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LONG-TERM ASPECTS OF STROKE. SURVIVAL, HEALTH-RELATED QUALITY OF LIFE AND COSTS

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Long-term aspects of stroke. Survival, health-related quality of life and costs
THESIS FOR DOCTORAL DEGREE (Ph.D.)

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To Eivind.

I will treasure the happy memory when you and Hilde came to Cape Town and visited me and my family. Rest in peace Eivind.

ABSTRACT

Stroke, a disease that affects millions of people globally every year, is an emergency situation requiring fast and immediate action in hospital. Acute stroke treatments have rapidly improved and been developed over the recent decades and stroke mortality is decreasing. However, many patients suffer from long-term health deficits, making stroke a condition with a vast spectrum of decreased functional outcomes with associated healthcare and ensuing societal costs. This thesis focuses on the impact of acute stroke in life after stroke.

Thrombolysis given as an acute treatment to ischemic stroke has well documented effect on improved functional outcome, but long-term survival after thrombolysis has been poorly investigated. We performed a three-year follow up on patients with ischemic stroke and did not find a significant difference in survival between patients receiving thrombolysis compared to those receiving standard of care (Study I). However, among those who survived the first seven days after the stroke, patients who received thrombolysis did have a significantly better survival compared to those who received standard of care.

Long-term deficits after stroke includes hemiparesis, depression, decreased cognition, communication deficits, and post-stroke fatigue, symptoms affecting health-related quality of life. With an increasing number of stroke-survivors the impact on patients and society are immense. We performed an investigation which showed that health-related quality of life and survival is associated with stroke related functional outcome (Study II). The study also showed that survival decreased and costs to healthcare increased with decreasing functional outcome after stroke. Further we investigated the impact of disability level on health-related quality of life over time and found that patients with the lower functional outcome after stroke subsequently decrease in health-related quality of life, whereas stroke survivors with a better functional outcome after stroke increased in health-related quality of life over time (Study III).

Studies II-III demonstrated that patients perceive life differently, depending on severity of their functional deficit, with many stroke patients suffering from low health-related quality of life. The diversity in needs from individual patients challenges healthcare provision when deciding on interventions required in order to improve health-related quality of life after stroke. Research on improving the life after stroke is likely to have the best impact if addressing areas directed by the patients. Therefore, we asked a large group of patients what research areas they prioritized in life after stroke (Study IV). We found that most stroke patients prioritize more research on balance and walking difficulties. The second most prioritized area was post-stroke fatigue, and that was in particular evident among younger stroke patients.

Together these results display the high need for both rehabilitation and further research to improve the quality of life and survival after stroke, and at the same time decrease the burden to healthcare and society.

LIST OF SCIENTIFIC PAPERS

I. *Effects of alteplase on survival after ischaemic stroke (IST-3): 3 year follow-up of a randomised, controlled, open-label trial.*
Berge E, Cohen G, Roaldsen MB, Lundström E, Isaksson E, **Rudberg AS**, Slot KB, Forbes J, Smith J, Drever J, Wardlaw JM, Lindley RI, Sandercock PA, Whiteley WN; IST-3 Collaborative Group.
Lancet Neurology. 2016 Sep;15(10):1028-34.

II. *Long-term health-related quality of life, survival and costs by different levels of functional outcome six months after stroke.*
Rudberg AS, Berge E, Gustavsson A, Näsman P, Lundström E.
European Stroke Journal. 2018 Jun;3(2):157-164.

III. *Health-related quality of life based on functional outcome. Results from the EFFECTS trial.*
Rudberg AS, Ernstsson O, Näsman P, Lundström E.
Manuscript.

IV. *Stroke survivors' priorities for research related to life after stroke.*
Rudberg AS, Berge E, Laska AC, Jutterström S, Näsman P, Sunnerhagen KS, Lundström E.
Topics in Stroke Rehabilitation. 2021 Mar;28(2):153-158.

Other related scientific papers not included in the thesis:

- *The FOCUS, AFFINITY and EFFECTS trials studying the effect(s) of fluoxetine in patients with a recent stroke: statistical and health economic analysis plan for the trials and for the individual patient data meta-analysis.*
Graham C, Lewis S, Forbes J, Mead G, Hackett ML, Hankey GJ, Gommans J, Nguyen HT, Lundström E, Isaksson E, Näsman P, **Rudberg AS**, Dennis M.
Trials. 2017 Dec 28;18(1):627.

- *Selective serotonin reuptake inhibitors (SSRIs) for stroke recovery.*
Legg LA, Tilney R, Hsieh CF, Wu S, Lundström E, **Rudberg AS**, Kutlubaev MA, Dennis M, Soleimani B, Barugh A, Hackett ML, Hankey GJ, Mead GE.
Cochrane Database Systematic Reviews. 2019 Nov 26;2019(11).

- *Fluoxetine for stroke recovery: Meta-analysis of randomized controlled trials.*
Mead GE, Legg L, Tilney R, Hsieh CF, Wu S, Lundström E, **Rudberg AS**, Kutlubaev M, Dennis MS, Soleimani B, Barugh A, Hackett ML, Hankey GJ.
International Journal of Stroke. 2020 Jun;15(4):365-376.

CONTENTS

LIST OF ABBREVIATIONS

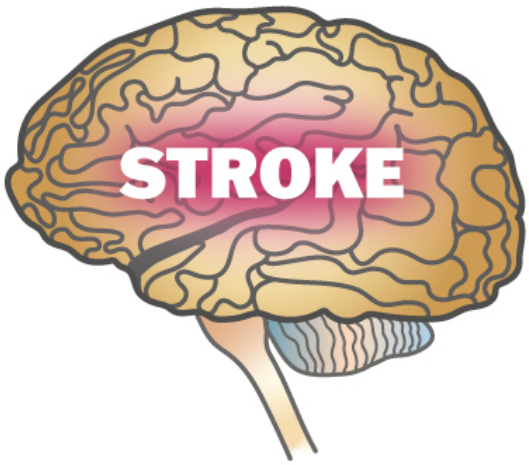
IS	Ischemic stroke
ICH	Intracerebral hemorrhage
SAH	Subarachnoid hemorrhage
TOAST	Trial of Org 10172 Acute Stroke Treatment
IVT	Intravenous thrombolysis
r-tPA	recombinant tissue plasminogen activator
tPA	tissue plasminogen activator
EPN	Etikprövningsnämnd/Etichal approval board
RCT	Randomized Controlled Trial
IST-3	The Third International Stroke Trial
EFFECTS	Efficacy oF Fluoxetine- a randomisED Controlled Trial in Stroke
HRQoL	Health-Related Quality of Life
NIHSS	National Institutes of Health Stroke Scale
mRS	modified Rankin Scale
OHS	Oxford Handicap Scale
OAC	Oral anticoagulant
FOCUS	Fluoxetine Or Control Under Supervision
AFFINITY	The Assessment oF FluoxetINe In sTroKe recoverY trial
EQ VAS	EQ-5D visual analouge scale
KPP	Cost-per patient registry
DRG	Diagnosis-related group
ICD	International Classification of Disease
HR	Hazard ratio
CI	Confidence Interval
SD	Standard deviation

1 INTRODUCTION

The word “Stroke” has been in use since the 17th century and the disease is today one of the leading causes of death and disability in the world. Even with improved detection of stroke, and new effective treatments over the recent decades, a growing body of literature urge that a going forward with ‘business as usual’, will not decrease the burden of stroke.

Fortunately, we have many tools to prevent, treat and manage stroke, and together with new and effective therapies, and if fully implemented, the opportunity exists to reduce the burden caused by stroke and its longstanding impact. Although, this will require the engagement and action of many involved, including patients and relatives, health professionals, clinical researchers, industry, and policymakers.

This thesis aims to put focus on the stroke patient and before we start I therefore would like to express my gratitude to every stroke patient involved in the studies. Without your willingness to contribute to stroke research, this would never have been possible.



2 BACKGROUND

2.1 STROKE DEFINITION

Stroke is clinically defined as "rapidly developing clinical signs of focal (or global) disturbance of cerebral function, lasting more than 24 hours or leading to death, with no apparent cause other than that of vascular origin", a definition that was introduced by the World Health Organization in the 1970's.[1, 2] Since then and due to advanced neuroimaging, the stroke definition has been upgraded by the American Heart Association, and the American Stroke Association to include both clinical and tissue criteria.[3] The upgraded definition is similar to the World Health Organization's 11th version of International Classification of disease (8B11).[4, 5] The definition of stroke includes acute ischemic stroke (IS), intracerebral hemorrhage (ICH), and subarachnoid hemorrhage (SAH).

A transient ischemic attack, traumatic bleedings, and stroke mimics such as migraine, seizure and psychiatric disorders are differentiated from the stroke definition.[6]

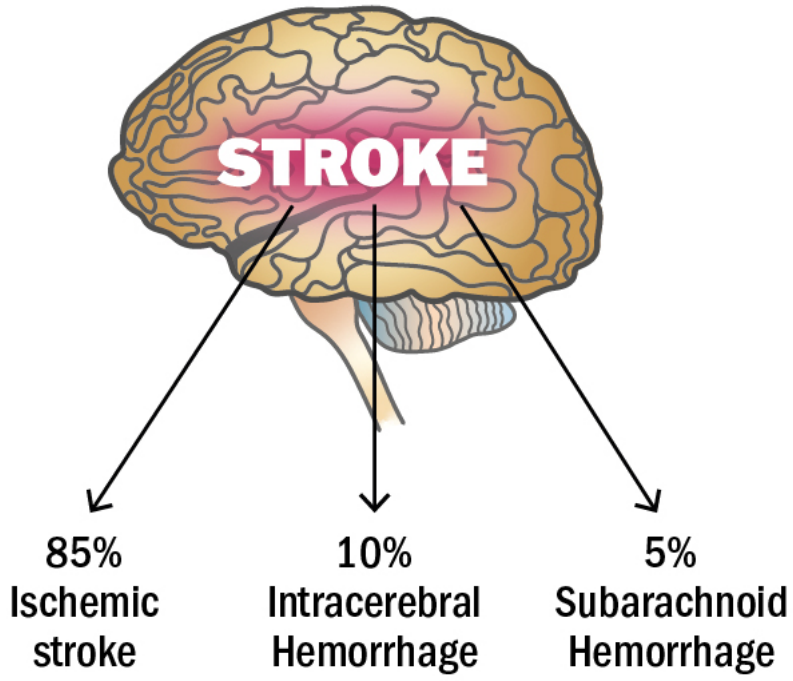


Figure 1. The proportions of acute ischemic stroke, intracerebral hemorrhage and subarachnoid hemorrhage included in the stroke definition.

2.2 EPIDEMIOLOGY OF STROKE

Globally, approximately 13.7 million people are affected by stroke each year, causing about 5.5 million deaths worldwide (2016).[7] In Sweden, as well as in many other countries, the incidence and mortality of stroke have decreased over the last decades probably due to better prevention of primary and secondary risk factors, and detection of stroke.[8, 9] In Sweden, approximately 25 000 people have a stroke annually (2019), which is a decrease of age-adjusted stroke incidence of almost 40% over the last 15 years.[10] Globally, stroke is estimated to affect more than 80 million stroke survivors, and in Sweden the figure is more than 100 000 people.[7, 10, 11] Stroke is globally, and in Sweden, one of the leading causes of neurological deficits in adults, and stroke survivors live with varying functional, emotional and cognitive deficits. Considering that stroke not only affects the life of the individual, but also that of their relatives, this places a huge burden on healthcare and society.[12, 13]

2.3 PATHOPHYSIOLOGY OF STROKE

2.3.1 Acute ischemic stroke

Acute ischemic stroke is caused by occlusion in a cerebral artery which causes decreased blood flow in the brain and provoke rapid death of neurons resulting in a core ischemic zone. Surrounding this area is the penumbra, consisting of cells at risk of damage if blood supply is not restored. Ischemic stroke can be classified into categories based on underlying pathophysiological mechanism. The most well-known classification system in research and in clinical practise is the Trial of Org 10172 in Acute Stroke Treatment (TOAST)[14], dividing ischemic stroke etiology into:

1) Large-artery atherosclerosis

2) Small artery occlusion

3) Cardio-embolism

4) Stroke of other determined etiology

5) Stroke of undetermined etiology

2.3.2 Acute hemorrhagic stroke

Acute hemorrhagic stroke is caused by spontaneously ruptured arteries in the brain which accumulate hematoma and compress surrounding brain tissue, impairing neural cells and destroying nerve paths. Acute hemorrhagic stroke is divided into ICH and SAH, where ICH causes approximately two thirds of all bleedings (often due to cerebral small vessel disease/hypertensive arteriopathy, and cerebral amyloid angiopathy) whereas SAH, mainly caused by aneurysm, but also by arteriovenous malformation, stands for a third of acute hemorrhagic stroke and more common in younger patients.[15-17]

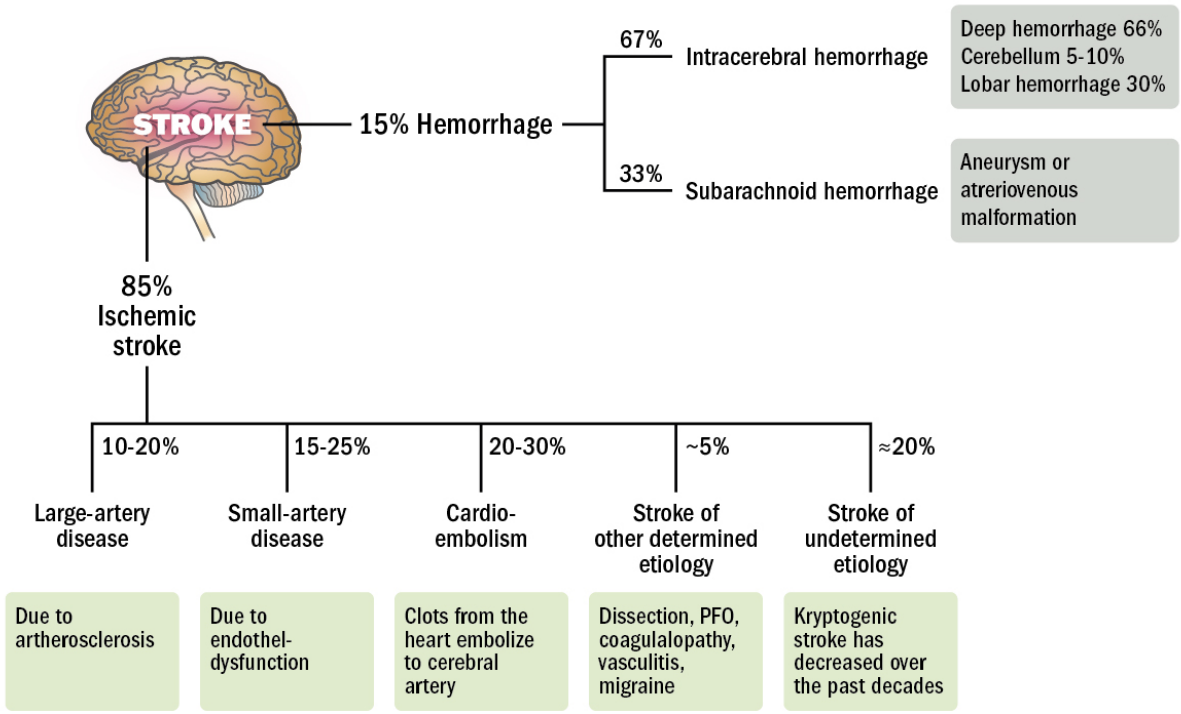


Figure 2. Subtype of stroke divided on ischemic stroke and hemorrhagic stroke

2.4 RISK FACTORS OF STROKE

Risk factors of stroke are divided into modifiable or unmodifiable.

Unmodifiable risk factors include older age, family history of stroke and sex. It also includes genetic factors, such as cerebral amyloid angiopathy, cerebral autosomal dominant arteriopathy with subcortical infarcts, and genetic variations increasing the risk of cardiovascular disease like atrial fibrillation, diabetes and hypertension.[18-20]

Important modifiable risk factors for ischemic stroke are factors predisposing for atherosclerosis such as hypertension, diabetes, hyperlipidemia, and smoking.[21] Cardiac disease such as myocardial infarction, atrial fibrillation, and valvular disease are important risk factors for cardio-embolic stroke. Other modifiable risk factors are abdominal obesity, diet, a physically inactive lifestyle, and high alcohol intake (more than 30 drinks per month). [21] The main risk factors for hemorrhagic stroke are hypertension, high alcohol intake, smoking, abdominal obesity, and diet.[21]

2.5 AGE DIFFERENCES IN STROKE

The incidence of stroke raises with age and the mean age for stroke onset in Europe, and in Sweden, is approximately 75 years of age.[22] There is a difference between sex and stroke incidence, where men have a lower mean age compared to women.[23] The etiology of stroke also differs between age groups, much due to the increase of predisposing risk factors for atherosclerosis, small vessel occlusion and atrial fibrillation which accompany older age.[24] Etiologies such as cervical artery dissection, patent foramen ovale, migraine and stroke of undetermined etiology are more prevalent in younger stroke patients. [25-27] The age of ICH-patients is slightly younger than for ischemic stroke patients.

2.6 ACUTE SYMPTOMS AND COMPLICATIONS OF STROKE

Symptoms of a stroke are widely heterogenous and depend on multiple factors, including the site of the cerebral lesion and the size of the lesion. Stroke can either affect the anterior circulation from the carotid arteries and their branches, or the posterior circulation from the vertebral and basilar arteries and their branches.

The anterior cerebral artery supplies the medial areas of the frontal and parietal lobes and corpus callosum. The middle cerebral arteries are the largest, and supply areas of the frontal, parietal, and temporal lobe surfaces, and are also the most common site for ischemic stroke. Branches of the anterior and middle cerebral arteries supply the basal ganglia and anterior limb of the internal capsule. Symptoms associated with supratentorial lesions are hemi symptoms on contralateral side, central facial palsy, aphasia, neglect, apraxia and cognitive changes.

The vertebral and basilar arteries provide the brain stem, cerebellum, posterior cerebral cortex, and medial temporal lobe. From the basilar artery, the posterior cerebral arteries bifurcate to supply the medial temporal and occipital lobes, hippocampus, and thalamus. Symptoms associated with infratentorial lesions are vertigo, nausea, headache, ataxia and visual defects.

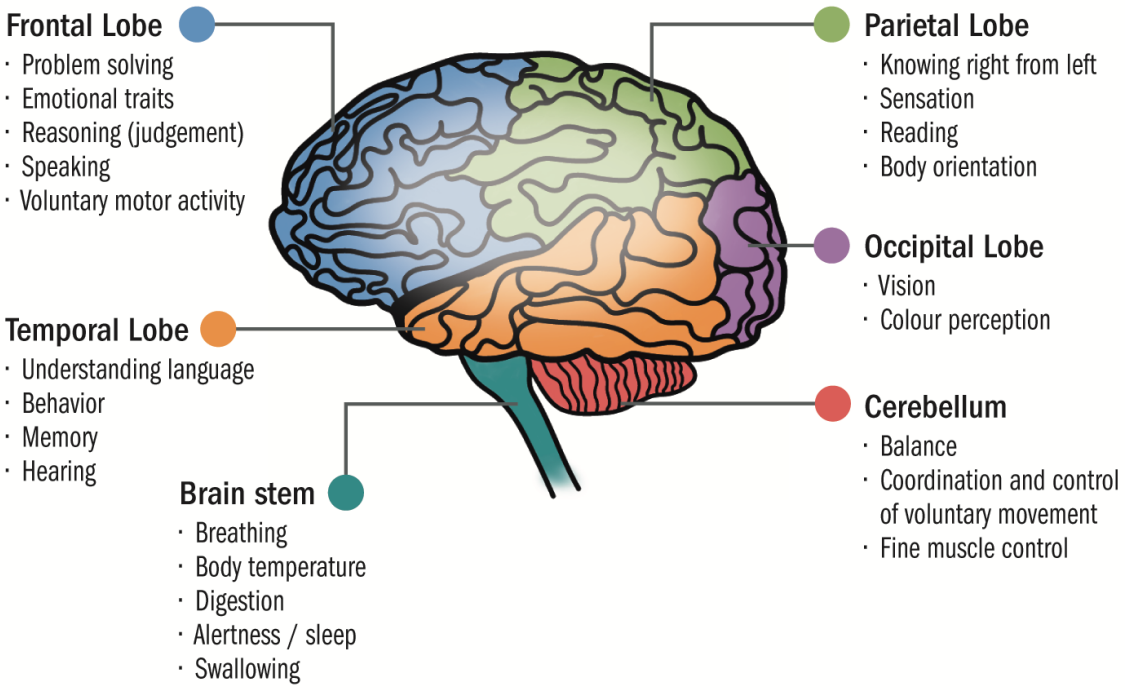


Figure 3. Symptoms associated with stroke and location in the brain.

Complications of acute stroke may include confusion, sleep difficulties, pneumonia, depression, incontinence, and swallowing dysfunction, which could lead to dehydration or undernutrition, or aspiration. Long periods of immobility can cause venous thrombosis, ulcers from pressure, deconditioning, urinary infections, and contractures which illustrates the wide variety of the impact an acute stroke might have on the individual patient in the acute phase. This in turn indicate the difficulty of regarding stroke patients as a homogenous population. There are similarities in underlying disease between stroke patients but the inter-individual difference in acute symptoms, complications and deficits after stroke is profound.

2.7 ACUTE TREATMENTS IN STROKE

2.7.1 Stroke unit

A stroke unit is a multidisciplinary team ward involving medical, nursing, paramedic, and therapy assessments and has been proven to be beneficial to both acute ischemic and acute hemorrhagic stroke patients.[28, 29] It includes early management policies, such as screening swallowing function, early mobilization, treatment of hypoxia and infections, and making early assessments for discharge and level of rehabilitation.[30] Stroke patients treated in stroke units are more likely to be alive, independent, and living at home one year after their stroke.[31, 32] A study showed that five years after stroke, patients treated in a stroke unit had a better functional outcome compared to patients treated in general wards.[33] Almost one in seven of acute stroke patients in Sweden is not admitted directly to a stroke unit, often due to lack of hospital beds. [34, 35]

2.7.2 Acute treatments of ischemic stroke

International, as well as national, clinical guidelines on acute ischemic stroke recommend stroke unit care, reperfusion by intravenous thrombolysis (IVT) and/or endovascular thrombectomy for stroke management.[36, 37]

2.7.2.1 Intravenous thrombolysis

IVT with alteplase is given to patients with ischemic stroke - if there are no contraindications- to restore blood flow which aims to rescue the penumbra, and treatment has to be started within 4.5 hours of the stroke onset. Since IVT is time dependent, the sooner it is started the better to improve functional outcome. The most severe risk of treatment is intracranial hemorrhage, and the risk increase with increasing stroke severity.[38]

IVT with alteplase for ischemic stroke was introduced in 1996, after approval by the U.S Food and Drug Administration, and has been shown to improve functional outcome 3 months after stroke.[39, 40] Initially, IVT was only given to ischemic stroke patients younger than 80 years of age who could be treated within 3 hours which was later expanded to 4.5 hours.[41, 42] The Third International Stroke Trial (IST-3), published in 2012, showed that patients older then 80 years of age also benefit from IVT.[43] Other studies have shown that IVT can improve functional outcome for selected patients up to 9 hours after last known well.[44, 45] With advanced neuroimaging IVT has now, for selected patients, extended to beyond 4.5 hours. The National Institute of Neurological Disorders and Stroke (NINDS) trial (n=624) and the IST-3 (n=3035) followed up participants' long-term survival after acute IVT for 12 months, and 18 months respectively, and the treatment was not shown to improve long-term survival. Thus, questions were raised about the long-term benefit of IVT.

IVT is administered as a bolus (10% of total dose) followed by a one-hour infusion of 0.9 mg/kg (maximum dose 90 mg). Actilyse® (alteplase) is a recombinant tissue plasminogen

activator (r-tPA). It is a serine protease inhibitor and binds to plasminogen, which itself is bound to the fibrin netting of the blood clot at the lysine binding site. It activates fibrin-bound plasminogen and converts it into plasmin. Plasmin catalyzes the breakdown of fibrin to its degradation products, resulting in the dissolution of the clot.[46, 47] Alteplase is metabolized in the liver, with a half-time in plasma of 4-5 min, and terminal in 40 min. It is licensed for patients older than 18 years of age. Tenecteplase, sometimes used off-label in acute ischemic stroke, is a tPA modified to have longer half-time and is currently being studied in ongoing stroke trials, e.g the TWIST-trial.[48]

2.7.2.2 Endovascular thrombectomy

Thrombectomy is the most recent treatment in acute stroke care, and since 2015, with a number of studies published showing improved functional outcome in selected patients, thrombectomy has now become an established treatment in acute stroke care.[49-53]

Thrombectomy is performed by neuro interventionists at a limited number of sites in Sweden, and have shown effect up to 24 hours of the stroke onset in large vessel occlusion stroke, using CT-angiography to visualize the occlusion. The most common procedure is catheter-based thrombectomy with an incision into the groin leading up to the clot through an artery, with a stent-retriever slid into the catheter to encase the blood clot. Even with a possible extended 24 hour window for the intervention, the sooner after stroke onset it is performed the better the outcome.[51]

2.7.3 Acute management for acute intracerebral hemorrhage

No studies have definitely proved any specific medical treatments for acute ICH.[54] Although, after an acute CT scan to determine ICH location, acute and intensive treatment of blood pressure management has been associated with an improvement in 30-day survival.[55] Anticoagulation reversal and neurosurgery may be beneficial but this has not yet been proven.[56] The main goal of acute management is to stabilize the patient and to prevent secondary brain injury. Some ICH patients may need immediate intensive care unit care, and if not, all ICH patients should be rapidly admitted to an acute stroke unit since the benefits for ICH patients are equivalent to that for acute ischemic stroke patients.[57] Management of complications such as raised intracranial pressure (caused by mass effect of bleed, oedema or hydrocephalus) could also be important for the acute care. ICH patients should be monitored to follow prognosis at stroke units for at least 24 to 48 hours.[54]

2.8 OUTCOME AFTER STROKE

2.8.1 Survival

Even with a decreasing mortality rate, stroke is still the second leading cause of death worldwide.[58] In all stroke, approximately 72-85% survive the first 30 days after onset, 43-69% survive one year, and 40-65% survive five years. [59-65] ICH patients have a worse prognosis compared to ischemic stroke, with a survival rate of 41-76% the first 30 days, as compared to ischemic stroke patients of which 79-95% are alive.[59, 63-64, 66-70] A corresponding difference between stroke type is seen at five years. Among ischemic stroke patients, mortality rate is highest among cardioembolic and large-artery occlusion stroke.[71-73] Further on, studies have shown that mortality rate increase with comorbidity such as atrial fibrillation, diabetes and smoking as well as decreased functional outcome.[74, 75] A Swedish study also showed that attempted suicide and completed suicide is more common among younger stroke patients with the highest risk within the first two years after stroke.[76]

2.8.2 Functional impairment and outcome

There are various functional disabilities after stroke, such as paresis, gait disorders, visual disorder and aphasia and stroke studies have shown that the unfavorable impact of long-term functional outcome in stroke survivors is substantial, from one year up to 15 years after stroke. [77-82] Due to neuroplasticity, many stroke patients do regain some functional abilities over time.[83] Stroke recovery is usually divided in different phases, the first being the acute recovery phase within seven days, the second being the sub-acute recovery phase lasting up to six months, and the third, the chronic phase, from six months and beyond.[84]

There is not a single measure of outcome which cover all areas of impairment, recovery and disability after stroke. Several tools have been validated and used in clinical practice and in stroke trials.[85] Two frequently used tools in stroke research are The National Institutes of Health Stroke Scale (NIHSS) and the modified Rankin Scale (mRS).

NIHSS is an assessment tool providing a measure of stroke-related neurological deficit, useful for early prognostication and serial assessment.[86-88] It was originally developed for use in thrombolysis studies and is also used for quality-based follow up in national registries. The NIHSS predicts lesion size, can present as a measure of stroke severity and be used as a predictor of short- and long-term outcome of stroke patients. The score ranges from 0 – 42, where 0 equals no deficit and the higher score the more severe stroke.

The mRS measures functional outcome, and was introduced in 1957 by Dr. John Rankin, initially as a 5-level measure.[89] Over the years mRS has been modified to a 7-level measure of functional outcome and is widely used as primary outcome measure in stroke studies.[90, 91] The current mRS ranges from 0 (no deficit) to 6 (death).

2.8.3 Health-related quality of life

Apart from functional disabilities, numerous stroke survivors suffer from long-term psychological deficits and the combination of the two may negatively impact health-related quality of life (HRQoL).[82] HRQoL mirrors a person's perception of how a health condition influences their physical, mental, social, and emotional health an also their ability to functionally perform everyday tasks. It has been defined as "The value assigned to duration of life as modified by the impairments, functional status, perceptions and social opportunities that are influenced by disease, injury, treatment or policy."[92]

Studies on post-stroke HRQoL have shown that factors such as the state of mental health and dependency before stroke, age, sex, educational level, socioeconomic level, social support and as well as plastic factors such as improvement of functional outcome are associated with post-stroke HRQoL.[93, 94-96] Other studies have also shown that anxiety, depression, fatigue, and apathy are seen in up to thirty percent of stroke patients.[97] Dementia and cognition deficits after first stroke, also known to affect HRQoL, are estimated to be approximately 10 percent, and after recurrent stroke the prevalence rises to thirty percent.[98] In recent years there has been increasing interest in the HRQoL of informal care givers and spouses, one study showing that lower HRQoL in stroke survivors was associated with lower HRQoL for their spouses.[99] Another Swedish study reported that the HRQoL of care givers was lower than the stroke patient they cared for, the most important determinants being own age and the patient's functional status.[100]

In a retrospective study from 2013 on stroke patients, the authors reported that the patient's assessment of mRS has a strong association with HRQoL at three months.[101] Other studies have shown less association between the level of mRS and HRQoL after stroke.[102]

Studies investigating the sub-acute phase of recovery after stroke showed that being dependent, severe cognitive impairment, being unemployed, affected HRQoL at three months, and another study showed that anxiety and upper-limb disability affect level of HRQoL six months after stroke.[103, 104] Studies measuring HRQoL in the chronic phase have found that disability, anxiety and depression are associated with lower scores for HRQoL five years after stroke, and that 23% of stroke survivors report very poor HRQoL seven years after stroke onset.[105, 106]

There are several instruments available to assess a person's health-related quality of life, ranging from generic instruments which may be used for any disease, to specific instruments used for a single health condition. Health-related quality of life is often a secondary outcome in stroke trials but remains to be the primary measure of effectiveness in economic evaluations when combined with information on patients' survival, referred to as quality adjusted life years (QALYs). The generic EQ-5D instrument is often recommended to be used in health-economic analysis.[107, 108]

2.9 COSTS AND STROKE

The economic burden of stroke is known to be high, and includes costs such as acute stroke treatments and initial rehabilitation at hospitals, outpatient appointments, medicine, long-term stroke care, and also loss of income from incapacity to work.[109, 110] When decision makers determine acceptability of new stroke treatments, they consider these costs and whether the new treatments provides enough benefit (measured in HRQoL) to the stroke patient to justify it.

Stroke is a condition with a vast spectrum of functional outcomes on which associated health care and societal costs depend. The acute treatment of stroke is complex (and costly) and includes effective treatments such as stroke unit care, intravenous thrombolysis, and most recently, thrombectomy, treatments which aim not only to save lives, but also to improve functional outcome after stroke. Ghatneker and colleagues calculated a societal lifetime cost to €68,800 per stroke patient in 2009 in Sweden (ADL support: 59%; productivity losses: 21%).[110] A recent report calculated cost in Europe 2017 to be €60 billion, the same report projected stroke care costs in Europe to increase with 44% between 2017 and 2040.[111] Heterogenous studies have illustrated the relationship between costs and outcomes based on functional outcome categories, usually measured by the modified Rankin Scale (mRS).[112-118] However, many of these studies failed to contribute to useful results that could be applicable in health economic evalutions.[119] A few studies (and only one in Sweden) have described long-term costs beyond a year, but these studies did not have large enough samples sizes and/or enough data on all the mRS categories to allow analyses on the full spectrum of mRS scores. [120-122]

2.10 LONG-TERM STROKE MANAGEMENT

Secondary prevention of stroke aims to minimize the risk of a recurrent stroke by treating identified risk factors such as hypertension, hyperlipidemia, diabetes, atrial fibrillation, carotid stenosis and also to encourage the patient to a healthier life-style.[34] Secondary prevention pharmaceutical treatments range from antithrombotic treatment with antiplatelets, anticoagulant treatment (OAC /Vitamin K-antagonists), antihypertensives and statins to diabetic treatment. Lifestyle guidance of stroke patients aims to encourage patients to quit smoking, reduce alcohol consumption, adopt a healthy diet and increase physical activity.[123] According to Swedish stroke recommendations, all stroke patients should have a follow-up at three to six months to identify unmet needs. However, it has been observed that many patients do not receive this kind of structured follow-up and this might have negative effects on patients' health.[35]

The goal of stroke rehabilitation is to help the patient relearn skills, optimize functions and level of independence after stroke, and to achieve the best possible quality of life.[124] The

severity of stroke complications and each person's ability to recover varies widely and may involve depression, epilepsy, spasticity and pain. Recommended post-stroke rehabilitation settings include inpatient rehabilitation units, outpatient units, skilled nursing facilities, and home-based rehabilitation programs allowing for flexibility of rehabilitation to meet a patient's individual needs. However, such facilities differ greatly between countries as well as within countries and many stroke patients report long-term unmet needs in life after stroke.[35, 125]

2.11 PATIENT ENGAGEMENT IN STROKE RESEARCH

In recent years there has been increasing interest in patients' and carers' engagement in taking part in research planning.[126, 127] Only a few studies have focused on stroke patients, often being small and using interview methods. For instance, Pollock et al, showed in a Scottish survey (n=28) that cognition was the most prioritized area of research for stroke patients.[128] In Sweden, no such studies have been performed.

The term patient engagement is not to be confused with the synonymously used patient-centered care. Although the concepts are related it is important to note that patient-centered care is a broader term: "a partnership among practitioners, patients, and their families (when appropriate) to ensure that decisions respect patients' wants, needs, and preferences and that patients have the education and support they need to make decisions and participate in their own care".[129] Patient engagement at the policy level, on the other hand, focuses on engaging in research planning, developing, implementing, and also evaluating national healthcare polices, and, it has been argued to improve health outcomes and reduce healthcare costs.[130] The purpose of patients' engagement in research planning and policy making, often described as public involvement, is to ensure that the health care system is oriented around and responsive to the affected patients' perspectives.

2.12 KNOWLEDGE GAP

Stroke is a heterogenous disease with various functional and mental deficits with long-term impact among stroke patients. We know that quality of life is affected by stroke, but we do not know to what extent, how it changes over time, or who is affected the most. We know that acute treatment, such as thrombolysis improve functional outcome after acute stroke, but we do not know if it improves long-term survival. We know that healthcare costs of stroke care are large, but we do not know the variation of these costs. We also know that it is important to do research on stroke patients, but we do not know which research areas the patients themselves consider to be the most important. In order to be able to make customized changes to maximize health-related quality of life and survival among stroke patients, and furthermore to evaluate these changes, it is crucial to better understand the variation in how stroke impacts patients.

3 RESEARCH AIMS

The overall aim of this thesis was to contribute to the understanding of the impact stroke has on the stroke survivor's life after stroke in terms of survival, health-related quality of life and costs since all these aspects are important when implementing and evaluating changes made to clinical practice.

Table 1. Specific knowledge gaps and aims of each project included in the thesis

Study	Knowledge gap	Aim
Study I:	Thrombolysis improves functional outcome if given to selected acute ischemic stroke patients, but we are lacking knowledge on long-term survival after thrombolysis.	To find out if intravenous thrombolysis in acute ischemic stroke lead to improvement in survival at three years after stroke
Study II:	We know that stroke impact life after stroke in terms of survival, health-related quality of life and costs to healthcare. But little is known of how functional outcome after stroke impact these aspects.	To find out the impact of life after stroke in terms of survival, health-related quality of life and costs, based on functional outcome after stroke
Study III:	We know that health-related quality of life is affected after stroke, but we do not know the variation in impact over time based on functional outcome.	How does stroke impact health-related quality of life based on functional outcome
Study IV:	Despite extensive ongoing stroke research, we do not know what research areas stroke patients prioritize in life after stroke, according to themselves.	To ask the patients what stroke research areas they prioritize in order to improve life after stroke

4 MATERIALS AND METHODS

The studies of this thesis are descriptive investigations of stroke patients, based on primary and secondary clinical data from two large randomized clinical drug trials.

4.1 MATERIAL

Clinical data on primary and secondary outcomes were retrieved from the Third International Stroke Trial (IST-3) and Efficacy of Fluoxetine- a randomized controlled Trial in Stroke (EFFECTS), to describe the impact on patients in life after stroke. In study II registry data from the Swedish National Patient Register which is held by the National Board of Health and Welfare was combined with clinical data from the IST-3.

4.2 PATIENT POPULATION

4.2.1 The Third International Stroke Trial

IST-3 was a pragmatic international, multi-center, randomized-controlled, open-treatment trial including 3035 ischemic stroke patients in 156 hospitals in 12 countries between year 2000, and 2011.[43] A protocol of the trial was published in 2006, with an initial aim of recruiting 6000 patients, and was later updated with a reduced aim of 3100 patients.[131-133] The sample size gave 80% power to detect an absolute difference of 4.7% in the primary outcome. Patients were randomized to the study via a telephone secure computerized central system or a web interface. Randomization was 1:1, and 1515 (50%) were allocated to the alteplase plus standard care group and 1520 (50%) were allocated to the standard care alone group. A statistical analysis plan was published in 2012, before the data was unblinded and analysed.[134]

The initial pilot phase was double-blinded and placebo-controlled, and the main phase was open control. After the pilot phase ended, additional measures were introduced to minimize bias in the assessment of early and late outcomes. If the patient had a clear indication for intravenous thrombolysis with rt-PA, they were to be treated in accordance with local guidelines, and if the patient had a clear contraindication to treatment they were not to be entered into the trial. Only if both the clinician and the patient felt that the treatment was promising but unproven, could the patient be included in the trial after written informed consent from the patient.

The primary outcome in IST-3 was independent and alive, defined by Oxford Handicap Scale (OHS) 0-2, at six months after given IVT (alteplase) within six hours of randomization compared to standard of care. The results showed improved functional outcome for patients

given IVT within six hours, also to patients older than 80 years of age, with the greatest benefit among patients treated within three hours. There was no upper age limit for inclusion, and more than half of the 3035 patients were aged over 80 years.

The protocol was approved by the Multicentre Research Ethics Committees, Scotland (reference MREC/99/0/78), and by local ethical committees in each participating country. Registry number ISRCTN25765518.

Inclusion criteria:

- Symptoms and signs of clinically definite acute stroke.
- Time of stroke onset is known and treatment can be started within six hours of onset.
- CT or MRI brain scanning has reliably excluded both intracranial hemorrhage and structural brain lesions which can mimic stroke (e.g cerebral tumour)

Exclusion criteria:

- The patient has previously been randomized in IST-3.
- Major surgery, trauma (e.g. major fall at time of stroke) or gastrointestinal or urinary tract hemorrhage within the previous 21 days. Arterial puncture at a non-compressible site within the previous 7 days.
- Any known defect in coagulation (e.g. currently on oral anticoagulants with an INR > 1.3 OR current treatment with heparin [unless APPT within normal laboratory limits] OR treatment with low molecular weight heparin or heparinoid OR treatment with ximelagatran).
- Known defect of clotting or platelet function (but patients on antiplatelet agents can be randomized).
- The patient is female and of childbearing potential (unless it is certain that pregnancy is not possible) or breast feeding.
- Hypo- or hyperglycemia sufficient to account for the neurological symptoms; the patient should be excluded if their blood glucose is < 3.0 or > 20.0 mmol/L (stick testing is a sufficiently accurate test for this purpose).
- Symptoms considered likely to resolve completely within the next few hours (i.e. a TIA).
- Patient has had a stroke within the previous 14 days or has had treatment for acute ischemic stroke with thrombolytic therapy within the past 14 days.
- Patient was already dependent in activities of daily living before the present acute stroke.
- Patient has other life-threatening illness (e.g. advanced cancer) likely to lead to death within a few months.

- Likely to be unavailable for follow-up e.g. no fixed home address.
- Patient has systolic blood pressure < 90 mm Hg or > 220 mm Hg or diastolic blood pressure < 40 mm Hg or > 130 mm Hg

4.2.1.1 Study I

A total of 1948 (64%) patients of the 3035 enrolled participants in IST-3 were scheduled for follow-up analysis of three-year survival after thrombolysis in UK, Sweden and Norway.

4.2.1.2 Study II

A total of 297 patients were included in the IST-3 trial in Sweden and included for the analysis in study II.

4.2.2 Efficacy of Fluoxetine- a randomized controlled Trial in Stroke

EFFECTS was a clinical randomized double-blinded placebo-controlled drug-trial including 1500 acute ischemic- and hemorrhagic stroke patients at 35 hospital in Sweden between the 20th October 2014, and 28th of June 2019.[135] Inclusion was performed 2-15 days after stroke onset. Last 12-month follow-up was on 8th of July 2020. Randomization was 1:1 via a web-based randomization system, where 750 participants were assigned to fluoxetine, and 750 participants were assigned to placebo. A protocol was published in 2015, and a statistical plan was published in 2017.[136, 137] EFFECTS was an independent trial in a collaboration of three international studies; FOCUS (n=3000) in the UK, and AFFINITY (n=1500) in Australia and Vietnam, with results published in 2019 and 2020 respectivly.[138, 139]

The primary objective in EFFECTS was functional outcome (mRS) after 20 mg fluoxetine given daily for six months compared to placebo. The results showed no improved functional outcome between the groups at six months. Neither did scores on the secondary outcome EQ-5D show a difference between fluoxetine and placebo (data on file). Similar results were presented for the FOCUS and AFFINITY trials.

EFFECTS was approved by the central medical ethics committee in Stockholm (2013/1265-31/2) and by the Swedish Medical Agency (5.1-2014-43006). It was registered in EudraCT, 2011-006130-16; ISRCTN, 13020412; and ClinicalTrials.gov; NCT02683213.

Inclusion criteria:

- Age ≥ 18 years
- Intracerebral hemorrhage or ischemic stroke
- Randomised between day 2 and 15

- Persisting focal neurological deficit present at the time of randomization severe enough to warrant treatment from the physicians AND the patient's perspective

Exclusion criteria:

- Subarachnoid hemorrhage, except where secondary to a primary intracerebral hemorrhage
- Unlikely to be available for follow-up for the next 12 months e.g. no fixed home address
- Unable to speak Swedish and no close family member available to help with follow up forms
- Other life-threatening illness (e.g. advanced cancer) that would make 12-month survival unlikely
- History of epileptic seizures.
- History of allergy or contraindications to fluoxetine including: Hepatic impairment (S-ASAT/ALAT > 3 upper normal limit) or Renal impairment (S-Creatinine levels > 180 micromolar/L)
- Pregnant or breastfeeding, women of childbearing age not taking contraception. Minimum contraception is an oral contraceptive. A human chorionic gonadotropin blood test is to be made prior randomization and after the end of trial medication.
- Previous drug overdose or attempted suicide
- Already enrolled into a Clinical Trial of Investigational Medicinal Products.
- Current or recent (within the last month) depression requiring treatment with a Selective Serotonin Reuptake Inhibitor (SSRI) antidepressant
- Patients who are unable give consent themselves
- Current use of medications which have serious interactions with fluoxetine.
- Use of any mono-amino-oxidase inhibitor during the last five weeks
- Fluoxetine in combination with metoprolol used in cardiac failure New York Heart Association Grade III B–IV

4.2.2.1 Study III

All patients who had completed the primary outcome (mRS) at six months in the EFFECTS study, were included in the investigation.

4.2.2.2 Study IV

All patients who had completed the 12 months follow-up in EFFECTS as of August 2018 were included in the investigation.

4.3 REGISTRY DATA

In study II, data on resource utilization was retrieved from the Swedish National Patient registry.[140] Linkage was performed via the unique Swedish identification number. For each inpatient stay and outpatient visit, the diagnosis-related group (DRG) and International Classification of Diseases–Tenth revision (ICD-10) codes, estimated to be valid in 85-95% of all inpatient diagnoses, were retrieved and multiplied by a unit cost retrieved from the Cost-per-patient database (KPP). Mortality was retrieved from Cause of Death Registry which has almost complete coverage in Sweden.

4.4 OUTCOME MEASURES

4.4.1 Oxford Handicap Scale

In studies I and II we used the patient-reported Oxford Handicap Scale (OHS), adapted from the modified Rankin Scale (mRS) to measure functional outcome. The OHS-scale was introduced by a stroke research team in 1989 and differs from mRS in wording, using "handicap" instead of "disability".[141]

Table 2. The Oxford Handicap Scale

OHS	
0	No symptoms.
1	Minor symptoms that do not interfere with lifestyle
2	Minor handicap, symptoms that lead to some restriction in lifestyle but do not interfere with the patient's capacity to look after himself
3	Moderate handicap, symptoms that significantly restrict lifestyle and prevent totally independent existence
4	Moderately severe handicap, symptoms that clearly prevent independent existence though not needing constant attention
5	Severe handicap, totally dependent patient requiring constant attention night and day
6	Dead

4.4.2 Modified Rankin Scale

In studies III and IV we used the patient-reported simplified modified Rankin Scale to measure functional outcome in calculated mRS-scores. Modified Rankin Scale is the most commonly used primary outcome in stroke trials.[142]

Table 3. The modified Rankin Scale

mRS	
0	No symptoms.
1	No significant disability. Able to carry out all usual activities, despite some symptoms.
2	Slight disability. Able to look after own affairs without assistance, but unable to carry out all previous activities.
3	Moderate disability. Requires some help, but able to walk unassisted.
4	Moderately severe disability. Unable to attend to own bodily needs without assistance, and unable to walk unassisted.
5	Severe disability. Requires constant nursing care and attention, bedridden, incontinent.
6	Dead

4.4.3 Survival

Data on mortality was retrieved either from trial data (IST-3) or from the Cause of Death register in project I and II.

4.4.4 Health-related quality of life

Health-related quality of life (HRQoL) was secondary outcomes in the the IST-3 and the EFFECTS trials and assessed by the patient-reported EQ-5D instrument, using either the EQ-5D 3L (IST-3) or the EQ-5D 5L (EFFECTS) version. In IST-3, HRQoL was assessed by EQ-5D 3L at six and eighteen months. In EFFECTS, HRQoL was assessed by EQ-5D 5L at baseline, six and twelve months.

The generic EQ-5D instrument consists of two parts.[108] The first part is a descriptive system in which respondents classify their own health in five dimensions—mobility, self-care, usual activities, pain/discomfort, and anxiety/depression—within three severity levels (no problems; some problems; severe problems) or five severity levels (no problems; some problems; moderate problems; severe problems; extreme problems) depending on version; EQ-5D 3L (used in study II) versus EQ-5D 5L (used in study III).

The second part is the EQ visual analog scale (EQ VAS), a vertical scale in which respondents report their current health between 0 (worst health you can imagine) and 100 (best health you can imagine). Both EQ-5D 3L and EQ-5D 5L have been validated on stroke patients.[102, 143]

The descriptive system generates health states, and combined with value sets, a single index value, the EQ-5D index (0 represents death; 1 represents full health), can be assigned to each health state. The EQ-5D index cannot measure a value higher than 1, but can measure a value below 0, for health states valued as worse than death. These values are available in country-specific value sets.[144, 145] The EQ-5D-3L illustrating 243 unique health profiles, and the EQ-5D-5L illustrating 3125 possible health profiles. The EQ-5D value sets have been obtained from samples of the general public, to ensure that they represent the societal perspective and preferences relevant to the users and also the funders of publicly funded healthcare systems.[146-148] In study II (EQ-5D-3L) we used a Swedish tariff, and in study III (EQ-5D-5L) we used the UK value set.[144, 145]

4.4.5 Costs

In study II, unit costs were collected from the KPP database held by the Swedish Associations and Local Authorities, as available from Diagnoses-Related Group (DRG)-code and the main International Classification of Disease (ICD)-code reported at each observation from the National Register. DRGs are based on ICD diagnoses, medical procedures, sex, age, discharge status, and complications or comorbidities.

4.4.6 Research priorities in life after stroke

A questionnaire was sent out between August and November in year 2018 to those participants who had completed the 12-months follow-up in the EFFECTS-trial as of August 2018. The questionnaire was constructed based on earlier literature in the area as well as "The action plan for stroke in Europe 2018 to 2030" defined by the Stroke Alliance for Europe.[128, 149] Stroke specialists within neurology, internal medicine, and rehabilitation medicine were involved in the outlining of the questionnaire. To ensure relevance of the questionnaire it was evaluated on patients and their informal carers in an outpatient clinic, and accordingly adjusted before it was sent out to the study participants. The final questionnaire consisted of eleven research areas including one free-text alternative. Patients were asked to tick two prioritized research areas important to them on which to conduct further research.

Table 4. Questionnaire in Study IV.

Please circle two areas that you, from your point of view, consider to be most important for stroke research in life after stroke:

1. Speech difficulties
2. Balance- and walking difficulties
3. Cognition and memory function
4. Visual problems
5. Aphasia
6. Upper and lower limb problems
7. Post-stroke fatigue
8. The impact of physical exercise on rehabilitation
9. The impact of lifestyle to avoid a new stroke
10. Depression/anxiety
Other:

4.5 STATISTICAL ANALYSIS

Categorical variables are measured on a nominal or an ordinal scale, and numerical variables on a ratio or interval scale. It is the nature of the variable (categorical or numerical) that decides which statistical method is the most appropriate to use. In the studies of this thesis, descriptive statistics on baseline characteristics were presented on nominal variables as proportions or frequencies, and on ordinal variables as mean, medians with interquartile range; and on numerical variables as means with standard deviation.

Study I:

We used time-to-event Kaplan-Meier survival estimates to analyze survival between patients treated with alteplase compared to standard of care. We assessed whether the effect of alteplase was modified by age and stroke severity. We used Cox-regression which is frequently used for survival data. The proportional hazards assume that the ratio of the hazards comparing different exposure groups remains constant over time. Since the hazards were non-proportional for the whole time period, we separately calculated hazard ratios (HR) in the early (≤7 days) and late (>7 days) time periods. HR represent the instantaneous risk of dying over the study period, as compared to relative risks and odds ratios which are cumulative over an entire study.

Study II:

We used time-to-event Kaplan–Meier estimates, unadjusted and adjusted for age, to assess survival up to 36 months by functional outcome (OHS 0-2 versus OHS 3-5) at six months. We used the Log-rank test to analyze the association between functional outcome at six months and survival up to 36 months. EQ-5D-index was stratified on OHS levels at six months (OHS0-5) and presented with number of observations, mean, standard deviation, and confidence interval. We used the ordinary least squares model to control for confounding. Costs were stratified on OHS levels (OHS 0-5) and presented as cumulative cost at 18 and 36 months, with its mean, median, standard deviation and confidence interval. For costs we used a generalized linear model with a logarithmic link function using a gamma distribution. This method was used due to the properties of cost values. Baseline variables were excluded (stepwise) from the models unless significant. For missing data on costs, we implemented an average cost as retrieved from the KPP-register.

Study III:

A Paretian Classification of Health Change was presented for the overall stroke group.[107] Changes in health state were summarized as improved if the patient reported better on at least one dimension and no worse on any other dimension, and as worsened if worse in at least one dimension and no better in any other dimension. Mixed change was defined as better in at least one dimension, but worse in at least one other. Prospectively collected data on EQ VAS and EQ-5D index at six and twelve months, stratified on mRS at six and twelve months, and presented with number of observations, mean, standard deviation, missing data and confidence interval. Differences in mean EQ VAS and EQ-5D index scores within each mRS group were tested using dependent t-test. Regression analyses (ordinary least square) were used to explore the impact of differences in baseline variables across mRS group on HRQoL at six months. Baseline variables were excluded (stepwise) from the model unless significant.

Study IV:

We compared baseline characteristics between respondents and non-responders. We used Chi-square-test to compare categorical data of questionnaire answers, and between sex and dichotomized age.

In all studies, P-values <0.05 was considered to be statistically significant.

Statistical analysis was carried out by Geoffrey Cohen, Melinda B Roaldsen, Jonathan Drever, Ann-Sofie Rudberg, Per Näsman and Anders Gustavsson, using either SAS for Windows, Software (version 9.4) or IBM SPSS Statistics for Mac (version 26), depending on project.

4.6 METHODICAL CONSIDERATION

Internal and external validity

The study design of the trials used in this thesis were randomized placebo-controlled clinical trials (RCT), which are ranked highest of scientific methods used in medical research. One advantage of RCTs is that the randomization reduces confounding. However, in studies II, III, IV we analyzed the study population as a cohort, thus eliminating the advantage of randomization.

The fact that we used patients included in clinical trials might cause selection bias, since it has been argued that selected patients are invited to participate in clinical trials. This aspect makes large scale generalizability more difficult, and could possibly contribute to overestimation of the results, or underestimation. Since the studies of this thesis are performed in high-income countries, making generalizability to middle-, and low-income countries limited, even though they could contribute to some insight in other contexts.

In the first two projects we used data from a clinical trial (IST-3) combined with registry data, retrieved from the National Patient Registry and Cost-per patient registry in Sweden. Combining clinical data with registry data made it possible to prospectively expand the investigations on the Swedish IST-3 stroke population, but does involve heterogeneity of the data sources. The advantage of using data from registries on hospital-care and out-patient visits was that recall bias was reduced. On the other hand, there are always uncertainties such as missing data, incomplete data and incorrect registration in registries.

In stroke research, there is an inconsistency in how the mRS is analyzed, with many stroke trials using dichotomous analysis, dividing the mRS into favorable versus unfavorable outcomes, while other studies used ordinal (shift) analysis, determining all changes across the mRS-scale. What the best dichotomy is, is subject to debate, where more recent trials often use 0–1 versus 2–6 instead of 0 to 2 versus 3–6.[150, 151] In our studies we used OHS 0-2 versus 3-6 (study I and II) when analyzing survival. In study III we used the full ordinal scale since current recommendations are leaning towards this. Further on, we used patient reported mRS as compared to clinically assessed mRS.[152] Whether assessed clinically or patient reported, the mRS value is restricted by potentially interobserver variability which might cause misclassification bias.[153, 154] Several attempts have been made to reduce bias in the clinically assessed mRS between raters, for example the introduction of a structured interview and video-based training and certification, but the effects have not been consistent.[155]

The EQ-5D, also a patient reported outcome, was originally developed to be a brief generic instrument to measure HRQoL that could be summarized in to one single value for each health profile, the EQ-5D index (also called EQ-5D values or utilities), using country-specific value-sets. Not all countries have developed such value-sets, and if not available the recommendation is to use a value set from a country that resembles the current country in terms of demographics, geography, or health care. Different EQ-5D value sets are based on various valuation techniques, such as the time trade-off (TTO), standard gamble (SG), VAS,

person trade-off or rank-based techniques. It is important to consider that regardless of which value set is used, they will all have a different influence on the results and may also introduce an exogenous source of variance that might cause bias. The first publication of a EQ-5D-3L value set was seen in 1997 by Dolan et al. and since then many country-specific value sets have been published (www.euroqol.org).[148] A Swedish value set on the EQ-5D-3L was published by Burström et al, and this is the value set we used in study II. For study III we used an interim value set, a mapping function between the EQ-5D-3L value sets and the EQ-5D-5L descriptive system since this has been recommended by NICE and frequently used internationally.[145] Studies of the EQ-5D-5L version have been conducted from 2012 and in 2020, and a Swedish value set was recently published by Burström et al.[156, 157]

The main difference between EQ-5D 3L and the newer EQ-5D-5L is that the number of severity levels in each dimension has increased from three levels to five. In a comparison of responsiveness in EQ-5D-3L versus EQ-5D-5L on stroke patients, Golicki et al showed that EQ-5D-3L indicated stronger levels of correlation with stroke clinical outcome measures than EQ-5D-5L, essentially meaning that the EQ-5D-3L index changes were bigger than the mean EQ-5D-5L index changes, but they also showed that the 5L-version changes were greater than EQ VAS changes. This is contrary to almost any other disease where EQ-5D-5L has shown better responsiveness to changes compared to the EQ-5D-3L. Notable is that this thesis does not attempt to provide the answer to whether EQ-5D is the best way going forward to evaluate a stroke patient's HRQoL after stroke, but the need to assess quality of life for stroke patients in the future. However, EQ-5D remains to be a widely used and acknowledged instrument, and has the advantage of often being recommended for use in health economic evaluations.

A methodical concern should also be raised about the questionnaire used in study IV. Since being used for the first time in this study, it is therefore not validated. Thus, any strong conclusions from the results are more difficult to draw. On the same note, research and methods involving public involvement is still an unexplored field, lacking both knowledge and experience among clinicians and researchers.[158]

4.7 ETHICAL CONSIDERATION

The studies of this thesis conform to good clinical practice and the Helsinki declaration, being approved by the regional ethics committee in Sweden (Studies I and II: EPN 2002-551, amendment 2007-06-27, amendment 2015-06-10, 2015/1018-32: study III EPN 2013/1265-31/2: study IV: 2013/1265-31/2). The Helsinki declaration was developed by the World Medical Association as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.[159]

An individual informed consent was obtained from all patients included in IST-3 and in EFFECTS trial. However, the acuity of thrombolysis makes the approach to obtain informed consent challenging in clinical trials, as well as in clinical practice.[160] In addition, the ability of a patients to give a written informed consent may influence the selection of patients who differ clinically from patients who are not able to provide this.

Information about study II was not included in the informed consent in IST-3, since the project was approved in an amendment after the main study was already finished. Although informed consent is essential in intervention studies to preserve the confidence of the public, it is generally not required for registry studies in Sweden.[161] In study II we combined registry-based data with clinical data retrieved from IST-3 and the additional imposed risk on the study participants, due to retrieving registry data, are few, but do include the risk of breaching the participants' integrity, if for instance personal identity data are mismanaged, or presented at a detailed level with very few persons. The risk of violating individual patients´ integrity within the context of our study is considered to be very low, since it was carried out on a larger set of anonymized data, generating results on an aggregated level. On the contrary, using already existing collected data to gain new knowledge with no further disturbance to the patients, could be argued to be an ethical advantage, as long as the benefit to society exceeds the risk of causing harm. The potential risk of backward identification of individuals that could occur when combining detailed data was reduced by the fact that we did not include identifiable characteristics in the dataset that were combined with the registry data.

In study IV we did not inform the patients about the study in the informed consent since this study, as with study II, was approved by an amendment after the inclusion in EFFECTS. The questionnaire was sent out to the participating patients in EFFECTS, along with a letter thanking them for their participation in the EFFECTS study and asking them to fill out the questionnaire voluntarily and return it in a prepaid envelope. It could be argued that this additional disturbance of the patients, asking them to fill in an extra questionnaire, would raise an ethical concern. However, since the return of the questionnaire from patients was voluntarily we did not send out any reminders as we decided beforehand to interpret a non-answer as a refusal to participate. We did, nevertheless, receive an 81% response rate.

There is a growing body of literature demonstrating sex differences in large clinical stroke trials, and an under-enrollment of women.[162-164] Explanations for the under-representation of women are not fully investigated, but factors such as older age, severe stroke, less access to

health care and transportation have been identified. On the same note, regardless of sex, an ethical concern should be raised about the diverseness of patients who are invited to participate in studies compared to those who are not. More trials are performed in larger cities and in areas close to university hospitals, making trials less accessible to the suburban population. Socioeconomic-, cognitive, and language factors may also influence who is included in trials. Another explanation might be low diverseness among researchers who include participants in trials, and extending the diverseness of people involved in research might be a way forward to expand the spectra of participants. It could also be argued that participants in clinical trials are offered more attention and extra care, which would raise an ethical concern along with the discussion above that only selected patients are invited to participate.

5 RESULTS

5.1 STUDY I:

In total, 1946 patients out of the 1948 patients that were scheduled for the analysis were included (England and Wales n=1342, Scotland n=104, Sweden n=297, and Norway n=203). Two patients were excluded from the analysis because they were randomized outside the six hours window, resulting in 967 (50%) in the alteplase plus standard care group and 979 (50%) in the standard care alone group. Compared to the total 3035 participants of the main study, this subset of participants was older, had higher systolic blood pressure, had atrial fibrillation more often, had more severe strokes, and were randomized to treatment earlier (Table 5).

Table 5. Baseline characteristics. Data are median (IQR) or n (%).

	Alteplase + standard care	**Standard care alone**
	n= 967	n=979
Age (years)	82 (73–86)	82 (72–86)
Women	498 (51%)	501 (51%)
National Institutes of Health Stroke Scale score	11 (7–18)	11 (7–17)
Systolic blood pressure (mm Hg)	156 (139–174)	156 (140–173)
Atrial fi brillation	313 (32%)	300 (31%)
Time to randomisation (h)	3.8 (2.8–4.7)	3.7 (2.8–4.7)

We found that patients treated with alteplase had a small but non-significant improvement in overall survival at three years of 3.6 % (95% CI -0.81 to 8.1) as shown in figure 4. In the alteplase group there was an increased risk of death during first seven days, where 99 (10%) of 967 participants in the alteplase plus standard care group died compared to 65 (7%) of 979 in the standard care alone group, HR 1.52 (95% CI 1.11 to 2.08), p=0.004). Among patients alive at seven days, patients treated with alteplase, had significantly better survival to three years (p=0.007), HR 0.78 (95% CI 0.68 to 0.90). There was no statistically significant effect modification by baseline onset to randomization, NIHSS or age. Participants who died during the first seven days, both in the alteplase plus standard care and standard care alone groups, had more severe stroke at baseline than those who survived the first seven days.

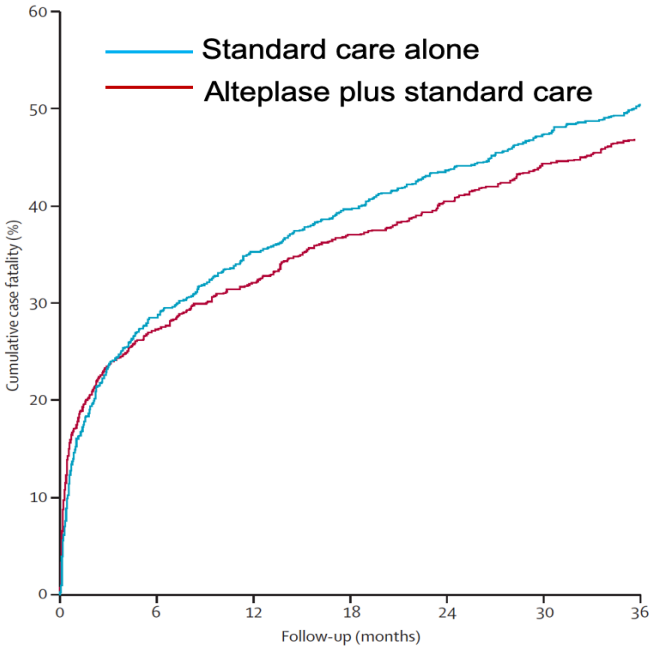


Figure 4. Three year cumulative mortality of 1946 patients divided to alteplase plus standard of care versus standard of care.

5.2 STUDY II:

All the 297 patients participating in the IST-3 study in Sweden had completed the OHS and were included in the analysis of Study II. Baseline characteristics is presented divided on functional outcome, measured by OHS at six months (Table 6).

Table 6. Baseline characteristics subdivided on functional outcome measured by Oxford Handicap Scale at six months.

	All	OHS 0	OHS 1	OHS 2	OHS 3	OHS 4	OHS 5	OHS 6
	n=297	n=36	n=50	n=48	n=41	n=23	n=42	n=57
Age, years								
Mean (SD)	81 (11)	76 (15)	75 (14)	82 (10)	81 (10)	80 (9)	84 (5)	86 (6)
Median (max/min)	83 (99/24)	83 (91/24)	81 (99/26)	85 (96/38)	83 (95/48)	83 (93/53)	85 (92/71)	87 (94/61)
Gender, n (%)								
Female	144 (49)	13 (36)	15 (30)	31 (65)	19 (46)	10 (44)	27 (64)	29 (51)
NIHSS n (%)								
Mean (SD)	10 (7)	5 (3)	7 (5)	8 (6)	10 (6)	9 (5)	15 (6)	14 (6)
0-5	95 (32)	24 (67)	28 (56)	18 (38)	10 (24)	7 (30)	2 (5)	6 (11)
6-14	125 (42)	11 (31)	19 (38)	23 (48)	22 (54)	13 (57)	16 (38)	21 (37)
15-24	75 (25)	1 (3)	3 (6)	7 (15)	9 (22)	3 (13)	23 (55)	29 (51)
>=25	2 (0.7)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2.4)	1 (2)
Living alone before admission, n (%)								
yes	135 (45.5)	16 (44)	18 (36)	25 (52)	21 (51)	11 (48)	25 (60)	19 (33)
Educational level, n (%)								
Elementary school or less	132 (44.6)	17 (47)	15 (30)	30 (63)	24 (59)	15 (65)	16 (38)	15 (27)
Completed elementary, and middle school	56 (19)	5 (14)	15 (30)	12 (25)	7 (17)	4 (17)	10 (24)	3 (5)
Completed high school	26 (9)	7 (19)	7 (14)	3 (6)	4 (10)	2 (9)	0	3 (5)
University	21 (7)	6 (17)	5 (10)	2 (4)	3 (7)	1 (4)	4 (10)	0 (0)
Unknown	61 (21)	1(3)	8 (16)	1 (2)	3 (7)	1 (4)	12 (29)	35 (63)
Missing								1

OHS=Oxford Handicap Scale. NIHSS= National Institutes of Handicap Stroke Scale
SD=standard deviation

We found that patients with a less functional handicap had a better survival, dichotomized on OHS 0-2 versus OHS 3-5 (Figure 5).

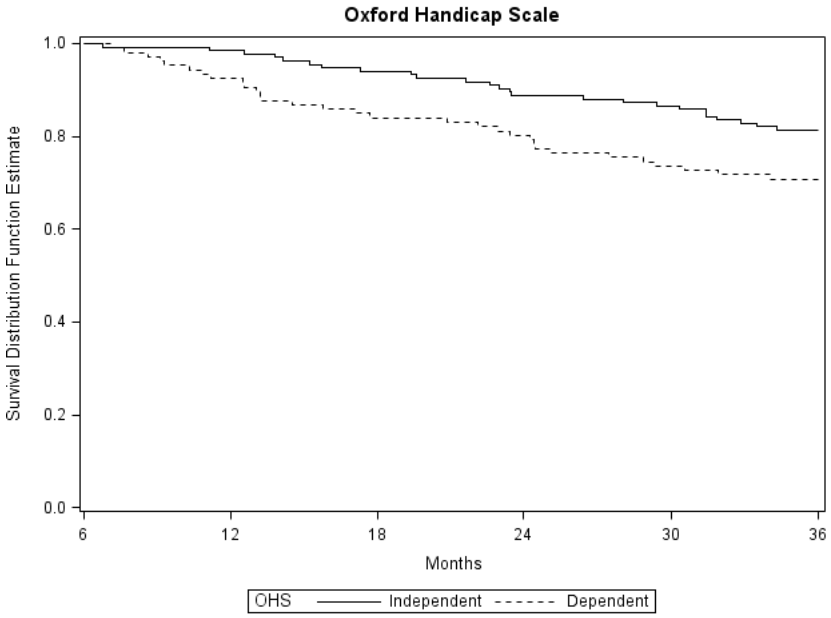


Figure 5. Kaplan–Meier survival curves up to 36 months by functional outcome, independent (OHS 0–2) versus dependent (OHS 3–5), at 6 months (p=0.038). The difference sustained when adjusting for age (p<0.01).

Patients with a less handicap level had a higher mean of health-related quality of life as measured by EQ-5D index at six and 18 months (Table 7). The findings remained stable when controlling for baseline differences across functional outcome groups, and the only significant predictor was age and only for the 18 months.

Table 7. Health-related quality of life by EQ-5D index at 6 and 18 months, subdivided on functional outcome (OHS) at six months

	Independent			Dependent			P-value*
	OHS 0	OHS 1	OHS 2	OHS 3	OHS 4	OHS 5	
6 months							
no of observations	n=36	n=50	n=48	n=41	n=23	n=42	
median (min/max)	0.97 (0.34/0.97)	0.92 (0.34/0.97)	0.79 (0.34/0.97)	0.74 (0.34/0.91)	0.66 (0.34/0.87)	0.58 (0.34/0.70)	
mean (SD)	0.92 (0.15)	0.80 (0.25)	0.76 (0.17)	0.68 (0.18)	0.61 (0.14)	0.56 (0.11)	<0.001
95% CI	0.87-0.97	0.73-0.87	0.71-0.81	0.62-0.73	0.55-0.68	0.53-0.59	
18 months							
no of observations	n=35	n=46	n=45	n=36	n=21	n=32	
median (min/max)	0.97 (0.34/0.97)	0.93 (0.34/0.97)	0.77 (0.34/0.97)	0.68 (0.34/0.97)	0.64 (0.34/0.77)	0.60(0.34/0.74)	
mean (SD)	0.82 (0.04)	0.86 (0.02)	0.73 (0.03)	0.68 (0.03)	0.61 (0.03)	0.57 (0.02)	<0.001
95% CI	0.75-0.90	0.81-0.91	0.68-0.80	0.62-0.74	0.55-0.66	0.53-0.61	

CI=Confidence interval; SD= standard deviation; OHS= Oxford Handicap Scale. *P value represents the mean difference in EQ-5D index between all groups of functional outcome OHS 0–5 using one-way ANOVA with Tukeys correction.

Differences in costs related to functional outcome after stroke, was mainly due to differences in mean number of days spent in hospital, ranging from eight to 42 days at six months, across OHS groups (Figure 6). However, the total cumulative costs at end of follow-up were lower among OHS 5 patients compared to OHS 4, and this group also utilized the least out-patient care resources. Males had a higher cost at OHS 0 compared to women, and women had a higher cost at OHS 1–5 compared to men. In the regression model, NIHSS at baseline was (together with OHS group) a significant predictor of 36 months total costs. Controlling for NIHSS changed the mean costs up to 16%.

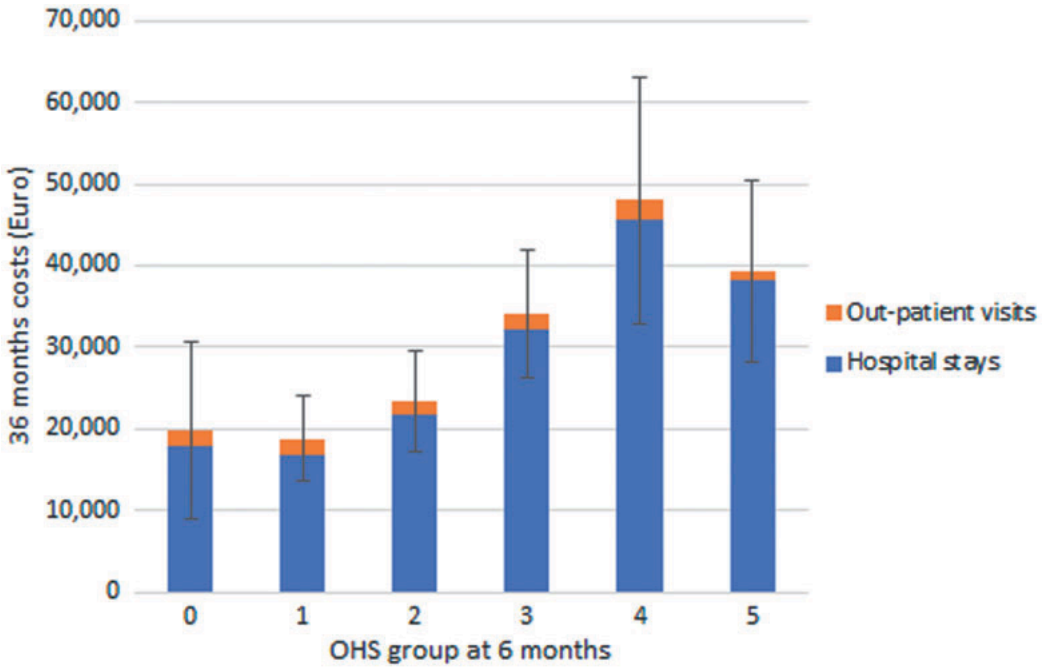


Figure 6. Cumulative 36 months mean total costs by functional level at six months, including 95% confidence intervals

5.3 STUDY III

Out of 1500 patients, 1479 patients completed the mRS at six months and were included in the analysis. Baseline characteristics on all patients, divided on functional outcome at 6 months is shown in table 8.

Table 8. Baseline characteristics divided on functional outcome as measured by mRS at six months.

Baseline characteristics	all	mRS 0	mRS 1	mRS 2	mRS 3	mRS 4	mRS 5	mRS 6
Number of patients, n (%)	1479	326 (22)	415 (28)	200 (14)	332 (22)	94 (6)	65 (4)	47 (3)
Age, mean years (SD)	71 (11)	69 (10)	69 (11)	66 (11)	74 (9)	77 (8)	77 (9)	78 (9)
Median (range)	72 (20-94)							
Sex								
Female, n (%)	569 (38)	113 (35)	152 (37)	63 (32)	138 (42)	51 (54)	33 (51)	19 (40)
Male, n (%)	910 (61)	213 (65)	263 (63)	137 (69)	194 (58)	43 (46)	32 (49)	28 (60)
NIHSS score, mean (SD)	5 (4)	3 (2)	3 (3)	5 (3)	6 (4)	8 (4)	10 (5)	7 (5)
median (range)	3 (0-26)	2 (0-11)	3 (0-17)	4 (0-16)	5 (0-26)	8 (1-20)	9 (1-24)	5 (0-20)
0-5, n (%)	1050 (71)	305 (94)	345 (83)	142 (71)	186 (56)	31 (33)	15 (23)	26 (55)
6-14, n (%)	382 (26)	21 (6)	68 (16)	57 (29)	130 (39)	57 (61)	36 (55)	13 (28)
15-24, n (%)	46 (3)	0 (0)	2 (1)	1 (1)	15 (5)	6 (6)	14 (22)	8 (17)
25-, n (%)	1 (0)	0 (0)	0 (0)	0 (0)	1 (0)	0 (0)	8 (17)	0 (0)
EQ VAS , mean (SD)	57 (22)	67 (19)	60 (21)	53 (20)	51 (23)	46 (22)	45 (24)	53 (25)
EQ-5D index, mean (SD)	0.48 (0.36)	0.73 (0.25)	0.58 (0.29)	0.39 (0.3)	0.35 (0.36)	0.16 (0.30)	0.13 (0.30)	0.32 (0.40)
Living arrangements before admission n (%)								
Living alone, n (%)	538 (36)	116 (36)	147 (35)	69 (35)	118 (36)	35 (37)	30 (46)	23 (49)
Living with someone, n (%)	940 (63)	210 (64)	268 (65)	130 (65)	214 (64)	59 (63)	35 (54)	24 (51)
Other living, n (%)	1 (0)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Independent before admission n (%)								
Yes, n (%)	1425 (96)	318 (98)	404 (97)	197 (99)	318 (96)	85 (90)	61 (93)	42 (89)
No, n (%)	54 (4)	8 (2)	11 (3)	3 (1)	14 (4)	9 (10)	4 (6)	5 (10)
Stroke type n (%)								
Ischemic stroke, n (%)	1295 (88)	292 (89)	377 (90)	172 (86)	282 (84)	76 (80)	56 (86)	40 (85)
Intracerebral stroke, n (%)	182 (12)	34 (10)	38 (9)	28 (14)	50 (15)	17 (18)	9 (14)	6 (13)
Non-stroke, n (%)	2 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)	1 (2)
Type of employment before admission n (%)								
Full-time work, n (%)	308 (21)	69 (21)	120 (29)	63 (32)	42 (13)	6 (6)	6 (9)	2 (4)
Part-time work, n (%)	67 (5)	24 (7)	16 (4)	13 (7)	13 (4)	0 (0)	1 (2)	0 (0)
Volonteer work, n (%)	2 (0)	0 (0)	1 (0)	0 (0)	1 (0)	0 (0)	0 (0)	0 (0)
Retired, n (%)	1069 (72)	227 (69)	268 (65)	114 (57)	270 (81)	88 (94)	57 (88)	45 (96)
Unemployed, n (%)	14 (1)	3 (1)	6 (1)	3 (2)	2 (1)	0 (0)	0 (0)	0 (0)
Other, n (%)	19 (1)	3 (1)	4 (1)	7 (4)	4 (1)	0 (0)	1 (2)	0 (0)

mRS=modified Rankin Scale. NIHSS= National Institutes of Health Stroke Scale. EQ VAS= EQ-5D visual analogue scale. SD= standard deviation. N=number of observations

In total, 1210 (82%) patients completed the EQ-5D at all time points; an additional 113 (8%) patients reported EQ-5D at some time point. In total, data on EQ-5D were missing for 156 (10%) individuals. Proxy response was reported for one individual at mRS 0; three individuals at mRS 1; five individuals at mRS 2; fifty-three individuals at mRS 3; twenty individuals at mRS 4; and thirty-one individuals at mRS 5. From baseline to twelve months, a total of 39% reported improved health, 17% reported worsened health, 40% reported a mixed change in health, and 5% reported no change in health (Figure 7).

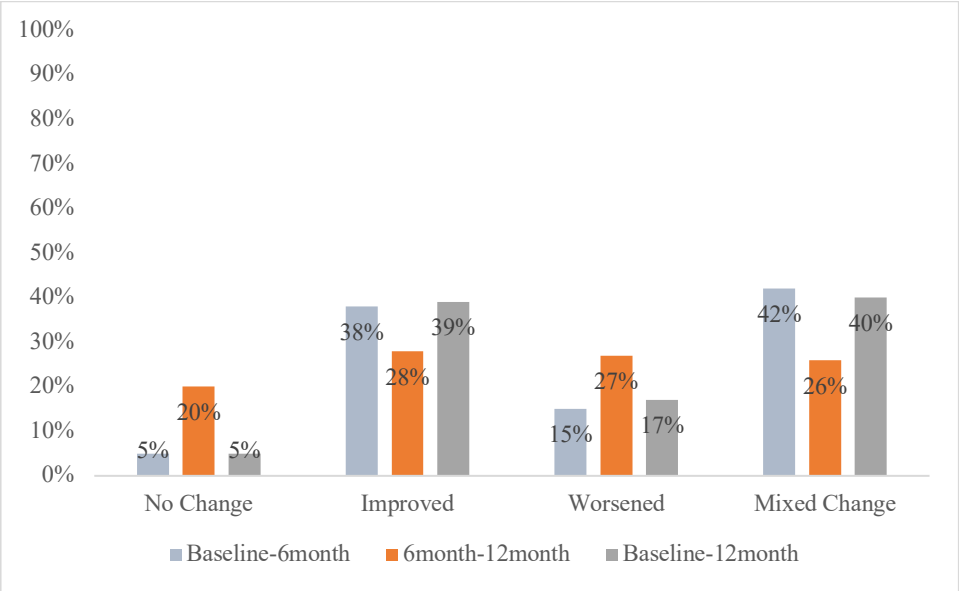


Figure 7. Health change for all stroke patients over time as measured by the EQ-5D-5L. Improved if the patient reported better within at least one dimension and no worse within any other dimension, and worsened if worse within at least one dimension and no better within any other dimension. Mixed change is defined as better within at least one dimension, but also worse within at least one other.

Overall, EQ VAS and EQ-5D index decreased with declining functional level at all time points, patients with mRS 0 had the highest mean, and mRS 5 had the lowest mean (Table 9).

Table 9. EQ-5D VAS and EQ-5D index at 6 and 12 months subdivided on functional outcome measured by modified Rankin Scale (mRS) at 6 and 12 months.

EQ VAS	6 months					12 months				
mRS	**n**	**mean**	**SD**	**CI**	**missing**	**n**	**mean**	**SD**	**CI**	**missing**
0	326	90	11	89-91	3	319	89	13	88-91	9
1	415	74	16	72-75	3	402	76	17	76-79	2
2	200	63	18	60-65	8	191	64	21	60-67	5
3	332	56	20	54-59	12	321	57	23	55-60	20
4	94	38	20	34-42	4	88	38	21	33-42	7
5	65	28	20	23-34	12	58	27	21	20-33	10
6	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
EQ-5D index	6 months					12 months				
mRS	**n**	**mean**	**SD**	**CI**	**missing**	**n**	**mean**	**SD**	**CI**	**missing**
0	326	0.88	0.14	0.86-0.89	5	319	0.87	0.15	0.86-0.89	11
1	415	0.77	0.16	0.75-0.78	8	402	0.76	0.17	0.75-0.78	5
2	200	0.63	0.20	0.60-0.66	13	191	0.64	0.23	0.61-0.67	6
3	332	0.54	0.23	0.52-0.57	17	321	0.53	0.26	0.50-0.56	21
4	94	0.15	0.28	0.09-0.21	4	88	0.20	0.30	0.14-0.27	6
5	65	´-0.08	0.20	-0.14-(-0.02)	14	58	0.02	0.28	-0.06-0.10	10
6	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

EQ VAS = EQ visual analogue scale. SD = standard deviation. CI = Confidence Interval

We found that people with lower functional outcome at six months (mRS 4 and 5) decrease in HRQoL both in EQ-5D VAS (Figure 8) and EQ-5D index (Figure 9) from baseline to six months, whereas patients with the better functional outcome (mRS 0-3) at six months improved in HRQoL from baseline to six months.

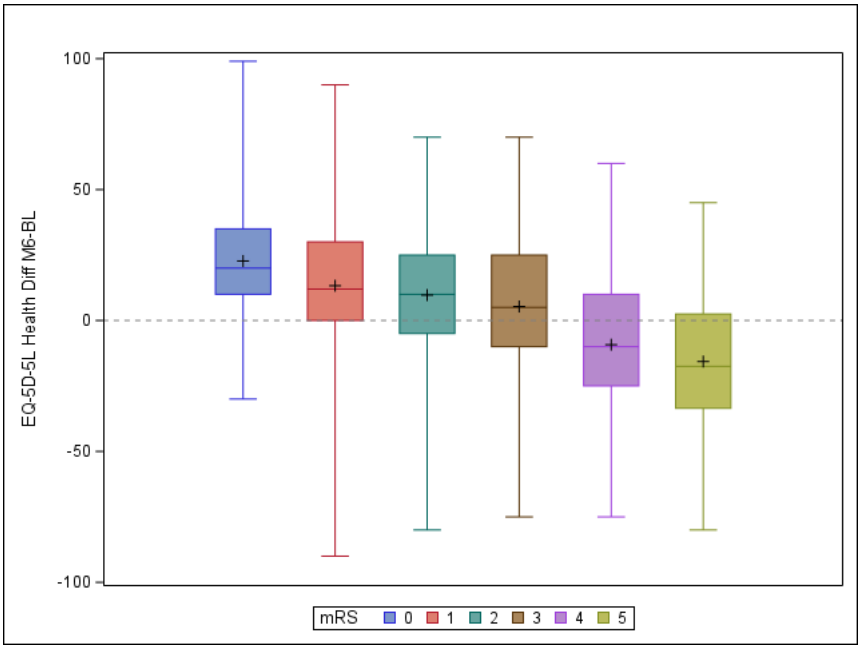


Figure 8: Changes in EQ-5D VAS score from baseline to six months, stratified by functional outcome (mRS) at six months, showing median, mean (+), upper and lower quartile, and min and max. P-values within each mRS-group: mRS 0 (<0.0001); mRS 1 (<0.0001) ; mRS 2 (<0.0001); mRS 3 (0.0013); mRS 4 (0.0027); mRS 5 (0.0014). Significance level was set to 0.05. mRS=modified Rankin Scale.

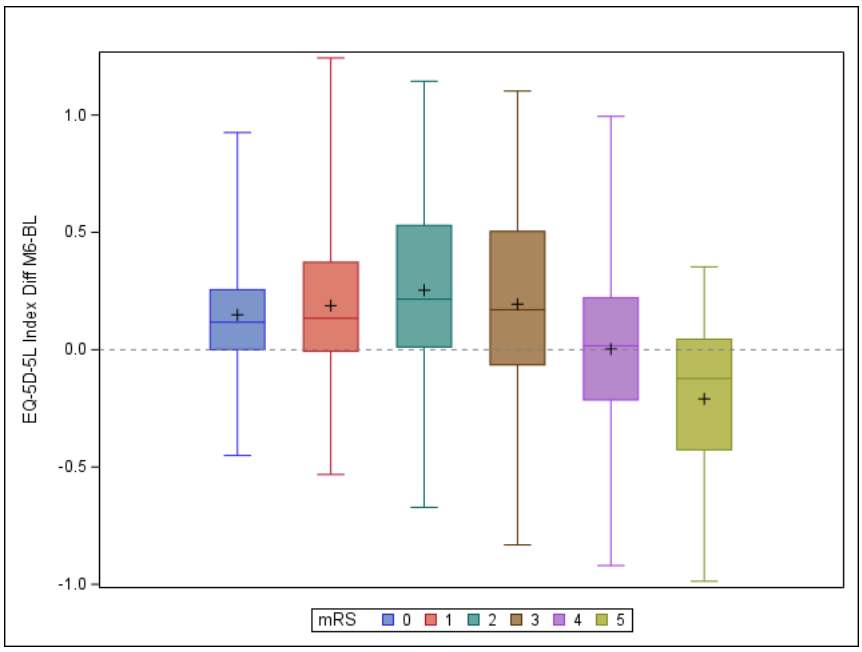


Figure 9: Changes in EQ-5D index from baseline to six months, stratified by functional outcome (mRS) at six months, showing median, mean (+), upper and lower quartile, and min and max. P-values within each mRS-group: mRS 0 (<0.0001); mRS 1 (<0.0001); mRS 2 (<0.0001); mRS 3 (<0.0001); mRS 4 (0.9504); mRS 5 (0.0003). Significance level was set to 0.05. mRS= modified Rankin Scale.

5.4 STUDY IV:

A total of 731questionnaires together with a prepaid envelope for the return was sent out. Out of these, 589 (81.1%) patients completed and returned the questionnaire. Five questionnaires were undelivered due to incorrect address. Baseline characteristics were compared with those responding to the questionnaire compared to those who did not and presented in table 10.

Table 10. Baseline characteristics of responders and non-responders to the questionnaire

	Responders	**Non-responders**	**Riksstroke 2018**
	(n=589)	(n=137)	
Sex, female	39 (190)	36 (50)	46%
Age, % ≥70	68	45	
Age at onset of stroke, median (min-max), years	72 (20-92)	68 (27-95)	75
Married	54 (318)	34 (47)	
Single	12 (71)	19 (26)	
Widow/widower	13 (74)	15 (20)	
Separated/divorced	7 (39)	11 (15)	
Partner	13 (77)	18 (24)	
Other	2 (10)	4 (5)	
Living alone	33 (197)	44 (61)	47%
Living together with someone	66 (391)	55 (76)	
Nursing homes	0	0	8%
Other	0.4 (1)	0	
Diabetes	18 (108)	24 (33)	23%
Previous coronary heart disease	15 (91)	15 (21)	
Previous stroke	16 (95)	16 (22)	21%
Previous intracranial haemorrhage	2 (13)	4 (6)	
Facial paresis	44 (261)	54 (60)	
Upper limb paresis	67 (393)	73 (82)	
Lower limb paresis	57 (335)	69 (77)	
Aphasia	17 (100)	14 (16)	
Homonymous hemianopsia	11 (63)	14 (16)	
Visuospatial symptoms	12 (72)	13 (14)	
Brainstem and cerebellar symptoms	19 (112)	12 (13)	
Other neurological defects	20 (115)	20 (22)	
NIHSS points sum, median (min-max)	3 (0-18)	4 (0-24)	3
MOCA total score, median (min-max)	24 (1-30)	24 (3-30)	
Ischemic Stroke	89 (524)	81 (110)	86%
Intracerebral Haemorrage	11 (64)	19 (26)	13%
Unknown	0.2 (1)	1 (1)	
Time stroke onset to questionnaire, median (min-max), months	27 (14-48)	27 (14-48)	

Presented as % (n) if not indicated otherwise. NIHSS = National Institutes of Health Stroke Scale. MOCA = Montreal Cognitive Assessment.

Balance and walking difficulties were the area of research most prioritized by the patients, chosen by 290 (49%). The second most prioritized area was Post-stroke fatigue, chosen by 173 (29%) patients. The alternative, Other, where patients were able to write a free text was chosen by 54 (9%) patients. The majority of questionnaires were filled out by the patients (93%), yet many commented that it was answered together with an informal carer. Out of the total questionnaires, 47 was filled out by informal carers and one by other personnel. There was a significant difference in area chosen between the age groups, dichotomized to < 70 years of age or ≥ 70 years of age, where older patients prioritized Balance and walking difficulties (p=0.002) and Speaking difficulties (p=0.045) to a higher degree. Younger patients prioritized Post-stroke fatigue (p<0.001). There were no differences between men and women in the response, except that more women (43 (11%) versus 11 (6%) men provided answers in the free text area Other (p=0.043).

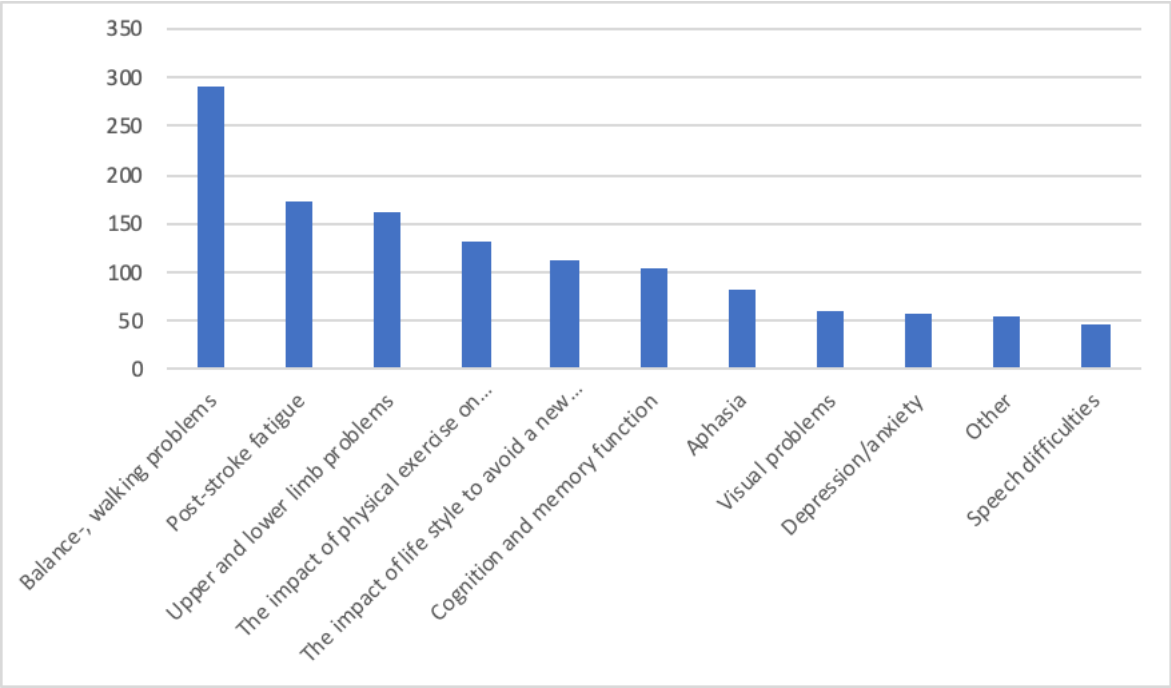


Figure 10. Number of answers on each research area. Each patient was asked to prioritize two areas. Thirty-one patients chose more than two areas. All priorities are presented in the figure.

6 DISCUSSION

6.1 MAIN FINDINGS

In study I we found a small, non-significant, decrease in three-year mortality in ischemic stroke patients, treated with IVT within six hours after onset. In those who survived the first seven days after treatment, there was a significant reduction in mortality. In study II we saw that a better functional outcome after stroke was associated with a better survival, and health-related quality of life. We also found an association with worse functional outcome and increased costs to healthcare. If established and new treatments could reduce short and long-term disability, this may have a substantial impact on survival, health-related quality of life and costs to the healthcare system. In study III we saw that patients with the worst functional outcome after stroke was associated with a decrease in health-related quality of life six months after stroke, whereas patients with the better functional outcome after stroke increased in health-related quality of life after stroke. Gaining knowledge of long-term impact by disability levels after stroke may reveal an important gap of unmet needs where we are able to make improvements. To further explore this critical gap of unmet needs we asked the stroke patients in study IV what area of research they prioritize in order to make life better after stroke, and they responded that they prioritized research to improve their outcomes in terms of walking and balance difficulties and to decrease post-stroke fatigue.

6.2 SURVIVAL

Treatments such as IVT represent an urgent decision, taken within minutes after first encounter with the patient, and is seldom an easy clinical decision considering the risk of causing an even worse acute outcome such as hemorrhagic bleeding or death. Treating a patient with IVT also requires providing information to the patient in a highly stressful situation. It may feel challenging to inform a patient of the pros and cons of potentially fatal treatment not knowing if the treatment will improve survival in long term. This has also caused debate and controversies among clinicians.[165]

In our study, we could not find a significant difference in survival between patients treated with alteplase plus standard care compared to standard care alone at three year follow-up. Patients were randomized to treatment within six hours from stroke onset. However, our study was published in 2016, and since then other studies on long-term survival and outcome after IVT have been performed. In 2018, Muruet et al. showed, from a cohort-study on the population-based South London Stroke Register of first-ever strokes, that in a 10-year period, ischemic stroke patients admitted to hospital within three hours of stroke onset and treated with IVT, lived one year longer than controls.[166] In the same study, improved functional outcome was seen up to five years after IVT compared to controls. We showed that a better functional outcome is associated with a better survival (Study II). Other studies have shown improved survival after IVT, a meta-analysis of six observational trials, including 16,000

acute ischemic stroke patients, found that compared with non-IVT treated patients, IVT treated patients had a 39% risk reduction of long-term mortality.[167] Taken together, IVT has now been proved to improve functional outcome and long-term survival after stroke, and the use of treatment has increased greatly over recent years. Still, with the decreasing risk of dying from stroke, the number of stroke survivors with varying degrees of sequalae increases. A longer life is valuable, yet, this very much depend on what a longer life provides in terms of health-related quality of life.

6.3 HEALTH-RELATED QUALITY OF LIFE

Stroke is a condition with a sometime high rate of poor outcomes and a perceived lack of effective treatments, and those stroke patients might be at risk of being vulnerable to therapeutic nihilism, especially ICH patients. Stroke patients who do receive and are suitable for today's stroke management in Sweden have a good chance of a favorable recovery, but not all patients do receive this, which subsequently could negatively affect long term health-related quality of life. In a best case scenario the acute stroke patient is admitted to a stroke unit or an intensive care unit if required. One purpose of the stroke unit is to make early multi-disciplinary discharge assessment to guide on the level of further rehabilitation. Those patients who are not perceived to benefit from rehabilitation and have a significant care need are discharged to nursing homes or palliative care, often with no further follow-up from stroke-teams or outpatient clinics, and directed to primary care. There is a risk that these patients do not improve in their functional outcome and end up in the worse functional outcome groups as classified by mRS. Interestingly, we found that patients in the lower mRS 4 and 5 at six months, have a decreased HRQoL from baseline to six months, whereas patients in mRS group 0-3 have an improved HRQoL at six months compared to baseline. The decline in HRQoL among mRS 4 and 5 could possibly be explained by lack of initial acute care, early and long-term rehabilitation, and/or stroke follow-up. However, other explanations such as co-morbidity, or unrealistic views of recovery goals, or the lack of social support are also possible as is factors of which we may not yet understand. Further, older age is known to be associated with an overall decrease in health-related quality of life. Interestingly though, a recent study showed that patients 80 years of age or older had a greater effect of endovascular thrombectomy in terms of improved health-related quality of life compared to younger patients receiving the same treatment.[168]

In order to improve health-related quality of life we need extensive knowledge on which stroke patients who suffer from reduced HRQoL and why. Our findings shed light on the need for stratification of research and clinical stroke management with regard to the functional level in a stroke patient. This is also consistent with a recent report identifying the fact that improving health-related quality of life of stroke patients is one of the key factors in order to decrease costs to health-care and the overall burden of stroke to the society.[111] The same authors projected future stroke care costs to increase drastically between 2017 and 2040 if changes are not implemented swiftly.

6.4 COSTS

It may seem evident that the cost of stroke healthcare is related to functional outcome after stroke, but the possible effect of our finding is worth some reflection. For example, we showed that there is a cost reduction between disability level OHS score 3 and 2. Hence, therapies that improve disability outcomes by ≥1 OHS/mRS points could have considerable economic impact. Another observation in our study was that patients with an OHS score of 4 (moderate disability) have higher costs than those at OHS 5 (severe disability). We could not explain this but it may be associated with patients with higher disability having decreased health expectations and therefore reduced use of services, or they may have a cognition or mental disorder, such as dementia or depression, that interferes with care seeking. Further research of this is required, and probably along with patient and caregiver interviews. A costs study similar to ours was recently published by Kim et al. in 2020. Kim and colleagues calculated the five-year direct costs for 11,136 patients with acute ischemic stroke in South Korea.[169] They found that the mean cumulative five-year costs after stroke were 117 576 USD, with the highest cost within the first year after stroke. After the first year, costs remained elevated. They also found that functional outcome is the most important contributor to long-term costs, and that level of mRS explained 60% of the cost variation.

Despite the benefit of reduction of stroke mortality, patients who survive stroke still have unacceptably high levels of functional impairments.[170] Our findings provide a monetary reason to develop acute and long-term stroke management that reduce long-term disability from stroke. Our findings also tell us something about the variation of direct long-term costs after stroke stratified by post stroke disability. Thus, we would be able to calculate the money saved by new stroke treatments, which, if they reduce disability after stroke, will be much more important to the patients and families with stroke than the money.

6.5 RESEARCH PRIORITIES ACCORDING TO PATIENTS IN LIFE AFTER STROKE

The guidelines of the Swedish National Board of Health and Welfare focus primarily on the acute stroke care and early rehabilitation. Long-term stroke care has received less attention and therefore also varies across the country. One reason might be that long-term stroke care is the responsibility of primary care and the municipality, and not much research regarding stroke patients is taking place in primary care settings. In Sweden, primary care services recommend that individuals initiate contact when problems occur and make their own choices regarding healthcare services. This in turn requires a high level of capability on the part of the patient with respect to navigating the healthcare system, which might result in further negative consequences for the individual.

Reports have shown that Swedish stroke patients' rehabilitation needs after stroke are not sufficiently met.[23, 35] This could be compared with the results in our studies, showing that health-related quality of life decreases with declining functional outcome (Study III) in addition to many patients prioritizing further research areas such as gait deficits and post-stroke fatigue (Study IV). In study III we have found that aspects which negatively impact stroke patients' health-related quality of life is the inability to perform usual activities, anxiety and pain, and one possible way forward to change this might be to improve areas, which patients themselves, cites as being prioritized research areas.

Research into the patient's perspective with respect to life after stroke has been poorly prioritized which is in good agreement with the authors of a Swedish focus group investigation, who also encouraged the implementation of larger studies.[171] The knowledge retrieved from our investigation could empower stroke patients and present an opportunity for collaborations with policy makers to solve problems, outline healthcare policy, and set priorities for the use of resources in the long-term care of stroke.

7 CONCLUSIONS

IVT should be given to acute ischemic stroke patients in order to improve short and long-term functional outcome. A better functional outcome is associated with better survival, health-related quality of life and decreased costs to the healthcare system. Patients with better functional outcome after stroke is associated with improved health-related quality of life over time compared to patients with the worse functional outcome which is associated with a decrease in health-related quality over time. One possible explanation, among others, to decreased health-related quality of life might be lack of proper acute care, follow-up and/or rehabilitation. Involving the patient and informal carer in stroke research might be an (cost-) efficient way forward to find the gap represented by the stroke patients' unmet needs in order to improve life after stroke.

We have shown that impact on life after stroke varies to a large extent depending on functional outcome. A stratified and comprehensive approach to stroke management and research is therefore warranted, which should not only include the stroke patients but also the informal caregivers. Health and social care systems in Sweden, as well as in other countries, need to be improved and decision makers and healthcare planners need to commit. Interventions need to be put in place in order to maximize long-term survival and health-related quality of life, and at the same time decrease costs to healthcare and society.

8 POINTS OF PERSPECTIVE

Across Sweden, as well as in other countries, we see declining birth rates, an aging population, and a reduction in people of working age, which will continue to alter the composition of the population in the world with a proportionate shift from younger to older. This is important not only because a decline in the proportion of younger people in Sweden is most likely leading to a reduction in economic activity and work production, but also since an increase in the proportion of older people results in an economic burden through the higher requirement for healthcare and pensions. As the majority of strokes affect older people, the number of individuals having and living with stroke is likely to increase, and with this also associated healthcare and societal costs. Living with stroke and depending on functional outcome has an impact on health-related quality of life and survival. In order to improve life after stroke we need further extensive knowledge on the stroke patients' situation in Sweden.

Despite our increasing ability in recent decades to provide treatments for stroke patients, there is still more that can be done to implement and customize treatments that we know are effective both in the acute phase and long-term. Moreover, more can be done in identifying new treatments and multi-disciplinary individual or group therapies to improve prognosis after stroke, both in terms of survival and health-related quality of life, and this could simultaneously also reduce costs. We know that acute treatment improves prognosis after stroke as does the increasing implementation of secondary prevention such as OAC, and we see an increasing use of these treatments. Still, there are very few treatments available for ICH-patients, a group of patients likely to rise with the increasing use of OAC.

The studies of this thesis reflect on the stroke management we perform in Sweden today, from angles that have only partly been explored before. With this knowledge, combined with other researchers´ studies several questions arise. Are we satisfied with the level of health stroke survivor report in Sweden today? If not, what can we do better and for whom? Would there be a reasonable cost associated with further improvements of the stroke management, and are these improvements worth the possible extra cost? Would there be more money to save if we make improvements compared to not making improvements? Can we afford *not* to improve life after stroke? Are there alternatives to finance better stroke management? What do the stroke patient and their families think, would they be willing to pay an extra cost to improve their health? How do we involve the patient? Most patients and relatives are concerned about their health situation which is a huge resource itself that needs to be acknowledged and acted upon, especially since an even larger burden of care will most likely be put on the patient itself and the informal carer in the future.

There is a risk that increasing costs of life after stroke will put an extra burden to already limited health and social care budgets. Therefore, Sweden, as well as other countries, must invest in stroke management and interventions not just to improve outcomes for stroke patients, but also to slow down costs and overall burden. In order to implement cost-effective treatments, we need to implement tools to evaluate whether our interventions are cost-

effective, and routinely collecting HRQoL in stroke patients is one way forward, also in acute care.

To improve stroke management requires clinicians' engagement, open-minded approaches and creative solutions at many levels, especially when it comes to involving the patient and the informal carer. Research evaluating clinical outcome, including HRQoL, for critically ill stroke patients admitted to intensive acute care versus those who are not, especially ICH patients, likewise how relatives and families are affected would be highly interesting, as would evaluating the effect on long-term costs. Further research on how patients and families are equipped for life after discharge from hospital would tell us something about the tools we provide to navigate the resources provided in primary care. To expand collaboration between stroke units at hospitals and primary care in terms of education, consultations, and research would be a possible way forward to improve stroke management, and this would require research to evaluate and to further underpin such collaborations.

Finally, for middle- and low-income countries acute treatment such as IVT and thrombectomy are seldom possible, often due to limited resources such as lack of neuroimaging along with far distances to hospitals and lengthy paramedic transports. At the same time, these countries experience an increasing incidence of life-style diseases such as diabetes, hypertension, obesity, heavy alcohol drinking and smoking, resulting in an increasing risk of stroke without any expanded resources or acute treatment possibilities. This will lead to large stroke populations with severe functional deficits. In these countries, the ability of clinical stroke management of stroke survivors with functional impairments will be critical, and research therefore also needs to be performed in different countries adapted to local conditions.

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10 SHORT POPULAR SCIENCE SUMMARIES OF THE THESIS

English:

Stroke is a disease that affects millions of people globally every year and it is an emergency situation requiring fast and immediate action in hospital. Improvement in acute stroke treatments has developed and improved rapidly over the last decades and mortality of stroke is decreasing. However, many people suffering a stroke experience long-term deficit, making stroke a condition with a vast spectrum of functional outcome on which associated health outcomes depend. In this thesis, we show that impact on life after stroke in terms of quality of life, survival and costs to health-care, varies to a large extent depending on severity level of functional outcome after stroke. We also asked the patients what research areas they prioritize in life after stroke and they reported research on balance and walking difficulties and post-stroke fatigue. A stratified and comprehensive approach to stroke management and research is therefore warranted, which should not only include the stroke patients but also the informal caregivers. Health and social care systems in Sweden, as well as in other countries, need to be improved and interventions need to be put in place in order to maximize long-term survival and health-related quality of life, and at the same time decrease costs to healthcare and society.

Svenska:

Stroke är en sjukdom som innefattar både hjärninfarkter och hjärnblödningar och kräver ett snabbt akut omhändertagande på sjukhus. Samtidigt så drabbas många strokepatienter av funktionsnedsättningar på lång sikt, vilket kan påverka livskvalitet och överlevnad negativt och samtidigt leda till ökade kostnader för sjukvården. Därför blir det viktigt att betrakta stroke som ett långvarigt sjukdomsförlopp och inte enbart ett akut sjukdomsförlopp. Behandlingen av stroke på sjukhus riktar in sig på det akuta omhändertagande vilket kan påverka överlevnad och funktionsförmåga, men hur stroke påverkar de patienter som överlever stroke på längre sikt vet vi mindre om. Vår forskning visade att överlevnad, livskvalitet och kostnader för sjukvården varierar beroende på vilken svårighetsgrad på funktionsnivå man har efter stroke. Vi frågade också strokepatienter vilka forskningsområden de tycker att vi ska prioritera i framtiden, och balans- och gångsvårigheter samt hjärntrötthet var de områden som prioriterades högst. Som strokeforskare måste vi nå ut längre med våra forskningsresultat än enbart till andra strokeforskare. Vi måste också nå ut till de som prioriterar och beslutar om hur vi finansierar våra insatser. Oavsett om man arbetar inom vården med målet att rädda liv och förbättra hälsa och livskvalitet för en strokepatient, *eller* om man är beslutsfattare/politiker och vill spara pengar för samhället så är vägen dit gemensam: att stärka vårdkedjan och omhändertagandet av alla strokepatienter.

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