑧ Posterior Communicating Artery (PCoA)

Posterior circulation

❶ Vertebral Artery
❷ Basilar Artery
❸ Posterior Cerebral Artery (PCA) segment P1
❹ Posterior Cerebral Artery (PCA) segment P2
❺ Superior Cerebellar Artery (SCbA)
❻ Anterior Inferior Cerebellar Artery (AICA)
❼ Posterior Inferior Cerebellar Artery (PICA)

Figure 1. Arteries in the circle of Willis

Clinical presentation of aneurysm rupture

When an intracranial aneurysm ruptures, blood leaks into the subarachnoid space and causes a SAH, classically characterized by explosive onset of severe headache, decreased level of consciousness, nuchal rigidity and vomiting.[58] Depending on the volume and the location of the bleeding, the aneurysm rupture may also produce hematomas; subdural, intracisternal, intracerebral, intraventricular, or a combination of

these.[16,59] During the rupture the intracranial pressure rises to diastolic blood pressure, and cerebral blood flow only occurs during the systolic phase. When the initial bleeding is not fatal, it is believed that the bleeding stops by a combination of coagulation and tamponade.[16] Symptoms of aneurysm rupture range from mild, transient headache to deep coma with failing vital signs. When there is a hemorrhage into the brain, or into the cranial nerves, or when the regional blood flow is diminished in important areas of the brain, focal neurological deficits accompany the symptoms.[58]

A commonly used scale for clinical assessment of the patient's level of consciousness is the Glasgow Coma Scale (GCS). In the GCS, three aspects of behavior are evaluated and summed; motor responsiveness, verbal performance and eye opening. The GCS values range from 3 to 15.[60]

For assessment of the patient's neurological grade, the Hunt and Hess classification (H&H) of SAH[61] is commonly used. H&H classifies the clinical condition into five grades, as follows:

I: Asymptomatic, or minimal headache and nuchal rigidity,

II: Moderate to severe headache, nuchal rigidity, no neurological deficits (except for cranial nerve palsies that may be present),

III: Confusion and drowsiness or mild focal deficits,

IV: Stupor, moderate to severe hemiparesis, possible early decerebrate rigidity and vegetative disturbances,

V: Deep coma, moribund appearance, decerebrate rigidity.[61]

Natural history without aneurysm occlusion

The prognosis of surviving patients depends on the severity of the initial bleed, the occurrence of complications and how successful the treatment to secure the aneurysm is.[62] The complications include both intracranial complications (such as recurrent bleeding, hydrocephalus, vasospasm), and systemic complications (such as fever, hyperglychaemia, hypertension/hypotension, pneumonia, hyponatremia, myocardial ischemia).[62] In an early study on hospitalized aneurysmal SAH patients with untreated aneurysms, recurrent hemorrhage occurred in 10% of cases during the first week, in 12% the second week, in 7% the third week, in 8% the fourth week, and in 14% of cases in weeks 5-12 after the onset.[63] Winn et al.[64] followed-up aneurysmal SAH patients with untreated aneurysms for up to 20 years, and reported a re-bleed rate average of at least 3% per year. The rate of fatal re-bleeds were 2% per year during the first decade.

2.6 MANAGEMENT OF ANEURYSMAL SAH

Before aneurysm securement

In the acute care after aneurysmal SAH, multidisciplinary collaboration between neurosurgeons, neuroradiologists, neurointensivists and specialist nurses is essential.[62] In Sweden all incidents of SAH are referred for treatment at intensive care units. Further medical investigations and aneurysm treatments are performed at neurosurgical departments.[65] During the intensive care period, highly advanced technological care is performed, including: continuous observations of neurological functions and vital parameters; detection and treatment of cerebral vasospasm; intracranial pressure monitoring; pain assessment and treatment; prevention of vein thrombosis and pulmonary embolism; pressure sore prophylaxis; and pharmaceutical administration.[62,66-69] At hospital admission most patients are too ill to assimilate information, thus during this first stage information is instead given to family members.[69]

Aneurysm occlusion

The treatment goal for ruptured intracranial aneurysms is to prevent re-bleeding by completely and permanently occluding the aneurysm thus excluding it from the cerebral circulation while preserving the blood flow in the parent artery and perforating vessels. The choice of therapy depends on factors such as the patient's age and condition, aneurysm location, aneurysm characteristics, and the occurrence of intracerebral hematoma. The two most common treatment alternatives are microsurgical clipping and endovascular coiling.[70] Surgical clipping is performed via a craniotomy, when a stable metal clip is placed across the neck of the aneurysm.[71] Endovascular coiling excludes the aneurysm from the circulation by embolization with detachable coils, filling the aneurysm sac.[70] Rapid advances in the 1990s in endovascular technology and techniques have led to an increasing number of aneurysms being treated with coiling[72] and have also decreased the proportion of earlier untreatable aneurysms.[73,74] Nowadays, assisting techniques could be used when the aneurysm neck is wide, such as deploying a stent over the aneurysm neck or balloon remodeling before coiling.[70,75] A small proportion of aneurysms are considered unable to be completely excluded from circulation by the usual methods; some of them can be treated by wrapping cotton, muslin, or adhesive material or muscle round the aneurysm, and sometimes the wrapping material is secured with a clip ligation.[76,77] Complex aneurysms can be treated with bypass surgery followed by trapping the parent artery.

Bypass surgery could be performed extracranial-intracranial or intracranial-intracranial.[78,79] The timing of treatment is most often divided as follows: early treatment within 0-3 days from rupture; intermediate treatment 4-7 days after rupture; and late treatment more than 7 days after rupture. It has been suggested that early and intermediate treatment improves outcomes after aneurysm rupture.[80] Benefits of early treatment are a reduction of risk of a re-bleed and safer prevention/treatment of cerebral vasospasm.[81]

After aneurysm securement

When the aneurysm is secured the care is continued at the intensive care unit with some adjustments: if the patient remains stable, neurological and vital parameter assessments are decreased and the patient's motor activity is gradually increased.[69] When the health condition has stabilized and the risk of cerebral vasospasm is low, the patient is transferred to a neurosurgical ward. Vital signs and neurological assessments should be performed every 4-8 hours and medications are to be maintained. Activity is further increased as tolerated by the patient. Physical and occupational therapy may be consulted for assessment of patient functioning and needs for rehabilitation.[69]

A commonly used scale to assess neurological outcome at hospital discharge is the Glasgow Outcome Scale (GOS), as recommended by the World Federation of Neurosurgical Societies in the assessment of outcomes after SAH.[82]

Table 1. Glasgow Outcome Scale[83]

Category	Description
1	Death
2	Persistent vegetative state
3	Severe disability, conscious but disabled, dependent on daily support
4	Moderate disability, disabled but independent
5	Good recovery, resumption of normal life although there may be minor deficits

After hospital discharge - rehabilitation

Effective rehabilitation requires multidisciplinary competence with experience of, and specialization in stroke care, from physicians, nurses, physiotherapists, occupational therapists and speech therapists. During rehabilitation, multidisciplinary interventions follow national guidelines and are usually specific and task-oriented, but should also be in accordance with the patient's own goals.[84]

The National Swedish Board of Health and Welfare recommends ensuring access to rehabilitation during the first post-stroke year,[65] but all aneurysmal SAH patients do not receive rehabilitation.

Follow-up and support

The follow-up of ischemic stroke patients after rehabilitation varies widely; from nothing at all, to outpatient therapy.[85] Kirkevold[85] describes the discharge from the rehabilitation unit as a transition into a new phase – patients struggle to return to their former life, they re-think who they are, what their priorities are, and emotionally processes losses – which could be considered a kind a grief work. Most of this adjustment process occurs after discharge from the stroke rehabilitation unit.

The Helsingborg Declaration 2006 on European Stroke Strategies is a statement of the overall aims and goals of stroke management in European countries to be achieved by 2015. The stated goal for the evaluation of stroke outcome and quality assessment is that all countries should have a system for the routine collection of data needed to evaluate the quality of stroke management.[84] One of the core indicators for assessment of quality of care is population-based monitoring of the incidence of stroke as well as case fatality.[84] In Sweden the stroke care is monitored by the Swedish Stroke Register (Riks-Stroke). Established in 1994, it includes all 76 hospitals in Sweden that admit acute stroke patients. This register follows patient outcomes (such as functional ability, perceived health, QoL and mood), quality of care and community support three months and one year after the stroke event. However, patients with the stroke type SAH are not eligible to be included in this register and, to date, the Riks-Stroke has not attempted to involve neurosurgery services in the collection of data.[32] Because there is no existing national SAH register, some epidemiological data are lacking for these patients. It is also unknown how aneurysmal SAH patients perceive quality of care or support.

2.7 MORTALITY AND DEATH CAUSES

The overall risk of death before receiving medical attention for aneurysmal SAH has in a meta-analysis been calculated to be 12.4% of cases.[86] Ruptured aneurysms in the posterior circulation of the brain are associated with a higher risk of death before hospital admission.[86]

A multicenter study on SAH epidemiology in 11 populations from Europe and China showed that the 28-day case fatality ranged from 23% to 62%, with a mean of 42%.[24] In a meta-analysis including 39 studies from Asia, Australia, New Zealand,

North America, South America and the Caribbean, the case fatality ranged 8.3 – 66.7%. In Finland and north Sweden the case fatality was found to be 44.4%. A Swedish study on SAH epidemiology from the Swedish hospital discharge and Cause of death registries showed a 28-day case fatality of 31.7%.[37] However, none of these studies distinguished aneurysmal SAH from other types of SAH, and SAH cases of non-aneurysmal origin have generally a better prognosis.[37] Information on the case fatality after aneurysmal SAH in Sweden is therefore insufficient.

The major causes of death the first month after aneurysmal SAH are the initial and recurrent bleeding.[87] In the International Subarachnoid Aneurysm Trial (ISAT) the most common death cause during the first year after the aneurysm rupture was complications of severe dependent survival (such as infections).[88] After the first year of the onset of aneurysmal SAH, the majority of deaths are cardiac-related or due to malignancies.[88-90]

2.8 SURVIVING ANEURYSMAL SAH AND LIVING WITH THE CONSEQUENCES

Survivors of aneurysmal SAH differ from other stroke survivors; the proportion of women is higher and the mean age at onset is approximately 20 years younger compared to other stroke types.[24,55] This younger mean age implies that SAH, to a larger extent, strikes people who are in their prime working years and thus they are likely to be responsible for young children.

Physical consequences

Well-known functional impairments after both ischemic and hemorrhagic strokes include motor impairments, sensory deficits, visual deficits, and speech and language disorders.[91] Motor impairments can affect movements of the face, arms and legs, which affect an individual's ability to perform activities of daily living.[92] Meta-analyses have been conducted to evaluate the percentage of patients being disabled following intracranial aneurysm rupture; for example, Hop et al.[93] analyzed disabilities 1-48 months after the onset and found that on average, 10-20% of survivors of aneurysmal SAH become so disabled that they lose their independence and have to rely on others to carry on in their daily lives. In the meta-analysis by Nieuwkamp et al.,[94] 55% of patients remained independent and 19% were dependent on help for activities of daily living 1-12 months after the onset. Carter et al.[95] followed 182 patients from 1-6 years

after SAH and found conflicting results: 76.2% had no disabilities, and only 3% were severely physically disabled.

About 20% of patients experience one or more epilepsy seizures after aneurysmal SAH, and most frequently the seizures are not recurrent.[96] Late epilepsy is, in the vast majority of patients, manifested within two years after the SAH. Epilepsy could be caused by the SAH itself, aneurysm treatment, or both.[96] The risk of epilepsy has been found to be significantly higher in patients treated with clipping. The suggested explanation for this is that during surgical procedures, disturbances of the cortical surface occur, due to dissection and retraction.[97] Other predictors that increase the risk of epilepsy have been found to be younger age,[96,97] a large amount of subarachnoid blood on CT scan, vasospasm, thromboembolic complications and MCA aneurysm location.[97] Epilepsy has a significant impact on individual patients and their families' lives due to driving prohibition, and having the condition may also affect their employment status.[97]

Hydrocephalus (HC) is a common sequel to aneurysmal SAH. In general, post-hemorrhagic HC is caused by obstructive mechanisms due to blood or adhesions blocking the cerebrospinal fluid circulation within ventricles and cisterns.[98] HC after SAH could be developed acutely or insidiously over weeks or months and could be classified into three temporal stages; acute (0-3 days after SAH), sub-acute (4-13 days after SAH) and chronic ($\geq$ 14 days after SAH).[99] Acute HC may resolve spontaneously, but in 18-20% of aneurysmal SAH patients chronic HC develops and a permanent cerebrospinal fluid shunt implantation is needed.[98-100] The risk of chronic HC has been found to be lower in patients treated with clipping, and the suggested explanation is that open surgery affords the opportunity to open cerebral cisterns and remove the clot and blood.[98] Chronic HC after aneurysmal SAH has been found to decrease physical HRQoL.[101]

Another problem that impacts upon the patients' lives is post-stroke fatigue, an overwhelming feeling of exhaustion that leads to the difficulty or inability to sustain even routine activities.[102,103] Staub & Bogousslavsky[103] argue that post-stroke fatigue is not a component of post-stroke depression, and that these two conditions develop independently of each other. Post-stroke sleep-wake disorders (SWD) may play a role in subjective fatigue because they may cause somnolence and fatigue.[103] SWD have previously been reported in 34-47% of cases 1-7 years after SAH.[104-106] Fatigue was reported by 17% of patients nearly nine years following aneurysmal SAH.[107] Stroke-

related features, such as location of stroke lesion and severity of neurological impairment, do not seem to play a role in post-stroke fatigue.[103]

Psychological consequences

Anxiety and depression after ischemic stroke is a well-known problem and it has been debated in the literature whether it is a reaction to the onset of disability and life changes, or if it is an organic result of biochemical changes from neurological damage.[108,109] Berry et al.[110] suggested several factors that may contribute to psychological distress in patients after aneurysmal SAH; a recent life threatening experience, fear of recurrent hemorrhages, anxiety over symptoms, lack of understanding of cognitive difficulties and changes in social roles.

Post-stroke depression is defined as a prominent and persistent mood disturbance, characterized by depressed mood, or lack of interest, or lack of pleasure in all or almost all activities.[111] Post-stroke depression prevalence ranges between 5 and 67% after all types of strokes. After two years, 18-55% (with a mean prevalence of 33%) of stroke survivors are depressed.[112] Depression after aneurysm rupture has been assessed at different time points. Studies have reported depression in 23-28% of cases 21-36 months after rupture; [113,114] Carter et al.[95] reported that 36.3% of respondents scored depression to some extent, and 23% scored for severe mood disturbances 1-6 years after the onset. Lindberg[115] followed-up respondents in mean seven years after SAH, and reported that 22% of respondents were depressed. Bellebaum et al.[116] reported that patients treated with clipping scored with significantly more depressive symptoms than coiled patients.

Visser-Meily et al.[114] reported anxiety symptoms in 32% of aneurysmal SAH patients 2-4 years after the rupture. Nearly nine years after aneurysmal SAH, Wermer et al.[107] reported 11% of patients scoring with anxiety symptoms.

Disorders of emotional expression control, also called emotional lability or emotionalism, is common after strokes in general, and is described as the lack of voluntary control of the expressions of crying, laughter, or both.[112] Emotionalism is an increase of the frequency of crying or laughing, that starts unexpectedly or with little warning.[117] It can be precipitated by nonspecific or inappropriate stimuli, or by an appropriate stimuli in an inappropriate context.[112]

Cognitive function after SAH has been assessed in several studies at different time points following aneurysm treatment, and assessments areas are both global cognition

and specific domains such as memory, perception and executive functions. Executive functions are the mental resources needed to control sequences of thoughts and the actions that are needed for planning, organizing, setting goals, follow-through activities and problem solving.[118]

Both Mayer et al.[119] and Hillis et al.[120] conducted cognitive testing in patients 3 months after aneurysmal SAH. Mayer et al.[119] found impairments in visual and verbal memory, reaction time, motor function, executive function, visuospatial function and language function, and Hillis et al.[120] found significant lower performance in memory tests. Significantly lower scores on memory tests were also found in SAH patients eight months after aneurysm rupture when compared to matched controls.[110] Sonesson et al.[121] reported that only 17.2% of patients with satisfactory neurological recoveries were cognitively unaffected or had very mild dysfunctions in mean 56 months after aneurysm rupture. Hütter and Gilsbach[122] followed aneurysm patients with good neurological outcome with cognitive tests 1-5 years after rupture and found that 54% of patients were substantially impaired in some aspects of cognitive capacity. Older patients had significantly worse cognitive problems than younger patients. Ogden et al.[105] followed patients 4-7 years after rupture and found that subjective memory difficulties were reported by 45.3% of patients. In a study on cognition five years after SAH in general, SAH patients performed significantly worse on all language- and information-processing speed tests when compared to matched controls.[123]

It has been proposed in the literature that aneurysm location may influence cognitive outcome, but the results are inconsistent. Both Tidswell et al.[124] and Stenhouse et al.[125] addressed cognitive function after aneurysm rupture in the ACoA, and found that patients with such aneurysms were not significantly more cognitively impaired compared to other aneurysm locations, however, the majority of patients in these studies, 65% and 59% respectively, did indicate cognitive problems. Hütter et al.[126] found that patients with ruptured left-sided MCA aneurysms had significantly more problems in cognition and communication compared to right-sided ones. They also found that aneurysms presenting with additional intraventricular hemorrhage had significantly more problems in cognition. In contrast, Haug et al.[127] found somewhat better cognitive performance for patients with MCA aneurysms compared to patients with ACoA aneurysms, attributed to the fact that a SAH from an ACoA aneurysm affects the medial part of the frontal lobes. In other studies, the aneurysm site has not shown any relation to cognitive outcome.[128] When cognition has been assessed in relation to treatment variables, results have shown no significant differences in

cognition when comparing treatment modalities, [128] or between late versus early aneurysm obliteration.[121]

It is well known that stroke may produce persistent personality disturbances, defined as a change from the previous characteristic personality, including labile, disinhibited, aggressive, apathetic, and paranoid types.[112] In an early study by Storey,[129] personality changes after SAH were assessed, mostly from the statements of close relatives, in 261 patients nearly three years after the onset. The results showed impaired personality in 41%, and improved personality in 5% of cases. Several changes in personality were described, such as more irritable, emotionally labile, withdrawn, selfish and suspicious. Ogden et al.[105] reported subjective experienced personality changes in 48.3% of cases in a sample of SAH patients 4-7 years after the onset. Examples of reported subjective changes in their study were that they were more irritable, had lowered self-confidence and increased emotionality. Wermer et al.[107] followed-up SAH patients nearly nine years after the onset and 59% of cases reported subjective personality changes, of which 13% reported positive personality changes. The most common changes were increased agitation, apathy and increased emotionality.

Social consequences

Daniel et al.[130] reviewed studies reporting social consequences of stroke (all stroke types) for working-aged adults. Slightly more than half of the patients who worked before the stroke had returned to paid employment 6-12 months after the onset. In studies quantifying social or leisure activities, a decrease of 15-79% was reported. In studies reporting consequences for family relationships, 5-54% of samples experienced family problems. Described effects for children of the patients included conflicts and an impact on caregiving. Deterioration in sexual relationships ranged from 5-76%.[130]

There are few studies reporting social consequences after aneurysmal SAH, and the findings in these studies are similar to those of Daniel et al.[130] Among patients returned to work, a large proportion report not being able to return to the previous level of employment, with shorter working hours and less responsibility.[105,107,131]

The burden on relatives and family strain after aneurysmal SAH has also been reported. Mezue et al.[132] describe that there is often a 'honeymoon period' after the patient's discharge, cushioned by the relatives' high expectations of recovery. However, as time passes, the reality of the permanence of the condition becomes

apparent and the significant others may not be able to cope with all of the changes that impact on their own lives. Pritchard et al.[133] depict these difficulties as dysfunctional stress on caregivers; that it was easier to deal with the initial crisis at the onset SAH than coping with the patient after they had returned home. The caregivers also described that their employment was affected.[133] Affected intimate relations due to a loss of libido has been reported,[131] and nearly nine years after aneurysmal SAH, 7% of respondents were divorced as a direct result of the consequences of the SAH.[107]

Dealing with changes

When experiencing a dramatic change in health status, such as a life-threatening disease, one's footing in life may be lost. The impact may be so complex that it intrudes on every aspect of the patient's reality; the previous reality does not exist and a new one has not yet been constructed. This alteration results in a period of uncertainty – a transition to something new.[134] Transition could be described as a period of instability; a passage from a fairly stable life phase, state or condition to another.[135] People do not experience transitions uniformly, even when the circumstances are similar. The meaning that the individual constructs out of an experience of transition depends on several dimensions, such as: duration, scope, reversibility, anticipation and voluntariness.[135] Different types of transitions have been identified: *health/illness transitions* could be caused by alterations in health status, such as moving from wellness to acute or chronic illness, or by moving between different levels in the health care system over the course of an illness. *Situational transitions* occur by a change of position or circumstance, for example, changes in family situations, in professional roles, or a near-death experience.[136] Transition implies adaptation to change, not to return to a pre-existing state.[137] Most transitions involve critical turning points or trigger points that are associated with an increased awareness of changed reality, its consequences and the permanency of the alteration.[134,139] These periods are associated with heightened vulnerability.[139] Two such trigger points have been identified during the first year after ischemic stroke; at discharge from rehabilitation clinic, and when returning to work or other meaningful activities outside their close social network, with increased needs at each point for consolation, emotional encouragement and help to interpret future possibilities and limitations.[85] Transitional experiences after aneurysmal SAH have not been described in the literature.

3 THESIS RATIONALE

Patients suffering from intracranial aneurysm rupture differ from ischemic stroke patients in some important aspects: they are younger at the onset, women are predominant and they are treated at neurosurgical clinics. Furthermore, they are not included in the Riks-Stroke register, and there is no national SAH register, thus existing epidemiological data are insufficient.

Although numerous studies on clinical outcomes after aneurysmal SAH have been conducted, there are still unexplored areas related to its long-term impact on life. Previous studies have looked at aspects of HRQoL in patients after intracranial aneurysm rupture but these are most frequently conducted during the first 18 months after the onset of aneurysm rupture. Most commonly, a cross-sectional design is used, and there are few studies that follow aneurysmal SAH patients longitudinally to detect changes over time. Long-term studies, with follow-up more than five years after the rupture, are scarce. Knowledge on the long term perceived consequences patients are suffering from after intracranial aneurysm rupture is therefore limited.

4 AIMS

The overall aim of the studies in this thesis was to describe impact on life up to ten years after intracranial aneurysm rupture in terms of health-related quality of life, changes in everyday life and descriptive epidemiology. This thesis is based on four papers with the following specific aims:

I. To describe changes and transitions in everyday life the first two years following an intracranial aneurysm rupture.

II. To describe epidemiology in relation to gender differences and treatment modalities ten years after intracranial aneurysm rupture.

III. To describe psychological, physical and cognitive functions ten years after intracranial aneurysm rupture, and to identify any differences in outcome variables between age-groups, gender or aneurysm locations.

IV. To measure HRQoL and to explore factors affecting HRQoL, ten years after aneurysmal subarachnoid hemorrhage.

5 MATERIAL AND METHODS

5.1 DESIGN

This thesis includes observational studies with different designs and approaches, depending on the purpose of the study. Table 2 shows an overview of the used designs in the papers included in this thesis.

Table 2. Overview of designs

Paper	Design	Approach	Type of data	Time-frame from aneurysm rupture
I	Prospective longitudinal	Mixed method	Self-reported outcomes	6 months, 1 year, 2 years
II	Retrospective cohort	Quantitative	Register data	10 years
III	Cross-sectional	Quantitative	Self-reported outcomes	10 years
IV	Retrospective cohort	Quantitative	Self-reported outcomes	10 years

5.2 SETTING AND SAMPLES

In this thesis project, two data collections were conducted. Patients in both data collections were recruited from a Swedish neurosurgical clinic in Stockholm County, covering approximately 2 million inhabitants. All patients in the aneurysm samples were acute admissions; patients treated for non-ruptured aneurysms were not included. The number of admitted patients with ruptured intracranial aneurysms at the clinic is about 100 per year. The clinic uses a clinical pathway protocol for ruptured aneurysms, including earliest possible aneurysm occlusion and aggressive anti-vasospasm treatment.[140] A return visit, with the possibility to meet the neurosurgeon or radiologist who conducted the aneurysm occlusion, is performed about three months after the rupture. Radiological follow-up is performed and is largely the same regardless of whether the patient was treated with open surgery or endovascularly. The only exception is that a conventional X-ray is also performed three months after the onset for endovascularly treated patients. Thereafter, all aneurysmal SAH patients are followed with angiograms at 1, 3, 5, 10 and 20 years after the onset.

Paper I.

Patients (n = 88) were prospectively consecutively recruited from 1st of March 2006. Inclusion criteria were: Swedish citizen (to enable follow-up and assess patient records); a sufficient health condition allowing participation (i.e. Glasgow Outcome Scale >2 at hospital discharge); and able to communicate in Swedish. Patients were

identified from International Classification of Disease codes (ICD-10)[141] in the hospital's statistics database of admitted patients (LISA), and from the neurosurgical clinic's intensive care unit SAH register. Figure 2 shows a flowchart of the sample in paper I. There were no significant differences between patients declining participation (n = 16) and those included in the study concerning rupture age, sex, aneurysm treatment, aneurysm locations, or GOS at hospital discharge.

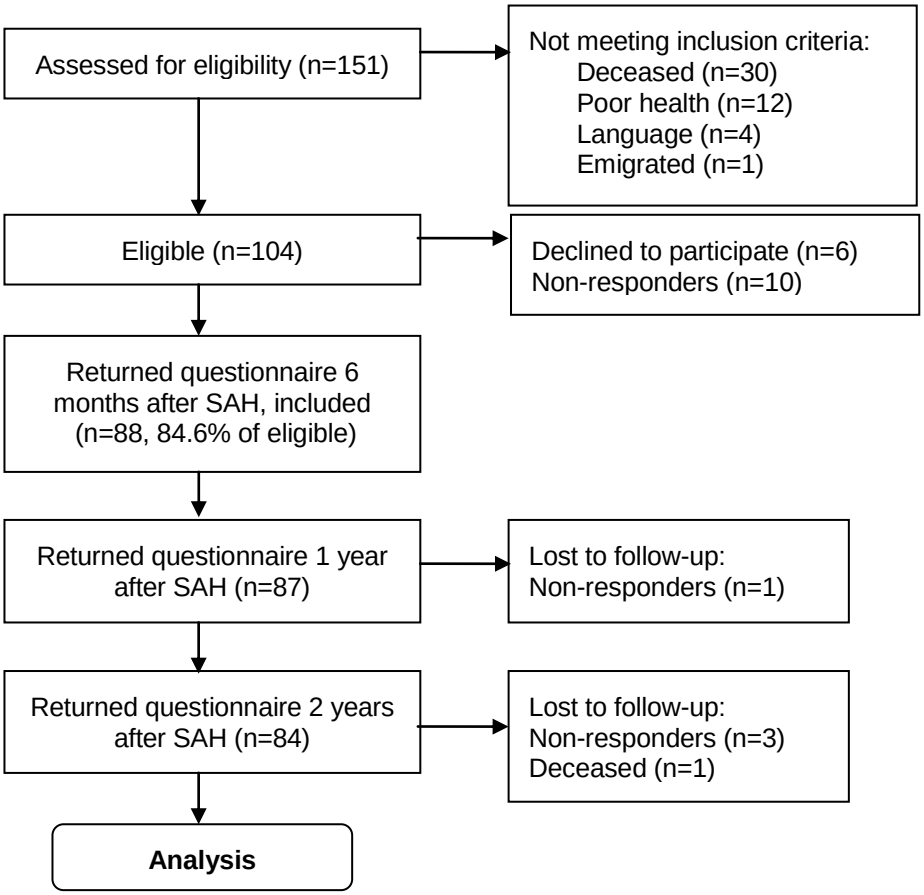


Figure 2. Sample in paper I

Paper II.

Included patients (n = 468) were retrospectively identified through clinical registers based on ICD-9 and ICD-10 diagnoses. All consecutive cases of aneurysmal SAH from 1 January 1996 to 31 December 1999 were eligible. The inclusion criteria were: Swedish citizenship, and living in Sweden for the ability to retrieve Swedish register data on survival and cause of death.

Papers III and IV

Survivors from the sample in paper II were assessed for further follow-up in papers III and IV. Inclusion criteria were: a sufficient health condition allowing participation; able to communicate in Swedish; and Swedish citizenship for the ability to follow-up and assess patient records. From the eligible 273 patients, 79.5% (n = 217) were included in papers III and IV. There were no significant differences between patients declining participation (n = 56) and those included in the study concerning age, sex, aneurysm treatment, aneurysm locations, or GOS at hospital discharge.

In paper IV a comparison sample from general population (n = 434) derived from the Stockholm Public Health Survey 2006 was used. The Stockholm Public Health Survey was sent from Stockholm County Council to monitor population health, and was sent to a representative sample of 57 000 persons aged 18-84 years in Stockholm County, with a response rate of 61%. Each respondent in the aneurysm sample was matched by age and sex to two controls, randomly selected by the statistical program SPSS. Figure 3 shows a flowchart of samples in papers II to IV. Characteristics of respondents in papers I-IV is presented in table 3.

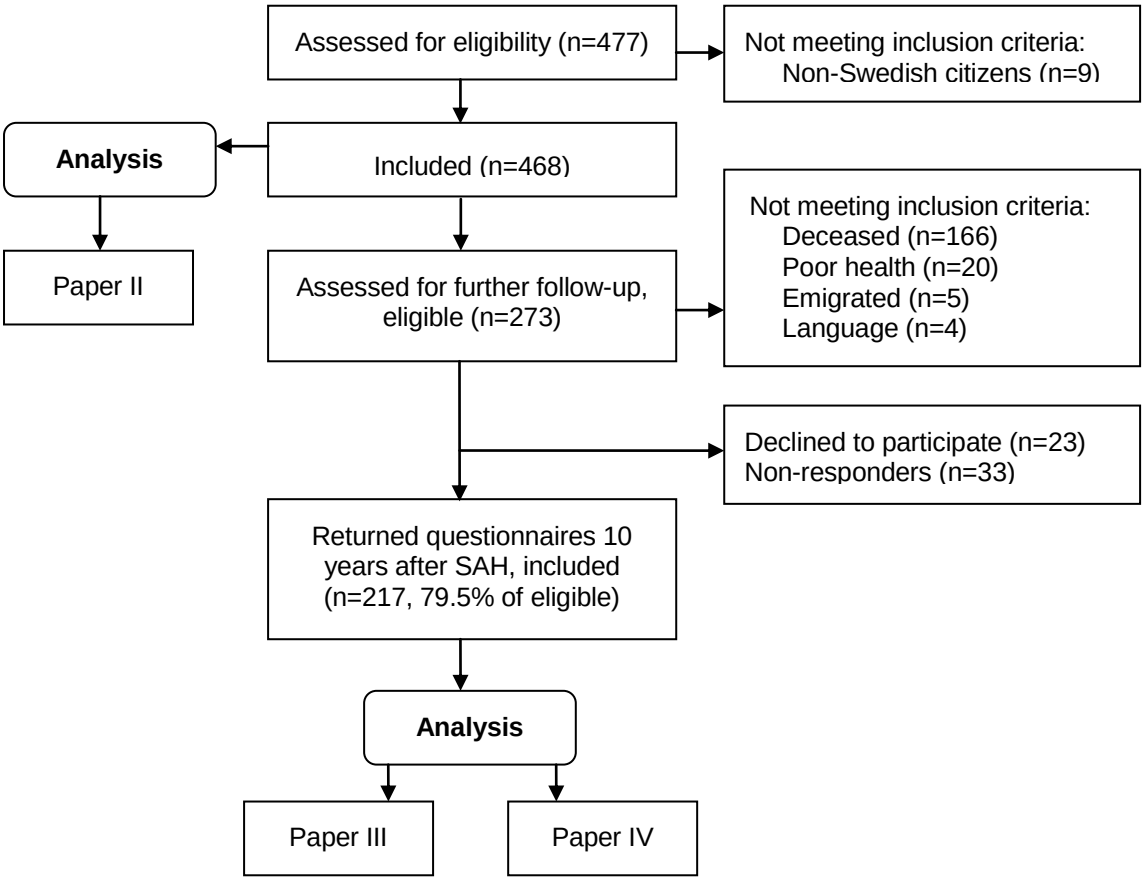


Figure 3. Aneurysm sample in papers II-IV

Table 3. Characteristics of respondents in papers I-IV

Paper	n	Age (years) at onset m (SD)	Age (years) at follow-up m (SD)	Males / females n (%)	H&H at admission n (%)	Treatment: O/E/C n (%)	GOS at discharge n (%)
I	88	52.6 (14.2)		30/58 (34/66)	I-III: 72 (82) IV-V: 16 (18)	34/54/0 (39/61/0)	3: 14 (16) 4: 24 (27) 5: 50 (57)
II	468	54.9 (13.2)		139/329 (30/70)	I-III: 289 (62) IV-V: 179 (38)	325/67/76 (70/14/16)	1: 89 (19) 2: 19 (4) 3: 93 (20) 4: 72 (15) 5: 195 (42)
III	217	50.6 (12.0)	60.7 (12.0)	63/154 (29/71)	I-III: 174 (80) IV-V: 43 (20)	181/35/1 (83/16/1)	2: 3 (1) 3: 38 (18) 4: 35 (16) 5: 141 (65)
IV	651:						
Aneurysm sample	217	50.6 (12.0)	60.7 (12.0)	63/154 (29/71)	I-III: 174 (80) IV-V: 43 (20)	181/35/1 (83/16/1)	2: 3 (1) 3: 38 (18) 4: 35 (16) 5: 141 (65)
Comparison sample	434		60.7 (11.9)	126/308 (29/71)			

Treatment: O/E/C = open surgery/endovascular procedure/conservative
H&H= Hunt and Hess classification of subarachnoid hemorrhages
GOS = Glasgow Outcome Scale

5.3 DATA COLLECTION

Clinical data were collected from digital and paper patient records, epidemiological data were retrieved from the Swedish Cause of Death Register and county council statistics from Swedish Association of Local Authorities and Regions.[142] Six instruments were used to assess different aspects of HRQoL. Used measurements, and clinical and diagnostic classifications are further described below.

5.3.1 Measurements

The used instruments, except for a study-specific questionnaire, were chosen on the basis of their previous use in studies on outcome assessment after ischemic stroke or in intracranial aneurysm populations. A short description of the used instruments, including validity and reliability testing, is given below. Table 4 presents an overview of used instruments and their relation to HRQoL domains described by de Haan et al.[10,11]

Table 4. HRQoL domains and aspects in relation to used instruments

Domain described by de Haan et al.[10,11]	HRQoL aspect	Instrument	Data collection method	Paper
Physical health	Physical symptoms	Study-specific	Questionnaire	I, III, IV
	Pain/discomfort	EQ-5D descriptive system	Questionnaire	IV
Functional health	Activity of daily living, mobility	Barthel Index	Telephone interview	III
	Mobility	EQ-5D descriptive system	Questionnaire	IV
	Self-care	EQ-5D descriptive system	Questionnaire	IV
Psychological health	State anxiety	State Trait Anxiety Inventory	Questionnaire	III
	Anxiety/ depression	Hospital Anxiety and Depression Scale	Questionnaire	III
		EQ-5D descriptive system	Questionnaire	IV
	Cognition	Telephone Interview for Cognitive Status	Telephone interview	III
	Mood	Study-specific	Questionnaire	I
	Personality	Study-specific	Questionnaire	I
	Overall perception of health	$EQ\text{-}5D_{index}$	Questionnaire	IV
		EQ VAS	Questionnaire	IV
Social health	Housing conditions	Study-specific	Questionnaire	I
	Working conditions	Study-specific	Questionnaire	I
	Social activities	Study-specific	Questionnaire	I
	Usual activities	EQ-5D descriptive system	Questionnaire	IV

State Trait Anxiety Inventory (STAI) is a measure of psychological status, and distinguishes between state and trait anxiety, measured on two different scales. State anxiety is a function of how an individual perceives stressors and how this fluctuates over time. Trait anxiety can be described as a relatively stable personal trait.[143] The initial version of STAI measured both state and trait anxiety on the same scale, but has later been modified to measure state and trait anxiety on two different scales. In paper III the later form of STAI state anxiety[144] was used. Construct validity of the STAI state has been evaluated in different groups and the results show higher mean values in

stressful situations than in non-stressful situations.[144] In a review study on STAI reliability of 59 studies, mean value for test-retest reliability of STAI state was 0.70 and mean internal consistency was 0.91.[145] The STAI state consists of 20 statements that encourage respondents to describe how they feel at a particular moment in time by rating on a four-point scale: not at all, somewhat, moderately and very much. The scores range from 20 to 80; higher scores indicate higher levels of anxiety. A cut-off score of 39 has been used to detect clinically significant symptoms of state anxiety.[146] STAI have previously been used in patients with ischemic stroke[147] and intracranial aneurysms.[148,149]

Hospital Anxiety and Depression Scale (HADS) is a 14-item measure for detecting states of anxiety and depression constructed by Zigmond and Snaith.[150] The statements are divided into two subscales; one for anxiety (HADS-A) and one for depression (HADS-D). Each subscale score ranges from 0-21; higher scores indicate severe anxiety or depression disorders. Scores ≥8 on HADS-A or HADS-D are considered to indicate anxiety and depression respectively, and are the most frequently used cut-off scores for subscales, with a sensitivity and a specificity for both subscales of approximately 80%. [151] Scores of 8-10 identify mild cases; scores of 11-15 identify moderate cases, and scores ≥16 identify severe cases on HADS subscales.[152,153] HADS could also be considered as a unidimensional scale of mental distress.[154] Using total HADS, a cut-off score of ≥11 has been used on a aneurysmal SAH population, [114] with a sensitivity of 89%, and a specificity of 66%. [155] HADS has, in several studies, been proven to be a valid and reliable instrument for anxiety and depression in patients with both somatic and mental problems, [151,155,156] and in stroke patients.[157] HADS has previously been used after aneurysmal SAH.[107,114,158,159]

The Barthel Index (BI) is a scale constructed by Mahoney and Barthel [160] that describes mobility and activities of daily living (ADL) using ten variables (feeding, transfers, grooming, toilet use, bathing, walking, climbing stairs, dressing, controlling bowels and controlling bladder). The sum of the scores range from 0-100; a higher score is associated with a greater likelihood of being able to live independently at home.[160] Scores lower than 60 indicate severe disability, 61-79 moderate disability, 80-99 mild disability and 100 no disability. [95,161] BI has been shown be a valid and reliable measure of ADL after stroke,[162,163] and also reliable when used in telephone interviews.[164] BI has been used after aneurysmal SAH in several studies.[89,95,158,159,165-168]

Telephone Interview for Cognitive Status (TICS) was developed by Brant, Spencer and Folstein[169] to enable easily accomplished and cost-effective screening of Alzheimer's disease patients. TICS has been shown to be a valid and reliable instrument to detect post-stroke dementia, [170,171] and has been used for cognitive assessment after aneurysmal SAH.[119,172,173] The TICS is a structured 11-item interview that evaluates orientation (to person, time and place), attention (counting backwards 20-1 and serial sevens), verbal memory (recall of a 10-item list), long-term memory (naming Swedish Prime minister and Minister for finance is used in the Swedish version), motor function (finger tap) and language (naming, repetitions and antonyms). The maximum score is 41 and the cut-off score <31 is used to predict cognitive impaired individuals.[169] With the mentioned cut-off score, TICS has a sensitivity of 94%, and a specificity of 100%.[169] Other cut-off score have also been used; Desmond et al.[170] used a cut-off of 25 with a sensitivity of 100% and a specificity of 83%. Barber & Stott[171] found that a cut-off score of 28 gave a sensitivity and specificity of 88% and 85% respectively.

The EQ-5D is a generic HRQoL instrument developed by a consortium of investigators,[174,175] and has been shown to be a valid and reliable measurement of HRQoL after stroke.[176-178] EQ-5D has previously been used in intracranial aneurysm populations.[168,179,180] The EQ-5D consists of two parts: (1) A descriptive system of health in five dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression), classified by the respondent within three levels (no problems, some problems and severe problems). In the mobility dimension the respondent reports the ability to walk about. The usual activities dimension is a social dimension and refers to work, study, housework, family or leisure activities. In the dimension self-care, the respondents report the abilities of eating, washing or dressing by themselves. The descriptive part produces a five-digit number describing a health profile, and the descriptive system generates 243 possible different health profiles that may be indexed in a health preference weight, the EQ-$5D_{index}$. There are several value sets that can be used to calculate an overall preference value.[181] Because there is no Swedish value set, the UK EQ-$5D_{index}$ value set[182] was used in this thesis.
(2) The second part of the instrument is the EQ VAS, a 100-point visual analogue scale with two anchor points where 0 represent worst imaginable health and 100 is best imaginable health.

A study-specific questionnaire was developed by the authors to collect data on physical symptoms, comorbidities, perceived recovery and social aspects of HRQoL (housing situation, work, economy, life-style, personality and family life. The study-specific questionnaire was developed from a literature review, interviewing patients and discussions with experts in the area.

5.3.2 Clinical classifications

At hospital admission the patient's level of consciousness was assessed with the Glasgow Coma Scale, GCS.[60] The patient's neurological status at admission was assessed with the Hunt and Hess classification (H&H) of SAH.[61] Neurological outcome at hospital discharge was assessed by clinicians with the Glasgow Outcome Scale, GOS.[83]

5.3.3 Diagnostic classifications

The International Classification of Diseases (ICD) is an international diagnostic classification for epidemiological, health management and clinical use. WHO nomenclature regulations stipulate the use of ICD in its most current revision for mortality and morbidity statistics by all WHO member states.[141] The ICD is revised periodically and is currently in its tenth revision, ICD-10. The previous revision, ICD-9, was used in Sweden between 1987 and 1996. For eligibility of the samples in this thesis, patients diagnosed with the following ICD codes were assessed; ICD-9 code 430 (SAH, ruptured aneurysm), and the ICD-10 codes: I60.0 –I60.9 (SAH of different origins). Only patients with verified ruptured aneurysms were included.

5.3.4 Procedures

Paper I: Patients were identified from the hospital's database of admitted patients, and controlled against the neurosurgical clinic's intensive care registry. A request of study participation, study information and questionnaires (STAI, HADS, EQ-5D, study-specific) along with informed consent were sent to the patients' homes approximately six months after the hospital admission. When questionnaires and signed consent forms were returned, a structured telephone interview was conducted (using BI and TICS), and to collect any missing data. The same procedures were repeated one year and two years after the rupture. One reminder call was made if the questionnaires were not returned within a two-week time period. Demographic data and clinical variables were retrospectively collected from digital patients' records. The data collection continued

from April 2006 to October 2009. In this thesis, only data from the study-specific questionnaire is presented.

Papers II-IV: Patients admitted for aneurysm rupture 1996-1999 were retrospectively identified through clinic patient registers based on ICD-9 and ICD-10 diagnoses. Living patients were identified through medical records, and they received a request of study participation along with informed consent, study information, and questionnaires (STAI, HADS, EQ-5D, study-specific) approximately ten years after aneurysm rupture. One reminder call was made if the questionnaire was not returned within a two-week time period. After signed consents and questionnaires were returned, a structured telephone interview was conducted for assessment of ADL and cognitive status. The data collection period for the data in papers III and IV continued in 2007-2008. Data on the diseased patients were obtained from paper and digital patient records and from the Swedish Cause of Death Register. The data collection in paper II was completed in December 2009.

5.4 DATA ANALYSIS

An overview of methods for analysis is presented in table 4, and analyses are described in detail below. Statistical significance was set at $p < 0.05$. Statistical analyses were performed by SPSS16.0 and SPSS 19.0 for Windows.

Table 5. Overview of statistical methods and qualitative analysis used in papers I-IV

Analyses	**Paper**			
	I	**II**	**III**	**IV**
Mann-Whitney U test		X	X	
Kruskal-Wallis one-way analysis of variance			X	
Spearman's rank correlation coefficient			X	
Multiple regression analysis				X
Logistic regression analysis			X	
Cronbach's alpha			X	
Chi-square test		X		
Fisher's exact test		X		X
Independent sample t-test		X		X
Kaplan-Meier analysis		X		
Log-rank test		X		
Qualitative content analysis	X			
Cochran's Q-test	X			

Paper I: The sample size was determined though a power calculation to detect a difference in the mean value of 5 points on the instrument State Trait Anxiety Inventory (STAI), with a statistical power of 80% and an alpha value of 0.05. The power calculation showed that that at least 28 individuals in each group (treatment type and gender) were needed.

An exploratory mixed methods approach was used, combining quantitative and qualitative data[183]. The purpose of choosing this approach was to create a complementarity; to be able to describe a fuller picture of perceived changes in life after aneurysm rupture, as well as to compare and contrast variables. During the data collection, intramethod mixing was used with a questionnaire that included both quantitative and qualitative components.[184] The quantitative and qualitative data were given equal priority and were analyzed parallel with statistics and qualitative content analysis.

The quantitative data were analyzed with descriptive statistics. Reported changes within everyday activities and within mood or personality were dichotomized into two categories and compared; no and small changes, versus moderate and large changes. To analyze differences between the three follow-up points, Cochran's Q-test was used.

The textual data were analyzed using manifest content analysis as described by Graneheim & Lundman.[185] Content analysis is a systematic research method to make valid inferences from verbal, visual or written data, in order to describe or quantify specific phenomena. Content analysis can be used alone or in conjunction with other methods. Analysis can be quantitative and merely count frequencies, or qualitative, aiming to provide knowledge and understanding of the phenomena under study.[186] Qualitative content analysis that describes the visible and obvious content are referred to as manifest analysis, and analysis of the underlying meaning is referred to as latent analysis.[185]

Before the analysis began, the material was read repeatedly to gain an overview. The analysis was thereafter carried out in a back-and-forth movement between the whole and parts of the text in the following steps: (1) the text was sorted into content areas according to specific topics in the questionnaire, (2) the text was divided into meaning units, relating to the central meaning of the content area, (3) the meaning units were condensed to shorten the text while preserving the central core, (4) the condensed meaning units were labeled with a code to enable abstraction, (5) sub-categories were formed by related codes, and (6) categories were formed by related sub-categories.

Paper II: In this paper epidemiological differences between men and women, and treatment modalities were examined. To analyze the overall gender distribution of aneurysm rupture, the Chi-square test was used. Fisher's exact test was used to analyze differences between patients treated with clipping and coiling, and differences between men and women. For normally distributed data such as age at aneurysm rupture and age at death, independent sample t-test was used. Mann-Whitney U test was used for comparing not normally distributed interval data, that is to say the differences in frequency of aneurysms between men and women. Ninety-five percent confidence intervals (CI) for proportions were calculated, estimated by normal binomial distribution. Kaplan-Meier analysis and log-rank test were used for testing equality of survival time across gender and treatment modalities. The incidence of ruptured aneurysms per 100 000 person-years was calculated from male, female and overall population data in Stockholm County per year from 1996-1999, [142] and were analyzed by calculating 95% CI according to method by Schoenberg.[187] In this method, table values based on Poisson distribution are used to calculate confidence intervals in neuro-epidemiologic studies.[187]

Paper III: Comparisons between the following groups were made: men and women, age groups and aneurysm location. In the analysis, three age groups were formed; 24-45, 46-65, and >65 years. Aneurysm locations were dichotomized into anterior and posterior circulation of the brain; aneurysms in the anterior circulation include all arteries forward of the posterior cerebral artery, and posterior circulation comprises the posterior cerebral artery and all arteries backwards.

Data were not normally distributed and nonparametric tests were used. For comparisons in three age groups, Kruskal-Wallis one-way analysis of variance was used. Mann-Whitney U test was used for comparisons between groups (anterior/posterior circulation of brain, respondents with/without untreated aneurysm or base remnant). Spearman's rank correlation coefficient was used for examining association between age and cognitive function on the TICS. The internal consistency of STAI, HADS and BI were calculated by using Cronbach's alpha. Logistic regression analysis was used to predict psychiatric disorder with HADS total as the dependent variable.

Paper IV: In this paper, respondents treated for aneurysm rupture were compared to a general population sample. Subgroup analyses in the aneurysm sample were

performed; respondents with comorbidities were compared with respondents without comorbidities, stratified into three age groups: 24-45, 46-65 and 66-90 years, due to the fact that comorbidities are more common with increasing age. Respondents differing in perceived recovery were compared and perceptions of recovery were dichotomized; respondents not at all or partly recovered were compared to respondents fully or mostly recovered. Respondents differing in neurological outcome on GOS at hospital discharge were compared; respondents assessed as GOS 2-3 were compared to GOS 4-5. Active aneurysm treatment modalities were compared; open surgery treated versus respondents treated with endovascular procedure. In this comparison one conservatively treated respondent was excluded. In order to investigate HRQoL in relation to close family support respondents differing in marital status were compared; those living alone were compared to those who were married and cohabitants. To analyze differences between groups, Fisher's exact test and t-test were used. Moderate and severe levels on EQ-5D dimensions were collapsed before analysis. Multiple regression analysis was used to study how the $EQ\text{-}5D_{index}$ varied with sex, age, comorbidity, perceived recovery, neurological outcome, aneurysm treatment and marital status. All explanatory variables were entered as dummy (0/1) variables.

6 ETHICAL CONSIDERATIONS

In Sweden, research involving humans is regulated in a legal act with the purpose of protecting individuals and human dignity when research is conducted.[188] The conducted data collections in this project followed the ethical principles of medical research involving humans outlined in the Helsinki Declaration.[189] The Declaration of Helsinki was adopted by the World Medical Association 1964, and was last amended in 2008. The Declaration of Helsinki is a statement of ethical principles for medical research involving humans and binds the researcher to protect life, health, dignity, integrity, right to self-determination, privacy and confidentiality for the research subjects.[189]

Before conducting the studies, an assessment of predictable risks and benefits was performed. Predictable risks for patients participating in this research project were assessed to be: possible increased anxiety due to follow-up sessions, and that some questions may be seen as intrusive and possibly violating their personal integrity. These risks were judged largely preventable through information concerning confidentiality and follow-up telephone calls. The predictable benefit for the respondents was that they may feel a sense of security when contacted and followed-up by someone familiar with the specific problems that may follow an intracranial aneurysm rupture.

Study information and consent forms were sent to the respondents along with the self-reported questionnaires. A signed informed consent form was obtained from each respondent. In the study information, voluntary participation was emphasized and confidentiality was guaranteed. The subjects were informed that their decision whether to participate or not, as well as interrupted participation, would not affect their ordinary or future care. All data collection was done with no possible dependent relationship between the researcher and the patients. To ensure confidentiality, all questionnaires were provided with a respondent-specific code number. The identifying code list was stored in a locked cabinet and kept separate from the completed questionnaires.

The Stockholm regional board for ethics of research involving humans approved the project (registration numbers 2006/1431-31/1, 2006/283-31/3).

7 RESULTS

The results from papers I, III and IV are presented in the form of the dimensions of HRQoL, formulated by de Haan et al.[10,11] and described in the background section of this thesis.

7.1 PHYSICAL DIMENSION OF HRQOL

During the first two years following an intracranial aneurysm rupture, several aspects of physical impact are described (paper I). A variety of physical symptoms originating from the aneurysm rupture were described, such as different types of pain, loss of smell or taste ability, and a sensitivity for stimuli. This sensitivity was expressed as sensitivity to sounds, strong light, and being in crowds or stressful situations. In papers I and III, problems with disruption of night sleep, daytime sleepiness and fatigue were reported. Problems in all these three areas were reported by 48.9% (n = 43) at six months, 57.5% (n = 50) at one year, and 46.4% (n = 39) at two years (paper I). At ten years, problems in all three areas were reported by 42.9% (n = 93) (paper III). Table 6 shows reported problems with night sleep, daytime sleepiness and fatigue at different time points.

Table 6. Reported sleep-wake disorders and fatigue 6 months, 1 year, 2 years (paper I) and 10 years (paper III) after aneurysmal SAH

Assessment area and degree of rated problems		Follow-up at 6 months, n = 88		Follow-up at 1 year, n = 87		Follow-up at 2 years, n = 84		Follow-up at 10 years, n = 217	
		n	(%)	n	%	n	%	n	%
Disruption of night sleep	None	35	(39.8)	32	(36.8)	34	(40.5)	89	(41.0)
	Some	27	(30.7)	30	(34.5)	33	(39.3)	61	(28.1)
	Moderate	19	(21.6)	17	(19.5)	10	(11.9)	38	(17.5)
	Severe	7	(8.0)	8	(9.2)	7	(8.3)	29	(13.4)
Daytime sleepiness	None	10	(11.4)	13	(14.9)	13	(15.5)	64	(29.5)
	Some	45	(51.1)	38	(43.7)	38	(45.2)	74	(34.1)
	Moderate	21	(23.9)	28	(32.2)	23	(27.4)	60	(27.6)
	Severe	12	(13.9)	8	(9.2)	10	(11.9)	19	(8.8)
Fatigue	None	23	(26.1)	18	(20.7)	27	(32.1)	79	(36.4)
	Some	32	(36.4)	34	(39.1)	26	(31.0)	67	(30.9)
	Moderate	24	(27.3)	25	(28.7)	25	(29.8)	49	(22.6)
	Severe	9	(10.2)	10	(11.5)	6	(7.1)	22	(10.1)

Post-stroke fatigue was described as chronic or extreme tiredness with an increasing need for rests or naps to manage the day. The post-stroke fatigue affected social life, working life and intimate relations (paper I).

7.2 FUNCTIONAL DIMENSION OF HRQOL

Mobility and activities of daily living ten years after the onset of aneurysmal SAH were assessed with the instrument BI (paper III). The values ranged from 20-100 and a majority of respondents (84.4%, n = 184) rated the maximum value of 100. A small proportion rated disabilities in varying degrees; 11.1% (n = 24) had mild physical disabilities, 1.4% (n = 3) had moderate disability and 2.8% (n = 6) had severe disability. Coefficient alpha for BI was 0.91.

Mobility ten years after the onset was also measured and compared to a general population sample in the dimension ‘mobility’ on the instrument EQ-5D (paper IV). The comparison showed significantly more problems with mobility in the aneurysm sample (table 7).

Ten years after aneurysmal SAH the aneurysm sample reported significantly more problems in the EQ-5D dimension self-care compared to the general population sample (table 7).

Table 7. Percentage (number) of respondents reporting no, moderate and severe problems in EQ-5D dimensions, EQ-5D$_{index}$ and EQ VAS values, aneurysm sample and general population sample (paper IV)

EQ-5D dimensions	Total					Men					Women				
	Aneurysm sample n = 217		General population sample n = 434			Aneurysm sample n = 63		General population sample n = 126			Aneurysm Sample n = 154		General population sample n = 308		
	%	(n)	%	(n)	*P* [a, b]	%	(n)	%	(n)	*P* [a, b]	%	(n)	%	(n)	*P* [a, b]
Mobility					<.001					.007					.010
No problems	71.0	(154)	83.6	(363)		68.2	(43)	85.7	(108)		72.1	(111)	82.8	(255)	
Moderate problems	26.7	(58)	16.4	(71)		27.0	(17)	14.3	(18)		26.6	(41)	17.2	(53)	
Severe problems	2.3	(5)	0.0	(0)		4.8	(3)	0.0	(0)		1.3	(2)	0.0	(0)	
Self-care					.002					.016					.026
No problems	92.6	(201)	97.9	(425)		92.0	(58)	99.2	(125)		92.9	(143)	97.4	(300)	
Moderate problems	6.0	(13)	1.4	(6)		4.8	(3)	0.8	(1)		6.5	(10)	1.6	(5)	
Severe problems	1.4	(3)	0.7	(3)		3.2	(2)	0.0	(0)		0.6	(1)	1.0	(3)	
Usual activities					<.001					<.001					.019
No problems	74.7	(162)	87.8	(381)		69.9	(44)	92.9	(117)		76.6	(118)	85.7	(264)	
Moderate problems	20.3	(44)	11.1	(48)		22.2	(14)	7.1	(9)		19.5	(30)	12.7	(39)	
Severe problems	5.1	(11)	1.2	(5)		7.9	(5)	0.0	(0)		3.9	(6)	1.6	(5)	
Pain/discomfort					.506					.760					.322
No problems	49.8	(108)	46.8	(203)		50.8	(32)	53.2	(67)		49.4	(76)	44.1	(136)	
Moderate problems	42.4	(92)	48.8	(212)		36.5	(23)	43.6	(55)		44.8	(69)	51.0	(157)	
Severe problems	7.8	(17)	4.4	(19)		12.7	(8)	3.2	(4)		5.8	(9)	4.9	(15)	
Anxiety/depression					.001					.045					.007
No problems	56.7	(123)	70.3	(305)		58.7	(37)	73.8	(93)		55.9	(86)	68.8	(212)	
Moderate problems	37.3	(81)	27.9	(121)		38.1	(24)	23.8	(30)		37.0	(57)	29.6	(91)	
Severe problems	6.0	(13)	1.8	(8)		3.2	(2)	2.4	(3)		7.1	(11)	1.6	(5)	
EQ-5D$_{index}$ mean (±SD)	0.74 (±0.31)		0.81 (±0.22)		<.001	0.71 (±0.36)		0.84 (±0.21)		.002	0.75 (±0.28)		0.80 (±0.22)		.029
EQ VAS mean (±SD)	70.7 (±22.1)		77.6 (±18.0)		<.001	71.4 (±21.5)		78.1 (±16.9)		.021	70.4 (±22.5)		77.4 (±18.4)		<.001

[a] Differences between aneurysm sample and general population sample

[b] Moderate and severe levels in EQ-5D dimensions collapsed before analysis

7.3 PSYCHOLOGICAL DIMENSION OF HRQOL

Cognitive function

During the first two years following aneurysmal SAH, the impact on cognition in terms of affected memory, executive functions and perception were described (paper I). Different aspects of memory problems were described, such as difficulty to remember names, words and places. The affected executive functions were expressed as: having difficulty to initiate, to concentrate, perform long-term planning and to maintain activities. Affected perceptions were expressed as having a slower perceptual speed, they felt slow in discussions, had poorer listening comprehension and had difficulty interpreting irony and witty humor.

Ten years after aneurysmal SAH, cognitive status was assessed using TICS (paper III). The values on TICS ranged between 13-40 points (md = 33.0, IQR = 31.0 – 36.0); 21.7% (n = 45) scored ≤ 30 which indicates impaired cognitive function. Respondents aged over 65 years (n = 76) scored significantly lower on TICS compared to younger age groups ($p < 0.001$). Higher age correlated negatively with cognitive function on TICS ($r_s = -0.322$, $p < 0.001$), indicating that higher age is related to decreased cognitive function.

Emotional status, mood and personality

The first two years following aneurysmal SAH, the majority of respondents rated changes in mood and/or personality to some extent: 73.9% (n = 65) at six months, 75.9% (n = 66) at one year, and 72.6 (n = 61) at the two-year follow-up (paper I). These changes were consistently reported during the follow-up points. Mood changes were expressed in the different aspects of feeling blue, being less happy and being depressed. An increased level of anxiety was also expressed; anxiety for a new SAH from the previously ruptured aneurysm or another aneurysm, concerns for their own abilities, and a general feeling of anxiety. The mood stability was also affected, with respondents reporting that they could not control their emotions, expressed as having mood swings, they were easily irritated and impatient, they were quick to anger, and that their anger was likely to 'explode'. Emotional lability was also expressed and was described as being more sensitive or sad, to cry for no reason and to cry easily.

The perceived changes in personality included altered behavior, new perspectives on life and new feelings. The altered behavior experiences could be placed on a continuum between two extremes; some respondents described their personality as more introvert, that they were calmer, more thoughtful, less spontaneous and more serious than before

the onset. Others described an opposite change to a more extrovert personality, to be more straightforward, more social, and more assertive after the onset. The new perspectives on life were expressed as: that they valued new or other things than before, that they were grateful to be alive, and that they prioritized differently after the onset. The respondents expressed that they felt more vulnerable after the onset; they felt insecure and had poorer self-esteem.

Ten years after aneurysmal SAH, symptoms of anxiety and depression were measured with STAI and HADS (paper III), and also with the dimension of anxiety/depression on the EQ-5D self-classifier (paper IV). The majority of respondents (52.5%, n = 114) scored higher than the Swedish population norm mean value of 33.2 on total STAI. Significantly more symptoms of anxiety and depression were found in respondents with ruptured aneurysms in the posterior circulation of brain. Table 8 shows the median and inter quartile range (IQR) on STAI and HADS for the total sample and anterior/posterior circulation, and values from two reference populations.

Table 8. Psychological function for total sample and by aneurysms in the anterior and posterior circulation, and reference groups (paper III)

Instrument	Aneurysm sample md (IQR)				Reference groups (Central tendency and dispersion)	
	Total sample *n* = 217	Anterior circulation *n* = 199	Posterior Circulation *n* = 18	*p*		
STAI [1)]	34.0 (28.0-47.0)	34.0 (27.0-46.0)	46.0 (39.0-56.5)	0.002	median 32 m (SD) = 33.2 (± 9.6)	Randomized Swedish sample, *n* = 180, 26-65 years[190]
HADS-A [2)]	5.0 (1.0-9.0)	4.0 (1.0-8.0)	9.0 (4.8-12.5)	0.001	Median 4.0 IQR = 2.0-7.0	Randomized Swedish sample, *n* = 624, 30-59 years[191]
HADS-D [2)]	4.0 (1.0-7.0)	3.0 (1.0-7.0)	6.5 (2.8-10.0)	0.036	Median 3.0 IQR = 1.0-6.0	
HADS total [3)]	8.0 (4.0-15.5)	8.0 (3.0-15.0)	15.0 (10.8-21.2)	0.001	Median 7.0 IQR = 4.0-12.0	

[1)] Higher scores STAI total indicate higher levels of anxiety
[2)] Higher scores on HADS subscales indicate more anxiety or depression
[3)] Higher scores on HADS total scale indicate psychiatric disorder

On the HADS anxiety subscale (HADS-A) 33.6% (n = 73) scored anxiety symptoms; 16.1% (n = 35) were identified as mild cases, 12.0% (n = 26) were moderate cases and 5.5% (n = 12) were severe cases. On the HADS depression subscale (HADS-D) 23.5% (n = 51) scored for depressive symptoms; 15.7% (n = 34) mild cases, 6.0% (n = 13) moderate cases and 1.8% (n = 4) severe cases. Respondents older than 65 years had

significantly lower scores on HADS-A compared to younger age-groups (p = 0.004). On HADS total scale 41.9% (n = 91) scored ≥ 11 points, indicating a psychiatric disorder. A logistic regression analysis showed that the primary predictor for a psychiatric disorder was aneurysm location. Aneurysm rupture in the posterior circulation of the brain increased the odds ratio for a psychiatric disorder (5.5, 95% CI = 2-17, p = 0.04), R^2 = 9% (χ^2 = 14.9, *df* = 4, p = 0.005).

Cronbach's alpha for STAI was 0.95. Alpha coefficient for total HADS was 0.91, and for HADS anxiety and depression subscales coefficients were 0.91 and 0.82, respectively.

On the EQ-5D self-classifier, the aneurysm sample reported significantly more problems (p < 0.001) in the dimension anxiety/depression compared to the general population sample (paper IV).

Overall perception of health

Overall perception of health was measured ten years after aneurysmal SAH with EQ-$5D_{index}$ and EQ VAS (paper IV). EQ-$5D_{index}$ ranged from -0.484 to 1.0; 78 respondents (35.9%) reported full health (1.0), and 6 respondents had index values below zero. In the EQ VAS, where overall health was reported, values ranged from 0-100, and full health (EQ VAS = 100) was rated by 5.1% (n = 11). When the aneurysm sample was compared to a matched general population sample (table 7), the aneurysm sample had significantly lower EQ-$5D_{index}$ and EQ VAS values. Subgroup analyses were performed in the aneurysm sample and the results showed that those with low perceived recovery had significantly lower EQ-$5D_{index}$ (m = 0.45 versus m = 0.85, p < 0.001) and EQ VAS values (m = 50.5 versus m = 78.6, p < 0.001). When respondents differing in neurological outcome were compared (GOS 2-3 versus GOS 4-5), those with worse neurological outcome had significantly lower EQ-$5D_{index}$ (m = 0.52 versus m =0.79, p < 0.001) and EQ VAS values (m = 50.5 versus m = 72.9, p = 0.002). Subgroup analyses were also performed between those with comorbidities (n = 99), and without comorbidities (n = 118), and the results showed significantly lower EQ-$5D_{index}$ (m = 0.81 versus 0.65, p < 0.001) and lower EQ VAS values (m = 76.0 versus 64.3, p < 0.001) for respondents with comorbidities. When controlling for age and sex in regression analyses it was shown that those with worse neurological outcome, with comorbidities and with low perceived recovery had significantly lower EQ-$5D_{index}$.

7.4 SOCIAL DIMENSION OF HRQOL

Several social consequences were revealed during the first two years following aneurysm rupture, with changes in social contacts and interactions (paper I). Most changes in family life were reported at 6 months. The most frequent type of change at all three follow-up points were changed social roles (n = 18), followed by separation or divorce (n = 8). Other described changes were to be unable take care of children (n = 2), and positive changes; that they had married or moved in together with a partner (n = 3). The respondents described that they were involved in fewer social activities, were less involved in the lives of others, that they had lost friends and had difficulties in interacting with others – leading to isolation. Some expressed that they chose to be lonely, while others described that loneliness was a consequence of people behaving differently towards them. The SAH had impacted on the close relationships with family and friends, described as changed social roles, separations and divorces, and altered friendship relations, but also that some relationships were valued more after the illness. The time to return to work ranged between 2.5 to 24.0 months (md = 5.0, IQR = 4.0-12.0) and the proportion that were working part- or full-time were 30.7% (n = 27) at six months, 36.8% (n = 32) at one year, and 51.2% (n = 43) two years after the onset. Those who had returned to work expressed difficulties in the working situation; they found it hard to manage the previous workload due to concentration difficulties and tiredness, and described different strategies to manage work, such as memorizing tasks beforehand, and adjustments that their employer had done to make it possible to manage workload. Examples given for adjustments were; holding a new position with less responsibility, other or easier tasks, shorter working hours, and help and support from colleagues.

At ten years post-aneurysm rupture, the social domain of HRQoL was assessed with the dimension ‘usual activities’ in the EQ-5D descriptive system (paper IV). The results showed a significantly higher proportion of aneurysm respondents scoring for problems compared to the general population sample (table 7).

7.5 EPIDEMIOLOGICAL OUTCOMES

Epidemiology was analyzed in relation to gender differences and treatment modalities (paper II). The female incidence was higher than that of men in all four followed year groups; table 9 shows the incidence per 100 000 person years in Stockholm 1996-1999.

Table 9. Incidence of aneurysmal SAH/100 000 person years in Stockholm County Council, 1996-1999 (paper II)

Year	All	Men	Women
1996	7.2 (6.0-8.6)	4.0 (2.8-5.6)	9.1 (7.3-11.2)
1997	7.1 (5.9-8.5)	4.5 (3.2-6.2)	9.5 (7.6-11.8)
1998	5.9 (4.9-7.2)	4.4 (3.1-6.0)	7.4 (5.8-9.5)
1999	5.7 (4.6-6.9)	2.7 (1.7-4.0)	8.5 (6.7-10.6)

95% CI is shown in parentheses

The women were older at the onset of aneurysm rupture (mean age 55.7 versus 52.8 years, $p = 0.027$) and they were diagnosed with significantly more aneurysms compared to the men; 88 of the women (26.7%, 95% CI: 22.0 – 31.5) and 23 of the men (16.5%, 95% CI: 10.4 – 22.7) were diagnosed with multiple aneurysms.

The majority of the ruptured aneurysms (n = 419, 89.5%) were located in the anterior circulation of the circle of Willis, and most common locations for both men and women were ACoA (n = 168, 35.9%) followed by MCA (n = 129, 27.6%). Significant gender differences ($p < 0.001$) in proportions were found when comparing aneurysm locations; aneurysms in the ICA area were more common in women (25.8%, n = 85) compared to the men (8.6%, n = 12). Aneurysms in the ACA area were more common in men (53.8%, n = 81) compared to the women (34.0%, n = 112).

Ten years after aneurysm rupture, 63.9% (n = 296) of patients were still alive. There were no significant differences in mean survival time between men and women; for men 6.8 years (95% CI: 6.1 – 7.5) versus 7.2 years (95% CI: 6.8 – 7.7) for women.

Comparison of mean survival time between treatment modalities showed significantly lower survival ($p < 0.001$) for conservatively treated patients (0.8 years, 95% CI: 0.3 – 1.4) compared to patients treated with clipping (8.4 years, 95% CI: 8.1 – 8.8) and endovascularly treated patients (8.2 years, 95% CI: 7.4 – 9.1).

The mortality was highest in the first month after the rupture, due to the initial hemorrhage. Deaths after the first year were not related to the ruptured aneurysm, but to cardiovascular diseases and malignancies.

8 DISCUSSION

8.1 GENERAL DISCUSSION

Impact on life

Aneurysmal SAH impacts upon life and health in several ways on a long-term basis after the onset. During the first two years, transitions are ongoing with changes in personality, social roles, abilities and behavior. Transitions and change are not synonymous; change is to substitute one thing for another and is an external process, while transition is an internal process that incorporates changes in identity, roles, relationships, abilities and behavior.[192] Transition requires that new knowledge is incorporated and that behaviors are altered and therefore requires people to change the definition of self in a social context.[138] Emotional distress in terms of anxiety, depression, insecurity and frustration are common during the transition process.[136] When successful transition has occurred, the distress gives way to well-being.[136] The results reveal transition in more than one area, or multiple transitions; [139] health /illness transition caused by the differences in health status after the aneurysm rupture with physical and psychological consequences, and also situational transition, caused by a changed family situation and changes in professional role. Some of the transitions seem to be sequential and overlap, while others seem to appear to be simultaneous.

The respondents in paper I expressed an increased level of anxiety and a more depressed mood than before the aneurysm rupture. This finding could be interpreted as process indicators, a response to changes in self-concept, self-esteem and social roles.[135] However, the high levels of anxiety and symptoms of depression seem to be continuous; when comparing reported problems on the dimension anxiety/depression the EQ-5D self-classifier (paper IV), the aneurysm respondents report significantly more problems than the general population sample, ten years after the onset.

Symptoms of depression were further assessed ten years after the aneurysm rupture (paper III), and the results showed that about a quarter of respondents scored for depressive symptoms. This proportion corresponds to results from previous studies 21-36 months after aneurysm rupture, [95,113,114] and 7-9 years after the onset.[107,115] When anxiety was assessed ten years after the onset (paper III), the median values were greater for the aneurysm respondents, when compared to Swedish norm populations.[190,191] Our results show that ten years after the onset, about one-third of respondents scored anxiety symptoms, which corroborates with the results by Visser-

Meily et al.[114] 36 months after aneurysmal SAH. The similarity in results between previous studies and our results on the proportion of respondents with symptoms of depression and anxiety indicates that the levels of anxiety and symptoms of depression may be unchanged many years after the onset. The highest levels of anxiety and the most symptoms of depression ten years after the onset were found in patients with ruptured aneurysms in the posterior circulation of the brain, which predominantly were treated endovacularly (paper III). Endovascular treatment, in the literature, is associated with more frequent radiological follow-up,[193] and it could then be suggested that recurrent follow-up sessions may serve as reminders of the previous aneurysm rupture and produce more anxiety and depression. However, the radiological follow-up at the clinic is similar between surgically- and endovacularly-treated patients and does not provide any explanation for this theory. One previous study has examined symptoms of anxiety and depression in relation to aneurysm location, but reported no significant differences.[107]

Decreased cognitive functions were described the first two years following aneurysm rupture, in terms of memory problems, lowered executive functions and a slower perceptual speed. When cognitive status was assessed ten years after the onset, 21.7% scored with cognitive impairments and had, on a group level, a lower cognitive function when compared to published norm data on healthy controls.[169] Our percentage of cognitively impaired differs largely to previous studies where the majority of patients were cognitively impaired up to five years after the onset.[121,122] It has to be considered that the TICS instrument does not provide a complete array of information on cognition; some of the respondents may suffer from clinically significant impairments that are not covered by the instrument.

Approximately one-third of respondents in papers I and III report moderate and severe problems with disruption of night sleep and daytime sleepiness. This proportion is similar to results from previous studies 1-7 years after aneurysmal SAH.[104-106] Sleep-wake disorders may play a role in fatigue,[103] about one-third of respondents also reported moderate and severe problems with fatigue. This is a higher percentage of respondents affected by fatigue than previously reported results by Wermer et al., [107] where 17% reported subjective fatigue nearly nine years after the onset. Post-stroke fatigue is a complex problem to study because of the diversity of its manifestations, there is a lack of objective instruments to measure it, and the underlying

neurobiological mechanisms are unknown.[103] The diversity of manifestations and lack of objective instruments to measure post-stroke fatigue may explain differences in proportions of affected patients between studies. Fatigue may have a major impact on quality of life after stroke, despite the fact that neurological or cognitive sequel cannot be found, and may prevent patients to resume social and professional activities.[103] This can be illustrated by the results in paper I, where fatigue is described to affect social life, working life and also intimate relations. Although fatigue is a well-known health problem after stroke, there is still insufficient evidence to guide the management of post-stroke fatigue.[194] Stone[195] describes cognitive difficulties and fatigue after hemorrhagic strokes as 'invisible' disabilities; when disabilities are not obvious, stroke patients may nevertheless live with impairments that limit their ability to fully meet social expectations.

Ten years after aneurysm rupture the majority of respondents scored the maximum value on BI, indicating they were managing activities of daily living independently, while a small proportion, 2.8%, scored severe physical disability (paper III). These results are similar to the results in paper IV, where 2.3% reported severe problems with mobility and 1.4% reported severe problems with self-care on the EQ-5D self-classifier. The meta-analyses by Nieuwkamp et al.[94] and Hop et al.[93] showed that 10-20% of respondents were dependent on help for activities on daily living after the onset. This discrepancy with the results in this thesis may be explained by the time of follow-up; the majority of participants in the aforementioned studies were followed-up during the first 12 months after the onset, and the physical ability is expected to improve to some degree after the first year. Although a small proportion of respondents were severely disabled, the results in paper IV show significantly more problems with mobility and self-care are present, when compared to the general population.

Social life is also affected in several ways after aneurysmal SAH; isolation from previous social life, changes in family life and in working life (paper I). Ten years after aneurysm rupture, respondents report significantly more problems with usual activities when compared to the general population (paper IV). Negative social consequences after stroke have been addressed in a systematic review reporting deterioration of leisure activities in 15-79% of cases, negative impact on family relationships 5-54%, and inability to return to work 0-100%.[130]

During the first two years after onset, social relationships were impacted with changed social roles in the family, separations and divorces and altered friendship relations. The literature describes that the family's ability to provide ongoing support is an important factor that may facilitate or inhibit the transition process.[196] Family disruption and disagreements may occur during transition, but as the transition process moves on, relationships may be restored with enhanced appreciation and closeness, which can be described in terms of family adaption.[136] However, when the partner or spouse fails to adapt to the new situation, the transition is then not only inhibited, but also, a separation or a divorce may further lead to a new transition.

Epidemiological outcomes

The incidence declined over time (paper II), which is similar to findings in previous studies.[23,37,197,198] A possible explanation for the declined incidence is a change in risk factors: the smoking prevalence decreased in Sweden from 1980 to 1999, in both men and women.[199] Alternatively, other risk factors increased during this period: the alcohol consumption increased significantly in both men and women,[200] and the proportion of overweight people increased, which might lead to an increased proportion of people suffering from hypertension. The hypertensive medical treatments increased from 1985 to 2002.[200] Another possible explanation is the increase of inhabitants in the Stockholm uptake area during 1996-1999; the population increased by 59 000 people,[142] and the increase was largest in the ages below 45 years. One might suggest that people in this age group have lower risk of aneurysmal SAH, as the average rupture age is about 49 years. [24]

The results in paper II show gender differences at the onset of SAH, but not in outcome at hospital discharge, mortality rates or survival times. The incidence was significantly higher in women and they were diagnosed with significantly more aneurysms; they were also significantly older at the onset. It has been suggested in the literature that the female sex hormones play an important role in the etiology, formation and growth of intracranial aneurysms, because the female predominance of aneurysmal SAH starts after menopause.[50,201] However, these results are somewhat inconsistent; estrogen is presumed to have an inhibitory effect on aneurysm formation, [201] while high-estrogen oral contraceptives have been reported to increase the risk of SAH.[45] The reasons for overall higher incidence in women are still unclear.[23]

In paper II survival times were also compared between treatment modalities. Conservatively treated patients had significantly lower survival than patients treated with clipping or endovascular procedures. This result is not surprising; conservative treatment (i.e. no aneurysm securement) remains the only alternative for patients with untreatable aneurysms and patients in poor clinical grade at hospital admission. The risk of a fatal re-bleeding is highest the first weeks after the rupture.[63] Survival times were equal between active treatment modalities (clipping versus coiling), which is contrary to the results of ISAT; one and five years after aneurysmal SAH significantly more deaths occurred among patients treated with clipping in ISAT.[88,202] The differences between our results and ISAT may be explained by differences in study design and sampling; in ISAT aneurysms should be suitable for both clipping and coiling, and patients were randomized. Since a large proportion of aneurysms are not suitable to both treatment modalities, aneurysms in the in the posterior circulation, MCA aneurysms and patients in poor clinical grade are under-represented in ISAT.[203] In paper II, a consecutive sample of all patients were chosen and aneurysm obliteration method was chosen from the best evident methods, depending on aneurysm location, aneurysm morphology and the patient's clinical condition.

How should follow-up be organized for aneurysmal SAH patients?

Follow-up care after ischemic stroke varies widely, [85] and because aneurysmal SAH patients are not included in the Riks-Stroke[32] register, important information is lacking for this patient group.

There are several reasons why aneurysmal SAH patients should be followed-up; firstly, in the absence of a national SAH register, the existing Swedish epidemiological data are insufficient. Previous studies either cover only parts of Sweden, or are based on retrospective data collection from the Swedish Discharge Register and the Swedish Cause of Death Register, including SAH of all origins. The differences between regions and time trends in incidence and mortality cannot be followed.

Secondly, for ischemic stroke patients, the Riks-Stroke register evaluates the perceived quality of care and community support, thus, for aneurysmal SAH patients these data are lacking.

Thirdly, ongoing transitions during the first two years indicate a need for support through the transitional processes. People in transition are vulnerable and may benefit from interventions to support them, providing knowledge of what to expect, support in the planning and preparation for different phases of the transition, and to find strategies

to manage the process effectively. Moreover, most of the adjustment to change occurs after being discharged from the stroke rehabilitation unit.

Liaison facilities, to assist the patient's transition from hospital to home, is a commonly expressed wish and need formulated by ischemic stroke patients.[204] The efficacy of stroke liaison interventions has recently been explored in a meta-analysis. The results showed that younger patients appeared to benefit in ADL score by the intervention. There also appeared to be significant benefits from liaison services' input to patients with mild to moderate disability.[205] However, in studies on stroke liaison facilities, the term 'liaison worker' spans different professions including nurses, psychologists, social workers and also persons from the voluntary sector. The liaison worker's knowledge and skills may influence the information provision and counseling.[205] Liaison services after aneurysmal SAH in terms of a neurovascular specialist nurse have previously been tested in an intervention study in the UK. The intervention group felt less anxious, and had better family relationships compared to the comparison group.[206] The intervention was also cost-saving due to earlier return to work for the intervention group.[207]

Fourth, the high levels of anxiety and symptoms of depression ten years after the onset indicate a need for support and/or counseling long after hospital discharge. Survivorship care plans (SCP) may be an applicable way to support these patients. SCPs are used in cancer care after completion of the primary treatment and each is a summary of treatments and a comprehensive plan for follow-up, aiming to inform the patient and the patient's primary care provider of any long-term effects, the timing and content of follow-up, recommendations regarding how to maintain health and well-being, and to identify psychosocial resources in their community.[208,209] SCPs help patients and care providers to know what needs to be done, and who is responsible for various aspects of a person's care.[208] In cancer care different models for delivering survivorship care are emerging: a shared-care model where specialists collaborate with primary health care providers, specialized survivorship clinics where multidisciplinary care is offered at one site, and nurse-led models in which nurses are responsible for follow-up care with oversight from physicians.[209]

Kirkevold[85] emphasizes that nurses are in a unique position to provide support to stroke survivors because of their prominent position in hospital and primary health care settings. Nurse-led follow-up interventions have previously been studied in other patient groups, at hospital clinics, [210] at outpatient clinics in primary health care,[211,212] or by telephone.[213-215] The results in this thesis show affected HRQoL, anxiety and

depression up to ten years after aneurysmal SAH; in the literature on nurse-led follow-up, interventions do not cover such a long time span. The length of follow-up varies considerably between studies; from 12 months to 5 years, [210,212,216] and results also vary considerably between studies; from improved survival and self-care behavior[210] to no significant differences in survival, psychological morbidity or HRQoL.[216]
Further research is needed to find an appropriate way to follow-up and support aneurysmal SAH patients.

8.2 METHODOLOGICAL CONSIDERATIONS

This thesis includes observational studies with different designs, whereof one study applied a mixed methods approach. The methodological strengths in this thesis are the long follow-up period, the homogenous samples of aneurysmal SAH patients and the response rates (84.6% in paper I, respectively 79.5% in papers III and IV). Another strength is the completeness of data, due to the strategy that telephone interviews were conducted after the return of questionnaires, which enabled collection of data missing from the questionnaires. Methodological considerations were made concerning internal, external and conclusion validity of quantitative findings, trustworthiness of qualitative findings as well as instrument validity and reliability.

Internal validity

Internal validity in this thesis was assessed in terms of the strength of the inferences in the results, and whether there were other possible explanations for the obtained results.[217] The risk of bias was assessed in the forms of selection of subjects, the way variables were measured, and if some not fully controlled confounding factors occurred.[218] Selection bias was limited by using consecutive samples and including all eligible patients admitted for intracranial aneurysm rupture (papers I-IV).

In paper II, the vast majority of the included patients came from the Stockholm County referral area; eleven patients came from other neurosurgical clinics due to temporal treatment inabilities or shortage of intensive care beds. Likewise, a small number of patients from the Stockholm referral area were initially treated at another neurosurgical clinic. To avoid overestimation in the incidence calculation, the eleven patients from other referral areas were excluded from the incidence analysis.

A potential selection bias is the exclusion criteria in studies III-IV (poor health condition precluding participation), leading to the possibility that patients worse off

after the aneurysmal SAH not were included. However, the excluded patients were not only those that recovered least well from aneurysmal SAH, they were excluded for other reasons, such as severe dementia, progressive cancer disease, psychiatric disease, or weakness attributed to older age. In study I, the exclusion criteria included a GOS score lower than 3, and the excluded patients (n = 12) were those worse off after aneurysmal SAH. Response rate and losses to follow-up are also connected with selection bias.[219] Paper I had a prospective longitudinal design, and one problem with this design may be the loss of some subjects between follow-up points.[219,220] In paper I, a total of 4 respondents were lost from first to last follow-up point, which was not considered to affect the results. The response rates were considered sufficient[221] in paper I (84.6% of eligible), and papers III-IV (79.5% of eligible).

Retrospective data were used to collect data on medical history from patient records in paper II. A major disadvantage when using retrospectively collected data is that the data were not originally collected for the purpose of the study.[220] If a prospective design would have been used in paper II, we would have been able to collect data on risk factors and more detailed data on medical history, but the data collection would have to proceed for 14 years to collect approximately the same data.

The term 'confounding' could be described as a confusion or mixing of effects; the effect of a variable is mixed with the effect of another variable, leading to bias.[218] HRQoL fluctuates and is variable over time.[8] When aspects of HRQoL are measured once, as in papers III and IV, numerous factors besides the aneurysm rupture may have affected the outcome at the time of the follow-up. Another possible confounder in paper III is that any previous history of depression and anxiety disorders before aneurysm rupture was not addressed. A limitation when using cross-sectional design is that measurements are conducted once, thus the independent variable of interest and the outcome are measured simultaneously and temporal associations cannot be established.[217,222,223]

External validity

External validity, the ability to generalize the study results to other populations outside the study setting and at other times,[217] was also assessed, and the results were considered to be representative of aneurysmal SAH patients in Sweden. The respondents in paper II were treated during 1996-1999, and the majority were treated with open surgery. Rapid development in endovascular techniques, and new research

findings from the ISAT study have led to larger proportions of patients in many countries now being treated endovascularly.[72,224] The rapid advances in both open surgery techniques and endovascular methodology have also decreased the proportion of earlier untreatable aneurysms.[73,74] The findings concerning HRQoL and aneurysm treatment in paper IV and survival times in relation to treatment modalities in paper II may therefore not be applicable to present conditions.

Conclusion validity

Since sampling fluctuations may result in a Type I or a Type II error, [225] the sampling was also assessed. The risk of conducting a Type I error (i.e. to reject the null hypothesis when it is true) was controlled by using a statistical significant level of at least 5% throughout all analyses. The risk of a Type II error, to accept the null hypothesis when it is false, increases when the sample size is small.[226] The samples in papers II-IV were consecutive and sample sizes were not based on sample size calculations. In paper II, the number of endovascularly treated patients was rather small, which may have ruled out a real difference (Type II error) when comparing survival times between active treatments. There is also a risk of Type II error in paper IV, as the number of respondents was small in some of the subgroup comparisons.

In paper I the sample was also consecutive and sample size was determined by a power calculation with 80% power and a significance level of 5% to detect a difference in the mean value of 5 points on the instrument STAI between groups (gender and aneurysm treatment). The power calculation showed that at least 28 individuals in each group were needed, which was taken into account during sampling; 30 men and 58 women were included, respectively 34 treated with open surgery and 54 endovascularly treated.

Trustworthiness

One strength in using a mixed methods approach and mixing qualitative and quantitative data is the opportunity to get a more complete picture of a phenomenon.[227] Criteria to evaluate quality in mixed methods research can be gathered from both quantitative and qualitative orientations.[228] In qualitative research validity, reliability and generalizability are assessed in terms of different aspects of trustworthiness,[185] such as transferability, dependability and confirmability.[185,229]

Credibility/believability is the goal to demonstrate that the study was conducted in a way to ensure that the subjects were appropriately identified and described,[229] and

refers to the focus of the study, the selection of context, study respondents and approach to data collection.[185] To establish credibility it is important to choose respondents with various experiences to get various answers to the research question, to collect a sufficient amount of data, and to select the most appropriate data collection method.[185] In the analysis phase, credibility deals with selecting suitable meaning units, and how well categories or themes cover the data. Credibility could be demonstrated by representative quotations from the transcribed text for the categories.[185] In paper I, a relatively large consecutive sample was used, with respondents differing in ages, sex, aneurysm treatment and background. The sub-categories were presented with representative quotations to enable readers to judge the appropriateness of the categorization. Examples of meaning units, condensation, codes and categorization from the analysis were provided.

Transferability could be explained as how well the analyst can argue the findings of the study to be useful to other in similar situations, with similar questions – how well findings can be transferred to other groups.[185,229] To enhance transferability, a careful description of context, selection of respondents, data collection and process of analysis is needed.[185] In order to enhance transferability in paper I, the context and characteristics of the respondents have been described, as well as the data collection methods and a thorough description of the analysis process. Considering the relatively large consecutive sample (n = 88) with respondents with varying background and experiences, and the similar care at neurosurgical departments and rehabilitation nationwide, the results are transferrable to other aneurysmal SAH patients in Sweden.

Dependability is the degree to which data changes over time and differences in the analyst's decisions during the analysis process. If the data is collected over a long time, there could be a risk of inconsistency in the data collection.[185] The data collection was longitudinal and continued over a long time (43 months), but was consistent with the same questionnaire during each follow-up, and the data analysis began when all data were collected.

Texts have no 'objective truth', meanings are always brought to it by the reader.[230] Although manifest content analysis describes the visible and obvious content and has less depth and abstraction than a latent analysis, some degree of interpretation always occurs,[185] and it is important to confirm and acknowledge whether another researcher could confirm the findings of the study, and if interpretations and logical inferences make sense to someone else.[229] The first author (AvV) has extensive clinical experience of patients treated for intracranial aneurysm rupture, and conducted the early stage

analysis of the data. Henceforth, during the following analysis process, discussions were made with the co-authors until agreement on how the data was coded and categorized, and on how well categories and sub-categories covered the data.

Instrument validity and reliability

Validity refers to what extent an instrument measures what it is supposed to measure, and validity has different aspects.[231] The instruments applied in this thesis have previously been shown to be valid and reliable instruments to use in stroke populations. In paper I, a study-specific questionnaire was used, developed from the literature review, interviewing patients and conducting discussions with experts in the field. The study-specific questionnaire was assessed to be face valid but further validity testing was not performed, which is a limitation in paper I. However, the respondents' answers adequately described the domain of interest of this study: changes and transitions. The questionnaire seemed easy and clear as none of the items had high rates of non-response.

Reliability refers to whether an instrument measures a target attribute consistently and to what extent that it measures true scores.[231] Reliability has different aspects; one aspect frequently evaluated in instruments with summing items is internal consistency, testing that the instrument items measure the intended attributes and nothing else.[231] Internal consistency is a property of the scores on an instrument for a particular population, not of the instrument itself.[232] In this thesis, internal consistency was tested for STAI, HADS (total and subscales) and BI using Cronbach's alpha. Cronbach's alpha should only be used in unidimensional instruments. For overall measures, where there are no assumptions that the individual items need to be correlated with each other, alpha coefficient is not useful.[233] In research, an alpha value of 0.7 to 0.8 is regarded as satisfactory for comparing groups.[234] The alpha coefficient for STAI, HADS and BI in paper III ranged from 0.82 to 0.91.

8.3 CLINICAL IMPLICATIONS

The results in these studies indicate a need for follow-up to enable support through the transitional process during the first two years, and for long-term support and/or counseling after aneurysmal SAH. This support should preferably be provided by nurses with extensive knowledge on the specific problems that could arise after aneurysmal SAH, irrespective if it is provided from the neurosurgery clinic or in primary health care.

To enable identification of patients needing support, some sort of screening for psychological distress and perceptions of health is needed. Screening could be performed with structured standardized instruments. If this screening is performed from the neurosurgical clinic, screening could be done in connection with scheduled radiological follow-up and could be a part of a survivorship care plan.

Follow-up of this patient group is also needed for reasons other than for long-term support: for assessment of quality of care, and to enable the monitoring of epidemiological parameters, such as incidence and mortality. Since SAH patients are not included in the Riks-Stroke register, a national SAH register is mandated.

8.4 FUTURE RESEARCH

This thesis contributes to the knowledge about the long-term consequences of life for patients who suffer from intracranial aneurysm rupture. Future research could build on this work by conducting longitudinal follow-up studies of HRQoL and the impact on everyday life beyond the first two years after aneurysmal SAH. For this purpose, both quantitative and in-depth qualitative interview studies are needed.

Future research to evaluate quality of care is recommended as these data are lacking for this patient group because they are not included in the Riks-Stroke register.

The results indicate a need for follow-up of aneurysmal SAH patients, and a need for support among certain subgroups of patients. The frequency and timing of follow-up needs to be investigated and identification of the support needs highlights the call for research focusing on nursing interventions to address these needs. Moreover, aneurysmal SAH strikes people at a younger age than other stroke types, therefore the patients are more likely to be responsible for young family members and the consequences of the aneurysm rupture may have a much wider impact on family relationships. It would therefore be valuable to explore the experiences and support needs of the significant others.

9 SUMMARY AND CONCLUSIONS

Ten years after aneurysmal SAH, the majority of patients were still alive. Differences between men and women were apparent in incidence and clinical presentation at the onset SAH, not in outcome at hospital discharge, mortality, or survival times. Survival time was equal between patients treated with clipping and endovascular procedures.

The findings show that aneurysmal SAH impacts upon life and health in several ways; the first two years is a vulnerable period when changes and transition are common. Most of the process to adjust to a changed reality occurs after an eventual rehabilitation, but it then follows that further support from health care may be insufficient. Ten years after aneurysmal SAH, overall HRQoL is lower than in the general population. Levels of anxiety and symptoms of depression are worse than in reference populations.

The results identify subgroups of aneurysmal SAH patients who might benefit from support: those with ruptured aneurysms in the posterior circulation of brain suffering from more symptoms of anxiety and depression, and the subgroups with significantly lower HRQoL; those with low neurological outcome at hospital discharge; those with comorbidities; and those with low perceived recovery.

10 SAMMANFATTNING (SUMMARY IN SWEDISH)

Bakgrund

Brustet pulsåderbråck i hjärnan är en livshotande sjukdom. Jämfört med andra typer av stroke drabbar denna typ av stroke i yngre åldrar och är vanligare hos kvinnor. Internationella studier har visat att andelen drabbade varierar mellan olika länder, befolkningsgrupper och regioner. Drabbade patienter behandlas på intensivvårdsavdelning och därefter på neurokirurgiska kliniker. För brustet pulsåderbråck finns två huvudsakliga behandlingsalternativ; öppen operation då en klämma sätts på pulsåderbråckets hals, eller endovaskulär behandling då kärlet behandlas inifrån genom embolisering under röntgengenomlysning. Efter utskrivning får en del patienterna rehabilitering, men detta gäller inte alla.

Ungefär 1/3 av dem som drabbas avlider under den första månaden. De som överlever kan ha fysiska restsymtom i form av bl.a. rörelsenedsättningar, känselbortfall, överväldigande trötthet, epilepsi och hydracefalus. Beskrivna psykologiska restsymtom är bl.a. ökad oro och depression, kognitiv nedsättning, personlighetsförändring och humörsvängningar. Även sociala konsekvenser finns beskrivna; svårigheter att återvända till arbetet, färre sociala aktiviteter och förändrade relationer i familjen. Tidigare studier har visat påverkad hälsorelaterad livskvalitet upp till fem år efter pulsåderbråcket. I Sverige inkluderas inte patienter med denna typ av stroke i det svenska strokeregistret, svensk data om antalet drabbade och uppföljning av dessa patienter saknas därför. Många internationella studier har genomförts på patienter som drabbats av brustet pulsåderbråck i hjärnan, men få studier har följt patienterna över tid, eller följt upp dessa patienter längre än fem år efter bristningen.

Syfte

Det övergripande syftet för avhandlingen var att beskriva påverkan på livet upp till tio år efter brustet pulsåderbråck i hjärnan i termer av hälsorelaterad livskvalitet, förändringar i det dagliga livet och beskrivande epidemiologi.

Studie I var en prospektiv longitudinell observationsstudie med syfte att beskriva förändringar och övergångar i det dagliga livet under de första två åren efter brustet pulsåderbråck. Urvalet togs konsekutivt, 88 personer inkluderades och följdes upp vid

tre tillfällen; sex månader, ett år och två år efter brustet pulsåderbråck. Data insamlades med ett studiespecifikt frågeformulär och analyserades med mixad metod där både kvalitativ- och kvantitativ ansats användes för att ge en fylligare bild av upplevda förändringar. Resultatet visade att majoriteten av deltagarna upplevde förändringar i det dagliga livet under de första två åren, och förändringarna pågick med liten skillnad över tid från sex månader till två år. Omvälvande inre förändringar (övergångar) upplevdes med ändrad personlighet, förändrade sociala roller och relationer, ändrade förmågor och beteenden.

Studie II var en retrospektiv kohortstudie med kvantitativ ansats, syftet var att beskriva epidemiologi i relation till könsskillnader och behandlingsmetoder tio år efter brustet pulsåderbråck. Urvalet togs konsekutivt och 468 personer inkluderades. Data insamlades från patientjournaler och Dödsorsaksregistret. Resultatet visade att incidensen sjönk under åren 1996 till 1999. Incidensen var högre hos kvinnor än hos män, de var också äldre när pulsåderbråcket brast och diagnosticerades med fler pulsåderbråck. Majoriteten (63.9 %) av patienterna levde tio år efter att pulsåderbråcket brustit. Dödligheten första månaden var 19.4 % och vanligaste orsaken var den initiala blödningen, efter det första året var de vanligaste dödsorsakerna hjärt-kärlsjukdomar och cancersjukdomar. Det fanns inga skillnader i dödlighet eller överlevnadstid mellan könen. Överlevnadstiden var likvärdig mellan dem som behandlats aktivt (öppen operation eller endovaskulärt).

Studie III var en tvärsnittsstudie med kvantitativ ansats, syftet var att beskriva psykologiska, fysiska och kognitiva funktioner tio år efter brustet pulsåderbråck i hjärnan, samt att identifiera skillnader i dessa variabler mellan åldergrupper, kön och olika lokalisationer för pulsåderbråcket. Urvalet bestod av de personer som var levande från urvalet i studie II, 217 personer inkluderades. Data samlades in med enkäter och telefonintervjuer. Resultatet visade att graden av oro och symtom på depression var högre tio år efter brustet pulsåderbråck än jämfört med i referenspopulationer i tidigare publicerade studier. De som haft ett pulsåderbråck i hjärnans bakre cirkulation skattade statistiskt högre grad av oro och mer symtom på depression. En liten andel (2.8 %) hade svår fysisk nedsättning, majoriteten klarade aktiviteter i dagligt liv självständigt. På gruppnivå var den kognitiva funktionen lägre än referenspopulation, 21.7 % hade värden under brytpunkten som indikerar nedsatt kognitiv förmåga.

Studie IV hade en retrospektiv kohortdesign med kvantitativ ansats. Syftet var att mäta hälsorelaterad livskvalitet, och utforska vilka faktorer som påverkar hälsorelaterad livskvalitet, tio år efter brustet pulsåderbråck i hjärnan. Samma urval som i studie III användes (217 personer), vilka jämfördes med ett matchat urval (434 personer) från normalpopulation hämtad från Folkhälsoenkäten i Stockholm 2006. Data insamlades med enkäten EQ-5D. Resultatet visade att tio år efter det att pulsåderbråcket brast är den hälsorelaterade livskvaliteten statistiskt sämre än hos normalpopulation. De som haft pulsåderbråck rapporterade fler och svårare problem med rörlighet, hygien, huvudsakliga aktiviteter och oro/nedstämdhet. Mest påverkad hälsorelaterad livskvalitet i pulsåderbråcksgruppen påvisades hos deltagare med sämre neurologisk status vid utskrivningen från sjukhus efter bristningen, deltagare med övrig sjuklighet och deltagare med låg grad av upplevd återhämtning.

Slutsatser

Resultatet från studierna visar att livet påverkas på flera sätt efter brustet pulsåderbråck; under de första två åren fortgår omvälvande förändringar, tio år efteråt är den hälsorelaterade livskvaliteten sämre än hos normalpopulation med hög grad av oro och symtom på depression. Resultatet indikerar ett behov av uppföljning av patienter som drabbats av brustet pulsåderbråck i hjärnan. Uppföljningar behövs för att utvärdera vård och behandling, studera epidemiologiska parametrar såsom incidens och mortalitet, och för att kunna identifiera patienter som är i behov av stödjande åtgärder. Ytterligare studier behövs för att utröna hur dessa patienter ska följas upp och stödjas.

11 ACKNOWLEDGEMENTS

First and foremost I want to express my sincere gratitude to all patients who kindly participated in the studies, answering questionnaires, contributing their time and were willing to share their experiences with me. I also wish to sincerely thank the following persons:

Associate professor *Christina Forsberg*, my main supervisor, for your knowledge and wisdom, for always having confidence in my ability when I was in doubt myself. Thank you for your support and for always being so calm.

Associate professor *Yvonne Wengström*, my co-supervisor, for sharing your knowledge, your valuable encouragement and support, and for all language improvements in the manuscripts.

Professor *Mikael Svensson*, my co-supervisor, for your outstanding knowledge in neurosurgery, for your always encouraging and constructive criticism.

Associate professor *Kristina Burström*, co-author in paper IV - for sharing some of your deep knowledge on the EQ-5D instrument, and for your thoroughness. You have taught me a lot about constructing tables.

All my colleagues at the Red Cross University College in Stockholm: thank you for your encouragement, support and sharing an interest in my research. Among my colleagues I'd like to especially thank my mentor, *Pia Holmér Pettersson*, for support throughout the years, and *Yvonne Törnqvist*, for relieving my workload in the operating room nursing program, which enabled research time, and for always being supportive and great fun to work with.

Vice-chancellor *Tommy Löfgren*, and director of studies *Marja Schuster* at the Red Cross University College, for giving me research time that facilitated the fulfillment of this thesis.

Dr. Göran Edner, for awakening my interest in research on intracranial aneurysms in the 1990s when you were the principal investigator and I was your center coordinator in the ISUIA study. Your deep engagement with the patients inspired me to start doing research.

Staff at Stockholm County Council Archive: *Marie Sjöberg* and *Maria Litton*, for picking out all the paper patient records (> 500) in papers II and III.

Pernilla Fagerström, administrator at the Swedish Cause of Death Register, for providing death causes for diseased patients in paper II.

Stockholm County Council, for providing data from the Stockholm Public Health Survey 2006 in paper IV.

Maria Eriksson, nurse and section leader at the neurosurgical intensive care unit at Karolinska University Hospital, for providing data from the clinic's SAH register in paper I.

Anna Blommengren and *Birgitta Olgren*, deputy chief nurse and chief nurse at the neurosurgical intensive care unit at Karolinska University Hospital, for reading the thesis frame with 'intensive care glasses' and being supportive.

Aileen Ireland, for her excellent proofreading skills.

Colleagues at the Department of Neurobiology, Care Sciences and Society, Division of Nursing, and fellow doctoral students are gratefully acknowledged for fruitful academic discussions throughout my PhD journey, and great fun during doctoral weeks. I especially would like to thank doctoral student *Ewa Wadhagen Wedholm,* for taking great interest in my research, and for reminding me to celebrate every step towards the doctoral degree (thank you for the Amarone wine!).

PhD *Anna Letterstål,* for encouragement during the PhD years and guiding the latter months of this process.

All my friends (no one named, no one forgotten) for your company, laughs and fun.

My (almost) mother and father in law, *Inga-Britta* and *Allan,* for your at all times warm consideration.

My mother *Ingalill*, and my sister *Eva and her family*, for being there for me, for believing in me, and giving me support.

Last, but by certainly no means least, a very special thank you to my dearest ones: My (almost) husband *Mats*, my children, *Emelie, Marcus* and *Ludvig*, for encouragement and support, for putting up with me and showing patience, and for just being there. I love you.

This thesis was supported with grants from the Red Cross University College in Stockholm; the Karolinska Institutet Foundations; the Centre for Health Care Sciences at Karolinska Institutet; the Swedish Stroke Association; the Capio Research Foundation, and Karolinska University Hospital, Department of Neurosurgery.

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