Upper extremity functioning during the first year after stroke

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Cover illustration: Individual patterns of change over time in upper extremity function, assessed with the Fugl-Meyer Assessment for Upper Extremity (FMA-UE) from 3 days to one year post stroke onset.

A comfort zone is a beautiful place, but nothing ever grows there.

Unknown

To Andreas, Axel and Elsa

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ABSTRACT

The overall aim of this thesis was to investigate upper extremity functioning during the first year after stroke from different perspectives.

Methods. All patients with first ever stroke, admitted to a stroke unit within 72 hours after stroke incidence were included during a period of 18 months. The prevalence of impaired upper extremity function was investigated within 72 hours. Differences in change over time in functioning (function and activity) between patients with ischemic and hemorrhagic stroke were explored. The possibility of a simple early assessment to predict the level of upper extremity motor function required for a drinking task was investigated, as well as the relationship between patient-perceived and assessed strength capacity. The studies are a part of the SALGOT-study (The Stroke Arm Longitudinal Study at the University of Gothenburg).

Main results. Of patients admitted to a stroke unit, 48% had impaired upper extremity function within 72 hours after stroke onset. In patients with impaired upper extremity function initially, those with hemorrhagic stroke had a larger improvement from 1 to 3 months in their function and activity compared to patients with ischemic stroke. Patients with hemorrhagic and ischemic stroke improved function and activity to a similar level 3 months and thereafter. Two items from the Action Research Arm Test (ARAT) used at 3 days post stroke could accurately predict the level of motor function required for a drinking task at three later time points during the first year post stroke. Assessed grip strength capacity and perceived strength at 10 days post stroke correlated highly, but some patients rated their strength differently compared to the assessment of strength capacity.

Conclusions and clinical implications. Fewer patients than previously described had impaired upper extremity function early after stroke which is

of importance in planning of care and rehabilitation. In patients with impaired upper extremity function, larger improvements of function and activity were seen after 1 month in those patients with hemorrhagic stroke compared to ischemic, but both stroke types reached a similar level at 3 months post stroke. These results together with the finding that early prediction of function is possible, and that a combination of patient-reported and objective strength assessment early after stroke may be valuable in planning of care, rehabilitation and goal setting, and therefore improve the overall rehabilitation process.

POPULÄRVETENSKAPLIG SAMMANFATTNING

Stroke är ett samlingsnamn för hjärninfarkt och hjärnblödning. Antalet personer som insjuknar i stroke varierar i världen, och i Sverige drabbas årligen 25-30 000 personer. Konsekvenser av en stroke kan se olika ut, men det är vanligt med nedsatt funktion och känsel i arm eller ben, eller påverkan på språk eller tankeförmåga och minne. Nedsatt arm- och handfunktion påverkar möjligheten att utföra aktiviteter. I akut skede har enligt tidigare studier 70-80% av patienterna nedsatt arm- och handfunktion, och ca 40% får kvarstående problem. Störst återhämtning av funktioner sker vanligen de första veckorna efter insjuknade, men individuella variationer förekommer.

Det övergripande syfte för avhandlingen var att studera funktion och aktivitetsförmåga i arm och hand under det första året efter stroke utifrån olika perspektiv. Avhandlingen omfattar fyra delarbeten, där patienter som vårdas för stroke på en strokeenhet inom 72 timmar efter insjuknade ingår. Samtliga delarbeten är en del av SALGOT-studien (The Stroke Arm Longitudinal Study at the University of Gothenburg).

I Studie I undersöktes förekomst av nedsatt arm- och handfunktion initialt efter insjuknade. Resultatet visade att 48% hade nedsatt arm- och handfunktion inom 72 timmar efter insjuknade. Dessa patienter var äldre, vårdades längre tid på strokeenheten och hade också en högre dödlighet än de patienter med god arm- och handfunktion.

I Studie II undersöktes eventuella skillnader mellan patienter som fått en infarkt eller blödning avseende återhämtning av motorisk funktion och aktivitetsförmåga i arm och hand under första året efter insjuknade. Patienter med blödning förbättrades mer de första 3 månaderna, jämfört med de som fått en infarkt. Båda grupperna hade ungefär samma nivå vid 3 månader och där efter. Högre ålder och mer uttalad stroke påverkade återhämtningen negativt i båda grupperna.

I Studie III undersöktes om en kort klinisk bedömning efter 3 dagar respektive 1 månad efter insjuknande, kunde förutsäga arm- och handfunktion som motsvarar att kunna dricka ur ett glas. Två delmoment från ett mer omfattande bedömningsinstrument användas. Den korta bedömningen visades ha god förmåga att förutsäga motorisk funktion motsvarande att kunna dricka ur ett glas efter 10 dagar, 1 månad och 1 år, och hade bäst

precision om patienten vid första bedömningen hade någon arm-handfunktion.

I Studie IV undersöktes överensstämmelse mellan patientens skattade styrka i arm och hand med en klinisk mätning av greppstyrka 10 dagar efter stroke. Majoriteten av patientens självskattade arm- och handstyrka överenstämde med den mätningen av handstyrka, men mindre del av patienterna över- eller underskattade sin styrka.

Sammanfattningsvis visar avhandlingen att färre än 50% av patienterna har nedsatt arm- och handfunktion i akut skede efter stroke, vilket skiljer sig från vad tidigare studier har visat. De patienter som hade nedsatt arm- och handfunktion visade sig ha sämre återhämtning under första året om de var äldre eller hade mer uttalad stroke. Patienter med blödning hade snabbare återhämtning de första månaderna, jämfört med de med infarkt, men vid 3 månader hade båda nått likvärdig funktion- och aktivitetnivå. Vidare visades att en kort, enkel, bedömning 3 dagar efter strokeinsjuknade kan förutsäga motorisk funktion som motsvarar att kunna dricka ur ett glas. Att kombinera patientskattning och klinisk funktionsbedömning tidigt efter stroke, ger olika perspektiv på funktion och tydliggör patientens kännedom om sin egen förmåga. Sammantaget kan resultaten bidra till ökad kunskap kring arm- och handfunktion och aktivitet efter stroke, som kan användas för bättre planering av vård och rehabilitering redan i tidigt skede efter strokeinsjuknande.

LIST OF PAPERS

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

I. Persson HC, Parziali M, Danielsson A, Sunnerhagen KS. Outcome and upper extremity function within 72 hours after first occasion of stroke in an unselected population at a stroke unit. A part of the SALGOT study. *BMC Neurol.* 2012;12:162.

II. Persson HC, Opheim A, Lundgren-Nilsson Å, Alt Murphy M, Danielsson A, Sunnerhagen KS. Differences in recovery of upper extremity functioning after ischemic and hemorrhagic stroke – a part of the SALGOT study. *Submitted manuscript*.

III. Persson HC, Alt Murphy M, Danielsson A, Lundgren-Nilsson Å, Sunnerhagen KS. A cohort study investigating a simple, early assessment to predict upper extremity function after stroke - a part of the SALGOT study. *BMC Neurol.* 2015;15:92.

IV. Persson HC, Danielsson A, Sunnerhagen KS. A cross sectional study of upper extremity strength ten days after a stroke; relationship between patient-reported and objective measures. *BMC Neurol.* 2015;15(1):178.

CONTENT

ABBREVIATIONS

ARAT	Action Research Arm Test
ARAT-2	Two items from ARAT, *Pour water from glass to glass* and *Place hand on top of head*
FMA-UE	Fugl Meyer Assessment of Upper Extremity
JAMAR	JAMAR Hand Dynamometer
ICF	International Classification of Functioning, Disability and Health
ICD-10	International Classification of Diseases, Tenth Revision
M-MAS UAS-95	Modified Motor Assessment Scale according to Uppsala Akademiska sjukhus
NIHSS	National Institutes of Health Stroke Scale
NPV	Negative Predicted Values
PCA	Principal Components Analysis
PPV	Positive Predicted Values
SALGOT	Stroke Arm Longitudinal Study at the University of Gothenburg
SIS	Stroke Impact Scale
TOAST	Trail of Org 10172 in Acute Stroke Treatment
WHO	World Health Organization

DEFINITIONS IN SHORT

Activity   The execution of a task or action by an individual *(WHO, 2001).*

Body Functions The physiological functions of body systems *(WHO, 2001).*

Body structures Anatomical parts of the body such as organs, limbs and their components *(WHO, 2001).*

Capacity   Ability to execute a task or an action in a standardised environmental *(WHO, 2001).*

Impairment   Problems in body function or structure as a significant deviation or loss *(WHO, 2001).*

Functioning   Umbrella term of Body Functions and Structures and Activities and Participation, positive aspects *(WHO, 2001).*

Participation   Involvement in a life situation *(WHO, 2001).*

Performance   What a person does in his or her current environmental *(WHO, 2001).*

INTRODUCTION

One in six people worldwide will have a stroke in their lifetime. Stroke has a great impact not only on the quality of life of the person, but also on their relatives and caregivers and could leave the person with multiple impairments and complex needs[1]. As the demands for efficiency in stroke care increases, knowledge of the prognosis of function and activity for patients is of importance in order to optimize stroke management, to reduce the suffering of individuals and their level of disability, as well as to use patients and financial resources optimally.

Paresis in an upper extremity is a common impairment after stroke[2,3]. Few up-to-date studies, have investigated upper extremity functioning (function and activity) in an unselected population during the first year after stroke onset[2-8]. The prevalence of impaired upper extremity, as well as different aspects of upper extremity function and activity needs to be further explored.

Stroke

Stroke includes three sub types; cerebral infarction (ischemic stroke), intracerebral hemorrhage, and subarachnoid hemorrhage[9,10]. According to the World Health Organization (WHO), stroke is defined as *rapidly developing clinical signs of focal (at times global) disturbance of cerebral function, lasting more than 24 hours or leading to death with no apparent cause other than that of vascular origin*[11]. In 2013, a more detailed definition of the stroke was published, including specific diagnosis according to imaging findings[9]. However, in this thesis the WHO definition of stroke is used; ischemic and intra cerebral hemorrhage (hemorrhagic) stroke are included in the thesis and subarachnoid hemorrhage is excluded.

Every year about 15 million people worldwide suffer a stroke where of 75-80% are living in low and middle-income countries[12,13]. In contrast to a decreased stroke incidence in high income countries, the prevalence of stroke has increased in low and middle income countries[12]. The prevalence of stroke types also varies globally. In high income countries, hemorrhagic stroke amounts to less than one third of the total stroke cases, compared to in low and middle income countries where nearly half of all stroke diagnoses are hemorrhagic[14]. People suffering a hemorrhagic stroke are younger compared to those with ischemic stroke[12]. Six million people die from stroke yearly around the world, which makes stroke the second leading cause of death[15].

The mortality of stroke is strongly influenced by each country's economic situation[14]. The total burden of stroke has increased around the world[12,13], and the burden of hemorrhagic stroke has been shown to be greater than of ischemic stroke, even if the total number of hemorrhagic strokes were lower[12]. Many people lives with long term impairments after stroke which has consequences that may restrict their possibility to participate in life as they wish. Approximately 50% of patients who survive their stroke require at least some assistance in their activities of daily living[16].

In Sweden, around 25-30 000 people suffer a stroke yearly[17], 18 000 of which are due to a first ever stroke. In 2014 the mean age of suffering a stroke was 75.6 years, women on mean being five years older than men[18].The stroke mortality in Sweden is 100 per 100 000 yearly[17], and stroke is the somatic disease that accounts for the largest number of days spent in Swedish hospitals.

Stroke in change

The characteristics of people who suffer from a stroke seemed to have changed over time, especially in high income countries. During recent decades, a higher proportion of patients have received primary prevention, such as lowering their blood pressure[19], which may have had an impact of stroke severity. The number of patients that have been treated with thrombolysis or thrombectomy[18], and the number of patients that have received care at stroke units has increased[20,21]. A higher proportion of patients survives their stroke[1,18] and is more likely to be discharged to their homes after their hospital stay than patients were previously[22]. Patients have also been shown to be more independent prior to their stroke than previously[12].

There has also been a change in the hospital admittance rate after a stroke. In accordance with the Swedish national guidelines[23,24]and the Swedish national stroke campaign[25], all patients with stroke symptoms should be immediately admitted to hospital as well as treated in hospital. In many countries, patients with no self-care problems or only mild motor impairments after their stroke have previously been treated as outpatients[8] and not admitted to hospital as a part of the ordinary routine. Also the duration of the in-hospital stay in Sweden and in many other high-income countries has decreased the recent decades[18,26] influencing demands on the care and the rehabilitation in the hospitals as well as the outpatient treatment facilities.

Classification of diseases and health status

The WHOs International Classification of Diseases, Tenth Revision (ICD-10), aims to standardize diagnostic classification of most diseases[27]. In this thesis, patients with stroke, diagnosis codes I61 intra cerebral hemorrhages (hemorrhagic stroke) and I63 ischemic stroke according to the ICD-10, were included.

As stroke is complex, multi-faceted and affects the total person, the bio-psycho-social model of International Classification of Functioning, Disability and Health (ICF)[28] provided by WHO, could be a useful tool to capture the many different facets of stroke. The ICF can be used when collecting and summarising data in the clinic and in a research context. The model provides a standardised language and theoretical framework for health and health-related states[28]. In the ICF model information is organised in two parts each with two components; Part 1, functioning and disabilities including a) body functions and structures, b) activities and participation. Part 2, contextual factors including c) environmental factors d) personal factors (Figure 1). Using the ICF model, the person's life circumstances can be analysed in a multi-perspective approach. A person's functioning in a specific domain is influenced by interaction between other factors or conditions (Figure 1).

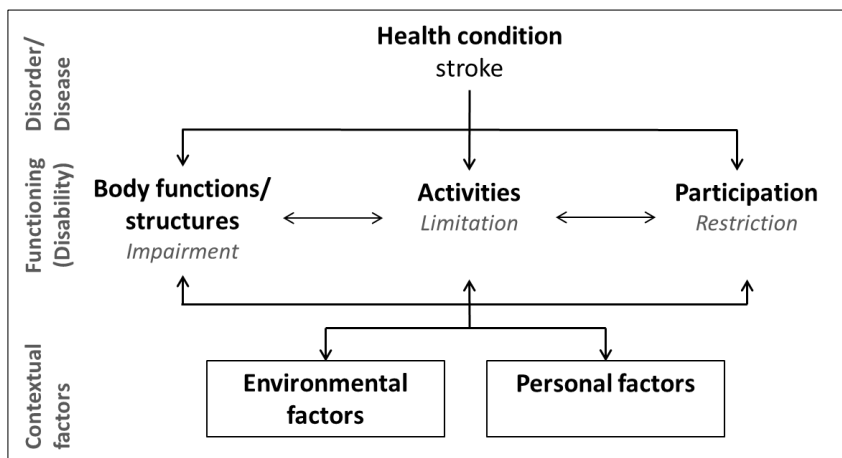Figure 1. *The model from the International Classification of Functioning, Disability and Health (ICF) illustrating the interactions between different components including contextual factors*

The components body functions and structures, activities and participation could be seen as functioning (positive) or disability (negative). Disability includes impairments, activity limitation and participation restrictions.

A combination of the ICF and ICD-10 provides a broad picture on health and health related conditions[28], since a diagnosis alone cannot explain a person's functional level, such as the ability to perform tasks in the environment[29]. The focus of this thesis has been stroke corresponding to ICD-10 codes I61 and I63 and upper extremity functioning (body functions/structures and activities).

Upper extremity

Arm and hand movements are used in many common daily tasks, involved in reaching, grasping and manipulation[30], and can be used in both unilateral or bilateral tasks. The upper extremity has a large degrees of freedom and the ability to take different positions. To perform a well-balanced and specific task, all different parts of the upper extremity (such as sensory motor function, coordination) need to contribute for optimal performance[31,32]. The hand function is complex and advanced, used to grasp objects of different shapes and sizes and coordinate isolated or more complex movements. The human hand has a unique function, where both position and length of the thumb are of importance[33].

Upper extremity after stroke

The most common impairment after stroke has been shown to be paresis[2] in the upper or lower limb. Clinically a paresis can be defined as a weakness (impairment) in the extremity, resulting in slower, less accurate and less efficient movements, compared to similar movements in persons with an intact neurological system[34,35]. Early after stroke the prevalence of upper extremity impairment has shown to be present in 70-80% of the patients[2,3,36]. Later after stroke, approximately 40-50% has remaining upper extremity impairments[3,37,38]. Upper extremity impairments after stroke have shown to have a significant impact on the person's ability to perform an activity using the upper limb and consequently negatively affected their quality of life[39,40]. As the impairment in upper extremity after stroke is common, focused research into the area has been rated as a top-ten topic both by patients and staff working with patients with stroke[41].

The severity of paresis strongly affects upper extremity function. Three weeks post stroke, the severity of the paresis explained 88% of the variance in upper extremity function, similarly at 3 months post stroke this was 80%[31]. The severity of paresis correlated with the ability to perform a movement or an action[31]. However, other factors than the severity of paresis may influence the upper extremity function and activity, such as impaired sensory

function[30,42], shoulder pain[43], spasticity[31,44], cognitive function[45] or environmental factors.

Stroke recovery

Recovery after stroke is a complex process including combination of spontaneous and learning-dependent processes[46,47], and the recovery profiles are characterized by high inter individual variability[8]. The major part of recovery usually takes place within the first few months and the speed slows down with time since stroke onset[47-50]. Most of the motor recovery follows a non-linear pattern, occurs in a limited time window within the early phase post stroke, where the exact length of the time window is not yet known[51]. After the early phase post stroke, recovery is mainly focused on brain reorganization, and neural plasticity allowing for damaged areas' functions to be taken over by other brain regions[52]. Around 20-40% of the patients shows increased neurological symptoms within the first days after stroke onset[53], but most patients improve their function thereafter if no other complications occur (such as an early recurrent stroke)[47]. The learning-dependent process includes restitution (restoring the functionality of damaged neural tissue), substitution (reorganisation of partly spared neural pathways to relearn lost functions) and compensation[46,47]. The degree of stroke recovery can be influenced by several factors, such as pre-stroke status, extent of the stroke, type/s, treatment therapies and comorbidities[52]. Within the first year after stroke onset, patients suffering a hemorrhagic stroke are often more severely impaired[54,55], have poorer long-term outcome[56-58] and have higher mortality than patients suffering an ischemic stroke. In addition, patients suffering a hemorrhagic stroke have shown to have increased mortality in the long-term, compared to a normal population[59]. Other factors such as cognitive functions (executive function, neglect, apraxia), language (aphasia), coping strategies and the family situation[53,60] may also influences the stroke recovery.

Many studies indicate that after 6-12 months upper extremity function seldom continues to improve[3,5,8,48,49,51]. Furthermore, even if the patient's capacity were high at discharge from hospital, the independence in activities in daily living have shown to decrease between 6-12 months, and within the same time frame, the need for support was expanded[61].

Recovery of upper extremity

Consistent with general stroke recovery the major part of recovery of function in the upper extremity appears within the first 3 months after stroke[3,62], and thereafter little improvement has been shown[3,50,62]. Maximum

arm function is achieved by 80% of the patients within 3 weeks after stroke onset and by 95% of the patients within 9 weeks[3]. Patients with mild stroke seem to have faster and to a higher extent recovery of motor function compared to patients with greater impairments[51,63]. It has been shown that a 40% improvement on an initial score of function (within first week after stroke onset) could correspond to the level of function at 6 months post stroke [50].

Stroke rehabilitation

The aim of rehabilitation is to regain the capacity of normal function and activity or as close to normally as possible[64]. The definition of rehabilitation according to the WHO is: *Rehabilitation of people with disabilities is a process aimed at enabling them to reach and maintain their optimal physical, sensory, intellectual, psychological and social functional levels. Rehabilitation provides disabled people with the tools they need to attain independence and self-determination*[65]. Rehabilitation is an active and dynamic process intended to maximise functional ability and minimise disability[66]. Furthermore, the care and rehabilitation has striven to become more person centred[67,68]. The process of stroke rehabilitation should include: 1) assessment to identify the patient's needs, 2) goal setting to define realistic and attainable goals; 3) interventions to assist in the achievement of said goals; and 4) reassessment to assess progress[46]. A motivated and engaged patient has greater ability to achieve good outcome from rehabilitation. The rehabilitation process should start as soon as possible after stroke onset[46,60].

The stroke rehabilitation is included in the discipline of Rehabilitation Medicine that focuses on patients with medical conditions that had led to long lasting, often complex disabilities. The discipline of Rehabilitation Medicine is a part of the patient's total rehabilitation within the health care system, and rehabilitation aims to build a bridge to a meaningful life for the patient. Different professions work together in the discipline of Rehabilitation Medicine, together with the patient, in a multidisciplinary team[64,66]. The complexity of the human in the rehabilitation process can be explored using the framework provided by the ICF[69].

Working multidisciplinary with specialized nursing staff is an important component in stroke rehabilitation, which initially takes place at stroke units[26,56,64]. A stroke unit is a ward exclusively for patients with stroke and is the basis of high quality stroke care[26]. In Sweden, a stroke unit could be defined as a designated unit at the hospital for acute stroke care, with a team approach that includes rehabilitation staff, team meetings and discharge

planning. The routine care at stroke units includes a structured analysis of function, activities and impairments as well as early mobilization and rehabilitation[26,60]. All the different aspects of physical, psychological, cognitive and social consequences of stroke both for the patient and their relatives, needs to be considered and taken into account by the multidisciplinary team[60]. Patients that have received organized inpatient stroke unit care have shown to be more likely to survive, regain independence and return home compared to patients with less-organized service[26,56].

One of the key disciplines in rehabilitation is physiotherapy[70]. According to the World Confederation for Physical Therapy (WCPT), *Physiotherapy provides services to individuals and populations to develop maintain and restore maximum movement and functional ability throughout the lifespan. This includes providing services in circumstances where movement and function are threatened by ageing, injury, pain, diseases, disorders, conditions or environmental factors. Functional movement is central to what it means to be healthy*[71]. The body of evidence of physiotherapy treatments following stroke is large and is growing[70,72]. Motor control theory is a cornerstone in physiotherapy rehabilitation after stroke. Several theories exist, though the task-oriented approach presented by Wollacott and Shumway-Cook[73] has had a large impact on the field of rehabilitation and physiotherapy. Training of motor control requires repeated actions (tasks) and ongoing practice[47,73,74]. The task-oriented approach of movement, focuses on the interaction of three factors; the individual, the task and the environment, all three of which are of important and interdependent[73]. There is good supporting evidence for task-specific or task-oriented training in all phases after stroke[70,75], but it has not been shown to be superior to other training concepts[72,76]. Task-oriented approach includes the following steps; 1) resolve, reduce or prevent impairment; 2) develop effective and efficient task- specific strategies; 3) adapt functional goal-oriented strategies in order to maximize participation and minimize disablement[73]. Task-oriented training assists the natural functional recovery and the intervention has been shown to have the largest effect at the level to which it is targeted (according to ICF)[46,47].

Rehabilitation of upper extremity

The optimal rehabilitation goal of the upper extremity function and activity after a stroke may be to restore functional use and ability to participate in the usual environment. Patients with increased stroke severity and more dependency in activities in daily living has shown to also have reduced use of upper extremity early after stroke[77] and after 1 year[78]. Different interventions

such as constraint-induced movement therapy (CIMT), repetitive task practice, mirror therapy, mental practice, interventions for sensory impairment and virtual reality can be useful at different time points during stroke rehabilitation[46,76]. Evidence based physiotherapy[70,72] and occupational therapy[46,79] promote the rehabilitation of upper extremity functioning after a stroke and aim to reduce impairments.

Measuring upper extremity after stroke

Measuring outcomes following stroke, has several purposes, such as being useful in clinical decision making for individual patients, improving the care and outcome for patients or providing data for research purpose[80]. Systematic routine measurements of impairments are critical for clinical decision making. There is no single measure that is specific and sensitive to all aspects of upper extremity function and activity, recovery or outcome post stroke. Different outcome measures according ICF levels need to be included if different aspects of function and activity are going to be captured[1,31,80,81].

Upper extremity measures can broadly be divided into two categories: 1) performance measures (clinician rates or times a series of upper extremity actions performed by the patients), and 2) self-reported measures (patient respond to questionnaires)[31]. Several performance measures capturing function and activity are available to measure the outcomes of stroke rehabilitation[31,81,82]. Recently, six measures of upper extremity functioning were identified, with high measurement quality and clinical utility, in an overview of systematic reviews [81]. The authors'[81] recommended the Fugl-Meyer Assessment of Upper extremity[83,84] at the level of Body function and structures, and the Action Research Arm Test (ARAT)[85,86], Box and Block Test (BBT), Chedoke Arm and Hand Activity Inventory (CAHAI), Wolf Motor Function Test (WMFT) and ABILHAND at the level of activity. Different measures seems to capture a similar perspective of function and activity[31], indicating it should be possible to choose the instrument that is best suited for the purpose for which context it is going to be used[31].

Self-reported tasks often reflect a person's perception of their performance in their own environment, and could therefore be seen as more complex compared to if the task is assessed at a clinic[87]. Performance based (including capacity measures) and self-reported measures[88] often cover different aspects of function and activity, but increases if the same aspects were assessed[88]. Even if self-reported problems were covered by items or domains in an outcome measure, discrepancy between patient-reported problems, and problems assessed with performance measures were seen[89]. Exploring

different aspects of functional limitations improves clinical practice[88,90], it is important that stroke care considers not only the obvious impairments discovered in functional assessments[88], but also includes the patients' perspective.

Outcome measures could also be used for the prediction of a functional outcome or recovery pattern. Accurate prognostic models with 100% certainty of the functional outcome after stroke are not yet available. A well-validated model of upper extremity recovery that generates accurate prediction of long-term use could be highly valuable in order to make informed decisions about treatment[91]. Function after stroke has shown to be predictable within the first days, despite individual differences in recovery or outcome[7,47,92]. Age, the initial severity of motor impairment or stroke severity are variables shown to be most important predictors of the upper extremity functional outcome[93-97]. A systematic review of prediction of upper extremity recovery[97] also showed that the number of motor-evoked and somatosensory-evoked potentials were strongly associated with a better upper extremity outcome. Measure of initial finger extension and shoulder abduction early post stroke has shown to be able to predict upper extremity activity corresponding to >10 points on the ARAT 6 months post stroke[7,98,99]. However, it is not clear if >10 points on the ARAT corresponds to an ability to use the upper extremity in an activity[100,101]. A combination of clinical assessment and transcranial magnetic stimulation or imaging[100,102,103] has also shown to increase the accuracy of prediction.

Psychometrics of measurements

When outcome measures are chosen to assess function and activity after stroke, the psychometrics needs to be considered. The level of the scale needs to be considered, there are four classic scale levels, nominal, ordinal, interval and ratio. The levels are based on to what extent a measure corresponds to a real number or a categorical system[104]. Nominal scales provide classification without order, such as gender or the Trial of Org 10172 in Acute Stroke Treatment (TOAST)[105]. Ordinal scales are measures in hierarchical order (as not difficult at all, a little difficult, somewhat difficult), such as questionnaires (Stroke Impact Scale) and assessment scales (such as FMA-UE or ARAT), but where the distance and rank between categories are not known[106]. The interval and ratio scale levels, are ordered categories with equal distance between items. Ratio scales have an absolute point of zero, which interval measures do not have[107].

A standardized outcome measure should have good clinical utility[81], be reliable, valid, and assess what it is intended to measures[104]. Firstly, the reliability includes that a measures should be repeatable, when administrated more than one time or by another rater[104,108]. Secondly, the validity includes to what extent a measure investigates what it is intended to measure. The validity comprises the appropriateness, meaningfulness and usefulness of the measures and of the interference that can be made from the score. The validity is achieved by accumulating evidence[104,108]. One aspect of the validity is the responsiveness, the measures ability to assess change over time also including clinically important change (minimal clinical important difference, MICD)[108]. Furthermore, important factors when selecting measures are the sensitivity to changes[107] and the stability of items over time[109]. The predictive properties of an outcome measure can be calculated using probabilities for a patient to be classified with or without a condition (at a later time point), using sensitivity, specificity and predictive values[104,110,111].

Lack of knowledge

Early after stroke, upper extremity impairment has been reported as one of the most common symptoms. Just as primary prevention has changed, medical treatment and rehabilitation after a stroke are changing[1,8,12,18,20,21,22]. Knowledge regarding the prevalence of upper extremity impairment needs to be updated. Upper extremity functioning after stroke needs to be explored in different perspectives according to the ICF model[28]. Both the patients' perspective/s and performance measures should be used[89,90,112,113], as the significance of person centred care is being emphasized within the field. Longitudinal upper extremity functional change in ischemic or hemorrhagic stroke has been sparsely investigated and findings have been inconclusive[54,55,114-117]. As hospitalisation time after stroke has become shorter, a reliable, valid and easily performed assessment, that can be made early post stroke and predict activity at a later time are needed in the clinic. Also the coherence between patient-reported and performance based measures in the very early phase after stroke has not yet been investigated.

AIM

The overall aim of this thesis was to investigate upper extremity functioning during the first year after stroke from different perspectives.

The specific aims were

I. To describe baseline characteristics, care pathway and discharge status as well as frequency of impaired arm and hand function in an unselected group of patients with first occasion of stroke, admitted to a stroke unit within 72 hours post stroke. A second aim was to explore factors associated with impaired upper extremity function and the impact on the patient's outcome.

II. To assess if there were differences in extent of change in upper extremity function and activity in patients with ischemic versus hemorrhagic stroke during the first year.

III. To investigate whether a sub-set of items from Action Research Arm Test (ARAT), administered at 3 days and 1 month post-stroke, could predict the level of upper extremity motor function required for a drinking task, at 10 days and at 1 and 12 months post stroke.

IV. To investigate the relationship between perceived upper extremity strength and clinically measured hand strength at 10 days post-stroke.

PATIENTS AND METHODS

This thesis comprises four quantitative studies; all are a part of the Stroke Arm Longitudinal Study at the University of Gothenburg study (SALGOT-study). The overall purpose of the SALGOT-study was to describe the longitudinal recovery of upper extremity function and activity in a non-selected sample with first ever clinical stroke, admitted to a stroke unit[118]. The inclusion of patients to the SALGOT-study required more time than expected and in order to investigate possible reasons for the low inclusion rate, Study I was conducted. The inclusion and exclusion criteria in Study I-IV are shown in Table 1.

Table 1. Inclusion and exclusion criteria in Study I-IV.

Inclusion/Exclusion	Criteria
Inclusion Study I-IV	1. first ever clinical stroke, defined according to WHO criteria by either imaging or clinical assessment[10]
	2. received treatment in the stroke unit within 3 days (±1),
	3. ≥18 years of age
	4. resident in the Gothenburg urban area (within 35 km from the hospital)
Inclusion Study II-IV	5. impaired upper extremity function 3 days after stroke onset
Exclusion Study I	1. upper extremity impairment prior to the stroke
Exclusion Study II-IV	1. an upper-extremity injury/condition prior to the stroke, that limited the functional use of the affected arm and/or hand
	2. severe multi-impairment or diminished physical condition before the stroke that will affect the arm function
	3. short life expectancy
	4. non-Swedish speaking prior to the stroke
Exclusion Study III	5. ≥66 points at FMA-UE[83,84] at 3 days post stroke
Exclusion Study IV	5. incomplete answers in the strength domain (domain one) of the SIS[119,120] or incomplete objective measure of hand strength (JAMAR hand dynamometer[121])

Abbreviations: FMA-UE Fugl-Meyer Assessment Scale for Upper Extremity; SIS, Stroke Impact Scale; WHO, World Health Organization

The study population

Patients were recruited to the Study I and to the SALGOT-study during a period of 17.5 months, between February 4, 2009 and December 2, 2010, with two breaks (in total 145 days) for administrative reasons, Figure 2. Patients were consecutively enrolled to the studies from the largest of three stroke units at the Sahlgrenska University Hospital in Gothenburg, Sweden.

At the time of recruitment, this stroke unit was the only unit where thrombolysis and thrombectomy were performed.

Study I comprised in total 642 patients. All patients with first ever stroke, >18 years old, resident in the Gothenburg urban area, admitted to the stroke unit within 72 hours after stroke onset and no prior upper extremity impaired function, were included. Patients were identified through the hospital record (ICD-10 code I61 and I63 as first or second diagnosis). Study II-IV included all patients (Study II) or sub samples (Study III and Study IV) from the SALGOT-study. Two patients were included in the SALGOT-study but not in Study I, these two had ia clinically confirmed stroke by a physician, however, at discharge they did not receive the diagnose I61, I63 (as first or second diagnosis), Figure 2.
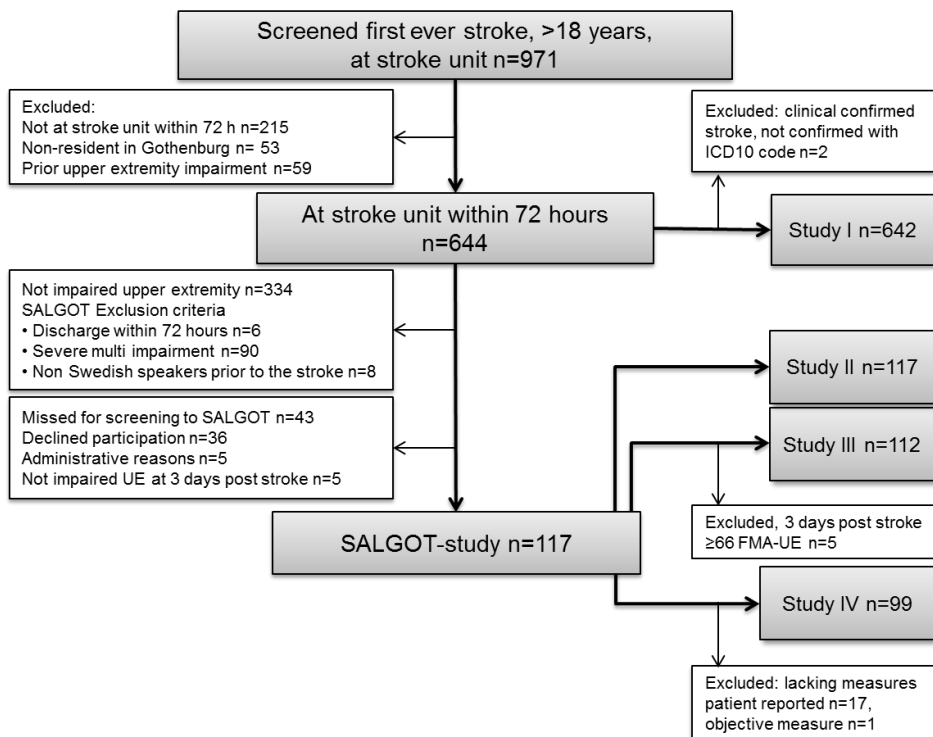

Figure 2. Description of inclusion process of the patients in Study I-IV.
Abbreviations: FMA-UE, Fugl Meyer Upper Extremity Assessment Scale; SALGOT, the Stroke Arm Longitudinal Study at the University of Gothenburg study

Definitions of impaired upper extremity function

Study I: Upper extremity function was assessed within 72 hours post stroke onset using item F, G and H from the Modified Motor Assessment Scale according to Uppsala Akademiska sjukhus(M-MAS UAS-95)[122,123]. The three items including upper arm function, hand movements and advanced hand activity were summed to a score of 0-15 points[122]. Impaired upper extremity function was defined as a ≤14 points.

Study II-IV: Impaired upper extremity function, 3 days post stroke onset was defined as <57 points on the ARAT (0-57 points)[85,86].

Study design

The SALGOT-study was planned with purpose to comprise the different domains of the ICF[28,118]. The study designs, analysis and data source of each study as well as the specific aims in SALGOT-study[118] are described in Table 2. The demographics of included patients in each study are provided in Table 3.

Table 2. An overview of the study design

Study	I	II	III	IV
Design	Cross sectional study	Longitudinal study	Cohort study	Cross sectional study
Analyses	Descriptive	Multivariate	Association Prediction	Association Agreement
Data source	Patients charts, The Riks-Stroke Collaboration	SALGOT-data	SALGOT-data	SALGOT-data
Specific aims in SALGOT-study	-	Follow recovery of upper extremity by using clinical measures of body function, activity and participation after stroke, (aim A).	To predict function at 12 months by analysis of data gathered at first week after onset of stroke, (aim D).	To gather the assessments of participants' self-perceived upper extremity function over the first year after stroke, (aim C).

Abbreviations: SALGOT, Stroke Arm Longitudinal Study at the University of Gothenburg

Table 3. Overview of the demographical and stroke characteristics of included patients

Study	I	II	III	IV
Patients, n	642	117	112	99
Age, years, mean (SD)	73 (14.2)	69 (13.0)	69 (13.0)	67 (12.7)
Males, %	55	56	55	42
Female, %	45	44	45	58
Ischemic stroke, %	90	84	83	82
Hemorrhagic stroke, %	10	16	17	18
Stroke severity NIHSS, md (q1-q3)	n=345 3 (1-9)	7 (3-13)	7 (3-13)	6 (3-11)
UE function at day 3 FMA-UE, md (q1-q3)	-	20 (4-56)	18 (4-55)	38 (4-56)
UE activity at day 3 ARAT, md (q1-q3)	-	n=114 4.5 (0-43)	4.5 (0-43)	n=96 12.5 (0-47)

Abbreviations: ARAT, The Action Research Arm Test; FMA-UE, Fugl-Meyer Assessment Scale for Upper Extremity; md, median; NIHSS, the National Institute of Health Stroke Scale; q1-q3, 1st and 3rd quartile values; SD, Standard Deviation; UE, upper extremity

Outcome measures

An overview of the main outcome measures used in this thesis, sorted according to ICF[28] is shown in Table 4. All outcome measures are generated from ordinal scales, except for strength in paretic hand which was measured with the JAMAR hand dynamometer (ratio level). A summary of the measurements characteristics and psychometric properties is provided in Table 5 below.

Table 4. Overview of measurement methods used in this thesis, categorized according to ICF

Measurements	Brief description	Study			
		I	II	III	IV
Body functions					
FMA-UE	Sensorimotor function		X	X	X
JAMAR	Grip strength				X
SIS, 2 questions*	Perceived hand strength				X
NIHSS, motor arm*	Neurological outcome, arm strength*	X	X	X	X
Activities					
M-MAS UAS-95					
F, G, H*	UE function and activity	X			
ARAT	Activity capacity		X	X	

*Subdomains/items

Abbreviations: ARAT, Action Research Arm Test; FMA-UE, Fugl-Meyer Assessment Scale for Upper Extremity; NIHSS, the National Institute of Health Stroke Scale; M-MAS UAS-95, Modified Motor Assessment Scale; SIS, Stroke Impact Scale; UE, upper extremity

Body functions

The Fugl-Meyer Assessment Scale (FMA)[83,124], includes an examination of the sensory motor function in the upper and lower limb[83]. The FMA is conducted following the hypothesis that the recovery of motor function follows stepwise; reflexes always precede volitional motor actions. Thereafter, active motion will appear, initially dependent on movement synergies, gradually decreasing dependency on synergies and finally selective limb movements with normal reflexes will be regained[83]. There are three different domains of the assessment; the motor function, the sensation and the passive range of motion/joint pain. The sensorimotor function was assessed using FMA-UE[83,124] where scoring is based on the ability to perform isolated movements both within and without the synergy patterns. FMA-UE is divided in four subscales; arm, wrist, hand and coordination. Sensation (0-12 points) was used as a descriptive characteristic, where a full score indicates normal sensation[83].

Grip strength in the paretic hand was measured in pounds (lb) using the JAMAR hand dynamometer, (Sammons Preston Rolyan, Bolingbrook, USA)[121]. The measurement was performed in a standardized manner described by Mathiowetz[121,125], with one modification; patients rested their arm and hand on a table during the measurement. Verbal encouragement from the physiotherapist was given, and the mean of three trials was used. The measured values were percentages of normalised age and sex values[125].

The Stroke Impact Scale (SIS) 3.0[119,120] is a stroke specific patient-reported health status measure. The SIS was developed on the basis of the perspectives of patients, caregivers and health professionals[119]. The SIS assess multidimensional stroke outcomes and includes eight domains (strength, hand function, activities of daily living, mobility, communication, emotion, memory and thinking, participation)[119,120].

To assess outcome and degree of recovery for patients with stroke the National Institute of Health Stroke Scale (NIHSS)[126] was used. The NIHSS comprises the following items; level of consciousness, eye movements, visual tests, face, extremity strength, ataxia, sensory function, language and speech, extinction and inattentions.

Activities

Upper extremity activity capacity was assessed using the Action Research Arm Test (ARAT)[85,86,127] which is intended to assess UE dexterity in basic movements. The ARAT consists of 19 items scores that are summed to 4 hierarchical sub scores; gross motor, grasp, grip and pinch. The ARAT is based on movement performance and on a time limit, and was performed following a standard approach[127,128].

The Modified Motor Assessment Scale (M-MAS UAS-95)[123] is developed from the original version of Motor Assessment Scale[122] designed to assess everyday motor function in patients with stroke. The assessment scale was developed on the basis of Carr and Shepherds theories of motor relearning after stroke[129] and assesse upper arm motor function and hand movements (F, G, H), sitting balance, transfers such as lying to sitting standing and walking[123].

Table 5. Overview of the characteristics and psychometric properties of the main measurements included in the thesis.

	Body function		Activities			
	FMA-UE Motor function[83]	JAMAR[121,125]	SIS[119,120]	NIHSS[126]	ARAT[85,86,127,128]	M-MAS UAS-95[122,123]
Type	Observational rating scale	Dynamometer, grip strength	Self-reported outcome	Observational rating scale	Observational rating scale	Observational rating scale
Scale level	Ordinal	Ratio (Pound)	Ordinal	Ordinal	Ordinal	Ordinal
Range sum score	0-66	Reference values	Each domain 0-100	0-46*	0-57	0-55
Number of items	33	-	59	13	19	11
Item range	0-2	-	1-5	Varies, 0-2, 3 or 4	0-3	1-5
Reliability	Excellent[31,124,130]	Excellent[31]	Excellent[31,119,120]	Adequate to Excelent[126,131,132]	Excellent[86,127,130]	Excellent[123]
Validity	Excellent[133-135]	Adequate to Excellent[136]	Excellent Strength domain[119]	Varies, Adequate-Excellent[132]	Excellent[137]	Adequate to Excellent[123]
Responsiveness	Large[84,138]	-	Large sub-acute[119]	-	Large[137,138]	-
MCID	7 points (10%) [139]	11-13 pounds[140]	Varies, within domains (4.5-17.8 points)[141]	2 points[82,126]	6 points (10%) [139]	-

Abbreviations: ARAT, Action Research Arm Test; FMA-UE, Fugl-Meyer Assessment Scale for Upper Extremity; JAMAR, Jamar Hand Dynamometer; M-MAS UAS-95, The Modified Motor Assessment Scale; MICD, minimal clinical important difference; NIHSS, the National Institute of Health Stroke Scale; SIS, Stroke Impact Scale; UE, upper extremity.

* NIHSS, lower total score indicate less severe stroke.

Reliability: Excellent ≥0.75, Adequate 0.-074 ICC, kappa statistics[142]

Validity: Excellent ≥0.60, Adequate 0.31-0.59 Construct/convergent, concurrent, Excellent ≥0.90, Adequate 0.70-0.89 ROC, ACU[142]

Responsiveness   < 0.5 small, 0.5-0.8 moderate, ≥0.8 large Standardised effect sizes, sensitive to change[142]

Descriptive variables

Outcome measures/variables used for description of the included population are described below and sorted according to ICF[28].

Body functions

Consciousness at arrival to hospital (Study I) was assessed using a modified version of the Reaction Level Scale (RLS-85)[143,144] according to criteria from the Riks-Stroke, The Swedish Stroke Register[145]. The patient's consciousness was stratified into three categories; Alert and oriented (RLS 1), drowsy or confused (RLS 2-3) and unconscious only responding to stimuli (RLS 4-8)[145].

Activities

The screening test Barrow Neurological Institute Screen for higher cerebral function (BNIS)[146] was developed to assess a variety of higher cerebral function. The BNIS has been shown to have good validity in a Swedish population with different neurological deceases (high sensitivity)[147,148], and to be useful as screening test in patients with ischemic stroke[149]. The BNIS pre-screening including three initial items assessing arousal level alertness, basic communication skills and level of cooperation was assessed (ordinal score 0-9 points).

The modified Rankin Scale (mRS)[150] 0-6 points, evaluates the patient over-all status after a stroke, at a seven grade ordinal scale. No symptoms at all corresponds to 0, and 5 corresponds to severe disability and 6 corresponds to death.

In order to detect cognitive impairment, a subset of items from the NIHSS score was used, entitled the COG-4[151]. The COG-4, is a comprehensive score of four items from NIHSS; orientation (item 1b), executive function, language and inattention. The COG-4 is used as screening of cognitive impairment and are scored 0-9 points, where 0 indicates no cognitive reduction[151].The COG-4 has been shown to have similar possibilities to detect severe cognitive impairment as the Mini-Mental State Examination (MMSE)[151,152].

Health condition/stroke specific

The stroke location was recorded from patients' charts, in Study I as right/left/bilateral/unclear and in Study II-IV right/left/bilateral/brain stem/unknown. Acute medical treatment (conservative, thrombolysis, thrombectomy), length of stay at stroke unit and care pathway were collected from patients' charts. The amount of in- or outpatient rehabilitation received

was noted at each assessment. Daily support in activities of daily living pre and post stroke, as well as mobility pre stroke was recorded from the Riks-Stroke register[145].

The causes of the ischemic stroke were defined and sub-categorized according to the classification system the SSS-TOAST (Stop Stroke Study Trial of Org 10172)[153], where each category consisting of subgroups according to evident, probable or possible. In a second step the SSS-TOAST were convert to the original classification of TOAST; the Trial of Org 10172 in Acute Stroke Treatment (TOAST)[105].

Using clinical neurological findings, the Oxfordshire Community Stroke Project classification (Bamford classification) divides ischemic stroke into four sub-groups according to stroke location[154]. The four groups are total anterior circulation infarct, TACI; partial anterior circulation infarct PACI; Lacunar anterior circulation infarct, LACI; and posterior circulation infarct, POCI[154].

Assessment procedure and data acquisition

In Study I, data from patients who received care at the stroke unit were gathered retrospectively from the medical charts. All patients with ICD-10 code I61 or I63 were screened for inclusion. More than 1800 charts were screened and patients with first ever stroke were included and those with recurrent stroke were omitted. The TOAST[105], the Bamford classification[154], the NIHSS[126] at onset and the mRS[150] at discharge from hospital were assessed from the patient's medical chart. A systematic error resulted in 52 patients not being correctly classified according to the TOAST criteria; therefore all charts were re-evaluated (by KSS) post publication of Study I. Also, patients with missing NIHSS scores were evaluated (by KSS) post publication of Study 1. Results from these evaluations are present within this thesis.

According to clinical practice, the M-MAS UAS-95[122,123] was performed as a screening of general function as well as upper extremity function, by the physiotherapists at the stroke unit within the first 3 days post stroke. The results were noted on a screening sheet by the physiotherapists at the stroke unit. In Study I the upper extremity function was determined from the patient's chart in by two of the authors (Study I, HCP and MP) and defined as impaired or not impaired in the following steps:

1) A documented assessment of the M-MAS UAS-95 (within 72 hours post stroke). The three items of upper arm function (item F), hand movements (item G) and advanced hand activities (item H) were summed, and impaired upper extremity function correspond to M-MAS UAS-95 <14 points.

2) Evaluation of other documented standardized assessment of upper extremity function (within 72 hours post stroke) by physiotherapist, occupational therapist or physicians at the stroke unit.

The upper extremity function was assessed with the M-MAS UAS-95 in 80.4% of patients, and in 19.6% of the patients, the two authors (HCP and MP) assessed the patients' charts according to the procedure. In a second step, a comparison of the evaluated upper extremity function and NIHSS at admission to hospital (sub score arm strength) was performed

Prior to start of inclusion to the SALGOT-study, a pilot study including five patients from a convenience sample at the stroke unit was conducted. The SALGOT-study protocol was revised (small changes) according to results of the pilot study.

In Study II-IV, patients were assessed at stroke onset, at 3 and 10 days and at 1, 3, 6, and 12 months post stroke, Figure 3. The SALGOT-study also comprises assessments at 3 and 6 weeks post stroke, as well as other outcome measures, not included in the present thesis.
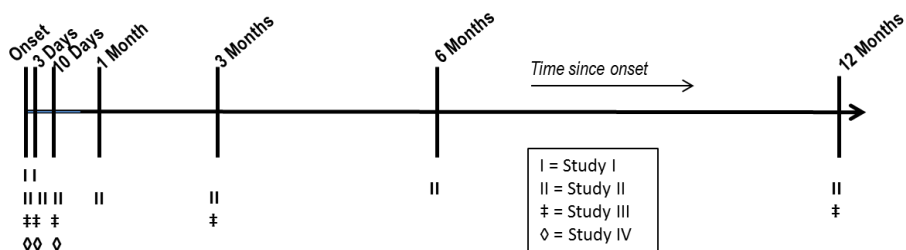

Figure 3. *Description of the time points for the assessments used in this thesis*

At each assessment, the clinical characteristics and status update questions (including living condition, amount and type of rehabilitation) were noted. This was followed by the BNIS pre-screening, which assessed the ability to participate in the following assessments. Outcome measures were thereafter administrated in a block randomized manner in order to minimize the

systematic bias. The two assessments of ARAT or JAMAR hand dynamometer were conducted in a random order. Next, the FMA-UE was assessed, and finally the SIS was recorded (Figure 4). The test order and the reasons for missed or unsuccessful test results were recorded in a test protocol.
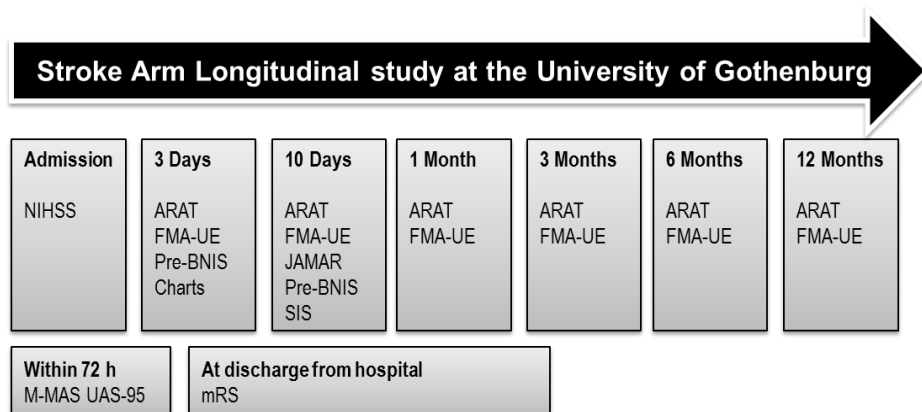

Stroke Arm Longitudinal study at the University of Gothenburg

Admission	3 Days	10 Days	1 Month	3 Months	6 Months	12 Months
NIHSS	ARAT FMA-UE Pre-BNIS Charts	ARAT FMA-UE JAMAR Pre-BNIS SIS	ARAT FMA-UE	ARAT FMA-UE	ARAT FMA-UE	ARAT FMA-UE

Within 72 h	At discharge from hospital
M-MAS UAS-95	mRS

Figure 4. *Illustration of main outcome measures at each time point after stroke onset.*
Abbreviations: ARAT, The Action Research Arm Test; FMA-UE, Fugl-Meyer Assessment
Scale for Upper Extremity; M-MAS UAS-95, The Modified Motor Assessment Scale;
NIHSS, the National Institute of Health Stroke Scale; SIS, the Stroke Impact Scale

Clinical characteristics were gathered at the first assessment, from the patients' charts, as well as from the Riks-Stroke[145] in Study II-IV. Also in Study II-IV values from TOAST, Bamford criteria and NIHSS at onset were assessed from the patients' charts.

In Study IV, 2 questions from the SIS 3.0[119,120] strength domain (domain 1), were used: *In the past week, how would you rate the strength of your;* 1a) *Arm that was most affected by your stroke?* 1b) *Grip of your hand that was most affected by your stroke?*. The patients rated their strength on a verbal, five point ordinal scale from *no strength at all* (1) to *a lot of strength* (5).

The majority of assessments in the SALGOT-study were performed at the hospital in a special test room, which was also used at the follow-up assessments. If the patient was unable to travel to the test room, assessments could be performed in the patient's home or in their current care setting. Three physiotherapists, not otherwise involved in the care, performed the assessments (after training) following a standardized protocol[118]. At the follow-up assessments, the physiotherapists were not familiar with the results from the previous assessment, except for the time point at 12 months, where

the patient received information on their results from all the assessments during the past year. If a patient not could contribute and participate in the assessment at 1 month, the patient only was followed at the 1 year follow up.

Care and rehabilitation

The studies in this thesis did not interfere with the routine care rehabilitation or care pathways of the included patents. Patients followed the ordinary planning of rehabilitation and discharge procedure. Patients received individually adjusted, functional, task-specific rehabilitation from the first day in the stroke unit. Rehabilitation in this thesis includes physiotherapy and/or occupational therapy and the amount of received rehabilitation at each assessment was recorded. Inpatient rehabilitation was defined as ongoing rehabilitation at the hospital (at stroke unit or rehabilitation unit), and outpatient rehabilitation as rehabilitation received when patients' lived at their own homes or at community care units.

Data analyses

The guidelines for reporting observational studies, Strengthening of Reporting of Observational Studies in Epidemiology (STROBE)[155] were followed.

Due to administrative reasons, 20 patients out of 117 in Study II and 18 patients out of 99 in Study III were not assessed using FMA-UE at 10 days post stroke, but were assessed with all other outcome measures at 10 days. In order to enable use of these 20 patients FMA-UE data, a score for each non-assessed patient was estimated in the following manner: The mean change from 3 to 10 days after onset for all patients assessed at both time points (Study II, n=97, Study III n=94) was calculated. By adding the mean change (this was 5 points) to each of the missing 20 (Study II) and 18 (Study III) patients' FMA-UE scores at 3 days, an estimated value at 10 days post stroke was obtained. The estimated value at assessment at 10 days could not exceed the score of the subsequent assessment.

In study III, the predictive validity of the FMA-UE$\geq$32 to correctly classify a patient's motor ability to drink from a glass (the drinking task) was investigated. In a previous publication from the SALGOT-data[156], patients were included if they could perform a drinking task. The drinking task included reaching, grasping, lifting the glass to drink a sip of water. All patients included in that study[156] had a score of $\geq$32 points on the FMA-UE, and therefore this cut-off was used to classify the ability to drink from a

glass. At 10 days, 1 and 12 months post stroke, the FMA-UE≥32 showed high sensitivity (97-100%) and high specificity (89-96%) to detect capacity to perform a drinking task, Table 6.

Table 6. Numbers of patients with capacity to perform a drinking task, divided into groups on FMA-UE≥32 points

Time since stroke onset	Capacity to perform drinking task	FMA-UE <32*	≥32*	Sensitivity (95% CI)	Specificity (95% CI)
10 days n=112	no	57	6	97%	89%
	yes	2	47	(0.88-1.0)	(0.77-0.96)
1 month n=103	no	44	4	100%	93%
	yes	0	55	(0.92-1.0)	0.84-0.98)
12 months n=73	no	22	2	100%	96%
	yes	0	49	(0.85-1.0)	(0.87-1.0)

(Conference interval 95%)*FMA-UE <32 correspond to severe upper extremity impairment, and FMA-UE ≥32 corresponds to mild/moderate upper extremity impairment
Abbreviations: CI, Confidence Interval; FMA-UE, Fugl-Meyer Assessment Scale for Upper Extremity

In Study IV, normative strength values according to Mathiowetz[125] were dichotomized using the cut off of 80%. The patient-reported strength (two items from SIS) was dichotomized, categories 1-3 corresponded to *perceived reduced strength in arm/hand* and 4-5 corresponded to *perceived good strength in the arm/hand*. *Perceived good strength* was assumed to correspond to ≥80% of normative strength values, versus *perceived reduced strength* was assumed to corresponded to <80% of normative strength values. Approximately 80% strength corresponded to normal function[157].

Statistical analyses

An overview of statistical methods used in this thesis is provided in Table 7.

Table 7. Overview of statistical methods used in this thesis

Statistics	Study I	II	III	IV
Descriptive statistic				
Mean (SD)	X	X	X	X
Median (q1-q3, range)	X	X	X	X
Proportions (absolute numbers, percentages)	X	X	X	X
Differences between groups				
Mann-Whitney *U*-test	X	X	X	
Independent sample *t*-test		X	X	
Fisher's exact test		X	X	
Change over time				
Mixed models repeated measurements		X		
Item reduction				
Principal components analysis (PCA)			X	
Receiver operation characteristic (ROC) curves			X	
Agreement				
Sensitivity, specificity			X	X
Percentage of agreement/percentages of correct classified			X	X
Positive and Negative predicted values (PPV, NPV)			X	X
Likelihood ratios			X	
Associations				
Spearman rank correlation	X		X	X

Abbreviations: SD, Standard Deviation; q1-q3, 1st and 3rd quartiles,

Descriptive statistics

Descriptive statistics were used for demographic data in order to describe the study population. Mean (SD) or median (range or 1st and 3rd quartiles) were used in accordance to the scale level. If an ordinal measure has been commonly reported with mean and SD, these values were also presented in addition to the median value.

Differences between groups

Independent t-test was used to investigate differences between groups in normally distributed data and in data at ratio level. Differences between two groups in ordinal level and dichotomized data were analysed using the Mann-Whitney U test and Fisher's exact test respectively.

25

Change over time

There is no non-parametric statistical method that handles differences between groups in longitudinal data. Therefore in Study II, in order to investigate extent of recovery regarding functioning as well as to explore differences between two types of stroke (hemorrhagic and ischemic stroke), the Mixed models repeated measurement[158-160] was used. The Mixed model repeated measurements enables maximum use of data as it can handle missing values, calculate individual changes over time as well as investigate differences in change over time between groups. Two separate models were used; one for motor function (FMA-UE) and one for activity capacity (ARAT) both including the independent variables; type of stroke, age and stroke severity. Differences between the two types of stroke were further investigated using values generated from Mixed models repeated measurements, where the impact of significant factors on change over time in function and activity were explored. Differences in the extent of change in motor function and activity capacity between the two types of stroke were calculated at four time periods; from 3 days to 1, 3, and 12 months post stroke respectively, as well as from 1 to 3 months. When calculating differences in changes in FMA-UE or ARAT scores, significant factors (from the Mixed models repeated measurements) were controlled for.

Item reductions

In order to achieve a clinical assessment with potential to be feasible in routine care at the stroke unit early after stroke, an assessment that was short and easy to perform was required. The hypothesis was; that ARAT has potential to detect limitations in upper extremity, the minimal number of items needed to capture most of the variation could be identified using principal components analysis (PCA) based on the SALGOT-population (n=117). Only components with eigenvalues ≥1 were selected and ARAT items with loading values greater than 0.6 were considered, according to Kaiser's criterion[159]. In the next step, the ARAT items with the most wide variation in difficulty (out of possible items), were identified according to Koh et al[161]. The selection of the sub-set of ARAT items was carried out by identification of an optimal cut-off level of the score and was valid to all time points of assessments during the year. This was identified using receiver operation characteristic (ROC) curves[162].

Agreement

Agreement between two types of outcome measures was investigated with 2-ways contingency tables. Sensitivity is the probability that a patient that has problems is classified correctly; specificity is the probability that a patient without problems is classified correctly. The predictive values could be

positive (PPV), indicating the probability that a patient without problems is classified as having problems, and negative (NPV) the probability that a patients having problems is classified as having no problems[104,110]. The Likelihood ratios, indicates the overall value of information of the predictive test and can be positive and negative[111]. In Study III and IV sensitivity, specificity, PPV, NPV, percentages of agreement/percentages of correctly classified patients, and likelihood ratios (positive, negative) were investigated at each time point including 95% confidence intervals (CIs)[110].

Associations

Spearmans rank correlation (rho) was used to investigate the associations of impaired upper extremity function and patient's care pathway (mortality, length of stay, discharge) (Study I). In Study III, rho was used to investigate relationship between ARAT items and in Study IV, correlations between perceived arm and hand strength and the measured strength (capacity).

Statistical software

Statistical analyses were mainly performed in the IBM Statistical Package for Social Sciences (SPSS version 21.0, for Windows). In Study II, the analysis using the Mixed models repeated measurements was performed using the Statistical Analysis Program, (SAS proc mix, version 9.3 SAS Institute Inc., Cary, N.C USA). The Confidence Intervals of likelihood ratios were analysed using the Prop CIs Package in R version 3.1.1 (2014-07-10).

Ethics

The SALGOT study received ethical approval by The Regional Ethical Review Board in Gothenburg, with the reference number 225-08, approved 5th of May 2008, Study II-IV. In Study I, a complementary approval (to 225-08) was needed, approval was received on the 10th of January 2011, reference number T801-10. In Study I, complementary data were collected from the patients' charts, and according to Swedish law on Data Protection Authority (Personuppgiftslagen, Swedish law No. SFS 1998:204) patients' informed consent is not mandatory when data is gathered for clinical use. Approval to read the patients charts was given from the responsible authority at the hospital and on the wards. All patients or next of kin gave informed oral and written consent for participation in the SALGOT-study (Study II-IV). The Helsinki Declaration[163] was followed. The SALGOT-study (included Study II-IV) was registered at the clinical trials.gov: NCT01115348, May 3, 2010.

RESULTS

The differences between included, non-included and drop-outs as well as the main findings from Study I-IV are presented in this section.

Drop-outs and non-included patients

Differences between included patients, drop-outs and non-included patients from Study I to the SALGOT-study were investigated. There were no differences in gender (p=0.477) or in stroke severity (p=0.157) in patients that were *missed for screening to SALGOT*, *declined participation* and *not included due to administrative reasons* (total n=84), compared to the included patients in the SALGOT-study (n=117), Figure 2. However, included patients were significantly younger (p=<0.001) with a mean age of 69.3 years, compared to the other group who had a mean age of 76.1 years. The percentage of patients with ischemic stroke was lower (74%) in the included patients compared with the other group (94%, p=0.029).

In Study I there were no differences in gender (p=0.134), type of stroke (p=0.134) or stroke severity (p=0.491) of patents with prior upper extremity impairment (n=59) compared to patients who were included in Study I (n=642).

In Study II, there were no drop-out from assessments at 3 and 10 days post stroke. The main reasons for drop-out at 12 months were in both ischemic and hemorrhagic stroke death, withdrawal from study or new stroke. Eight patients could not contribute in the assessment at 1 month and these patients were only followed at the 12 month assessment; two out of these eight patients participated in the follow-up at 12 months whereof both lived at nursing homes and had full support in their activities of daily living and had low or no function or activity in upper extremity; an additional two patients survived the first year after stroke, of which one declined to participate, and one had moved from the area at the 12 months follow-up; four patients died within the first 12 months.

In Study III, there were no drop-out from assessments at 3 and 10 days post stroke. At assessment at 1 and 12 months, 9 respective 39 patients did not participate, and the reasons for non-assessed in each group are specified in Figure 5. The reasons for drop-out at 12 months did not differ in patients with initially severe or moderate/mild impairment regarding; type of stroke, stroke severity, initial upper extremity function (severe or moderate/mild) or gender.

However, the patients that participated at the 12 months assessment were significantly (p=0.017) younger compared to the drop-outs.
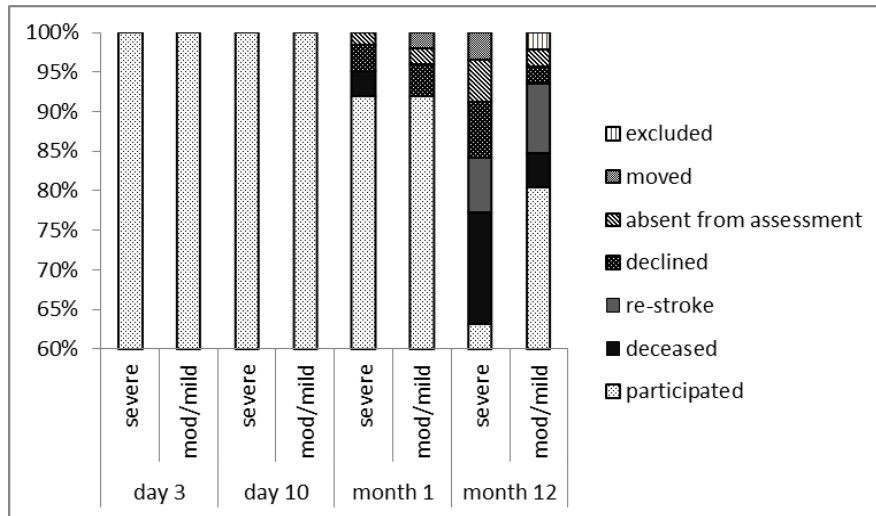

Figure 5. *Patients assessed and non-assessed including the reasons for drop-out (Study III). The population was divided due to upper extremity function at stroke onset; severe FMA-UE ≥32, mod/mild FMA-UE <32. Note that the vertical axis starts at 60%, all patients below 60% participated. Abbreviations: Mod, moderate*

In Study IV, no differences between included (n=99) and non-included patients (n=18) from the SAGLOT-study were seen in gender and type of stroke (ischemic or hemorrhagic stroke). However, the non-included patients were older (p=0.02) and had a significant more severe stroke at onset (higher NIHSS score, p= <0.001).

Prevalence of impaired upper extremity function

In total, 642 patients with first ever hemorrhagic or ischemic stroke, admitted to the stroke unit at Sahlgrenska University hospital were included in Study I. Re-evaluated values of the TOAST and NIHSS score (post publication of Study I) are shown in Table 8, cardio-aortic embolism was the most common cause of stroke (41%) followed by small artery occlusion (30%). The frequency of cardio-aortic embolism and small artery occlusion were the two categories of TOAST that showed different values (Table 8) compared to the published results in Study 1. However, these differences did not affect the main results in Study I. The NIHSS-score was re-evaluated in total 565 patients with a mean of 6.0, median of 3.0 points (min-max 0-33), Table 8,

similar results as present in Study I, n=345man 5.5, median 3.0, min-max 0.33).

Table 8. Characteristics of included patients in Study I, re-evaluated.

n = 642		
TOAST-criteria, causes of ischemic stroke, n (%)	Large artery atherosclerosis	102 (18)
	Cardio-aortic embolism	236 (41)
	Small artery occlusion	171 (30)
	Other causes	25 (4)
	Undetermined cause	14 (2)
	Unclear	27 (5)
NIHSS 0-42 points, n=565		Mean 5.5 Md 3.0 min-max 0-33

Abbreviations: NIHSS, the National Institute of Health Stroke Scale; Md, Median; TOAST, the Trial of Org 10172 in Acute Stroke Treatment

The most frequent subtype according to Bamford classification was the Lacunar stroke, present in 44% of the study population. Out of the patients with first ever stroke, admitted to the stroke unit within 72 hours, 48% had impaired upper extremity function, Study I, Figure 1.

Impaired upper extremity function correlated to higher age (p=<0.004). There were no differences between patients (ischemic) who had received treatment with thrombolysis (8.9%), or patients not treated with thrombolysis (p=<0.482) regarding upper extremity function assessed within 72 hours. Patients with the Bamford classification TACI had impaired upper extremity function more often (p=<0.001) than patients classified as LACI or PACI (p<0.031). Of the 642 patients admitted to stroke unit, 71 patients (11.1%) died during the stay at the stroke unit, and 571 (88.9%) survived, Figure 6.
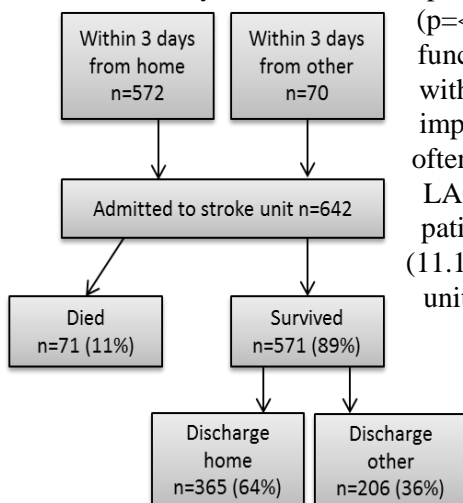

Figure 6. *Care pathway of included 642 patients in Study I.*

Differences in recovery of functioning

The extents of change over time in function and activity during the first year were investigated in the 98 patients with ischemic stroke and the 19 patients with hemorrhagic stroke. The amount and type of rehabilitation during the first year varied between the two types of stroke. As seen (Figure 7), some patients with ischemic stroke were discharged at 10 days post stroke, compared to patients with hemorrhagic stroke, who were discharged at 1 month post stroke at the earliest. Nearly all patients were discharged from hospital at 3 months post stroke.
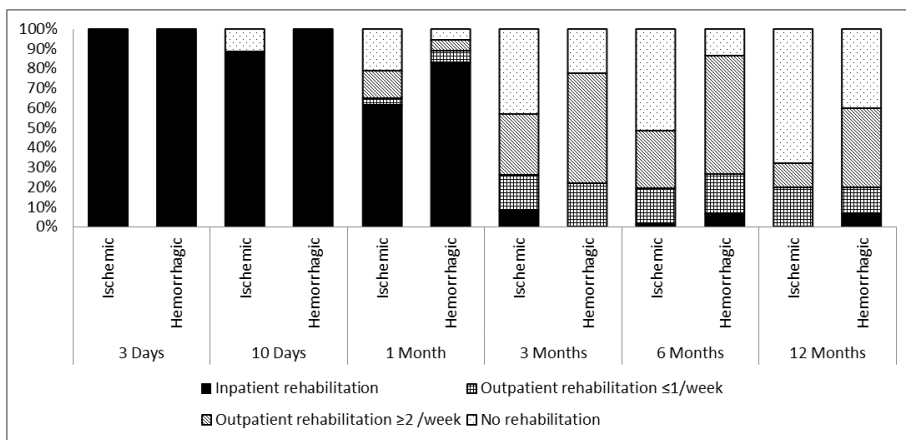
Figure 7. *Rehabilitation received in patients with ischemic vs. hemorrhagic stroke*

Individual scores of function (FMA-UE) and activity (ARAT) during the first year post stroke showed wide variations in both types of stroke. There was a tendency to a lower initial score in patients with hemorrhagic stroke compared to patients with ischemic stroke, however the initial differences between stroke types were not statistically significant ($p=0.164$, $p=0.104$). A higher age and higher score on NIHSS (initial stroke severity) had a negative impact on change over time in upper extremity function and activity in both sub-types of stroke, during the first year. The time since onset and type of stroke (interaction) had a statistically significant impact on the extent of change over time in both sub-types. Significant improvements in function and activity scores during the first month were shown in both sub-types of stroke (compared to at 12 months), and both stroke types reached approximately the same level of function and activity at 3, 6 and 12 months, Figure 8.
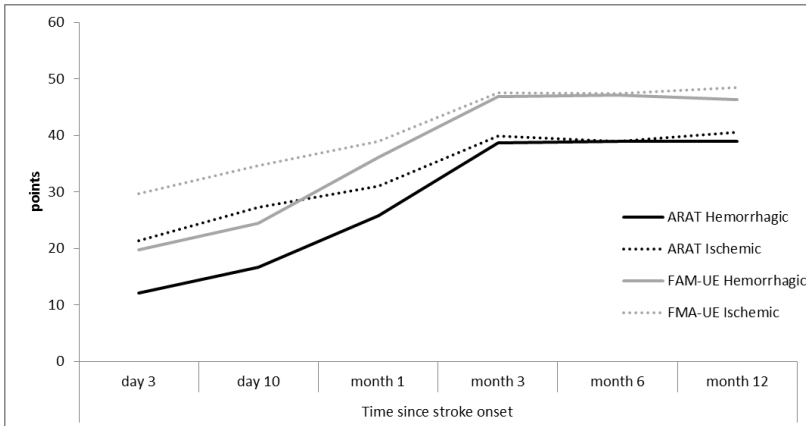
Figure 8. *The extent of change over time in function (FMA-UE) and activity (ARAT)*
during the first year (mean scores), in hemorrhagic and ischemic stroke.

To further explore differences in the extent of change in function and activity
between patients with ischemic or hemorrhagic stroke, four time periods were
investigated using mean values of FMA-UE and ARAT, adjusted for
significant variables (age and initial stroke severity). Patients with
hemorrhagic stroke gained more functioning compared to patients with
ischemic stroke from onset to one year; in function 13.2 points on FMA-UE
(p=0.0015) and in activity 13.8 points on ARAT (p=0.002). The largest
differences (in the shortest time period) in the extent of change over time
between stroke types were seen between 1 to 3 months post stroke, where
patients with hemorrhagic stroke improved their motor function (FMA-UE
8.6 points) and their activity (ARAT 10.9 points) more than patients with
ischemic stroke. These findings indicate that patients with hemorrhagic
stroke may have a different pattern in change over time in the first 3 months
post stroke, compared to patients with ischemic stroke, but both groups reach
similar results at 3 months and thereafter.

Prediction of function

In Study III, items from the ARAT was explored using PCA-analysis, in order to identify the possible fewest items needed for capturing most of the
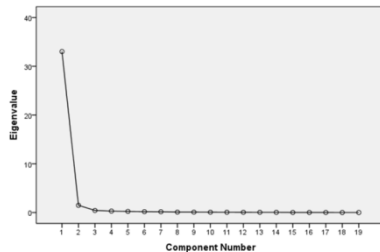
variance in upper extremity activity. The PCA-analysis identified all items to one factor, and two items with eigenvalues ≥1, see Figure 9. These items together explained 95.1% of the total variance.

Figure 9. *Scree plot of items included in ARAT, eigenvalues of each item.*

All ARAT items had a loading value >0.875, indicating that any of the items could be included in a sub-set with potential to detect motor function required for a drinking task extremity functioning. According to the item selection process, Study III, Figure 1, a sub-set of two feasible items was chosen. The two items were *Pour water from glass to glass* and *Place hand on top of head* and they comprised the ARAT-2, with a score 0-6. To predict motor function required for a drinking task at 10 days, 1 and 12 months post stroke, a cut-off level of 2 points was identified using ROC-curves (Study III). Using the ARAT-2, the possibilities of the items to correctly classify patients, at each assessment, were 81-92%, Table 9.

Table 9. *Percentages of correctly classified level of upper extremity motor function (FMA-UE) required for a drinking task, using ARAT-2*

	ARAT-2 Score	FMA UE <32	≥32	Percentages of correct classified, (CI 95%)
3 days - 10 days (n=112)	0-1	58	3	96% (0.70-0.89)
	2-6	1	50	
3 days -1 month (n=103)	0-1	44	13	87% (0.80-0.93)
	2-6	0	46	
3 days - 12 months (n=73)	0-1	22	14	81% (0.70-0.89)
	2-6	0	37	
1 month – 12 months (n=72)	0-1	22	6	92% (0.95-0.97)
	2-6	0	44	

Abbreviations: ARAT, Action Research Arm Test; ARAT-2, items *Pour water from glass to glass* and *Place hand on top of head*; CI, Confidence Interval; FMA-UE, Fugl-Meyer Assessment Scale for Upper Extremity
*FMA-UE <32 correspond to severe upper extremity impairment, and FMA-UE ≥32 corresponds to mild/moderate upper extremity impairment

In summary, using ARAT-2 had a high probability of accurately predict the motor function required for the drinking task in patients with >2 points (high specificity, high NPV, high negative likelihood ratios), during the first year. The lower percentages of correctly classified patients from 3 days to 12 months (81%), as well as lower specificity, lower PPV and lower positive likelihood ratios indicated less acuracy in ARAT-2 to predict patients with very little arm and hand activity (ARAT-2 ≤1) at 3 days post stroke. A more detailed description of the ARAT-2 sensitivity, specificity, predictive values and likelihood ratios at the different time points are present in Study III.

Patients' perception in relation to capacity measurement

In Study IV, higher levels of perceived arm and grip strength were associated with higher capacity measured grip strength (Study IV, Figure 1b) except for in category 5 (a lot of strength), only rated by only four patients. The correlations at 10 days post stroke in patient's perception of strength in their arm/hand and capacity measured grip strength were 0.82 (p=<0.001) and 0.87 (p=<0.001) respectively.

When dichotomizing patient-reported strength (dichotomized SIS) and capacity measured strength (dichotomised at 80%), high sensitivity (0.86-0.87) and high PPV (0.86-0.91) values were found (Study IV, Table 2). The high PPV indicated that patients with normal (>80%) upper extremity strength assessed their strength more correctly compared to those with impaired strength. Lower specificity (0.62-0.77) and NPV (0.64-0.67) were shown between the two measurements.

Summary of results

The SALGOT-study aimed to describe recovery in function and activity longitudinally from stroke onset to one year post stroke. The individual scores in FMA-UE for each patient are illustrated in Figure 10, were a wide dispersion in recovery of function could be seen over the first year after stroke onset. A summary of main results from Studies I-IV, is shown in Figure 11.
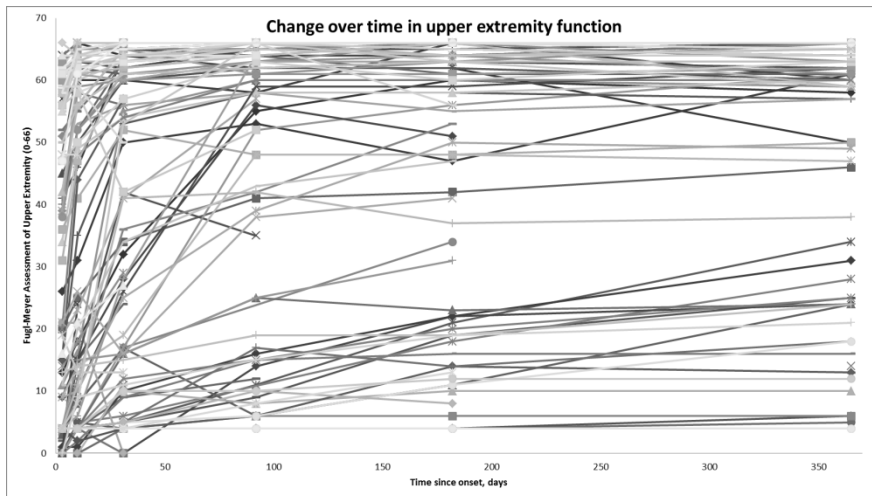

Figure 10. *Individual scores at each assessment on Fugl-Meyer Assessment of Upper Extremity, illustrating sensory motor function in upper extremity from day 3 to 12 months post stroke. Each line represents one of the 117 patients in SALGOT-study.*
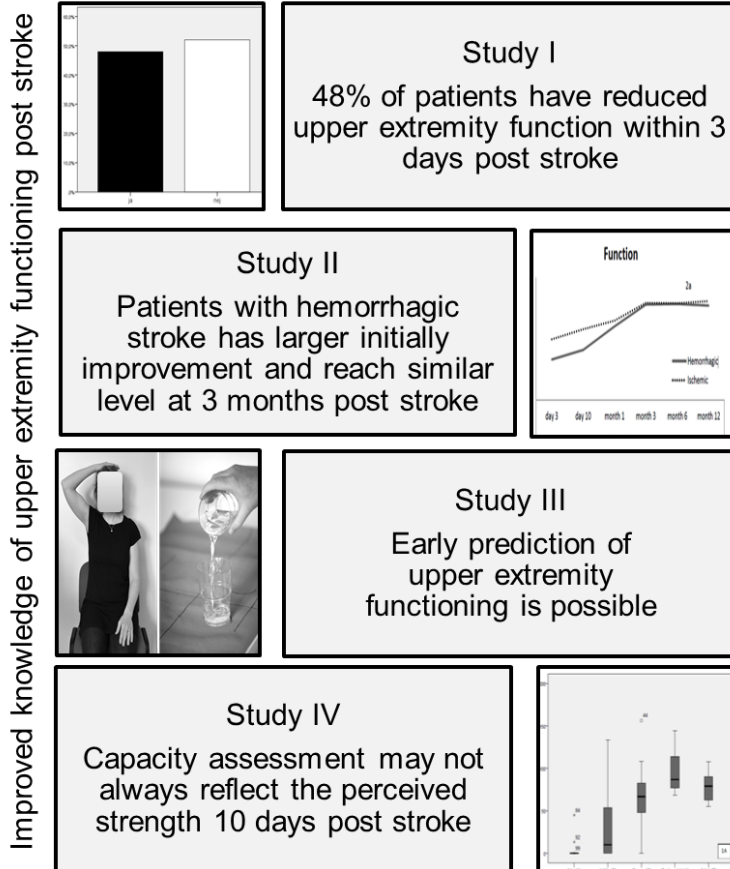
Figure 11. *Summary of results included in the thesis.*

DISCUSSION

The focus of this thesis was to investigate upper extremity functioning after stroke from different perspectives. All patients with their first ever stroke and admitted to a stroke unit were included. Patients with impaired upper extremity function were followed during the first year post stroke in the longitudinal SALGOT-study. The data collected enabled analysis of upper extremity function and activity in different aspects, in a cohort of patients with stroke. This thesis has aimed to capture upper extremity functioning according to the ICF domains, body function and activity using capacity and patient-reported outcome measures.

Prevalence of impaired upper extremity function

The finding that 48% of all patients at the stroke unit had impaired upper extremity function within 72 hours post stroke was lower than expected and gave an explanation to why inclusion to SALGOT-study required more time than expected (Study I). Patients with impaired upper extremity function were older, had a more severe stroke and they also required a longer stay in the stroke unit, compared to patients without upper extremity impairment. The result that less than half of patients at a stroke unit had impaired upper extremity function is a new finding, where previous studies have reported frequencies of 70-80%[2,3,36]. The difference in prevalence may have several potential explanations. First; regarding the study population, only patients admitted to the stroke unit within 72 hours with a first ever stroke were included. This is in contrast to the Copenhagen study[3] which also included patients with recurrent stroke. Furthermore, patients' who were admitted to other wards at the hospital or needed neuro surgical care[164] were not included in Study I. Second; stroke care has changed since data collection for the previous studies[2,3,36]. It is reasonable to believe that decreased stroke severity[1,18] may have an impact on prevalence and on severity of upper extremity function. Improved primary prevention[19], acute medical treatment[1,18], an increasing numbers of patients receiving care at stroke units may also affect the frequency of upper extremity impairment[20,21,26]. Third; even if the number of patients with stroke that are treated in hospitals with stroke has not increased, people today might be more aware of the symptoms of stroke[23-25], and immediately seek hospital care. These factors combined may result in a larger number of patients with mild symptoms that is received stroke unit care[24]. Taken together, these findings are novel and need to be confirmed in other studies with different samples of patients.

Study I also showed that the impaired upper extremity function was more common in patients with a total anterior circulation stroke(p=<0.001), than in other Bamford classifications. Total anterior circulation corresponds to higher mortality and a larger infarct[53], and the correlation to impaired upper extremity function, may not be surprising. A higher age was associated with impaired upper extremity function which also correlated to a longer stay in the stroke unit.

Aspects of functioning

Stroke severity and age were shown to have significant negative impact on the extent of change in upper extremity function and activity during the first year, in both patients with ischemic and hemorrhagic stroke (Study II). However the stroke severity and age did not explain the differences seen between the two types of stroke in gained motor function and activity. Patients with hemorrhagic stroke improved more in function and activity, with the largest improvement seen between 1 month and 3 months. Similar to others[3,6,48,62] little improvement of function and activity were found beyond 3 months, where both stroke types reached approximately similar levels. A potential reason for patients with hemorrhagic stroke showing the larger improvement 1-3 months after stroke could be the stroke unit setting of the SALGOT-study witch excluded those patients with more severe hemorrhagic stroke. As wide inter-individual variations were shown in the change over time within first year, this, together with the type of stroke needs to be considered when planning for care and rehabilitation (to individual based), as well as in goal setting. Furthermore, the different patterns due to type of stroke from 3 days to 3 months could be of importance in prediction models of upper extremity function or activity, but these findings should also be confirmed in larger studies.

The level of motor function required for a drinking task at 10 days, 1 month and 12 months was possible to predict 3 days post stroke in patients with initial impaired upper extremity function (Study III). Two items from the ARAT; *Pour water from glass to glass* and *Place hand on top of head*, called the ARAT-2, demonstrated high predictive values, were easily performed and have the potential to be clinically feasible to use within the first days post stroke. An early time point of prediction is important if the test is going to be used as guide for clinicians', in goal setting, therapy selection or discharge planning[94,95]. The prediction test should also be short and easily performed[94] as the time required to administer a measure strongly influences implementation into clinical practice[31].

The prediction model ARAT-2 has similarities to other prediction models. Presence of finger extension and shoulder abduction early post stroke have been shown to be important predictors[7,98-100,103], and are functions partly also required to receive initiate points on ARAT-2. Just like the ARAT-2, these models have a lower correct prediction in patients with an initially low motor function (lower specificity)[7,98-100,103,165]. Careful frequent follow-ups of patients with an initially poor prognosis for upper extremity capacity have been suggested[165] to determine progress of recovery. A correct prediction increases if the early clinical assessments are followed by neuroimaging of patients with poor function[102,166,167]. However, that model may be complicated (and expensive), and complex models have shown to be a barrier to implementation in routine care[94] and were shown to have approximately similar prediction[166] as in ARAT-2.

The predictive properties of ARAT-2 were tested in an unselected sample of patients, including patients with hemorrhagic stroke. The practical use of prediction of upper extremity functioning is a research field that is ongoing[165], but is currently focused on patients with ischemic stroke[7,98-100,103,165]. Findings in Study II indicate that the pathway of recovery (function and activity) may differ from onset to 3 months post stroke, but not thereafter, due to stroke type. These findings may be of importance in the continued research, as patients with hemorrhagic stroke seldom are included in predictive models.

Different prediction studies have often used different outcome measures and this complicates comparison between studies. The motor function required for a drinking task (FMA-UE$\geq$32) was used as the outcome in Study III, and correlated highly to a real drinking task. An ARAT score greater than 10 points has also been used as outcome measure[7], however, whether this cut-off automatically reflects recovery of function or the ability to use the arm in a meaningful activity, is descussed[100,101,168]. To compare different prediction models, in order to detect the best possible prediction model, could be a subject for further studies, also comprising patients with hemorrhagic stroke. Furthermore, how the lever of motor function required for a drinking task can be transferred to other activities needs to be further explored.

A major part of a patient's perceived upper extremity strength was confirmed with grip strength capacity measurements (Study IV). However, those patients' who rated their strength differently with the results of grip-strength capacity measures are important to follow-up more closely since their perception may deviate in both directions, which requires flexibility in goal setting and planning. Self-reported and capacity assessed function capture

different perspectives[88] and the use of both types of measurements could be appropriate early after stroke. The use of self-reported function early after stroke onset is not yet as common as the use of capacity scores[88], and these novel findings indicate that self-rating could be a complement to capacity measures. The agreement of dichotomized perceived strength and capacity assessed strength, showed lower NPV, indicated that patients might be unaware of their strength reduction. There were 15-20% of the patients that over- or under-estimated their strength 10 days post stroke. Awareness of the own function and activity is required for a patient to be motivated in the rehabilitation process[169]. There might be differences between those patients that over- and under estimate their function, which is needed to take into account in planning the rehabilitation[170]. Patients who over-estimate their function need intervention aimed at increasing awareness (such as feedback)[171], and those patients that under-estimated need to be encouraged in performing activities that they are actually capable of doing. This may emphasize why it could be important in clinical practice, to distinguish between patients that overestimate their level of function and these who underestimate[170].

There are several other potential factors that may influence a patient's upper extremity function and activity within the first year. The family support, the use of the paretic arm, the patient's capacity to cope in their new situation, or the rehabilitation received are some factors that could be important[53].

Methodological considerations

Measurements

Data in this were thesis was predominantly gathered using ordinal scales, and sum-scores were analysed with non-parametric statistics. However, when summing ordinal scales, some problems can arise[80,106]. Scores have a minimum and a maximum level, which gives a floor and a ceiling effect on the scale and only patients who fall within the range of the scale can achieve relevant measures[106]. If a maximum score is reached early after stroke onset, only the initially changes could be detected and none beyond that. The ARAT and FMA-UE floor effects have shown to be larger early after stroke onset, and the ceiling effect increases with time since onset[130]. The ceiling effect in both FMA-UE and ARAT was shown to be rather large in Study II and Study III, as has been seen previously when using these scales[172]. In order to minimise the ceiling effect, measures at different levels according to the ICF were used.

It cannot be assumed that the scores from ordinal scales are proportional and that the distance between and within item scale steps are equal[80,106]. Despite being aware of this, sum-scores of ordinal scales were used in this thesis. The FMA-UE has demonstrated unidimensional hierarchy in the early and late phases after stroke[173,174], also shown in the ARAT[161] which is one requirement for be used as a sum score in the clinical setting. Importantly, unidimensional hierarchy is only one aspect of linearity of a scale. Transformations of the scales to interval level measures using the mathematic based Rasch model would improve the psychometric properties. Studies[109,175-177] have used the Rasch model in FMA-UE and ARAT, however, two of the studies aimed to reduce the number of items[176,178] and it is unclear if the original form of the measure was used[175,176,179]. Continued research is needed on the psychometric properties of both regarding ARAT and FMA-UE.

Dichotomisation of ordinal sum scores was used in Study III and VI with two different purposes. In Study III, the purpose was to explore a measure (ARAT-2) with potential to be feasible in clinical routine, and to detect the minimal level of function required for an activity. In Study IV the purpose was to investigate differences between different types of outcome measures. Dichotomisation of a summed ordinal scale score, could increase the feasibility of it to be clinically useful, on the other hand it reduces information, which could lead to a reduced ability to detect changes or shifts that may be of clinical importances[82]. The difficulties with ordinal scales and potential un-equal distances between score levels and items, may be less of a problem if the sum score is dichotomized. The importance to explore correlations of cut-offs between commonly used measures[168] or different types of instruments according to ICF levels has been emphasised. Furthermore, also to explore cut-offs to identify the ability to use the impaired upper extremity in activities of daily living[180]. The cut off of FMA-UE≥32 (Study III) was used as corresponding to detect the motor function required for a drinking task (activity) and was based on a previous study from the SALGOT-population[156]. Interestingly, this cut off was recently[168] supported as indicating limited to full arm and hand capacity (corresponding to >22 points on the ARAT). In Study IV, it was assumed that 80% of normal strength[157] corresponds to good perceived strength. Another study have shown that 75% of normal strength[181] could be plausible to correspond to normal strength. If a different cut-off would have been chosen, this could have influenced the result. Furthermore, also another cut-off of the two SIS questions could have had impact on final results.

Another methodological issue was that the SIS has not been validated prior to 1 month post stroke[120]. It is possible that patients early after stroke have not

been active enough to fully be aware of the consequences of their stroke. As only two questions from the SIS were used, this might be a minor issue in this thesis. Self-perceived hand function could also have been explored using the hand function domain in SIS, commonly reported in studies later after stroke onset[90,101,112,182]. Ten days after stroke onset, the two questions from SIS were assumed to have ecological validity and the two questions were preferable compared to the full hand function domain.

Data collection and handling

The retrospective design of gathering data to Study I, reading patients' charts lead to incomplete data sets. Only 53% of the patients in Study I had a NIHSS-score noted in their charts. In cases where the NIHSS-score was not formally assessed, the score was evaluated from the patients chart, a procedure which has shown to have a high degree of reliability and validity[183]. However, this re-assessment of 220 patients revealed only a small change in mean value (5.5 compared to 6) compared to the published data in Study I, and did not affect the main result. Also the TOAST categories were re-evaluated post publication of Study I. The 52 patients not correctly classified according to TOAST were a systematic error, and importantly this did not affect the main results in Study I. Furthermore, regarding classification of TOAST, the SSS-TOAST criterion[153] was used. The use of SSS-TOAST compared to ordinary TOAST may decreases the proportion of patients with undetermined cause[53].

Grip strength was assessed using the JAMAR hand dynamometer. With a hand held dynamometer it may be more difficult to detect low grip strength, compared to the Grippit[184] which is securely attached to a table and assesses grip strength over a 10-second period[185]. To increase the patients' ability to participate even when having low muscle strength, the weight of the arm was off-loaded by resting on a table. This was different from the JAMAR manual[121]. Grip strength values were calculated from percentages of normative values, but could also have been reported as percentage of the unaffected side. However, as the "non-affected" arm may be affected as well[186], normative values were preferred in the current study. Different ways of reporting strength, such as percentage values of normative or the non-affected arm, may affect the ability to compare results between studies.

In order to enable use of longitudinal data in 20 patients (Study II) in 18 patients (Study III) respectively, missing values of FMA-UE at 10 days were estimated and imputed based on each patient's individual score 3 days post stroke, according to the described procedure. Importantly, these patients were assessed with all other measures at 10 days post stroke, but not with FMA-

UE. There are other possible procedures to impute values, but the chosen procedure was considered as the most appropriate and gentle handling of data, taking the patients' change over time in function into account.

Some statistical issues also need to be discussed. To fully make use of information gathered in longitudinal analysis (Study II), a multivariable analysis with the Mixed models repeated measurements was used. This model is based on parametric statistics, enabled longitudinal analysis of extent of recovery in motor function (FMA-UE) and in activity (ARAT) between type of stroke, and the impact of explanatory factors. A rule of thumb states that for each included variable about 10 patients[53,187] in each category should be included. The relatively small number of patients with hemorrhagic stroke enabled that only the most important variables according to literature qualified. This may have led to incomplete models and uncertainly of the accuracy of the results. Therefore further research is needed in other samples of patients, and studies could also include other explanatory factors such as the level of cognitive function, amount of rehabilitation, comorbidity or medical treatment. Furthermore, the use of parametric statistics with ordinal data limits the ability to draw conclusions of the magnitude of the estimates.

Multivariate regression analysis of prediction models is common[7,98-100,103], and was also considered in Study III and IV. A regression model would have enabled correction for confounding variables[158,162], such as age or stroke severity. Data needs to fulfil several criteria to be useful in a regression model, such as, 10 patients per explanatory variable and about 5 patients in each of the response-categories. When these considerations were taken into account when planning Study III and IV, it was decided that regression models would have been affected (by dichotomisation or excluded important variables), and therefor 2-way contingency tables were used.

Generalisability

Research need to connect to other findings in order to be useful in a larger context. In quantitative research, the generalizability of results may be influenced by several factors, such as the study setting, selection of patients and study drop-out.

The setting of the present studies is in a high income country, at a stroke unit at a University Hospital, with tax-funded care and rehabilitation. This influences the results[22,188], and should be considered when generalising any results from the present studies. The selection process for Study I and the

SALGOT-study aimed to cover an unselected sample of patients with first ever stroke. The detailed information of the included, excluded, non-included and drop-outs, provides information about the generalisability. The included patients in the SALGOT-study were younger compared to non-included which need to be taken into account. Also, 90 patients were excluded from the SALGOT-study due to severe multiple impairments. Furthermore, the SALGOT-study inclusion criteria excluded patients with a more severe stroke, those patients with stroke not admitted to the stroke unit[164] and patients with subarachnoid hemorrhage[189]. A considerable effort was made in order to minimise the study drop-out, but still from SALGOT-study at 12 months this was 35% (Study II, Study IV), compared to the estimated 30%[118]. The majority of the drop-out were deaths, new stroke or withdrawal from the study (Study II, Study III).

The STROBE guidelines[155], were followed. The STROBE guidelines provide an item checklist, aiming to improve the quality of reporting findings from studies[155]. This may also emphasizes the ability to generalise the findings. In total, the generalisability of findings from these studies may be limited to patients with stroke in high income countries that receive care at a stroke unit and those who have a similar care and rehabilitation system as in the present studies. Furthermore, patients in the SALGOT-study were younger and less multi impaired compared to a general stroke unit population.

Strengths and limitations

Strengths with this thesis are the investigation of the different aspects of upper extremity function and activity during the first year after stroke. The thesis includes clinical outcome measures that cover functioning at the level of body functions and at activities according to ICF, however, there is a lack of the participation perspective and more extensively self-reported measures. Some of this information has been gathered within the SALGOT-study and will be analysed in other studies.

The thesis comprises a well-defined group, with detailed information of the included and the non-included patients as well as the drop-outs. The early inclusion of patients with first ever stroke, both ischemic and hemorrhagic stroke, as well as the duration of follow-ups during the first year are strengths. The retrospective data collection in Study I, is a limitation, and led to incomplete data sets. However, a strength in Study I is the inclusion of all patients over that time period. The rate of drop-outs from the SALGOT-study (Study II-IV) must be considered as a limitation however.

Non-motor aspects after stroke have not been in the focus of this thesis and unexplored factors may have had an impact on upper extremity function and activity. Particularly common after stroke could be aphasia, neglect, and cognitive deficits only briefly explored within this thesis. Other factors, that impact on results, such as medical treatment with thrombolysis or thrombectomy, motivation, sensory function or lower limb function, has not been explored.

Clinical implications

Findings from this thesis increase the knowledge regarding patients with impaired upper extremity function after a first ever stroke and aim to improve care and rehabilitation. Less than 50% of patients at a stroke unit had impaired upper extremity function within 72 hours after stroke onset. Impairment was correlated with a more severe stroke and a longer stay at the stroke unit. The findings indicate that an early assessment of upper extremity function is of importance in planning for the patient's further need for rehabilitation and care.

Furthermore, the findings in this thesis could be useful in the rehabilitation of upper extremity function and activity after stroke. Age and stroke severity significantly influenced the change over time, but did not explain the differences seen between stroke types. Patients with hemorrhagic stroke had a lower initial functional level and improved significantly more compared to patients with ischemic stroke. This emphasizes the importance of rehabilitation planning to be individual basis and include regular follow-ups of both function and activity.

In order to predict the upper extremity motor function required for a drinking task, the ARAT-2 has potential to be useful at 3 days post stroke at a stroke unit. ARAT-2 requires no special equipment and the early prediction may improve the planning of care as well as rehabilitation towards training or compensations.

The discrepancy between patient-perceived strength and capacity assessed strength could indicate a patient's lack of awareness of their reduced grip strength early after stroke onset. In the clinical setting, the use of a combination of self-perceived function and capacity measures could improve patients' awareness of functioning or lack thereof which may further could facilitate the rehabilitation process.

CONCLUSION

- This thesis shows that 48% of patients in a stroke unit with first ever stroke had impaired upper extremity function within 72 hours after onset. Impaired upper extremity function was associated with higher age, higher mortality and longer stay at the stroke unit.

- A steeper recovery pattern was seen for the patients with hemorrhagic stroke compared to ischemic stroke, however starting from a lower level of functioning. At 3 months and thereafter, the differences between the groups were no longer present. Poor initial motor function or activity capacity could mislead expertise and exclude patients with hemorrhagic stroke from intensive rehabilitation.

- The ARAT-2, when assessed at 3 days post stroke had high possibility to predict the level of motor function required for a drinking task at 10 days, 1 and 12 months. The ARAT-2 demonstrated high predictive values, is easy to perform and has potential to be clinically feasible.

- Ten days after stroke, a patient's perception of arm and hand strength was not always reflected in objective capacity strength. A combination of the measurements is needed to enhance the setting of realistic goals early after stroke, and to increase the knowledge of patient's awareness of function.

FUTURE PERSPECTIVES

Several issues and ideas for future research have arisen during the work on this thesis

- The prevalence of impaired upper extremity function needs to be explored in other cohorts.

- Larger samples of patients with hemorrhagic stroke should be followed regarding change over time in upper extremity function and activity.

- The psychometric properties of the ARAT-2 and the feasibility in a clinical setting need to be explored as well as the predicative capability in a prospective study.

- The patient perspective of upper extremity function and activity should be continuously studied and qualitative analysis could also be used. The patient's perspective of function and activity also needs to be captured very early after stroke.

- The SALGOT-study comprises more longitudinal data, which enables the possibility of continued analysis of the patient perspective of functioning. Furthermore, movement analysis of longitudinal upper extremity function and activity captured with kinematic analysis would provide detailed information of the change over time.

- Further research on the long-term consequences of impaired upper extremity function and activity its impact on daily life and ability to participate in society would be interesting.

- In order to enable the use of data correctly, psychometric analysis of the FMA-UE with transformations into interval level measures is needed.

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