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Aphasia after Ischemic Stroke

Diagnosis, Incidence, and Outcome

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Aphasia after Ischemic Stroke

Diagnosis, Incidence, and Outcome

Angelina Grönberg

LUND UNIVERSITY

DOCTORAL DISSERTATION

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Aphasia after Ischemic Stroke - Diagnosis, Incidence, and Outcome

Abstract

Background: Aphasia is a common symptom after ischemic stroke, however, up-to-date, and detailed knowledge of its current occurrence, effects and outcome is needed. Recent advances in stroke management and prevention may have affected aphasia after ischemic stroke.

Aims: To investigate and update aphasia epidemiology after ischemic stroke and explore prognosis and recovery of aphasia, including potential factors important for recovery.

Methods:

Paper I: A cohort of consecutive first-ever ischemic stroke patients (n=221) included in Lund Stroke Register (LSR) were examined with the National Institutes of Health Stroke Scale (NIHSS), item 9 “best language” to detect aphasia after ischemic stroke. Diagnosis using NIHSS was compared with an aphasia evaluation with the Language Screening Test (LAST) performed by a Speech Language Therapist (SLT).

Paper II: A hospital-based cohort of consecutive first-ever ischemic stroke patients was prospectively included using LSR. Incidence rate of aphasia was calculated and adjusted to European Standard Population. A retrospective search in LSR was performed to compare incidence rates of aphasia between 2005-2006 and 2017-2018.

Paper III: A follow-up aphasia evaluation with NIHSS item 9 was performed median day 5 on the cohort from paper II to assess the short-term prognosis of aphasia and factors influencing favorable aphasia outcome.

Paper IV: The cohort of patients with aphasia (from paper I) who were alive and available for aphasia assessment were followed-up in-person at 1-, 3- and 12-months post stroke regarding recovery of aphasia, including language impairment and self-perceived health-related quality of life.

Results:

Paper I: NIHSS diagnosed 23% of all stroke patients with aphasia at median day 3 post stroke, compared to 26% detected with LAST. The sensitivity of NIHSS was 72% and the specificity is 95%. All patients with severe to global aphasia were correctly diagnosed, however mild aphasias might be misdiagnosed.

Paper II: The initial incidence of aphasia after stroke remained stable at 30%, with 35 of 100 000 person-years in the Swedish population having aphasia after first-ever IS. Stroke severity was the most important factor for aphasia and may contribute to several of the negative factors associated with aphasia.

Paper III: The short-term prognosis of aphasia was favorable for a majority of patients, with 57% showing improvement within a median of 5 days post-stroke. However, 61% had remaining aphasia, with approximately half (48%) of the patients having severe to global aphasia. Predictors of poor aphasia outcome include stroke severity, pre-stroke mRS and number of stroke risk factors.

Paper IV: Chronic aphasia at 12 months post stroke was observed in 61% of patients with initial aphasia. The prevalence of aphasia after ischemic stroke was 15%. Most recovery of aphasia occurred within the first months after onset, however, individual variations exist. People with aphasia perceive that aphasia has negative impact on their communication, participation and emotional well-being, consequences which remained up to 12 months post-stroke.

Conclusions: Aphasia remains a common and significant symptom after ischemic stroke, emphasizing the importance for prompt and early detection of aphasia. Aphasia prognosis has improved over the past decade, however, the long-term effects of aphasia for the individual patient and their overall outcome of aphasia is still substantial.

Key words
Aphasia, stroke, epidemiology, diagnosis, incidence, prognosis, outcome, health-related quality of life

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MADE IN SWEDEN

To my family

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List of papers

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I. Grönberg, A, Henriksson, I, Lindgren, A. Accuracy of NIH Stroke Scale for Diagnosing Aphasia. *Acta Neurologica Scandinavica*. 2021;143:375-382. https://doi.org/10.1111/ane.13388

II. Grönberg, A, Henriksson, I., Stenman, M, Lindgren, AG. Incidence of Aphasia in Ischemic Stroke. *Neuroepidemiology*. 2022;56:174-182. https://doi.org/10.1111/ane.13388

III. Grönberg, A, Henriksson, I, Stenman, M, Lindgren, AG. Short-Term Prognosis of Aphasia: Factors Influencing Favorable Outcome Including Possible Effects of Recanalization Treatment. Unpublished manuscript.

IV. Grönberg, A, Henriksson, I, Lindgren, AG. Long-Term Prognosis and Health-Related Quality of Life for People with Aphasia after Ischemic Stroke. Unpublished manuscript.

Abbreviations

A-FROM	Aphasia Framework for Outcome Measurement
AIQ	Aphasia Impact Questionnaire
CAT	Comprehensive Aphasia Test
CE	Cardioembolic stroke subtype
CI	Confidence interval
HRQoL	Health-related quality of life
ICD-10	International Statistical Classification of Diseases and Health
ICF	International Classification of Functioning, Disability and Health
IS	Ischemic stroke
IQR	Interquartile range
LAA	Large artery atherosclerosis stroke subtype
LACI	Lacunar infarct
LAST	Language Screening Test
LSR	Lund Stroke Register
mRS	Modified Rankin Scale
NIHSS	National Institutes of Health Stroke Scale
OC	Other determined etiology of stroke subtype
OCSP	The Oxfordshire Community Stroke Project
PACI	Partial anterior circulation infarct
POCI	Posterior circulation infarct
PWA	People with aphasia
SAO	Small artery occlusion stroke subtype
STAO	Short-term aphasia outcome
TACI	Total anterior circulation infarct
TOAST	Trial of Org 10172 in Acute Stroke Treatment
UND	Undetermined etiology of stroke subtype
WHO	World Health Organization

Introduction

Aphasia

Aphasia is an acquired language disorder with symptoms that can affect all components of language (phonology, morphology, syntax, semantics, pragmatics) and can be present in all language modalities (speech, comprehension, reading and writing) to different degrees, in both the input (comprehension) and output modes (expression).[1]

Several different definitions of aphasia have been proposed, reflecting different perspectives and theoretical frameworks of language. These include: 1) the neurological, 2) neurolinguistic, 3) cognitive and 4) functional (communication impairment).[1] Regardless of perspective, most definitions have common elements centering on the neurological impairments impeding language, defining aphasia as:

1. A language-level disorder (not somatic sensory, motor, psychiatric or intellectual)
2. Includes components of comprehension and expression
3. An acquired disorder with a neurological cause that affects already mastered language abilities
4. Multimodal in nature

After the World Health Organization's (WHO) International Classification of Functioning, Disability and Health (ICF)[2] emphasis on the consequences of impairments, an up-to-date definition of aphasia was established and is used throughout the thesis:

> Aphasia is an acquired impairment of language function and modalities, resulting from a brain lesion and affects a person´s communicative and social functioning, quality of life and the quality of life of his or her next of kin.[3]

Aphasia, and the consequential symptoms it entails, is heterogenous, affecting different language functions, different combinations of these, and to different extents. The clinical presentation of aphasia can therefore vary widely between individuals.[1,4] It is essential to promptly detect and diagnose aphasia after stroke, including patients with only mild language deficits.[5] At the individual level, aphasia can be devastating and is a condition that has one of the largest negative impacts on a person´s health-related quality of life, leading to worse psychosocial well-being compared to aging peers[6,7] and impacts overall stroke rehabilitation outcome.[8]

This thesis aims to contribute to advancing the knowledge of the burden of aphasia by studying the epidemiology and outcome of aphasia after ischemic stroke, identifying new insights into which stroke patients acquire aphasia, and how aphasia affects the individual. In-depth knowledge of stroke and aphasia is vital to accurately diagnose, prognosticate and establish further appropriate treatments of aphasia and how to improve life after stroke and aphasia. As one of the first epidemiological studies of aphasia after first-ever ischemic stroke in Sweden, this thesis aims to facilitate organization and planning of evidence-based aphasia care.

Elements of Neurology Essential for Language Functions

The neural basis of language was long considered to be a simple model consisting of Broca´s area, the Wernicke´s area and the arcuate fasciculus connecting the two.[1] These traditionally important brain areas are illustrated in Figure 1. Today, however, it has been recognized that language is made possible through an intrinsic neural system, not limited to these two brain regions. Recent studies of the neural basis of language have therefore acknowledged large areas of the frontal, parietal, and temporal lobes[9] and multiple stream models.[10,11] These advances in language research have led to new maps of the anatomy of language, incorporating brain regions, both hemispheres, processing streams, and neural networks.[10-12]

To summarize, language is a highly complex function, involving considerable parts of the central nervous system and few brain locations can be impaired without resulting in some deficits of language.[1] Figure 2 shows areas of left and right brain regions that are important and represent language function.

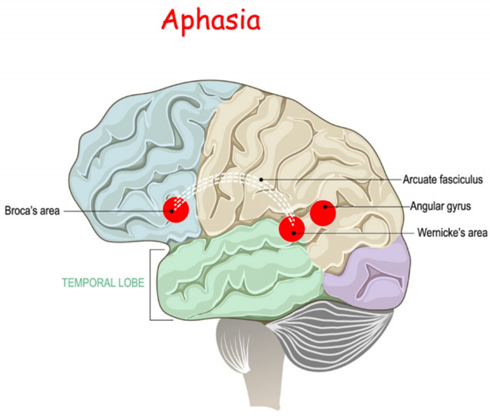

Figure 1. Traditional brain regions important for language function. Image used with permission under license from Shutterstock Inc.

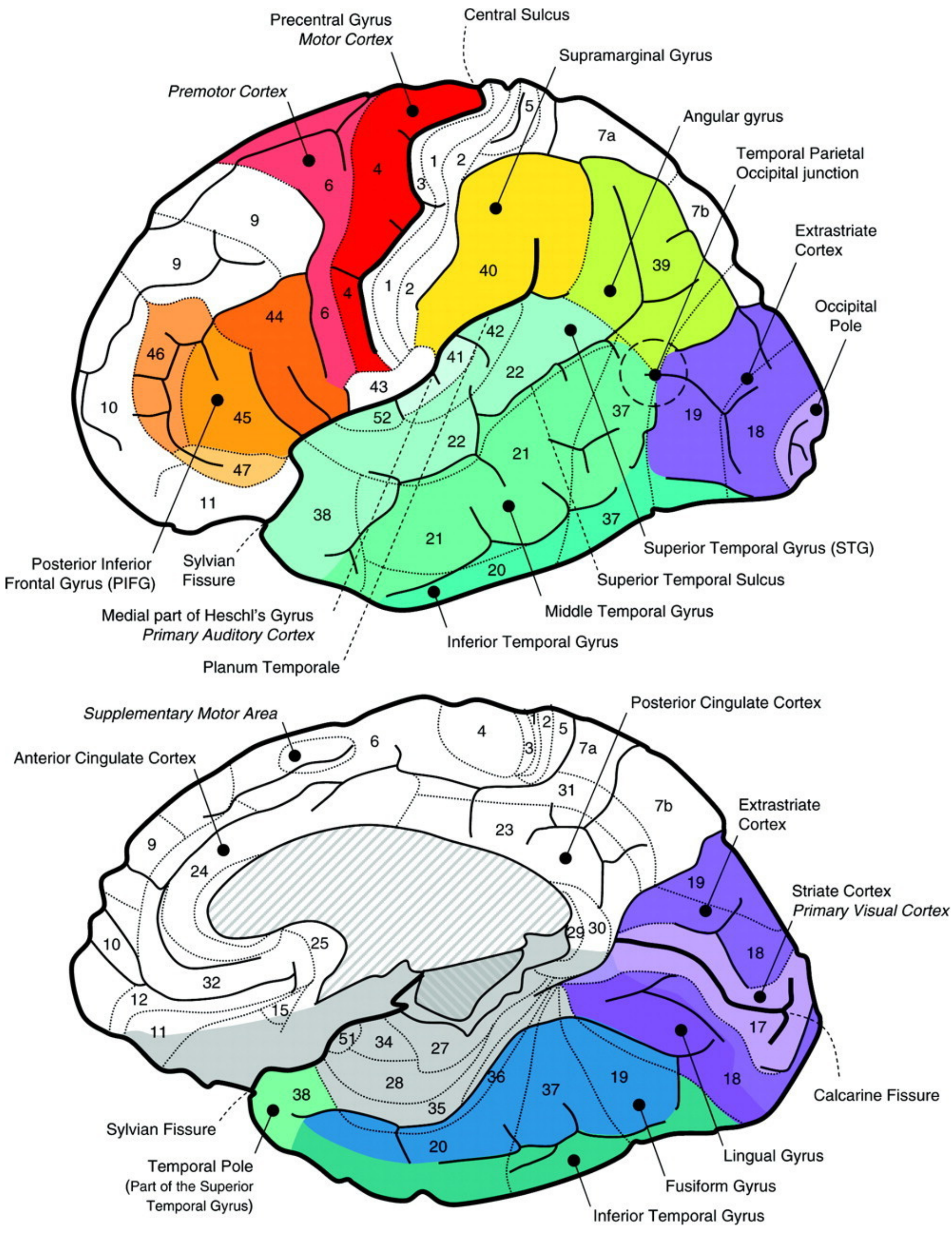

Figure 2. Main brain regions involved in language processing. Top picture: lateral view of the left hemisphere of the brain. Bottom picture: medial view of the right hemisphere of the brain. Image reprinted with permission from Physiological Reviews, Démonet, J.F. et al. Renewal of the Neurophysiology of Language: Functional Neuroimaging.[13] Copyright (2005) with permission from The American Physiological Society.

Symptomology of Aphasia

Aphasia is heterogenous with a considerable variety of language symptoms, affected to different degrees and in various constellations. Different terminology and classifications have been used to describe aphasia symptoms into syndromes with traditional models being based mostly on lesion location. Table 1 demonstrates the main aphasia syndromes according to the most commonly used Boston Classification System. Aphasia syndromes and their typical language symptoms are shown in Table 2. Language deficits are often divided into the two categories *receptive* or *expressive* language deficits; receptive being difficulties deriving meaning from language, whereas expressive is difficulty in the production of language.

Table 1. Aphasia syndromes according to Boston Classification System

Aphasia syndrome	Fluent? Is the speech fluent?	Comprehends? Can the person comprehend ?	Repeats? Can the person repeat words or phrases?
Global	No	No	No
Mixed transcortical aphasia	No	No	Yes
Broca's aphasia	No	Yes	No
Transcortical motor aphasia	No	Yes	Yes
Wernicke's aphasia	Yes	No	No
Transcortical sensory aphasia	Yes	No	Yes
Conduction aphasia	Yes	Yes	No
Anomic aphasia	Yes	Yes	Yes

Over the history of aphasia research, several models have been proposed to describe and analyze aphasia. The connectionist model of Geschwind[14] and the functional center model of Luria,[15] have through analysis of chronic language disorders emphasized the critical and often consistent relationship between lesion site and linguistic function. Since then, however, the effects of age, gender, and different linguistic structures of different languages have provided knowledge on the neural basis of language. Studies of language processing in the healthy brain has furthermore provided knowledge of brain structures important for language processing and how language networks serve language. These advances in research on the neural basis and neuroscience of language have led to new insights and approaches to the neurobiology of language, details of which are, however, outside the scope of this thesis. A summary of common aphasia symptoms is presented in Table 3.

Table 2. Aphasia syndromes and their typical language symptoms

Aphasia syndrome	Language symptoms
Global	Most severe form of aphasia Impairment of all language modalities (speaking, comprehension, reading, writing) Limited to no spoken output Poor to no language comprehension
Mixed transcortical	Non-fluent, often only speaks when spoken to Echolalia – repeats others´ words or phrases Poor comprehension Poor word retrieval Difficulty reading and writing
Broca´s	Difficulty speaking fluently, frequently speaking in short sentences Poor word retrieval (nouns better than verbs), often omits small words Slow speaking rate with articulatory disruption, dysprosody Typically better comprehension of language Difficulty reading and spelling
Transcortical Motor	Difficulty speaking fluently, can repeat Difficulty with word retrieval Good comprehension and motor speech production
Wernicke´s	Fluent speech, freqently long sentences with no meaning Neologisms, often difficult to follow what the person says Deficits of language comprehension, poor awareness of their deficts Poor reading and writing
Transcortical Sensory	Fluent speech with frequent paraphasias, good repetition Good articulation, rate and prosody, poor awareness Difficulty with language comprehension
Conduction	Fluent speech Difficulty with word retrieval, including phonemic paraphasias Articulation may appear impaired due to sound substitutions Fair to good comprehension
Anomic	Mild form of aphasia, fluent speech Difficulty with word retrieval (may appear near normal) Good language comprehension, articulation and prosody Often spared reading

Table 3. Aphasia symptoms and their corresponding description

Aphasia symptom	Description
Anomia	Difficulty with word retrieval. A primary symptom for most aphasia subtypes
Agrammatism	Difficulty producing grammatical structures, omission of function words
Agraphia	Writing impairment, often co-occuring with other langauge impairments
Alexia	Reading impairment, often co-occuring with other langauge impairments
Expressive language deficits	Difficulty in the production of language; deficits in communicating one's thoughts with others via any modality: e.g. speaking, writing
Paragrammatism	Errorfilled misuse and overuse of grammatical structures
Paraphasia	Word production errors. Paraphasias are classified into different types
Formal phonological	Word production errors phonologically related to the target word
Semantic	Word production errors semantically related to the target word
Nonword phonological	Word production errorors that result in a nonword that is phonologically similar to the target word
Neologism	Word production errors that result in a nonword; “new word”
Perseveration	Recurrence or continued production of a previously produced word or phrase
Receptive language deficits	Difficulties in understanding language and the communication of others, via any modality: e.g. auditory comprehension, text
Repetition deficits	Difficulties in repeting a word or phrase
Verbal stereotypies	Repeated forms of words, nonwords, or phrases. May be the only utterances produced

Impact of Aphasia

Impact on the Individual

Communication is a vital aspect of daily functioning, and it is through language and communication one can establish relationships, expression of oneself and participate in society.

Aphasia has significant negative impact on several aspects of outcome after stroke.[16] Stroke patients with aphasia have poorer functional outcome than stroke patients without aphasia[17] and the presence of aphasia impacts and disrupts rehabilitation,[18] one aspect being due to difficulties with patient-provider communication.[19] The patients' well-being, independence, social participation and quality of life are also affected and aphasia is often associated with depression.[20] People with aphasia (PWA) have a lower likelihood of returning to work,[21] and usually need long contact with healthcare professionals. Aphasia changes everyday life dramatically for PWA including the lives of their families.

Language is used daily and frequently, hence a wide range of consequences of language deficits like aphasia, are to be expected. Aphasia affects the ability to share ideas, feelings, ask and answer questions, i.e communication with family as well as the broader society.[22,23] On an individual level language is needed for learning, developing, and using essential community services.

Aphasia and impairment of communication affect participation in life activities immediately after the stroke, as well as in the long-term perspective. It is important to identify problems early with a thorough and holistic assessment. It is equally important to identify strengths and compensatory strategies that can enable the person with stroke and aphasia to maximize independence and to re-enter life activities with as much competency and confidence as possible.[24]

Considering the immense impact aphasia has on an individual, therapy should not only rehabilitate language functions and work with strategies of communication, but also focus on participation and well-being of the patient.[25-28] Treatment should be relevant to the individual and the patient should be included in the treatment decision-making process of the standard of care.[29]

Impact on Society

As described above, aphasia is one of the most severe symptoms after stroke,[30] with evidence of limited activity, decreased social networks and support, and higher incidence of depression.[5,7,27,31,32] In addition, PWA of working age are often unemployed or underemployed and unable to fulfill their pre-stroke roles and responsibilities.[33]

For society, aphasia adds to the cost of care, consequently, caring for stroke patients with aphasia is higher than for stroke patients without aphasia,[34] due to for example longer hospital stays.[35] In addition to the aforementioned poor outcomes, aphasia significantly correlates with greater use of both in- and outpatient health care services, subsequently leading to greater costs.[36] Aphasia treatments are under continuous development and refinement. Since aphasia therapy has been shown to be effective, the importance of rehabilitation of aphasia has been highlighted,[37] and may further add to the cost of initial care.

Stroke

Stroke has been defined by the WHO 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," and is the most used definition of stroke.[38] Stroke is the second most common cause of death worldwide and a leading cause of disability.[39,40] Stroke is also the major cause of aphasia and accounts for approximately 85% of all instances of aphasia.[41]

Stroke is classified into three different subtypes: intracerebral haemorrhage (ICH), subarachnoid haemorrhage (SAH), and ischemic stroke (IS); haemorrhage being the cause of 15% of strokes[42] and IS being the most common, accountable for approximately 85% of all strokes.[43]

As shown in Figure 3, an ischemic stroke is caused by disruption of blood supply by an acute occlusion of a brain artery.

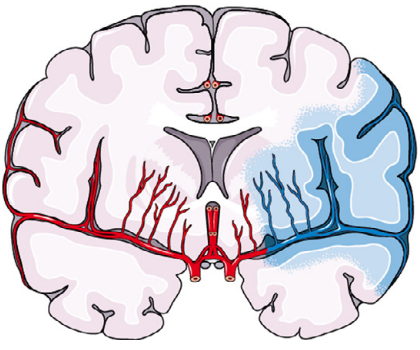

Figure 3. Ischemic stroke, blockage of blood vessels and lack of blood flow to affected area (blue). Image from Servier Medical Art, licensed under a Creative Commons Attribution 3.0 Unported License.

Stroke Epidemiology

Stroke remains a major health problem, yet the epidemiology of stroke is rapidly changing. Although stroke mortality has decreased over the past decades, the absolute number of people who have had a stroke has increased, and more people are living with the consequences of stroke.[39] The Global Burden of Stroke (GBD) has attributed this increase of stroke cases to population growth and an ageing population, and projects that it will continue.[44] Nevertheless, stroke incidence rates have declined in high-income countries while the incidence rates have increased in low- and middle-income countries.[45] Decline in high-income countries, despite an ageing population, have been suggested to be due to improved treatment of stroke risk factors, such as hypertension, diabetes, and atrial fibrillation, as well as a decrease in smoking habits among the population.[46] National stroke guidelines[47] for stroke care in Sweden have also been implemented, addressing the diagnostics, treatment and rehabilitation of stroke which possibly has contributed to the awareness of stroke and its risk factors.

In Sweden, there are approximately 25 000 first-ever stroke cases each year.[48] During the 21st century, the stroke incidence rate (number of people having a stroke per 100 000 inhabitants/year), and mortality of stroke have steadily decreased.[48] The age-adjusted incidence rate (adjusted to the European Standard Population from 2013) of stroke in Sweden has been estimated to be 167 cases per 100 000 person-years in 2015-2016, the incidence rate of IS being 107 per 100 000 person-years.[49]

Stroke occurs at all ages, but is more common among the elderly, with approximately three-quarters of all strokes occurring in persons aged 65 years or older.[50] A majority, 74%, of the individuals who had a first-ever stroke in Sweden in 2020 were 70 years or older, and both incidence and mortality increase significantly with age.[48] Stroke incidence and mortality are higher for men, than for women. However, due to that women have longer life expectancy and have higher stroke incidence at older ages, women have been shown to have more stroke events than men.[51]

Acute Stroke Treatment

When a patient presents with neurological deficits in the acute phase of ischemic stroke, the primary goal is to determine treatment options aiming to restore blood supply to the brain.[52] Two main treatment options for reperfusion are thrombolysis and thrombectomy that have been introduced and refined during the last decades.[53] The advances in acute stroke treatment and prevention may have affected stroke epidemiology as well as stroke outcome, including possible changes of aphasia after ischemic stroke.

Burden of Stroke

Aside from stroke remaining one of the leading causes of death, stroke is also the most common cause of acquired disability among adults, leading to one or more impairments that affect everyday life activities for individuals.[54] The proportion of stroke patients with neurological deficits is considerable, with 50-85% experiencing motor deficits, approximately 50% having cognitive deficits, and 30% having deficits within communication.[68] In addition, many stroke patients also have symptoms of anxiety and depression.[69]

In the Helsingborg Declaration of 2006, the goal for 2015 focused on all stroke patients having access to specialized stroke rehabilitation.[55] Stroke causes a high overall economic burden and rehabilitation is the main contributor to post-stroke care costs with considerable expenses for society.[56,57] The one-year societal costs for inpatient rehabilitation for one stroke patient, have been estimated at $70,601 and many stroke patients do not receive adequate rehabilitation, despite the effect of rehabilitation being undisputed.[58]

The range of support someone may need after a stroke is visualized in Figure 4, where aphasia and speech and language therapy is one of several aspects being addressed within the care of stroke patients.

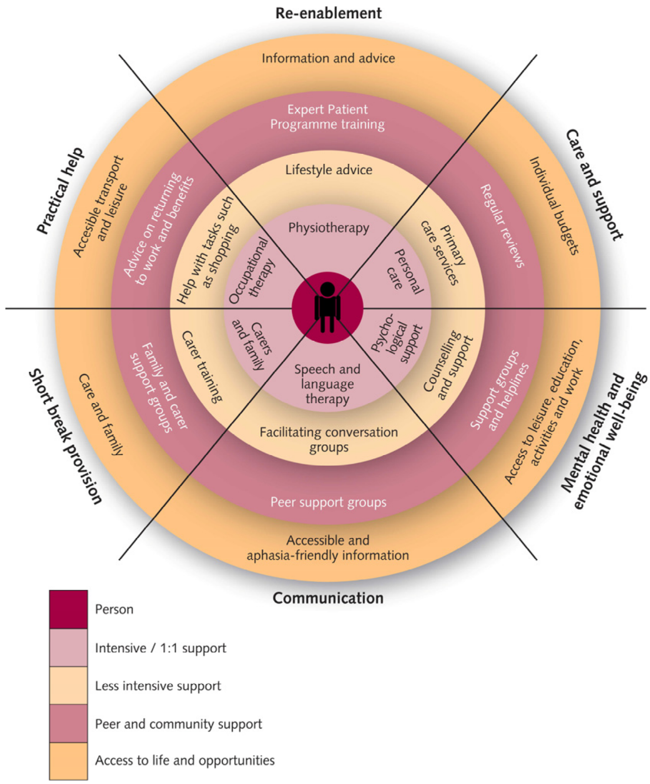

Figure 4. Range of support an individual may need after a stroke.[59] The image provides an overview of 6 domains with different levels of interventions and rehabilitation a stroke patient may be in need of. The different domains may include aspects on mobility, communication, everyday life activities, nutrition, visual deficits and illustrates different levels of support available in each domain. Image reprint with permission from Open Government Licence v3.0. Crown copyright 2007.

Stroke Risk Factors

Stroke risk factors increase an individual´s susceptibility in developing a stroke and contribute to many stroke events. Presented in Table 4 are the major risk factors[60,61] divided into non-modifiable or modifiable,[62] where the latter may be targeted for intervention and reduce the risk of stroke. A world-wide population-based study has identified 10 modifiable risk factors that account for 90% of the risk for stroke, suggesting that stroke largely may be a preventable disease.[61] There are also relations between risk factors, with for example a sedentary lifestyle affecting blood pressure and body mass index (BMI), and BMI affecting the risk of diabetes mellitus.

Table 4. Risk factors for stroke

Non-modifiable risk factors	Modifiable risk factors
Age	Hypertension
Sex	Diabetes mellitus
Previous stroke/TIA	Atrial fibrillation
Genetics*	Hypercholesterolemia
Ethnicity*	Smoking
	Heart disease
	BMI*
	Alcohol consumtion*

*Risk factors not addressed within the scope of this thesis.

Hypertension is the most significant risk factor for stroke among the modifiable stroke risk factors and a high proportion of strokes can be prevented with treatment reducing blood pressure.[39,63] The risk of ischemic stroke is twofold for persons with diabetes mellitus, and persons with atrial fibrillation have high risk of a cardioembolic ischemic stroke.[61]

Among lifestyle risk factors, smoking and BMI may increase the risk of developing stroke. Smoking, often due to the development of atherosclerosis,[64] and BMI have been shown to be related to high blood pressure and diabetes mellitus.[61]

Out of the non-modifiable risk factors, age is of most importance for stroke, doubling the risk every 10 years after the age of 55 years.[50] The male gender is also a risk factor for stroke.[51]

Pathogenetic Mechanisms of Stroke

The Trial of ORG 10172 in Acute Stroke Treatment (TOAST) classification is one of the most common methods for classifying pathogenetic mechanisms of ischemic stroke.[65] TOAST classifies ischemic stroke into 5 different categories:

1. Cardioembolic (CE)
2. Large artery atherosclerosis (LAA)
3. Small artery occlusion (SAO)
4. Other determined etiology (OT)
5. Undetermined etiology (UND)

Table 5. Overview of TOAST classification system

Features	TOAST subtype			
	LAA	CE	SAO	Other causes
Clinical				
Cortical or cerebellar dysfunction	+	+	+	+/-
Lacunar syndrome	-	-	+	+/-
Brain imaging				
Infarct >1.5 cm cortical, cerebellar, brain stem, subcortical	+	+	-	+/-
Infarct <1.5 cm subcortical or brainstem	-	-	+/-	+/-
Diagnostic workup				
Stenosis	+	-	-	-
Cardiac source	-	+	-	-
Other abnormalities	-	-	-	+

LAA: large artery atherosclerosis; CE: cardioembolic stroke; SAO: small artery occlusion; Other causes: other determined etiology or undetermined etiology. Adapted from Adams et al.[65]

Cardioembolic Stroke

Cardioembolic stroke (CE) indicates an ischemic stroke with a cardiac source, where a blood clot is formed in the heart and ascends to occlude a cerebral artery. CE often causes more severe strokes than other stroke subtypes and has the highest fatality.[66] CE is common in European countries, responsible for approximately 25-30% of all IS.[67,68] CE may cause lesions in several cerebrovascular regions and often has sudden and maximal neurological deficits at onset.[66]

Large Artery Atherosclerosis Stroke

Large artery atherosclerosis stroke (LAA) is a common IS subtype in Western countries and accounts for approximately 10-15% of ischemic strokes.[68,69] Plaques due to atherosclerosis causes occlusion or stenosis (>50%) of a major cerebral artery or branch cerebral cortical artery.[65] LAA typically causes cortico-subcortical infarcts and clinical symptoms include those of cortical impairment (e.g. aphasia), brainstem, or cerebellar dysfunction.

Small Artery Occlusion Stroke

Small artery occlusion stroke (SAO) constitutes approximately 25% of ischemic strokes in Western countries.[68] This subtype results in small subcortical infarcts often referred to as lacunar strokes and is defined by the clinical syndrome and size of the infarct.[70] Clinical symptoms are e.g. motor, sensory, ataxia, and dysarthria.[71]

Stroke of Other Determined Etiology

Other specific causes of ischemic stroke include patients with rare causes of stroke,[65] such as e.g. dissection, stroke in the setting of migraine, sickle cell anemia and hematologic disorders.[72] This subtype accounts for about 3% of IS.[68]

Stroke of Undetermined Etiology

Stroke of undetermined etiology is a heterogeneous group in the TOAST classification system and constitutes nearly 35% of IS, where no single pathogenetic mechanism of ischemic stroke can be identified.[72] This can be due to patients having inadequate stroke evaluation, when two or more causes of stroke mechanism have been identified, or when thorough evaluation has been performed but does not yield a pathogenetic mechanism. The latter is often referred to as cryptogenic stroke.[73]

Classification of Stroke Symptoms

The Oxfordshire Community Stroke Project

The Oxfordshire Community Stroke Project (OCSP)[74] is a classification system using clinical stroke symptoms and the anatomical localization of the stroke to characterize clinical stroke syndromes into different subtypes. The OCSP is used to predict the extent of the stroke and the area of the brain affected. The four subtypes are:

1. Total anterior circulation infarct (TACI)
2. Partial anterior circulation infarct (PACI)
3. Posterior circulation infarct (POCI)
4. Lacunar infarct (LACI)

In summary, stroke is a heterogenous disease with different causes and risk factors contributing to the development of stroke and different symptoms. Even though stroke incidence has declined, since stroke is a major cause of disability among the adult population, the overall burden of stroke, remains profound. Aphasia is one of several stroke symptoms that needs further epidemiological study with focus on its effects on the individual.

Aphasia after Ischemic Stroke

Aphasia Epidemiology after Ischemic Stroke

The consequences of brain damage from ischemic stroke vary greatly with many symptoms affecting directly or indirectly the disruption of communication. There is great diversity in the presentation of communication and language symptoms after stroke.[24,75] Epidemiological studies of aphasia vary widely with different diagnostic criteria for aphasia.[76] Historically, the proportion of ischemic stroke patients with aphasia has been reported to be approximately 30%.[17] However, estimations have varied between 19% and 62% of ischemic stroke patients having aphasia,[77-80] with few studies of aphasia epidemiology in Sweden.[17,81]

The presence of aphasia after stroke has in more recent studies been shown to increase with age,[79,80] and stroke patients with aphasia are older than stroke patients without aphasia.[76] Aphasia is represented almost equally between genders,[82,83] however studies have shown trends toward a higher risk of females having aphasia in comparison to males.[79] This may be due to the longer life expectancy of women, which has shown to result in disproportionately more women living with communication and functional impairments after stroke.[84,85]

PWA often present with more severe strokes[76] and consequently, more severe disabilities. PWA therefore also have higher mortality, longer hospital-stays, and are often in need of long-term care.[17,76]

Aphasia as a major stroke symptom persists,[86] with a reported prevalence of 24% of stroke patients having aphasia at 3 months,[21] and prevalence rates remaining high for years after stroke onset.[17] However, previous data on recovery of aphasia after stroke vary[82,87] depending on i.e. the timing of assessment, type of assessment and patient enrollment criteria. This emphasizes the need for comprehensive studies with long-term follow up of aphasia after stroke.

Stroke Localization and Aphasia

Language functions are mainly situated in the left hemisphere of the brain, and damage to regions of the brain devoted to language processing results in a loss of the ability to interpret or express thoughts in the form of language. Damage to regions of the perisylvian area, parts of the insula and/or subcortical regions are central for language and can cause aphasia.[1] Strokes affecting the left middle cerebral artery often causes aphasia, and more extensive damage is usually associated with severe aphasia.[1]

Although the left hemisphere of the brain has long been linked with language, and regions that can be considered especially important in the network for speech and language functions, not surprisingly causing aphasia, this does not suggest that other regions are not also crucial for communication and language impairment.[10] The classical brain areas for language, compared to a more up-to-date image of anatomical regions and networks important for language are visualized in Figure 1 and Figure 2 presented above. The right cerebral hemisphere also contributes to cognitive functions that underlie language processing and communication, and right hemispheric lesions can therefore result in communications disorders with substantial impact.[75]

Depending on the size and location of the damaged brain area the capability to express or to comprehend spoken or written language[88] is affected to different extents.

Diagnosis of Aphasia after Ischemic Stroke

The primary purpose of aphasia assessment is to determine the presence or absence of a language disorder, and if present, its characteristics, and to provide a differential diagnosis, as well as a preliminary prognosis.[30]

Screening can be defined as an initial method used to quickly identify PWA and ensure prompt referral to a speech and language therapist (SLT); SLT bed-side assessments evaluate a range of language skills and confirms a definite diagnosis of language impairment and aids in appropriate follow-up procedures; SLT comprehensive standardized language assessments, are designed to evaluate all aspects of language function, where clinicians can acquire an in-depth understanding of a person´s aphasia, identifying aphasia symptoms, plan treatment and measure recovery. Hence, evaluation of language entails identifying clinical manifestations, specific language symptoms, and the type and severity of a person´s aphasia. Aphasia diagnosis has evolved beyond the approach of classifying patients into syndromes and instead focuses on individualized patient symptoms. The SLT will also establish the level of a patients´ functional communication abilities with regards to patient strengths and weaknesses. Aphasia assessment can assist in identifying patients who are likely to benefit from language rehabilitation, as well as guide treatment planning and communication partner training for patients and their next of kin.[5]

Recovery of Stroke and Aphasia

Recovery of language is a complex process and many factors have been proposed to influence the recovery of aphasia, such as age at onset, initial severity of aphasia, amount and timing of therapy, lesion size and site. Most individuals with aphasia experience some degree of recovery of language function after a stroke.[89] Recovery after stroke is time-dependent, with the greatest recovery taking place early after stroke onset and decreasing over time.[90] In the acute early period (first ~ 48 hrs), reperfusion of the ischemic penumbra can lead to rapid improvement and resolution of aphasia symptoms.[5,89] Additional recovery may take place through various mechanisms of neuroplasticity, where modifications in the organizations of neurons occur with increased activity in different brain regions and/or recruitment of the contralateral hemisphere.[91] Recovery of aphasia has been shown to include both undamaged portions of the language network in the left hemisphere and/or homologous right hemisphere areas.

Language function has been reported to substantially improve during the first weeks after ischemic stroke,[92] expressive language function showing most recovery.[90] Yet, stroke patients with first-ever stroke and aphasia show a great variability in language recovery.[93] Studies have shown that neuroplasticity is enhanced the first 3-6 months post stroke and suggests that recovery first and foremost occurs during the first few months after stroke and thereafter reaches a plateau.[94] Figure 5 shows the schematic trajectory of language recovery after stroke.

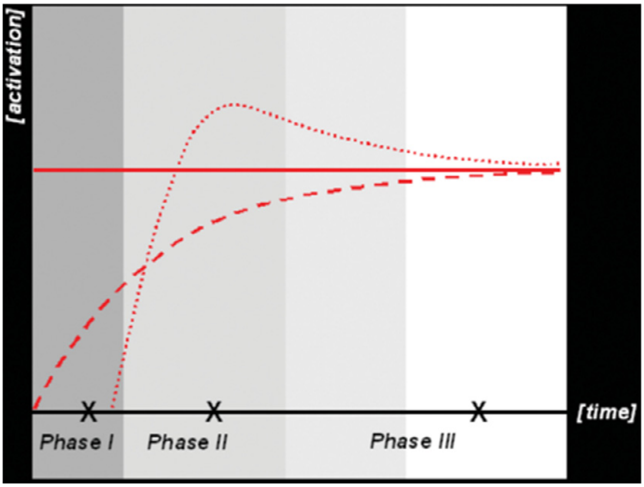

Figure 5. Model with three phases of language recovery. Phase I: acute phase characterized by loss of function; Phase II: subacute phase upregulation of the language network; Phase III: consolidation and normalization of activation. Language recovery relate to fMRI activation patterns with crosses (X) indicating time of fMRI performed in the study. Controls (—), left language areas (- - -) and right language areas of patients with aphasia (……).. Image reprinted with permission from Brain, Saur, D. et al. Dynamics of language reorganization after stroke.[95] Copyright (2006) with permission from Oxford University Press.

However, studies have contradicted this critical time window for recovery[96] with patients demonstrating language improvement with therapy many years post stroke onset[97] and studies have observed reorganization of language networks even in the chronic phase.[98] Nevertheless, most changes of aphasia symptoms occur up to 2-3 months post onset[5,81,82] and by 6 months aphasia is considered to be chronic.[99,100]

The proportional recovery rule of stroke is a model that has assumed that patients with mild deficits are more likely to make a good recovery, reporting that patients recover on average 70% of their lost function.[91] This view has however, been challenged, based on the non-negligible number of patients who do not follow this recovery rule ("non-fitters"). Patients with initial severe deficits, may demonstrate a range of recovery, from almost no recovery to very strong recovery.[5]

There is a lack of studies of aphasia recovery with consecutive enrolment and studies on aphasia prognosis from the acute phase to a longer follow-up perspective, have previously been poorly documented.[17] Several factors need to be considered when determining the outcome and recovery of aphasia after stroke. While outcome refers to a specific degree of function at the specific time of assessment, recovery incorporates improvement or deterioration of a condition using repeated measures and therefore better explains and provides knowledge of changes over time.[101] Patient-related variables (age, gender, education and cognition) have been suggested not to influence aphasia prognosis, while stroke-related variables such as initial stroke and aphasia severity and lesion location, have been associated with recovery.[87,102,103] However, factors affecting aphasia recovery is still controversial with studies also contradicting the abovementioned results.[81,104]

It has been argued that aphasia treatment focused on a particular language domain would result in recruitment of different aspects of the language network and different linguistic components (semantics, phonology and syntax) have been shown to recover at different points in time and to different extents.[105] Who, what and when to treat patients with aphasia to optimise recovery is still unclear.[106]

Studies concerning prevalence and prognosis of aphasia report considerable ranges of recovery, from 18% of people with initial aphasia having resolved aphasia by 3 months,[21] to other studies showing resolved aphasia in up to 74% of PWA by 6 months.[87] Future work, like that of this thesis, clearly documenting aphasia in relation to outcome and factors influencing recovery, are therefore warranted.

In conclusion, aphasia is a disorder of language with a variety of symptoms and a complex profile. It is one of several debilitating consequences of ischemic stroke, and poses a major disability for the patient and negatively impacts rehabilitation[18] and overall stroke outcome.[16] Moreover, aphasia is a condition that has one of the greatest negative impacts on a person´s health-related quality of life.[107] Language function has been shown to improve, however, the degree of recovery varies, and prognosticating aphasia recovery is difficult, even for skilled clinicians. Although treatment of stroke has improved, patients are left with disability impacting their functional communication and quality of life.[21,31]

Ensuring accurate diagnosis of aphasia after ischemic stroke have important implications in stroke healthcare. This thesis provides knowledge about aphasia after ischemic stroke and can serve as a basis for administration of timely and efficient care for stroke patients with aphasia as well as facilitate monitoring of recovery.

Measuring Outcome and Health-Related Quality of Life

Aphasia affects several aspects of language and communication and subsequently also health-related quality of life. Morbidity rates after stroke are high,[54] with approximately a third of all stroke survivors living with the aftereffects of stroke, being disabled and/or having poor cognitive ability and mental health.[54] Life after stroke has only recently been regarded as a separate entity within stroke research and the WHO has emphasized the importance of providing long-term support for stroke patients, as well as to prioritize how to identify and improve life after stroke.[54,108,109] Knowledge of persisting stroke symptoms is important to assess as a basis for rehabilitation and outcome, ensuring that medical care is meeting its targets for each patient.[110]

Definitions and Terminology

Defining health, quality of life and health-related quality of life has proven challenging. A widely used definition of health was provided by the WHO,[111] who defined health as:

> "A state of complete physical, mental and social well-being, and not merely the absence of disease and infirmity."

Definitions of quality of life and health-related quality of life have similarly been subject for discussion.[112] Quality of life is a broad concept describing an individual´s perception of well-being, comprising several different domains, including, but not limited to: physical, psychological, social relationships, and the environment. WHO´s commonly used definition of quality of life[108] is:

> "An individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns."

Health-Related Quality of Life (HRQoL) is defined as the effect a specific health status has on a person's self-perceived quality of life,[112] as described above.

The International Classification of Functioning, Disability and Health

The International Classification of Functioning, Disability and Health (ICF)[2] provides a framework for classification of health conditions among three domains: body functions and structure, activity, and participation,[2] as shown in Figure 6.

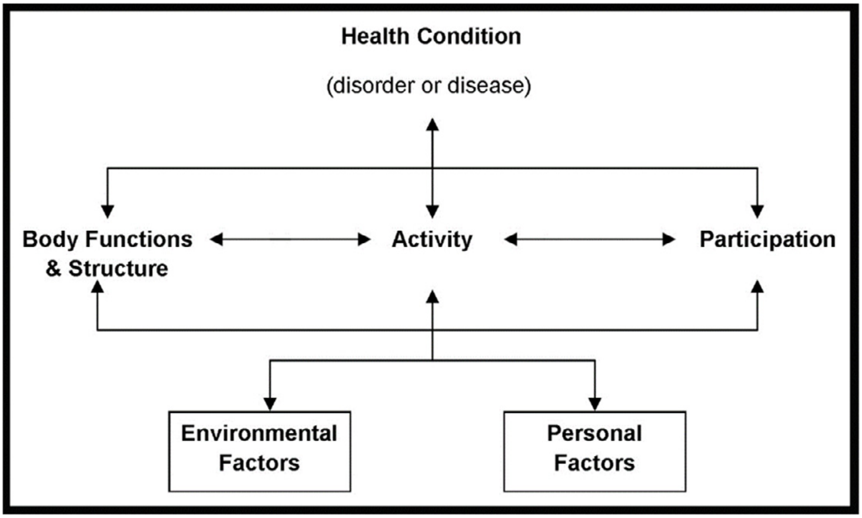

Figure 6. The International classification of functioning, Disability and Health (ICF) Framework. Image reprinted with permission from the World Health Organization.[2]

Incorporating the ICF framework into the assessment and treatment of aphasia and communication disorders has recently been given more emphasis.[24] Assessments that previously only focused on the disability of an individual, now focus on the effect aphasia may have on a person's participation in daily activities and quality of life. More attention has been applied to the conversation and interaction between PWA and their next of kin, including both the person with aphasia and their communication partner in the rehabilitation process.[24] The ICF framework therefore allows for classification of aphasia intervention that includes both impairment-based (improving language functions) and functionally oriented aspects (communication),[29,113] emphasizing that rehabilitation should be person-centered.[29]

Aphasia: Framework for Outcome Measurement

Living with Aphasia - Framework for Outcome Measurement (A-FROM) is an aphasia-friendly framework developed on the basis of the ICF-framework, though with specific adaptations relevant for PWA.[114] A-FROM also includes concepts of well-being and quality of life, aspects that are not captured within the ICF-framework.

As shown in Figure 7, A-FROM focuses on outcomes relevant to living with aphasia by incorporating the impact language and communication disability has on aphasia. It illustrates the domains of ICF, incorporating language impairment, with participation, the environment and personal factors,[115] while also relating to the quality of life for PWA.[114]

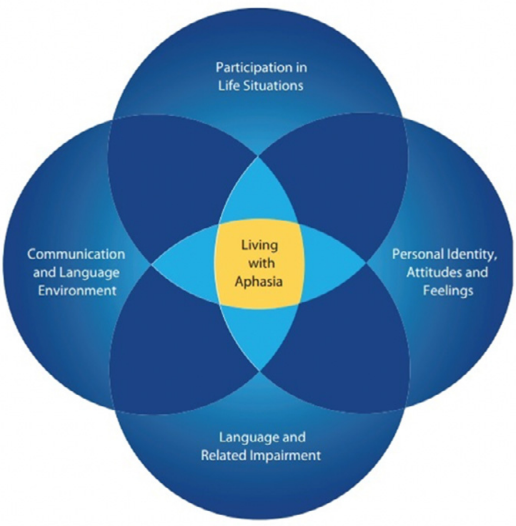

Figure 7. The Aphasia Framework for Outcome Measure (A-FROM). The image illustrates a conceptual base for capturing domains of intervention and outcomes relevant to people living with aphasia. Language impairment is equivalent to language symptoms; environment incorporates factors that facilitate or are barriers to communication; participation is relationships and activities in daily life; personal factors are inherent characteristics and attitudes of the person. Image reprinted with permission from Taylor and Francis Ltd. Kagan, A. et al. Counting what counts: a framework for capturing real-life outcomes of aphasia intervention.[114]

Measures of Neurological Impairment

The National Institutes of Health Stroke Scale

The National Institutes of Health Stroke Scale (NIHSS) is a standardized and globally used screening tool to measure stroke severity. It has become the standard for routine assessment of neurological deficits in the acute phase of stroke.[116] The scale is used both clinically and in research[116] and entails global stroke symptoms, such as level of consciousness, orientation, visual deficits, motor and sensory deficits, language, speech, ataxia and neglect.[117] Neurological symptoms are scored between 0-42 points, where zero indicates no impairment and higher scores indicate more severe stroke symptoms. It has been recommended for use in epidemiological stroke studies,[39] as well as for use as an outcome measure in studies concerning stroke treatment.[118]

NIHSS has excellent reliability and validity[118-120] when assessed by a person with NIHSS-certification and correlates well with infarct size and functional outcome after stroke.[121-123] NIHSS was not originally designed to capture specific neurological deficits, but instead to standardize global testing of patients in clinical trials.[116] However, it has gradually been implemented as a screening tool not only in the acute phase to measure stroke severity, but also to measure and follow recovery of stroke symptoms, [101] although it has its limitations for this use (see "Discussion" section below)

NIHSS item 9 "Best Language" evaluates aphasia in stroke and has been used in studies to detect post-stroke aphasia.[82,124,125] It is derived from the Boston Diagnostic of Aphasia Examination,[126] and language symptoms evaluated with NIHSS item 9 include: speech fluency (picture description) illustrated in Figure 8; naming (naming objects); and reading aloud (reading sentences). The aphasia item is stratified into 4 categories listed below.

NIHSS[116,127] definitions for item 9:

0 = No aphasia; normal language.

1 = Mild-to-moderate aphasia; some obvious loss of fluency or facility of comprehension, without significant limitation on ideas expressed or form of expression. Reduction of speech and/or comprehension, however, makes conversation about provided materials difficult or impossible.

2 = Severe aphasia; all communication is through fragmentary expression; great need for inference, questioning, and guessing by the listener. Range of information that can be exchanged is limited; listener carries burden of communication.

3 = Mute, global aphasia; no usable speech or auditory comprehension.

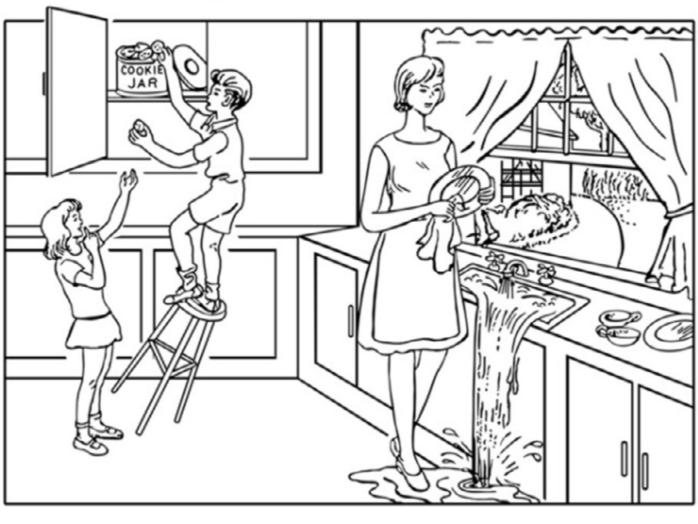

Figure 8. The "cookie theft picture" in NIHSS is used to evaluate language function and aphasia after stroke. Image reprint with permission from Mapi Research Trust. NIHSS: National Institutes of Health Stroke Scale.

Measures of Language Functions

The Language Screening Test

The Language Screening Test (LAST)[128] is a screening tool developed to evaluate language function for patients with acute stroke. Among several other possible aphasia screening tools for language evaluation,[129,130] LAST,[128] has high diagnostic accuracy, comprehensive validation and is recommended for use in acute stroke care.[130-133] LAST is specifically constructed to avoid subtests of language potentially affected by other stroke symptoms, e.g. hemiplegia and dysfunction of executive function. LAST includes 5 subtests with a total of 15 items within language. Expressive speech is tested by 3 subtests: naming, repetition, and automatic speech. Comprehension of spoken language is tested by 2 subtests: word comprehension and verbal instructions.[128] Each item is scored either correct (1 point) or incorrect (0 points) with a maximum score of 15 points (range 0-15, where 0-14 indicate aphasia and 15 no aphasia). The test duration is approximately 2 minutes.

The Comprehensive Aphasia Test

The Comprehensive Aphasia Test[134] (CAT) is a standardized test to measure language performance, screen for cognitive deficits associated with aphasia, and investigate the impact these impairments have on PWA. The language domain covers essential language modalities and levels of linguistic analysis.[135] It is based on current neuropsychological theory of language, identifying the impaired underlying language process by examining specific psycholinguistic functions.[136] Parameters such as frequency, familiarity, imageability (to which extent a word will evoke a mental image), and morphological complexity are varied and controlled for within the specific language subtests. CAT was originally developed in English, but has been cross-linguistically and culturally adapted to a wide range of languages,[135] implementing it as one of the first aphasia assessment tools for comparative international research within the field of aphasia.[135,137]

CAT is designed to: 1) screen for cognitive deficits (Part I of CAT); 2) assess language impairment (Part II: language comprehension; Part III: expressive language); and 3) monitor changes in aphasia over time.[134,136] CAT aphasia assessment also includes a patient-reported outcome measure (Aphasia Impact Questionnaire, described under "Measures of Health-Related Quality of Life") to: 1) examine the consequences aphasia has on an individual's everyday life and emotional well-being and 2) monitor the consequences of aphasia over time. The test provides a summary of linguistic abilities and impairments needed for planning language rehabilitation, monitor language recovery as well as measure outcome at each impairment level.

The cognitive screening in CAT provides the clinician with an initial evaluation of cognitive functions that may impact the ability of PWA to improve and benefit from language therapy.[138]

The language parts of CAT assess language performance within all language domains and covers auditory comprehension, written comprehension, oral reading, verbal expression, written expression, and repetition.

The overarching goals of CAT are:

1. Diagnosis of impairment and severity of the language disorder including measuring changes over time
2. Aid in impairment-based treatment planning as well as targeting intervention that is relevant and meaningful to PWA, involving PWA in the rehabilitation process
3. Investigate the disability and impact of aphasia on the individual

Measures of Health-Related Quality of Life

The Aphasia Impact Questionnaire

The Aphasia Impact Questionnaire (AIQ) was designed to capture the effect aphasia has on a person´s subjective and self-perceived communication, participation, and emotional well-being.[139,140] The perception and self-perceived experiences of aphasia have been emphasized and need to be recognized in the planning of rehabilitation.[141] AIQ was developed in collaboration with PWA,[139] incorporating the social model of disability[142] to measure and address how PWA experience life with aphasia.

AIQ has an aphasia-friendly design to make it more accessible for PWA by using established methods including: key words in bold, large font, few items per page and supporting pictures,[143,144] as seen in Figure 9.

Figure 9. Example of a supporting picture in Aphasia Impact Questionnaire that illustrates and aids PWA in comprehending questions on how reading abilities may affect health-related quality of life. Image reprint with permission from © 2018 Kate Swinburn.

The administration of AIQ has also been adapted for PWA, with instructions for the health care professional to provide as much assistance, support and feedback as required, to make the questionnaire as accessible as possible to the person with aphasia.[140] Supported conversation techniques[145,146] and the use of rewording, repeating and prompting are therefore encouraged.[140]

AIQ consists of 21 items and scores range from 0 to 4 on every item: lower scores indicate better perceived HRQoL.[138] AIQ, similarly as A-FROM, focuses on the impact aphasia has on the individual and comprises of three sections:

1. Communication
2. Participation
3. Emotional well-being

In the first section of AIQ, "Communication," the person with aphasia reports their views on daily communication situations. The section aims to assess the self-perceived practical limitations aphasia causes on communication for a person with aphasia. The effects of deficits within expression, comprehension, reading and writing are all investigated.[140]

The second section, "Participation", investigates the restrictions aphasia has on a person´s everyday life. The questions relate both to social participation and activities of daily living, aspects that have been specifically shown to be negatively affected by aphasia.[7,141]

The final section of AIQ "Emotional well-being," assesses the emotional impact aphasia can have on an individual. The emotional aspects presented in AIQ are a subset of emotions previously reported to be commonly experienced by PWA and have been identified through qualitative interviews with PWA.[139,147,148] This section aims to obtain the self-perceived perspective aphasia has on emotional well-being.

In summary, aphasia is a multimodal language disorder, and affects all aspects of the ICF-framework, which emphasizes the need for a holistic approach when treating people with aphasia. Focus should, therefore, not only aim at rehabilitating language functions and working with strategies of communication, but also be targeting participation and the well-being of the patient.

This thesis assumes the ICF-approach, including the abovementioned aspects, from detection of aphasia at the impairment level of the language disorder to the self-reported effects aphasia has on the individual patient.

This thesis provides knowledge on how sensitive and accurate diagnostic methods for aphasia are, as well as current prevalence and recovery of aphasia after ischemic stroke. This knowledge is essential to characterize and provide appropriate healthcare for PWA. Incorporating the patient-centered perspective, may also provide insights in the overall burden of aphasia and be of importance for future research aspects of rehabilitation and management of aphasia after ischemic stroke.

Knowledge Gaps

- An initial evaluation and diagnosis of aphasia is usually performed in the acute stage of stroke with NIHSS. It is important to ascertain the validity of this measure for diagnosing aphasia. This knowledge is a prerequisite in the subsequent provision of health care and for referrals for language evaluation.
- The described epidemiology of aphasia in stroke has varied in studies. New acute stroke treatment, stroke prevention methods, and an aging population may contribute to differences in aphasia incidence and prevalence. Up-to-date, accurate knowledge of aphasia epidemiology and risk factors affecting aphasia after first-ever ischemic stroke, is needed to assess rehabilitation needs for PWA as well as to inform policymakers.
- Knowledge of the short-term prognosis of aphasia and factors influencing aphasia outcome can serve as basis to accurately assess rehabilitation needs and support the planning of adequate resources in stroke rehabilitation services.
- Longitudinal, long-term studies of aphasia outcome and recovery after ischemic stroke are scarce, and few entail all ICF's aspects of aphasia. Aphasia prognosis at the level of language impairment, as well as patient-reported data are needed to identify and consider the patients' own views on their disability. This may serve as a basis for further research focus and to ascertain treatment for PWA, including both language therapy as well as the effect aphasia has on HRQoL.

Aims

The overall aim of this thesis was to evaluate and describe the current epidemiology and outcome of aphasia after ischemic stroke, including the impact aphasia has on health-related quality of life for people with aphasia and factors associated with favorable aphasia outcome.

The included studies highlight all aspects of ICF – from the health condition (aphasia) and its function and impairment, to activity and participation (the impact aphasia has on a patient), as well as related personal and environmental factors. The studies provide insights and knowledge of value for diagnostics and future treatment and care of people with aphasia.

The specific aims were to:
Validate methods to diagnose aphasia in the acute phase of ischemic stroke and detect factors and symptoms related to an incorrect aphasia diagnosis (paper I)

- Report the current incidence and severity of aphasia after first-ever ischemic stroke and investigate potential temporal changes of aphasia incidence (paper II)
- Identify pathogenetic mechanisms and risk factors associated with aphasia (paper II)
- Assess the short-term prognosis of aphasia after ischemic stroke (paper III)
- Study the relation between factors influencing favorable and poor aphasia short-term outcome (paper III)
- Assess the long-term outcome and prognosis of aphasia (paper IV)
- Investigate the health-related quality of life for PWA (paper IV)
- Examine factors associated with aphasia and health-related quality of life (paper IV)

Methods

All papers in this thesis (I-IV) are based on the hospital-based Lund Stroke Register (LSR) cohort of patients with first-ever ischemic stroke between 1 March 2017 to 31 May 2018. An overview of the methods used are shown in Table 6.

Table 6. Overview of the four studies included in the thesis

	Paper I	Paper II	Paper III	Paper IV
Study periods	15 months: 1 Mar 2017 - 31 May 2018	12 months: 1 Mar 2017 – 28 Feb 2018 and 1 Mar 2005 – 28 Feb 2006	15 months: 1 Mar 2017 - 31 May 2018	15 months: 1 Mar 2017 - 31 May 2018
Patients	221	369 and 308	391	221
Study area	Eight municipalities adjacent to Skåne University Hospital, Lund			
Study cohort	Prospective and consecutive case ascertainment through LSR			
	LSR-Speech Study	LSR	LSR	LSR-Speech Study
Method of language assessment	NIHSS item 9 and LAST	NIHSS item 9	NIHSS item 9	LAST, CAT, AIQ
Time of assessment	Day 3 and day 4	Day 0	Day 0 and day 3- ≤15	Day 4 and 1-, 3-,12-months
Study design	Prospective observational cohort study			
Study focus	Validate NIHSS for diagnosing aphasia	Aphasia incidence after IS and factors related to aphasia	Short-term outcome of aphasia and factors associated with favorable outcome	Long-term prognosis and health-related quality of life for people with aphasia
Outcome measures	Comparison of language assessment methods	Incidence of aphasia and risk factors in the two time periods.	Aphasia outcome	Follow-up assessment of language impairment and health-related quality of life.

LSR: Lund Stroke Register, NIHSS: National Institutes of Health Stroke Scale, LAST: Language Screening Test, CAT: Comprehensive Aphasia Test, AIQ: Aphasia Impact Questionniare.

Lund Stroke Register (LSR) (papers II and III)

The LSR is an ongoing prospective and longitudinal observational study that started March 1, 2001. The study area comprises of eight municipalities (Burlöv, Eslöv, Hörby, Höör, Kävlinge, Lomma, Lund, Staffanstorp) that represent the local catchment area of Skåne University Hospital, SUHL, Lund. SUHL is the only hospital designated for acute care of stroke patients for this area and patients are routinely treated in the acute phase of stroke at SUHL.[149] The study area had a population of 284 003 inhabitants (all ages) as of December 31, 2017[150] with 8% ≥75 years and 50% females.[150]

For possible inclusion to LSR, research nurses screen patient lists on weekdays from the SUHL Emergency Department as well as inpatient and outpatients lists at the Department of Neurology at SUHL. All patients with first-ever stroke (except iatrogenic stroke), according to the WHO definition,[38] receive information about participation in the LSR study. Patients are reviewed case-by-case to confirm a stroke diagnosis. The following measures are taken by the research nurses to validate a first-ever stroke prior to inclusion: 1) review patients' medical charts; 2) ask patients for previous medical history; 3) search the LSR-database for prior inclusion.

Informed consent is required for inclusion in LSR, and patients´ next of kin are consulted for patients when needed.

In paper II, incidence rates of aphasia after ischemic stroke were compared to a LSR cohort from the same study area during the years of 2005-2006. Population data were obtained from Statistics Sweden.[150] Incidence rates were age and gender standardized to the Swedish population as of December 31, 2017,[150] and to the European Standard Population from 2013.[151]

Study Population

Inclusion Criteria (all papers)

- Adult age at stroke onset
- First-ever ischemic stroke (WHO definition)[38]
- Resident within the catchment area of LSR at stroke onset
- Consent to participate

Lund Stroke Register Speech Study (papers I and IV)

LSR Speech was a sub-study to LSR and focused on language impairment after stroke. Patients with aphasia were provided with aphasia-friendly information regarding the purpose of the study with modifications to make information more accessible for PWA. Established methods included key words in bold, few items per page, large font, and supporting pictures.[143,144] Next of kin were also consulted before inclusion of PWA who could not provide clear verbal consent. PWA were interviewed and assessed by a Speech and Language Therapist (SLT) specialized in aphasia and experienced in facilitating communication with PWA.

Additional Exclusion Criteria at Inclusion (papers I and IV)

- Non-native Swedish speaker
- Reduced level of consciousness (according to Reaction Level Scale 85)[152]
- Concomitant disease that may affect language function
- Previously diagnosed cognitive impairment and/or severe psychiatric diagnosis

In total, 221 patients were screened for aphasia during the 15-month period of inclusion by a research nurse and SLT. Patients were screened for aphasia using The National Institutes of Health Stroke Scale (NIHSS) item 9 and the Language Screening Test (LAST) (as described in detail below in the section "Outcome Measures"). Follow-up assessments were performed for the cohort of 60 patients with aphasia at baseline (paper I, III, IV, see "Follow-up Procedures" below). Baseline characteristics were collected through interviews with patients and/or their next of kin as well as reviewing medical records (described in detail belowin "Definitions of Clinical Assessments").

Follow-up Procedures

Papers I and III

In paper I and III the follow-up assessments were in-hospital and performed at a median of 4 days and day 3 - ≤15 days post stroke, respectively. Evaluation of aphasia was performed by SLT using LAST (paper I) and by a research nurse using NIHSS item 9 (paper III). Baseline characteristics were collected through medical charts and by asking the patients and/or their next of kin. The baseline characteristics are described in detail below in the section: "Definitions of Clinical Assessments."

Paper II

In paper II, comparisons with the LSR cohort from the years of 2005-2006 was conducted and data concerning baseline characteristics and stroke risk factors were collected (described in detail below in "Definitions of Clinical Assessments").

Paper IV

Data in paper IV were derived from assessments conducted at 1 month, 3 months, and 12 months after stroke onset. All patients with aphasia in the acute phase of stroke according to LAST were included in the study. Aphasia follow-up evaluations were conducted by appointments in the hospital, in short-term care facilities or via home visits.

Patients were 1) given a follow-up assessment appointment before hospital discharge; or 2) contacted by telephone to schedule a follow-up assessment. Patients who were not reachable via telephone received an invitation by letter describing the follow-up evaluation, including an appointment. Patients´ records were checked to determine that the patients were alive before contacting the patients.

At follow-up, patients were evaluated regarding their aphasia with the Comprehensive Aphasia Test (CAT) (described in detail below in "Outcome Measures," "Measures of Language Impairment") which includes a cognitive screening.

Patients with remaining aphasia according to CAT at 3 months (n=30) also completed the Aphasia Impact Questionnaire (AIQ) (described in detail below in "Outcome Measures," "Measures of Health-Related Quality of Life") to assess their health-related quality of life at 3- and 12-months post stroke.

Definitions of Clinical Assessments

Baseline Characteristics

Baseline characteristics are described in all the thesis' papers. In papers II, III and IV baseline characteristics are analyzed as possibly associated factors related to aphasia outcome and selected because of their potential role in the development and risk of stroke.[60,61,153]

Data on demographic factors, risk factors, stroke severity (NIHSS), pre-stroke modified Rankin Scale (mRS; described below) and mortality are routinely gathered within LSR. Data regarding whether care was provided at a dedicated stroke unit or not, length of stay at hospital and discharge location: home or patient care facility, were also collected. The thesis author collected data via medical records or patient interviews if data were missing and a neurology physician was consulted if needed.

NIHSS was assessed by a NIHSS-certified research nurse via in person examinations during the patient's hospital stay. Retrospective review of patients´ medical records were performed by NIHSS-certified health care staff, including the thesis author, if the research nurse had not performed an in-person NIHSS evaluation.[154,155] Patients worst NIHSS score at stroke onset, before acute stroke treatment, was recorded. A physician assessed pathogenetic stroke mechanism using TOAST,[65] and evaluated clinical stroke mechanism with OCSP.[74]

Hypertension was defined as previously diagnosed blood pressure >140/90 mmHg, blood pressure >140/90 mmHg at discharge, or treatment with antihypertensive medication during the last 2 weeks.[156] Diabetes mellitus was defined as having 1) a prior diagnosis of diabetes; 2) newly diagnosed diabetes at time of discharge; 3) non-fasting plasma glucose levels >11 mmol/L.[156] Heart disease was defined as any of the following: ischemic heart disease, myocardial infarction, angina pectoris, heart failure, heart surgery (valve or bypass), atrial fibrillation or atrial flutter, as well as pacemaker. Atrial fibrillation was defined as: atrial fibrillation or paroxysmal atrial fibrillation confirmed by electrocardiogram.

Hypercholesterolemia was defined as: 1) previously diagnosed; 2) total cholesterol blood levels >5 mmol/L or LDL >3 mmol/L; 3) oral pharmacological treatment in the last two weeks before stroke onset.

The modified Rankin Scale (mRS) assesses limitations of activity with scores ranging from 0-6 (5= worst outcome, 6= death).[157] A mRS score of patient activity *pre-stroke* was recorded.

Criteria for Exclusion to LSR Speech Study (paper I and paper IV)

Reduced level of consciousness was defined as Reaction Level Scale (RLS 85)[152] > 2.

Non-native Swedish speaker was defined as not having Swedish as one of their first languages.[158] The definition of native language was: acquisition of the language in childhood by being immersed in the language of the surrounding environment.

Diagnosed cognitive impairment was defined as a diagnosis of cognitive impairment or a prior diagnose of dementia in medical records (ICD-10 diagnosis codes F00-F09).

Severe psychiatric diagnosis was defined as a psychiatric diagnosis (according to ICD-10) requiring current in-hospitalization.

Concomitant disease that can affect language function was defined as brain tumors, epilepsy, trauma or progressive neurological diseases.[1]

Outcome Measures

Several outcome measures were used at follow-up to assess different aspects of language function and its effect for PWA. They are presented below along with a description of what outcome type they measure. Each outcome measure has also previously been described in detail above (see “Introduction:” “Measures of Neurological Impairment,” “Measures of Language Functions,” “Measures of Health-Related Quality of Life”).

Measures of Neurological Impairment

National Institutes of Health Stroke Scale (NIHSS)

The National Institutes of Health Stroke Scale (NIHSS) is a globally widespread measure of stroke severity and neurological deficits that is used both clinically and in research. As previously described NIHSS measures neurological stroke symptoms and is often used at stroke onset and/or contact with healthcare as routine assessment[116] to guide course of stroke treatment[118] as well as prognostication of stroke symptoms.[159,160]

NIHSS item 9, "Best Language" was validated (paper I) and used at stroke onset (paper II, III) and as short-term follow-up evaluation of aphasia (paper III) to detect remaining aphasia and were conducted in-person before hospital discharge.

Measures of Language Impairment

The Language Screening Test (LAST)

LAST (scores 0-15; ≤ 14 = aphasia) was used to detect aphasia after ischemic stroke in the acute phase of stroke (paper I and IV), at median day 4. All LAST evaluations were conducted in-person before patients were discharged from the hospital. LAST was also performed at follow-up assessment at 1 month, 3 months and 12 months post stroke, however these LAST data are not reported in the present thesis.

The Comprehensive Aphasia Test (CAT)

CAT was used as follow-up evaluation of language functions, including cognitive performance. CAT (scores 0-439, not including word fluency; 0 = worst language impairment) was performed at clinical follow-up assessments in paper IV at 1 month, 3 months and 12 months post stroke. It takes approximately 90 minutes to complete.[138] All evaluations were performed in-person either at SUHL out-patient clinic, at short-term care facilities, or via home visits.

CAT results were analyzed using the total score, as well as analyzing each CAT domain: 1) cognition (the cognitive screen); 2) language comprehension; 3) expressive language. CAT subitems of specific language symptoms were also stratified by their language domain according to the test manual of CAT.[134,138] The cut-off score for aphasia was 402 points (including the cognitive screening) and 370 points (only language items), and/or below cut-off scores in one or more language domain(s).[138]

Measures of Health-Related Quality of Life

The Aphasia Impact Questionnaire (AIQ)

PWA underwent a self-reported aphasia-adapted Health-Related Quality of Life (HRQoL) evaluation by completing the Aphasia Impact Questionnaire (AIQ)[139] at 3- and 12-months follow-up (paper IV). Patients who were not able to complete AIQ themselves, received support from a next of kin or a SLT in reading and interpretating the questions in the form. PWA were interviewed in-person by the thesis author, specialized in aphasia and trained in facilitating communication for PWA.

The AIQ (total score 105; 5 point-scale; scores on each item 0-4; 4= worst self-perceived HRQoL) variable was analyzed as continuous.

Statistical Methods

An overview of the statistical methods performed in papers I-IV are presented in Table 7. Statistical calculations in the thesis were performed with the SPSS software package 25. Non-parametric tests were used when data were non-normally distributed. Comparisons between groups were tested with Chi-square, Fisher's exact test (categorical variables), or Mann-Whitney U-test (non-parametric continuous variables and ordinal variables). The alpha level for all calculations in the thesis was $p<0.05$.

Table 7. Overview of the statistical methods used in Papers I - IV

	Paper I	Paper II	Paper III	Paper IV
Chi-square test	X	X	X	X
Mann-Whitney U-Test	X	X	X	X
Pearson´s correlation				X
Logistic regression		X	X	
Linear regression				X
ROC-analysis	X			
Sensitivity, Specificty, PPV, NPV	X			
Paired-sample t-test				X
Wilcoxon signed-rank test			X	

PPV: positive predictive value, NPV: negative predictive value

Paper I

The diagnostic accuracy of NIHSS item 9, using LAST as reference standard was determined by analyzing: 1) Sensitivity and specificity; 2) Positive predictive value and negative predictive value; 3) Likelihood-ratios; and 4) The means of receiver operating characteristic (ROC) analysis, calculating the area under the curve (AUC). There were no missing data on the index test or reference standard. Associations between age and NIHSS at baseline between patients with and without aphasia were compared using the Mann-Whitney U-test.

Paper II

In paper II, incidence rates of aphasia were calculated using the direct method and were age- and gender- standardized to the Swedish population and the European Standard Population from 2013.[151] Population statistics for the Swedish population were obtained from Statistics Sweden[150] and standardized to the population as of December 31, 2017.[150] Incidence rates for 2005-2006 were also standardized to the Swedish population of 2017 to perform comparisons between the two time periods.

Associations between aphasia and age (unadjusted and adjusted for stroke severity), gender, education, stroke mechanism and stroke risk factors were examined using logistic regression analyses. Associations between aphasia and stroke severity were examined using the total NIHSS score excluding the aphasia item of NIHSS (item 9).

Paper III

In paper III, the incidences of aphasia at stroke onset and at median day 5 post stroke were calculated. Statistical analyses were performed using Wilcoxon signed-rank test to compare and analyze the same individual at baseline (initial aphasia at stroke onset, score on NIHSS item 9), and at median day 5 follow-up assessment of aphasia. This method was also used to compare outcome of aphasia for patients treated with recanalization treatment in comparison to aphasia patients who did not receive recanalization treatment.

Outcome of aphasia was dichotomized according to patients´ results on NIHSS item 9 to 1) favorable aphasia outcome or 2) poor aphasia outcome, as described below.

Definitions of aphasia outcome:

- Resolved aphasia: a score of zero on NIHSS item 9.
- Improvement of aphasia: decrease of ≥1 point on the NIHSS item 9
- Unchanged outcome of aphasia: same score on NIHSS item 9
- Deterioration of aphasia: increase of ≥1 point on NIHSS item 9

Favorable aphasia outcome was defined as resolved or improved aphasia according to NIHSS item 9. Poor aphasia outcome was defined as unchanged or deterioration of aphasia, including deceased patients.

Logistic regression was performed for univariable and multivariable analyses of clinical and demographic factors for favorable and poor aphasia outcome. Age, pre-stroke mRS, stroke severity (NIHSS excluding the aphasia item 9), recanalization treatment, higher education yes/no, stroke risk factors yes/no for each factor and number of inherent stroke risk factors were analyzed.

Paper IV

In paper IV, linear regression was performed to analyze and explore the association between self-perceived HRQoL (according to AIQ) and aphasia severity, adjusting for possible confounding effects of age and stroke severity (NIHSS excluding the aphasia item 9).

Pearson´s correlation was used to examine the relation between self-perceived HRQoL with: 1) severity of language impairment (total score on CAT); 2) cognitive function (part I of CAT); 3) language comprehension (part 2 of CAT); 3) expressive language (part 3 of CAT); and 4) language subitems of CAT: speech comprehension, language comprehension, naming, reading and writing.

In addition, potential temporal changes of HRQoL were analyzed comparing the same individual at 3 months and 12 months follow-up using paired sample t-test.

Ethical Approval

All studies in this thesis were approved by the Regional Ethical Committee in Lund, Sweden, with the diary numbers 2016/179 and 2016/999 and adhere to the Declaration of Helsinki.[161] Participants in the studies provided oral and written consent. When unable to do so, their next of kin were consulted before inclusion in the study. Participants with severe aphasia were assessed for inclusion by consulting their next of kin. Ethical considerations concerning the wish of the patient who cannot advocate for her/himself were ensured by providing aphasia friendly material (easy language, large font, pictures when necessary), and being receptive to non-verbal communication of consent or decline. Information to patients with aphasia was also given and explained at several time points to further assure consent. Participation, though time-consuming and sometimes strenuous, did not entail any direct risks for the patient.

Results

Paper I

We screened first-ever stroke patients over a 15-month period from 1 March 2017 to 31 May 2018. In total, 221 of 275 eligible patients participated in the study. The median age of the included patients was 75 years and 48% were female. Baseline characteristics of the cohort with comparison of stroke patients with and without aphasia are presented in Table 8.

Table 8. Baseline characteristics of the patient cohort

Variable	All patients (n=221)	Patients without aphasia (n=163)	Patients with aphasia (n=58)	*p*-value
Age, years, median (IQR)	75 (68-81)	74 (66-80)	78 (72-86)	0.002
Female gender, n (%)	105 (48)	75 (46)	30 (52)	0.454
Total NIHSS score, median (IQR)	4 (2-7)	3 (1-6)	7 (4-16)	< 0.000
Acute recanalization treatment, n (%)	48 (22)	28 (17)	20 (35)	0.006
Educational level, n (%)				0.4
Low ≤ 9 years	93 (42)	66 (40)	27 (47)	-
Middle ≥10≤12 years	55 (25)	39 (24)	16 (27)	-
High ≥12 years	73 (33)	58 (36)	15 (26)	-

NIHSS: National Institutes of Health Stroke Scale; IQR: Interquartile range. Definition of aphasia was ≤ 14 points on the Language Screening Test (LAST).

Diagnosing aphasia with NIHSS item 9, yielded 50 patients (23%) with aphasia. Most patients had mild to moderate aphasia (n=29, 58%), followed by 24% (n=12) with severe aphasia, and 18% (n=9) with global aphasia. When compared to aphasia assessment with LAST, performed by the SLT, 26% (n=58) of patients had aphasia (i.e. a score ≤14) with a median LAST score of 11 (IQR 6-14).

According to LAST, naming difficulties (79%) were the most common language symptoms, followed by deficits with verbal instructions (64%), and difficulties with the repetition tasks (62%).

As shown in Figure 10, the sensitivity of NIHSS item 9 was 72% (95% CI 0.59-0.83) and the specificity was 95% (95% CI 0.91-0.98) when using LAST as the reference test.

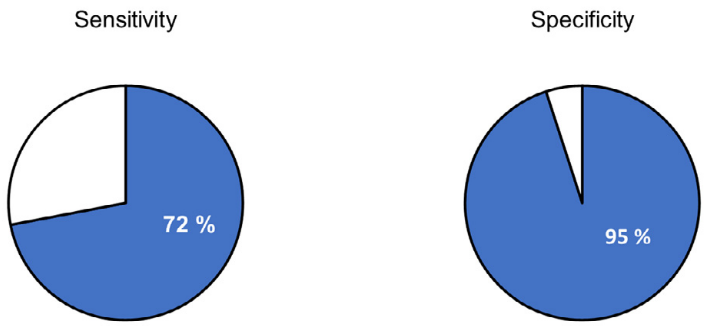

Figure 10. Sensitivity and specificity of NIHSS item 9, as shown in blue. NIHSS: National Institutes of Health Stroke Scale

ROC analysis showed that NIHSS item 9 can discriminate between stroke patients with and without aphasia with acceptable certainty and good diagnostic value[162] (AUC=0.85, 95% CI 0.78-0.92), Figure 11.

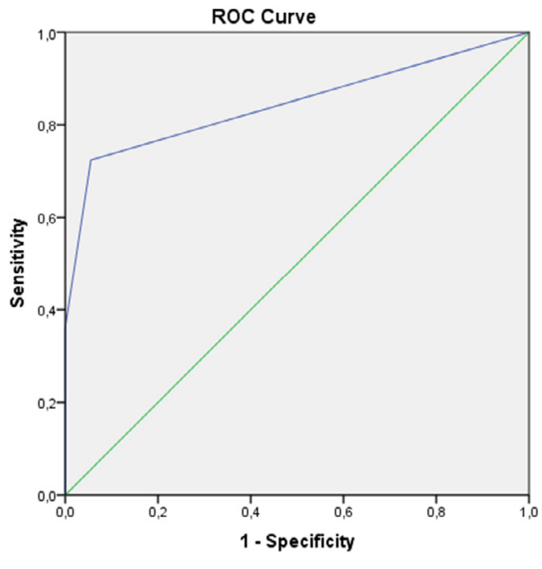

Figure 11. Receiver operating curve of NIHSS item 9 compared to LAST. NIHSS: National Institutes of Health Stroke Scale; LAST: the Language Screening Test.

The most common reasons for incorrect diagnosis were presence of motor speech disorders or predominately language comprehension deficits. Figure 12 displays false-negative and false-positive distributions of NIHSS item 9 and lists probable explanations for an incorrect diagnosis. False-negative subjects, i.e., patients who were not diagnosed with aphasia according to NIHSS item 9 had mild to moderate aphasia. Deficits within both expressive speech and/or comprehension were observed on LAST.

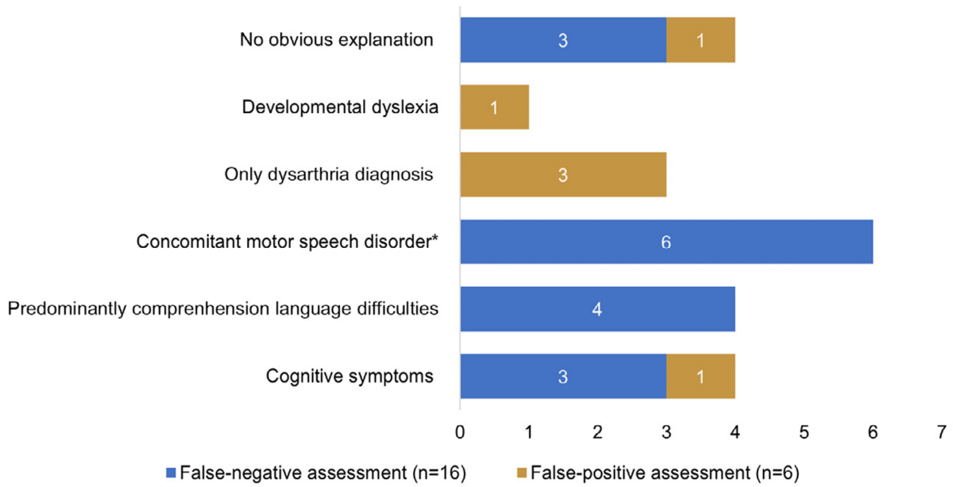

Figure 12. Distribution of false-negative and false-positive assessment of NIHSS compared to reference test LAST, including possible explanations for incorrect aphasia diagnosis with NIHSS. False-negative assessment: NIHSS item 9=0, but LAST<14; False-positive assessment: NIHSS item 9=1, but LAST=15; *dysarthria according to NIHSS item 10. NIHSS: National Institutes of Health Stroke Scale; LAST: Language Screening Test.

The predictive value of a positive test (PPV) was 84% and the predictive value of a negative test (NPV) was 91%. As presented in Figure 13, all patients with severe to global aphasia were correctly diagnosed with aphasia, whereas patients with mild to moderate aphasia were correctly diagnosed as having aphasia in 70% and correctly diagnosed as not having aphasia in 91%.

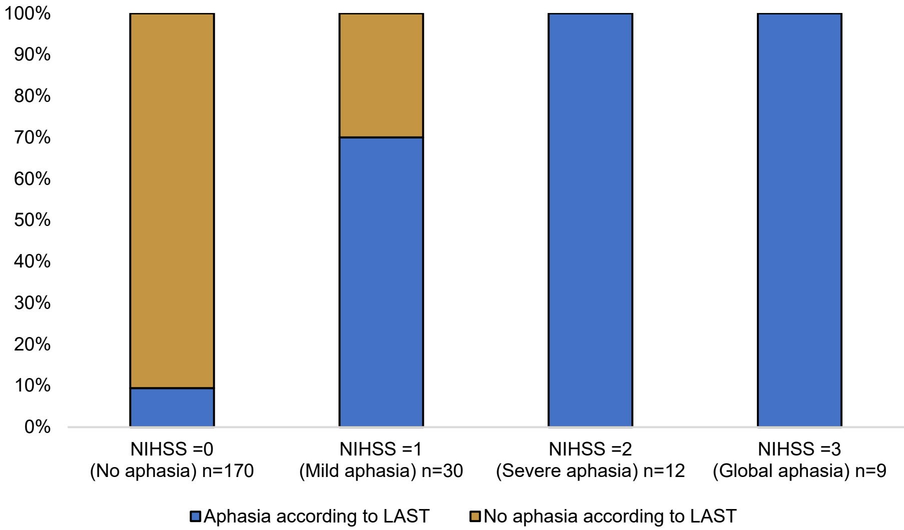

Figure 13. Diagnostic accuracy of NIHSS item 9 for diagnosing aphasia. Image reprinted with permission from Acta Neurologica Scandinavica, Gronberg et al., Accuracy of NIH Stroke Scale for Diagnosing Aphasia, 2021, vol 143, pp 375-382. NIHSS: National Institutes of Health Stroke Scale; LAST: Language Screening Test.

Paper II

To account for potential seasonal variations of stroke incidence the study cohort in paper II lapsed over 1 year, 1 March 2017 to 28 February 2018. A total of 338 patients were diagnosed with a first-ever ischemic stroke between March 1, 2017, and February 28, 2018. After exclusion due to deceased patients and patients not consenting to LSR, a total of 308 patients were included with a median age of 76 years (IQR 69-82 years) and 152 (49%) patients were female. Baseline characteristics of the cohort, including comparisons of stroke patients with and without aphasia, are presented in Table 9.

Stroke and Aphasia Incidence Rate

The sex- and age- standardized incidence rate of first-ever ischemic stroke was 108 per 100 000 person-years (95% CI: 97-121) adjusted to the European Standard Population (ESP) of 2013.[151]

The overall incidence rate of aphasia after ischemic stroke amounted to 31 per 100 000 person-years (95% CI: 25-38) adjusted to ESP. There was no significant difference in the aphasia incidence rate between females and males.

Temporal Trends in Aphasia Incidence

The study observed no significant temporal changes in the proportion of patients with aphasia in the acute phase of stroke between the two time periods. In year 2005-2006, 27% (95% CI: 23-32%) had aphasia as compared to 30% (95% CI: 25-35%) in year 2017-2018.

The incidence rate of aphasia followed the decreased stroke incidence rate of approximately 30% reported during the same time period, from 44 per 100 000 person-years with aphasia in 2005-2006 (95% CI: 37-54) to 31 per 100 000 person-years in 2017-2018 (95% CI: 25-38). There was a significant decrease of aphasia incidence rate for men (p<0.001) but not women. Figure 14 demonstrates aphasia incidences rates between 2005-2006 and 2017-2018.

Table 9. Baseline characteristics of ischemic stroke patients with and without aphasia year 2017-2018

	Patients with First-ever Ischemic Stroke			
Variable	Patients without aphasia (n=217)	Patients with aphasia (n=91)	All patients n=308	OR (95% CI)
Age, years, median (IQR)	74 (68-81)	78 (72-86)	76 (69-82)	1.04 (1.02-1.06)
Female gender, n (%)	101 (47)	51 (56)	152 (49)	1.46 (0.90-2.40)
Baseline NIHSS, median (IQR)	3 (1-5)	10 (4-19)	4 (2-7)	1.25 (1.18-1.32)
Stroke risk factors, n (%)				
Hypertension	172 (79)	70 (77)	242 (79)	0.87 (0.48-1.57)
Diabetes Mellitus	72 (33)	28 (31)	100 (33)	0.90 (0.53-1.52)
Atrial fibrillation	62 (29)	34 (37)	96 (31)	1.49 (0.90-2.50)
Hypercholesterolemia	123 (57)	47 (52)	170 (55)	0.82 (0.50-1.33)
Smoking	38 (18)	11 (12)	49 (16)	0.66 (0.32-1.35)
Previous TIA	43 (20)	14 (15)	57 (19)	0.74 (0.38-1.42)
Ischemic heart disease	50 (23)	24 (26)	74 (24)	1.20 (0.68-2.10)
Heart disease	97 (45)	48 (53)	145 (47)	1.38 (0.85-2.26)
Educational level, n (%)				
Low ≤ 9 years	107 (49)	49 (54)	156 (51)	Ref
Middle ≥10≤12 years	53 (24)	18 (20)	71 (23)	0.74 (0.39 - 1.40)
High ≥12 years	57 (26)	24 (26)	81 (26)	0.92 (0.51-1.66)

NIHSS: total score on National Institutes of Health Stroke Scale; TIA: Transient Ischemic Attack; IQR: Interquartile range; OR: odds ratio, CI: confidence interval.

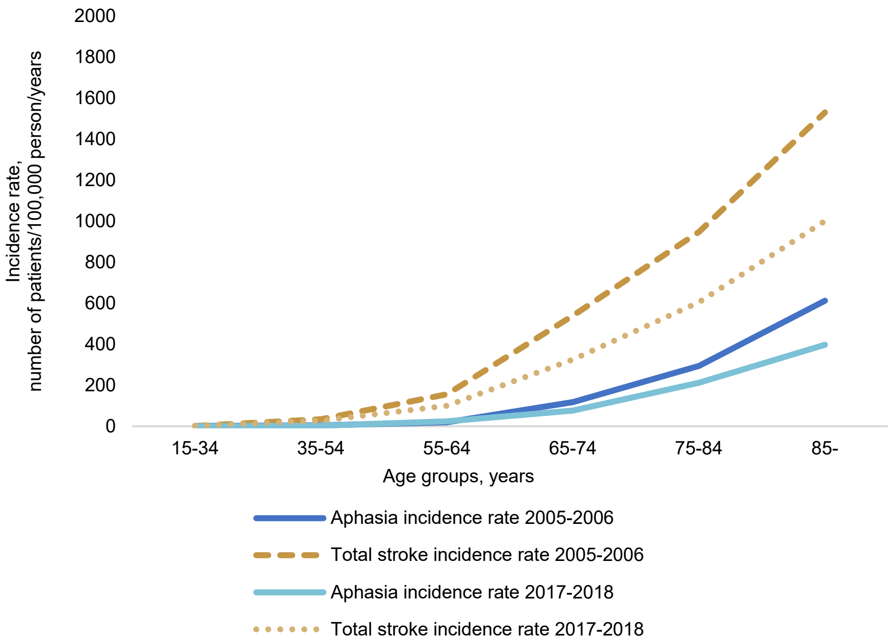

Figure 14. Incidence rate of ischemic stroke patients with and without aphasia year 2005-2006 and 2017-2018, stratified by age and adjusted to the European Standard Population from 2013. Definition of aphasia: NIHSS item 9 score >0. NIHSS: National Institutes of Health Stroke Scale. Image reprinted with permission from Neuroepidemiology, Grönberg et al., Incidence of Aphasia in Ischemic Stroke, 2022, vol 56, pp 174-182.

As shown in Figure 15 stroke severity according to NIHSS (including item 9) remained stable between 2005-2006 (median NIHSS=4) and 2017-2018 (median NIHSS=4; p=0.44). Likewise, there was no difference between aphasia severity year 2005-2006 and year 2017-2018 (p=0.35), and no difference between gender.

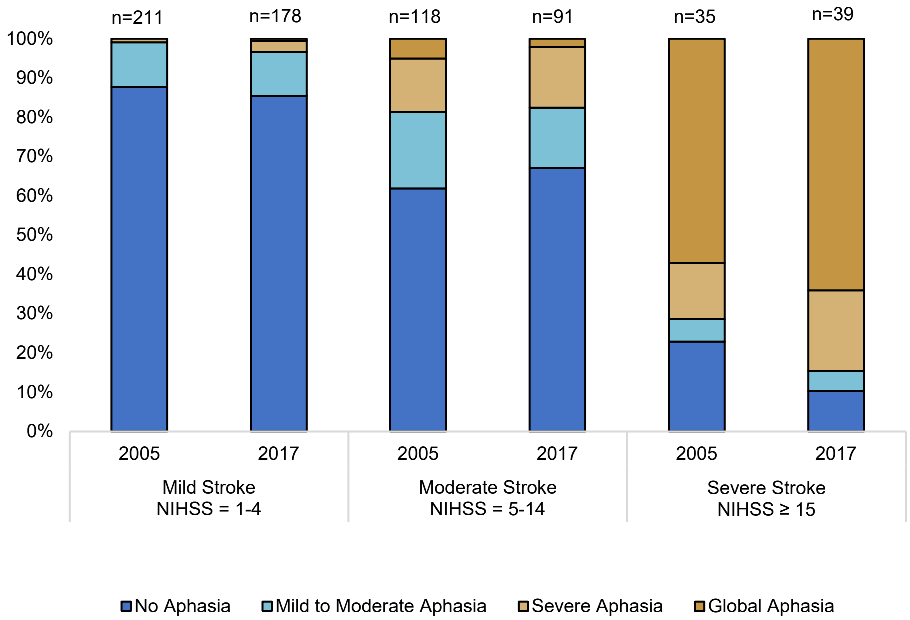

Figure 15. Proportions of aphasia severity relative to stroke severity 2005-2006 and 2017-2018. Definition of aphasia: NIHSS item 9 score >0. NIHSS: National Institutes of Health Stroke Scale. Image reprinted with permission from Neuroepidemiology, Grönberg et al., Incidence of Aphasia in Ischemic Stroke, 2022, vol 56, pp 174-182.

The 1- year mortality of stroke patients with aphasia year 2005-2006 and 2017-2018 was similar, 4% vs 6%, respectively (p=0.08). However, stroke patients with aphasia had significantly higher mortality when compared to stroke patients without aphasia (p=0.01), both year 2005-2006 and year 2017-2018.

Characteristics of Patients with Aphasia

The prevalence of aphasia increased significantly with stroke severity (NIHSS excluding the aphasia component, $p<0.001$). Each 1-point increase on NIHSS increased the odds of aphasia by 19% (OR, 1.19; CI: 1.13-1.26).

Patients with aphasia had higher age and had more severe strokes according to baseline NIHSS (Table 9) compared with stroke patients without aphasia. Patients with aphasia also had longer hospital stays, median 8 days compared to 4 days for stroke patients without aphasia; OR, 1.08; 95% CI: 1.04-1.12). Corresponding associations remained after adjusting for NIHSS scores (excluding the aphasia component).

Patients with aphasia had a higher in-hospital mortality, 18% compared to 2% for stroke patients without aphasia (OR, 9.05; 95% CI: 3.20-25.54). The discharge location also differed between stroke patients with and without aphasia, with 25% of patients with aphasia being discharged to a short-term care facility as compared to 13% of patients without aphasia. However, these factors were no longer significant when adjusting for stroke severity. The occurrence of stroke risk factors (Table 9) did not differ between stroke patients with and without aphasia.

The underlying pathogenetic mechanism for 36% of stroke patients with aphasia was CE. Even though CE was significantly more common in patients with aphasia (OR, 1.81; 95% CI: 1.06-3.06), the association was not significant after adjusting for stroke severity (OR, 1.18; 95% CI: 0.61-2.29). Figure 16 illustrates TOAST and OCSP classifications of patients with and without aphasia.

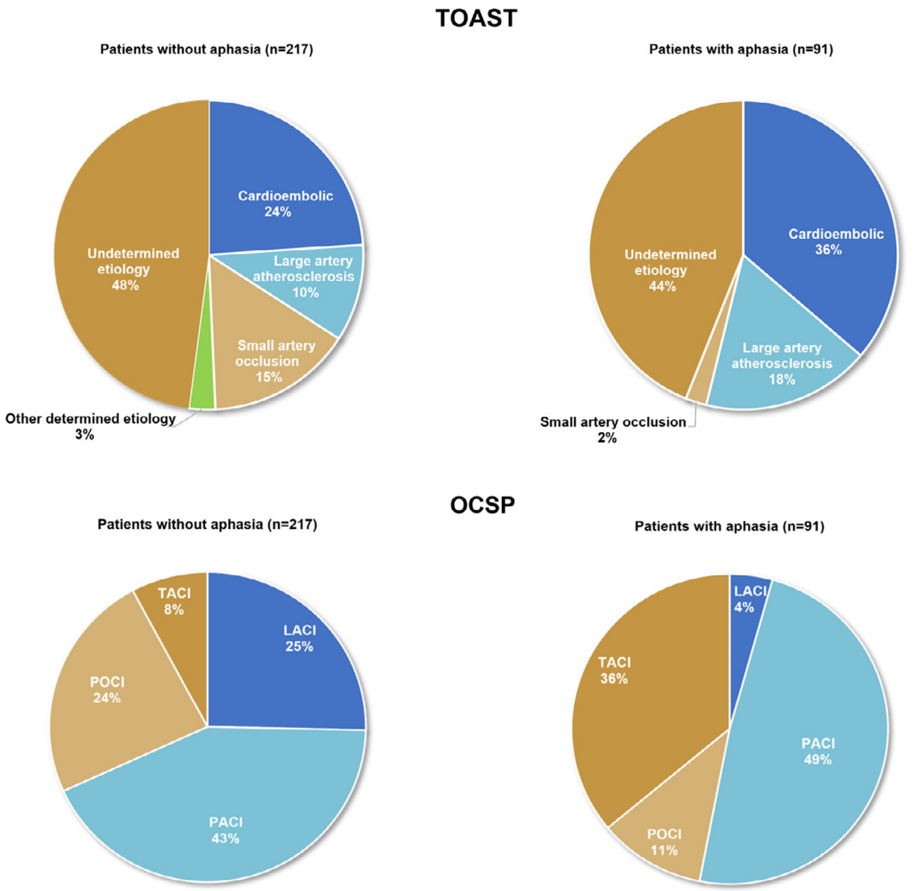

Figure 16. Baseline TOAST classification (top image) and OCSP (bottom image) of stroke patients with and without aphasia. TOAST: Trial of Org 10172 in Acute Stroke Treatment; OCSP: The Oxfordshire Community Stroke Project; TAC:, total anterior circulation infarct; PACI: partial anterior circulation infarct; POCI: posterior circulation infarct; LACI: lacunar infar

Paper III

In paper III, the same cohort was the basis as in paper II. However, in paper III, the study period was over a 15-month period, 1 March 2018 to 31 May 2018 (as opposed to only 12 months in paper II). All alive patients with initial aphasia (n=95) were followed-up and again screened for aphasia with the NIHSS item 9 at median day 5 post stroke.

Short-term aphasia outcome (STAO) after stroke onset was defined as the difference between the initial aphasia assessment at stroke onset and the re-assessment of NIHSS item 9 (median day 5) (definition of aphasia outcome is described in detail in “Statistical Methods” above).

In this analysis, aphasia was observed in 27% (n=107) of patients in the acute phase of stroke. Aphasia severity was distributed as follows: 40% (n=43) with mild to moderate aphasia, 30% (n=32) with severe aphasia, and 30% (n=32) with global aphasia. At median day 5, 89% were alive and re-assessed with NIHSS, detecting 61% (n=58) with remaining aphasia.

Aphasia improved for 57% (54 of 95 alive patients) of patients with initial aphasia and among these 39% (n=37) had resolved aphasia. Even though patients across all severities of aphasia demonstrated improvement, patients with less severe aphasia were more likely to improve. In the cohort, roughly half (52%) had remaining mild to moderate aphasia, whereas 24% had severe and global aphasia, respectively. Patients that had not improved in their aphasia status, had either unchanged aphasia, observed in 37% (n=35) or had deteriorated in their aphasia (6%, n=6).

The short-term prevalence of aphasia was 15% (95% CI:12-19%) at median day 5 among all stroke survivors (n=58 patients with aphasia of total n=375).

Figure 17 illustrates patient flow of all PWA (including deceased) and the proportion of patients with aphasia at stroke onset and median day 5 and their aphasia severity.

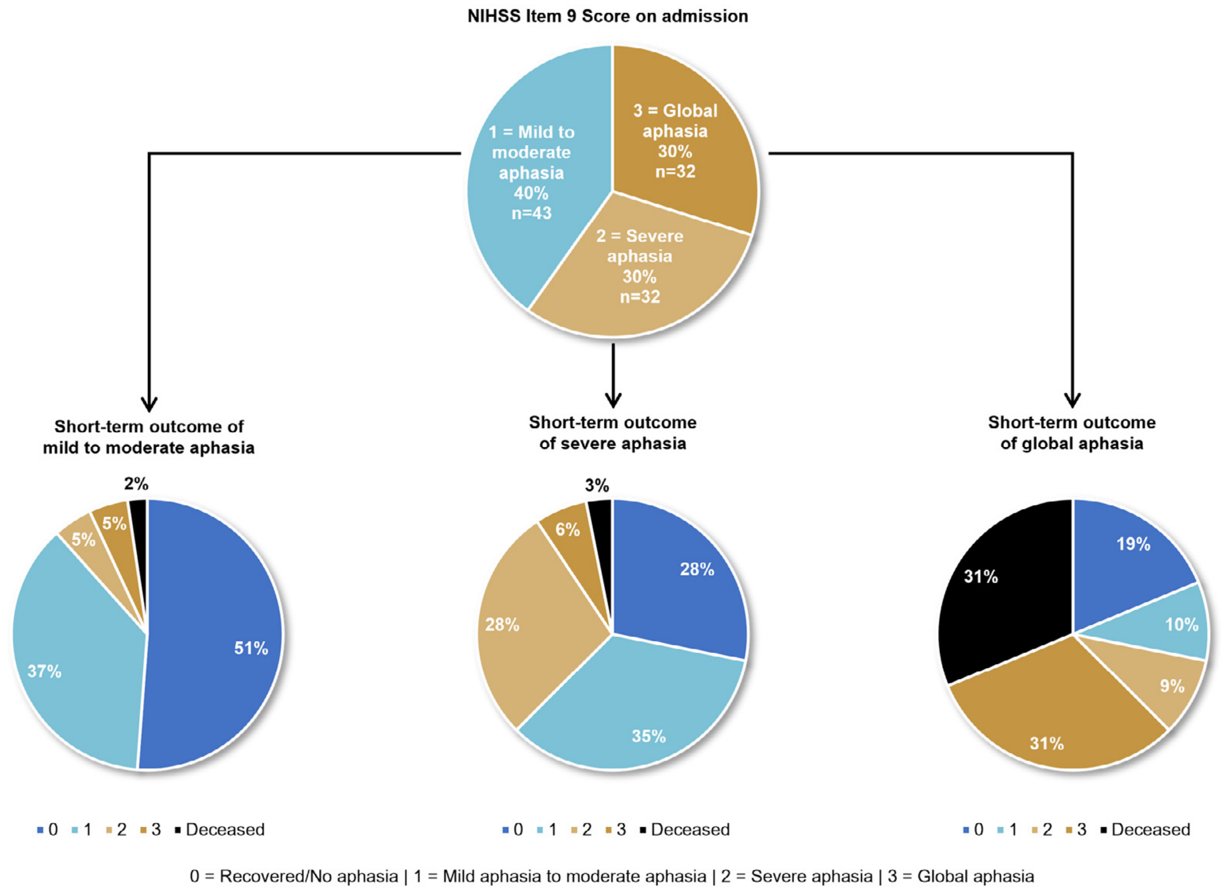

Figure 17. Patients with aphasia at stroke onset and their outcome regarding aphasia at median day 5 post stroke according to NIHSS item 9. NIHSS: National Institutes of Health Stroke Scale.

The significantly higher mortality rate for PWA was related to initial stroke severity (NIHSS excluding the aphasia component) and age.

Factors Associated with Favorable and Poor Short-term Aphasia Outcome

Baseline characteristics in relation to favorable and poor aphasia outcome are presented in Table 10. Stroke severity (NIHSS excluding aphasia component) was a significant independent predictor for aphasia outcome, i.e., patients with aphasia with favorable STAO had significantly less severe strokes (p=0.03).

Table 10. Baseline characteristics of patients with aphasia with favorable and poor short-term aphasia outcome

Variable	All patients	Favorable outcome	Poor outcome	*p*-value
Number of patients	107	54	53	-
Age, years (median)	79 (71-86)	76 (70-86)	80 (74-87)	0.14
Gender, female (%)	57 (53)	30 (56)	18 (44)	0.63
Education ≥12 years, n (%)	29 (27)	16 (30)	13 (25)	0.55
Pre-stroke mRS (>0) n, (%)	32 (30)	11 (20)	21 (40)	0.03
Baseline total NIHSS, median (IQR)	9 (4-19)	7 (4-15)	13 (5-22)	0.03
Baseline NIHSS excluding item 9	7 (3-16)	5 (2-12)	12 (3-20)	0.02
Stroke risk factors, n (%)				
Hypertension	80 (75)	40 (50)	40 (50)	0.87
Diabetes mellitus	32 (30)	13 (41)	19 (59)	0.19
Atrial fibrillation	38 (36)	18 (47)	20 (53)	0.63
Heart disease	54 (51)	23 (43)	31 (57)	0.10
Ischemic heart disease	28 (26)	8 (29)	20 (71)	0.009
Hypercholesterolemia	58 (54)	32 (55)	26 (45)	0.29
Previous TIA	15 (14)	6 (40)	9 (60)	0.54
Current smoking	14 (13)	5 (36)	9 (64)	0.24
Recanalization therapy	39 (36)	16 (41)	23 (59)	0.14

Favorable outcome: favorable short-term aphasia outcome, defined as improved or resolved aphasia according to NIHSS item 9; Poor outcome: poor short-term aphasia outcome (including death), defined as unchanged or deteriorated aphasia according to NIHSS item 9. mRS: modified Rankin Scale; NIHSS: National Institutes of Health Stroke Scale.

However, initial aphasia severity did not significantly predict short-term aphasia outcome and both favorable and poor STAO was observed in patients with severe aphasia deficits. Nonetheless, global aphasia was more often associated with poor aphasia outcome, with 37% of patients showing favorable outcome compared to 63% having poor aphasia outcome. Figure 18 visualizes aphasia outcome in relation to aphasia severity.

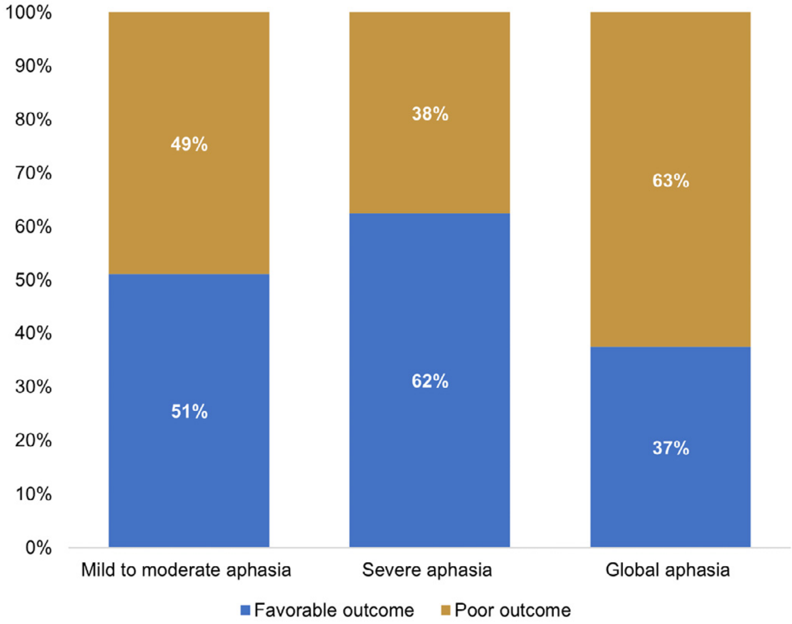

Figure 18. Proportions of patients with favorable and poor aphasia outcome in relation to aphasia severity according to National Institutes of Health Stroke Scale item 9. Number of patients with mild to moderate aphasia n=43, severe aphasia n=32, global aphasia n=32.

The odds of having favorable STAO was significantly worse for patients with the stroke mechanisms CE or LAA compared to patients with UND (CE vs UND: OR 0.35; 95% CI:0.13-0.93, p=0.04 and LAA vs UND: OR 0.27; 95% CI:0.09-0.82, p=0.02). TACI according to OCSP was also significantly related to poor STAO, with 47% of patients having poor outcome compared to 22% with favorable aphasia outcome; p=0.01).

Ischemic heart disease (OR 0.29; 95% CI:0.11-0.73; p=0.009) was negatively associated with favorable STAO. No other stroke risk factors were independently associated with outcome, however, as demonstrated in Figure 19, the total number of stroke risk factors (hypertension, diabetes mellitus, hypercholesterolemia, previous TIA, ischemic heart disease and current smoking) negatively impacted favorable aphasia outcome (p<0.05).

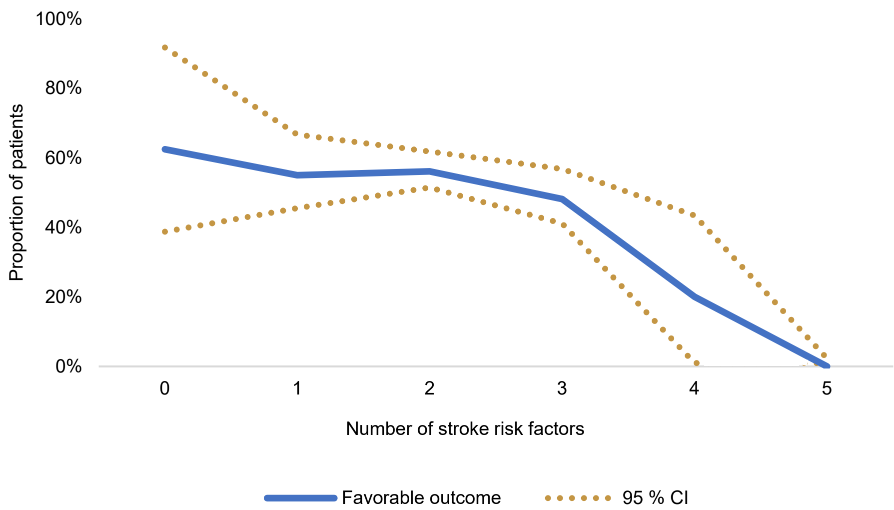

Figure 19. Number of stroke risk factors in relation to favorable short-term aphasia outcome (defined as improved or resolved aphasia according to NIHSS item 9) (n=54). Stroke risk factors include: hypertension, diabetes mellitus, hypercholesterolemia, previous TIA, ischemic heart disease and current smoking. NIHSS: National Institutes of Health Stroke Scale; CI: confidence intervall.

Favorable STAO was also related to pre-stroke mRS, with an odds ratio of 2.57 (95% CI:1.08-6.07) for favorable STAO for patients with pre-stroke mRS score of 0. Favorable or poor aphasia outcome was not significantly related to gender (p=0.63), age (p=0.14), or education (p=0.55).

Acute Recanalization Treatment

Acute recanalization treatment was more often provided to stroke patients with aphasia, with 36% receiving treatment in comparison to 11% of stroke patients without aphasia (p<0.001). The odds ratio for receiving acute recanalization treatment was 4.68 (95% CI:2.72-8.05), for patients with aphasia compared with stroke patients without aphasia. However, when adjusting for stroke severity (NIHSS excluding the aphasia component) the high proportion of treatment was only significant regarding thrombolysis and not for thrombectomy.

Regardless of acute stroke recanalization treatment, significant improvement of aphasia (from onset to median day 5) was seen in the total cohort of PWA. However, the patients treated and not treated with recanalization treatment differed concerning several factors, including: stroke and aphasia severity, stroke pathogenetic mechanism, and clinical stroke location according to OCSP.

Paper IV

Paper IV is based on the same cohort of patients as in paper I, but two additional patients with aphasia according to SLT evaluation (but not according to the screening instrument LAST) were included in the study. Thus, the total number of PWA in the cohort was 60 participants. All people with aphasia according to assessment with CAT, were followed-up at 1 month, 3 months, and 12 months post stroke.

Study Cohort and Loss to Follow-up

In total, at 12 months follow-up, 13% (n=8) of the 60 patients with aphasia at baseline had died and n=1 participant was lost to follow-up. A flow-chart of the study cohort, including reasons for loss to follow-up and aphasia outcome are presented in Figure 20.

Figure 20. Flow-chart of people with aphasia after ischemic stroke from median 4 days post stroke to follow-up 12 months post stroke. IS: ischemic stroke; CAT: Comprehensive Aphasia Test.

Prognosis of Aphasia

Aphasia at baseline (median day 4) was observed in 27% (n=60 of a total of 221 screened IS patients) of stroke patients according to aphasia assessment performed by SLT. Characteristics of the participants are presented in Table 11.

Table 11. Baseline characteristics of 60 patients with initial aphasia after ischemic stroke

Variable	Number of patients
Age, years, median (IQR)	78 (72-85)
Female gender, n (%)	29 (49)
NIHSS at baseline, median (IQR)	6 (4-16)
mRS=0 before stroke onset, n (%)	47 (78)
Fully awake at admission,* n (%)	51 (85)
Educational level, n (%)	
Low ≤ 9 years	28 (47)
Middle ≥10≤12 years	15 (25)
High ≥12 years	17 (28)

NIHSS: National Institues of Health Stroke Scale; CAT: Comprehensive Aphasia Test; AIQ: Aphasia Impact Questionnaire; mRS: modified Rankin Scale where mRS=0 is no symptoms; IQR: interquartile range; *Defined as Reaction Level Scale 85=1.[152]

At language assessment 1 month post stroke, 74% (n=40 of 54 PWA) had remaining aphasia whereas 26% (n=14 of 54) had completely recovered from their aphasia according to assessment with CAT (4 PWA had died before follow-up assessment and 2 PWA were too sick to perform assessment at 1 month and were deceased within 12 months). Figure 21 illustrates the proportion of PWA at baseline and at 1, 3-, and 12-months follow-up evaluations.

At 3 months, 37 patients diagnosed with aphasia at 1 month performed subsequent follow-up (n=2 additional patients had died, n=1 lost to follow-up) and in total, 67% (n=34 of 54) had remaining aphasia. At follow-up 12 months post stroke, 61% (95% CI 47%-74%) of all alive patients who presented with aphasia at baseline had remaining (chronic) aphasia (n=2 additional patients had died before follow-up).

The 12-month prevalence of aphasia post stroke was 15% (95% CI 11%-20%), i.e. n=30 PWA of total 202 alive patients with ischemic stroke.

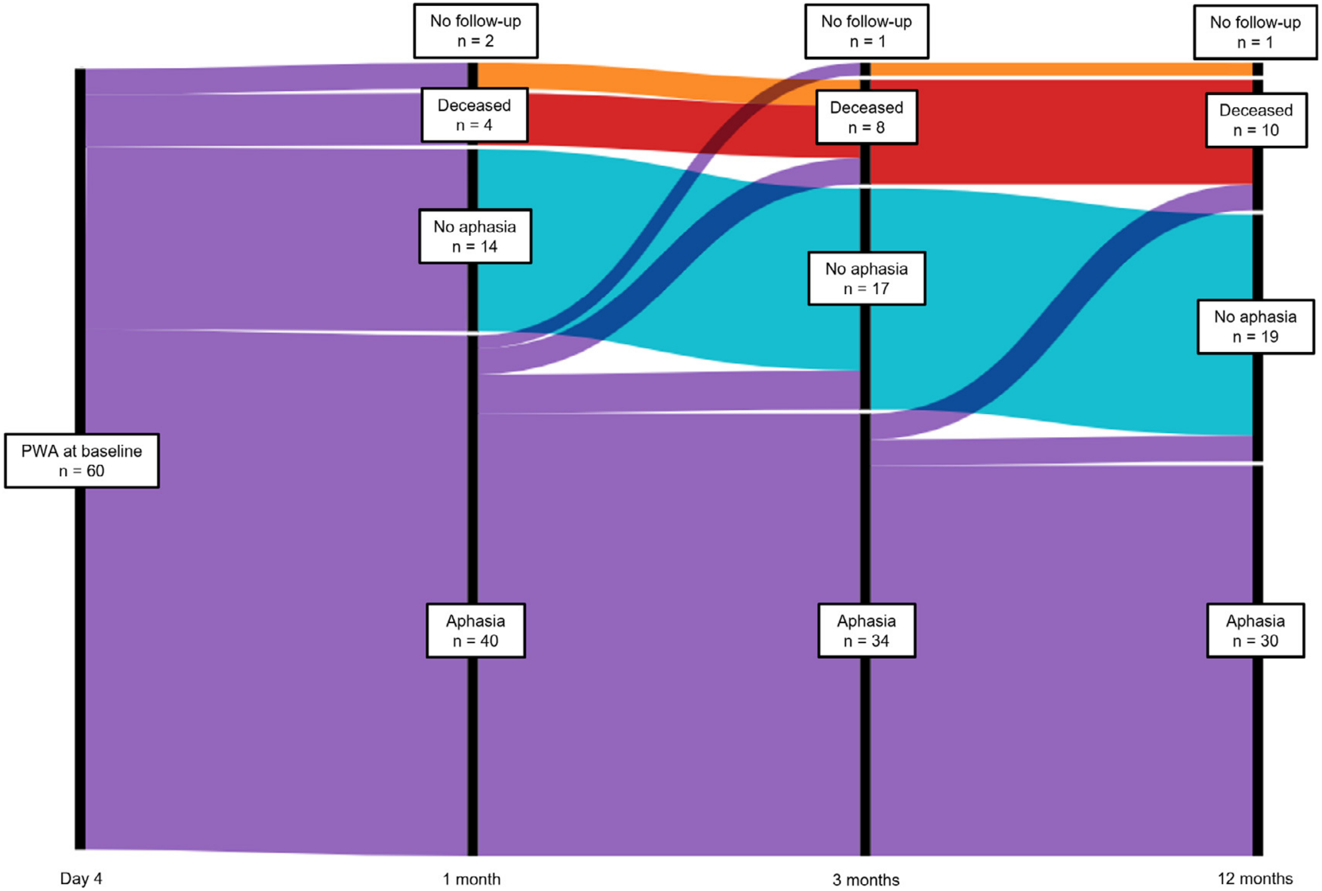

Figure 21. People with aphasia at baseline (median day 4 post stroke) and their outcome at 1 month, 3 months, and 12 months post stroke. PWA: people with aphasia. PWA: people with aphasia. Definition of aphasia: NIHSS item 9 score >0. NIHSS: National Institutes of Health Stroke Scale.

Of the total cohort of 60 patients with aphasia at baseline, complete recovery from aphasia was observed in 32% (n=19) of patients at 12 months (95% CI: 21%-44%). However, 50% (n=30) of patients had chronic aphasia (95% CI: 38%-62%), defined as remaining aphasia according to CAT at 12 months, and 1% (n=1) was lost to follow-up. The 1-year mortality rate of PWA was high, with almost every fifth (17%) patient with aphasia in the acute phase of stroke had died at year post stroke onset (n=10, 95% CI 9%-28%).

Language Impairment

Aphasia patients had language deficits across all language domains of CAT, as shown in Figure 22. Most of the language improvement was seen during the first 3 months after stroke, whereas the proportion of PWA remained relatively stable between 3 months and 12 months after stroke (67% vs 61%).

Language improvement from 1 month to 12 months post stroke was seen for 87% of PWA, though the range of improvement was wide (Figure 22). PWA demonstrated significant improvement in the domains of naming (p=0.01), comprehension of written language (p=0.01), and repetition (p=0.03). On the contrary PWA showed no significant improvement regarding comprehension of spoken language (p=0.18), cognition (p=0.10), reading (p=0.10) or writing (p=0.18).

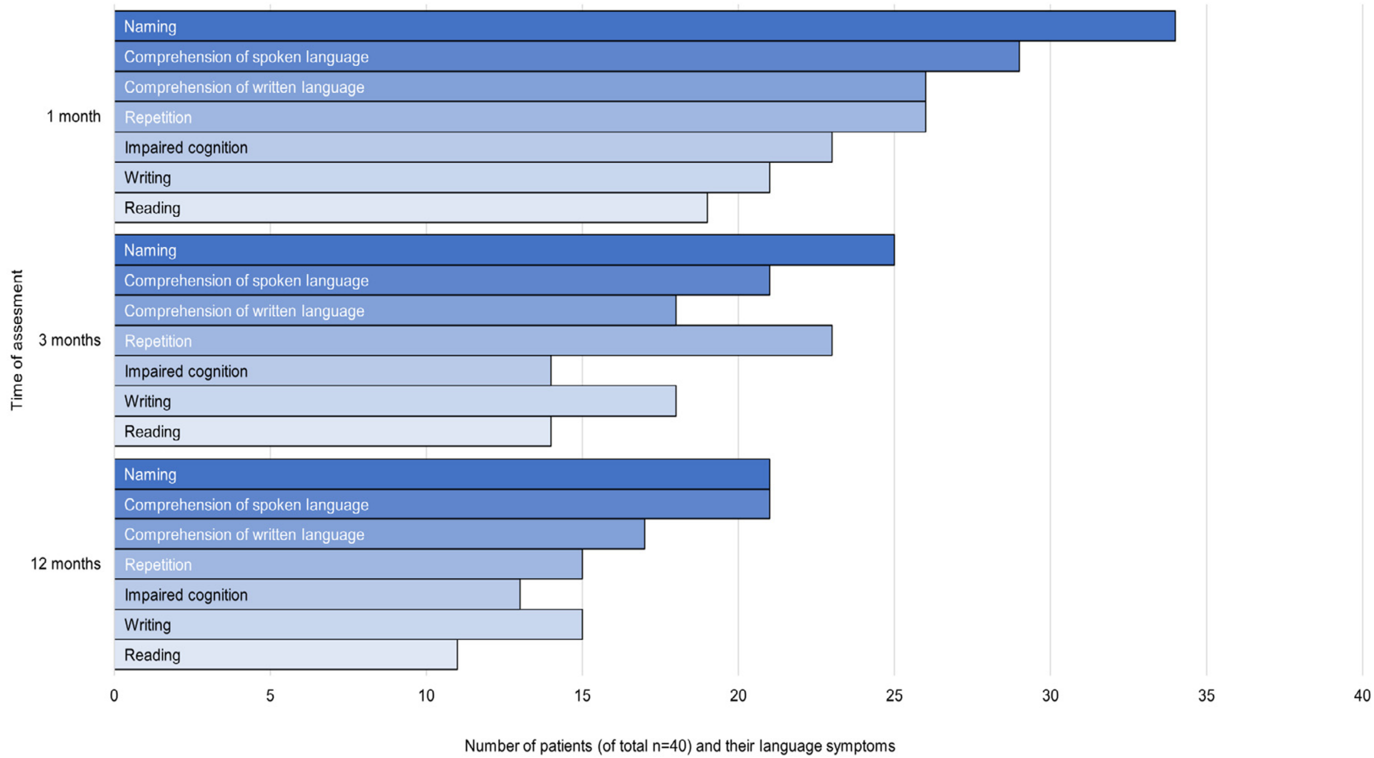

Figure 22. Language impairments (subitems on the Comprehensive Aphasia Test, CAT) at 1 month, 3 months and 12 months post stroke for n=40 patients with aphasia. Significant improvement was observed within naming, comprehension of written language and repetition from 1 to 12 months.

Health-related Quality of Life for People with Aphasia

When Health-related Quality of Life (HRQoL) was measured with the Aphasia Impact Questionnaire (AIQ) at 3 months post stroke, PWA reported that aphasia had a negative effect on aspects of communication, level of participation, as well as having a negative impact on their emotional well-being.

Effects on communication were reported among 87% of PWA and deficits within both comprehension, expression, reading, and writing affected the ability to communicate. Writing was strongly associated with HRQoL, with 70% reporting an effect on HRQoL, followed by 57% reporting deficits withing reading and speech production affecting HRQoL. Table 12 shows associations between health-related quality of life and different language symptoms.

Similarly, a majority of PWA (73%, n=22) reported that aphasia had negative consequences on their level of participation, with diminished ability to perform everyday activities (70%, n =21) as well as recreational activities (43%, n=9).

The emotional well-being was also affected by aphasia for 87% of PWA (n=26). Symptoms included: feelings of isolation (67%), frustration (70%), and helplessness (57%). In addition, 63% (n=19) respectively, felt worried or depressed.

PWA described similar HRQoL at 3- and 12- months post stroke. At 12 months aphasia remained negatively related to communication (90%, n=27), participation (77%, n=23), and emotional well-being (83%, n=25). There was no difference in HRQoL between genders.

Temporal Change of Health-related Quality of Life for People with Aphasia

There was no statistically significant temporal change of HRQoL (according to total score on AIQ) between 3 and 12 months. When comparing results of the first AIQ assessment at 3 months with the 12-month follow-up assessment, the total cohort of PWA showed no statistical improvement concerning communication, participation or emotional well-being, however individual improvements and deteriorations were observed. Figure 23 shows the proportion of patients reporting negative consequences of their aphasia.

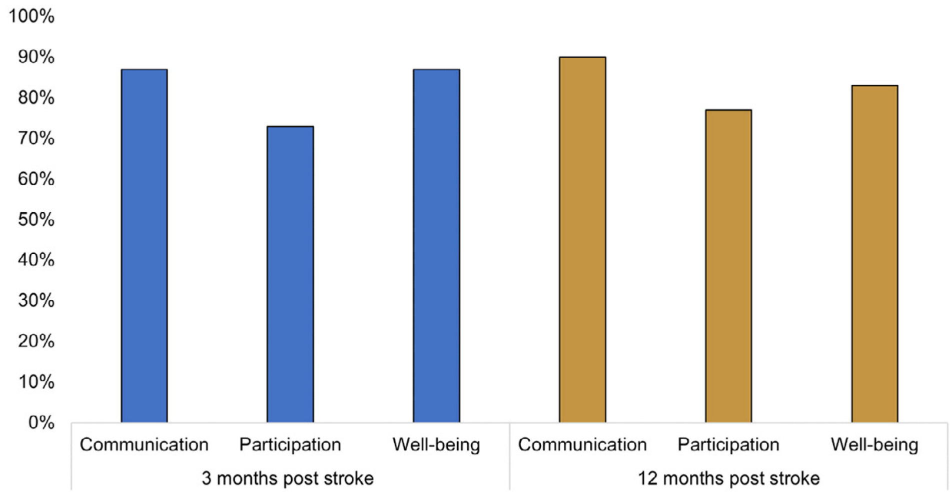

Figure 23. Proportion of people with aphasia (according to Comprehensive Aphasia Test) who experience negative communication, participation and emotional well-being at 3- and 12- months post stroke according to the Aphasia Impact Questionnaire.

Factors Associated with Health-related Quality of Life at 3 Months

Aphasia severity (according to CAT evaluation) was significantly related to AIQ HRQoL ($p<0.001$) as presented in Figure 24. Less severe aphasia was associated with improved HRQoL and for every 10-point increase of scores on CAT, AIQ scores decreased with 1.0 (95% CI: -1.4, -0.6). The association remained significant after adjusting for stroke severity (total NIHSS excluding aphasia component) and age (β -0.9 95% CI -1.3, -0.5; $p<0.001$).

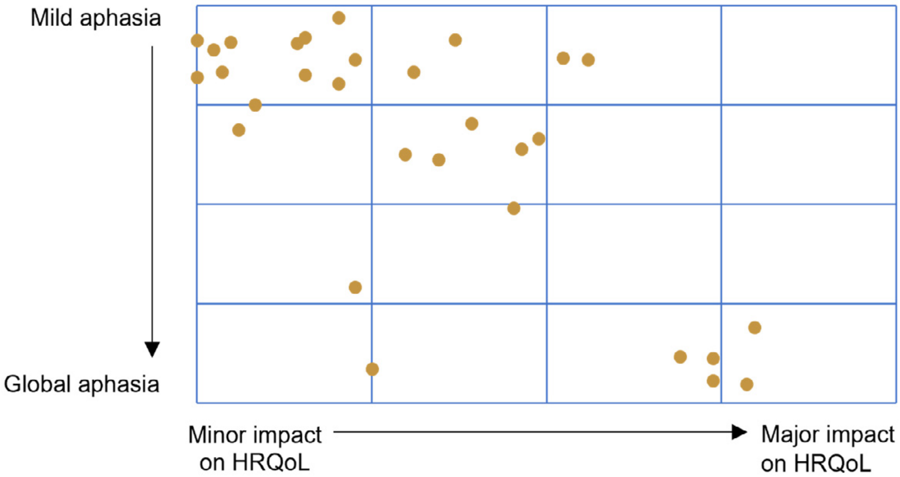

Figure 24. Scatter diagram of PWA (n=30) and their aphasia severity according to CAT in relation to self-reported HRQoL according to score on AIQ. CAT scores range from 0 points, global aphasia to mild aphasia, <402 points and/or below CAT cut-off scores in 1 or more language subitem(s).[138] AIQ scores range from 0 (no or minor impact) to maximum score of 84 (major impact). PWA: people with aphasia; CAT: Comprehensive Aphasia Test; AIQ: Aphasia Impact Questionnaire.

Table 12 displays correlations between language symptoms and self-reported HRQoL according to AIQ evaluation at 3- and 12- months. Cognition, language comprehension and expressive language was significantly related to HRQoL. The strongest association was seen for cognition, where for every 10-point increase on the cognitive assessment of CAT, scores on AIQ decreased with 12.8 (95% CI: -16.6, -7.4; $p<0.001$). Hence, a better cognitive function was associated with better HRQoL. The relationship remained significant at 11.8 (95% CI: 16.8, 6.8; $p<0.001$) after adjusting for stroke severity (total NIHSS excluding aphasia component) and age.

PWA also reported a significant association between language comprehension and HRQoL. For every 10-point CAT increase on language comprehension, AIQ scores decreased with 3.5 (95% CI: -5.3, -1.8; p<0.001). The decrease remained significant at 3.1 (95% CI -4.9, -1.2; p=0.002) when adjusting for stroke severity (total NIHSS excluding aphasia component) and age.

Expressive language and HRQoL showed a significant association, however, not as strong as for cognition or language comprehension (β -1.4 95% CI -2.0, -0.8; p<0.001). Neither gender, age, nor education significantly affected the overall HRQoL.

Table 12. Assessment with the Comprehensive Aphasia Test at 3- and 12- months post stroke and associations between language symptoms and health-related quality of life (according to the Aphasia Impact Questionnaire)

Comprehensive Aphasia Test (CAT)	3 months		12 months	
	Pearson´s correlation, *r*	*p*-value	Pearson´s correlation, *r*	*p*-value
Total score on CAT	-0.694	<0.001	-0.537	0.002
CAT part 1: Cognitive screen	-0.725	<0.001	-0.561	0.002
CAT part 2: Language comprehension	-0.619	<0.001	-0.567	0.002
CAT part 3: Expressive language	-0.685	<0.001	-0.532	0.003
CAT language subitems				
Speech comprehension	-0.585	0.001	-0.475	0.009
Reading comprehension	-0.631	<0.001	-0.533	0.003
Naming	-0.632	<0.001	-0.568	0.001
Reading	-0.606	0.001	-0.536	0.003
Writing	-0.743	<0.001	-0.591	0.001

Pearson´s correlation between scores on CAT and scores on AIQ. A negative correlation indicates that higher scores on CAT (less severity of aphasia) correlates with lower scores on AIQ (better HRQoL). CAT: Comprehensive Aphasia Test; AIQ: Aphasia Impact Questionnaire.

Discussion

Methodological Considerations

There are several aspects of methodology that need to be taken into consideration when interpretating study results. Methodological issues can influence and affect the results and their generalizability and may occur at several different phases: during the design of the study, collection of data, analyses of data, or when data is being presented.

This thesis is based on observational studies and aspects important to consider in this type of study include: selection bias, ambiguity of measurements performed in the study and confounding factors. These factors can potentially impact the validity of the study and consequently the implications of the studies' results.

Patient Inclusion and Potential Selection Bias

Lund Stroke Register (Paper II and III)

The case selection in the included parts of Lund Stroke Register does not fulfill all criteria for optimal population-based incidence stroke studies. However, it is prospective in its design and has multiple overlapping sources of detecting patients with stroke and adheres to the standard definition and core criteria for stroke studies.[163] Several of the criteria for advanced stroke studies are also fulfilled, e.g hot pursuit of stroke cases, classification of the stroke, collecting data on stroke risk factors and use of follow-up methods.

LSR uses these standard methods of data collection, case ascertainment and data presentation, which advances our knowledge on stroke, as well as enhances the comparability and generalizability of the results.

Paper II

The incidence rate of stroke patients with aphasia might have been affected by the study design, which was hospital-based as opposed to fully population-based, and therefore not adhering to all the criteria for stroke incidence studies.[163] However, the prospective methods used in LSR has in previous studies showed that LSR detects approximately 91% of all stroke cases in the population cohort. Stroke patients not detected by LSR more often lived in nursing homes, had more severe neurological impairment and higher fatality rate.[164] Nonetheless, this could introduce a selection bias in the cohort and affect the generalizability to the general population. Accurate incidence rates can only be estimated if *all* stroke patients were included. In the present study methodological aspects to consider are excluded patients with very mild strokes that may not seek health care, those who die before health care professionals are consulted, and those patients where a diagnosis of stroke is not documented due to a major illness pre-stroke event.

Comparing incidence rates from different time periods may also have been influenced by different methods of detecting aphasia year 2005-2006 and 2017-2018. In the latter years, assessments were performed in person and with a SLT specialized in aphasia in the research team, which may have biased the result comparison.

To conclude, the incidence rates of aphasia described in this thesis adheres to most, yet not all criteria for population-based incidence stroke studies. However, the case ascertainment including all stroke patients by the WHO definition of stroke and with no exclusion criteria,[38] suggests that the results should be generalizable and representative to a hospitalized stroke patient cohort.

Lund Stroke Register Speech Study (Paper I and IV)

Stroke patients with aphasia are a heterogeneous group that presents with a variety of characteristics concerning personal, language (including multilingual), stroke, and language impairment, as well as other co-morbidities. These aspects were considered in patient selection for the Lund Stroke Register Speech Study, since they may have impacted the findings.[165]

The patient selection for the Lund Stroke Register Speech Study had another objective than that of LSR. Therefore, inclusion criteria commonly used in studies of language were added. The generalizability of the results may therefore have been reduced. However, the aim of the study was not to study the whole stroke population, but rather specifically stroke patients with aphasia, establishing the current short-term outcome (paper III), long-term outcome (paper IV) and health-related quality of life for this subgroup of stroke patients (paper IV). Hence, not knowing the premorbid language level of a person not having Swedish as a native language, could have affected the results of language assessments, classifying a person with poor Swedish language skills incorrectly as being aphasic. Other diagnoses affecting cognition or mental health and severe uncorrected hearing problems, could also have affected the results.

Therefore, even though the inclusion criteria pose a risk of selection bias, the lack of specific exclusion criteria would on the contrary pose a risk of information bias with measurement errors misclassifying patients with aphasia (further discussed under "measurements" below). In summary, the cohort obtained was selected to be representative of hospitalized PWA after ischemic stroke, however results may not be generalizable to patients not cared for at hospital or patients with other prior medical diagnosis.

Attrition Bias (loss to follow-up)

Data on aphasia outcome (papers III and IV) was obtained and dependent of the follow-up examinations of participants with aphasia included in the cohort. There is a risk of bias in the outcome data if stroke patients with aphasia declined follow-up assessment or could not be contacted, with missing data as a result for these participants.[166]

Loss to follow-up therefore risks compromise the validity of a study, and the importance of attrition bias therefore needs to be considered. Considering factors of gender, age, and distance to the study center, it is possible to mitigate loss to follow-up.[167]

In paper III, all patients alive performed a follow-up assessment and no patients were lost to follow-up. It should be noted, though, that patients who did not actively consent to participate in LSR were not included, and 3% declined initial participation in LSR.

In the follow-up assessment at 1 month, 3 months and 12 months post stroke in paper IV, a few patients (n=3) were lost to follow-up. At 1 month, 2 patients declined follow-up due to illness (both of whom died within 12 months), representing 3% (2 of 60 patients) of the total cohort. At 3 months, 1 patient did not consent to continued aphasia evaluation, constituting 2% of the cohort (1 out of 54 patients), but at 12 months there was no further loss to follow-up.

Summarizing the total cohort of alive patients at 12 months, only 1 patient declined follow-up (1 out of initial 60 PWA at baseline), however 10 patients were deceased within the study time period, constituting a substantial 17% of patients of whom the outcome of aphasia is not reported. Loss to follow-up is important to consider in determining a study's validity, since patients lost to follow-up can have a different prognosis in comparison to those PWA who completed the study.[168]

To mitigate loss to follow-up, home-visits were offered to participants who could not come to the hospital for an examination. This is especially important for patients who live further away from the study center, who have an decreased likelihood of completing the follow-up assessments compared to patients who live closer to the study center.[169] To summarize, the loss to follow-up only constitutes a small proportion of the cohort, and substantial attrition bias is therefore not as likely.

Measurements

Bias arising from measurement error (also known as observational bias or information bias) refers to misclassifications due to flaws in measurements, affecting the accuracy and quality of information collected.[170] Measurement errors can either overestimate or underestimate the true results of the study.

Paper I, II and III – National Institutes of Health Stroke Scale

In paper I, we validated NIHSS item 9 for its use as a diagnostic screening tool to detect aphasia after ischemic stroke. The Language Screening Test (LAST)[128] was used as reference standard since it has been recommended for screening for language impairments in acute stroke settings.[47,130] Validation of a NIHSS item 9 aphasia diagnosis with other assessments than LAST might have yielded other results. However, LAST has high diagnostic accuracy[128] and all assessments were performed by a SLT specialized in neurological communication disorders. LAST is also specifically designed to avoid subtests of language that can be affected by other stroke symptoms. Furthermore, if lengthier aphasia assessments had been used, loss to follow-up might have been larger, constituting information bias instead.

In paper II and III, NIHSS item 9 was used to detect aphasia. As discussed above, the use of other language tests, for example, including assessments of all language modalities, might have affected outcome results. However, the objective was to calculate the initial incidence of aphasia in the acute stroke patient and few other tests would have been feasible to perform in this setting. The use of a standardised language battery may be confounded by the rapid changes of language symptoms in the hyperacute phase. The use of more complex material, and distinguishing language from executive dysfunction, memory or attention deficits are also not feasible in the acute setting.

Screening methods such as NIHSS item 9 for evaluation of aphasia have strengths and limitations. Strengths regarding NIHSS item 9 include that NIHSS is globally known and used by a vast majority of clinicians working with stroke, therefore facilitating comparison of research results and ensuring capture of most stroke patients. Limitations include that this scale was not originally designed to diagnose stroke symptoms like aphasia, making it difficult to assess specific language symptoms or the severity of aphasia with NIHSS item 9.[116] It is also a coarse instrument for aphasia, not adapted to the target language or culture, making it susceptible to bias within these two aspects.[171] In the study of incidence, the importance of having a representative cohort including all possible study subjects (in this case stroke patients) is vital. NIHSS is a valuable tool in this aspect for initial assessment in the stroke emergency setting[118] where it is a an instrument already implemented and integrated in clinical use. The NIHSS has also shown excellent reliability, with high inter- and intraobserver reliability, as well as high validity and reliability when applied to retrospective medical chart reviews.[155,172] Furthermore, even though neurologists and SLTs spend years of training to assess aphasia and patients with neurological deficits, the first clinician to assess the stroke patient in the acute phase of stroke, is often another health care practitioner. NIHSS can be performed by all trained health-care providers with continued high validity and reliability which provides the clinician and researcher with an accurate and quick assessment of stroke symptoms. Nevertheless, there may be bias in the incidence of aphasia between year 2005-2006 and year 2017-2018 due to different routines and management in the assessment of aphasia using NIHSS. Differences in availability of specialized SLT to consult and/or assess patients may also have affected the reported incidence, perhaps detecting additional patients with aphasia during 2017-2018 that were not detected year 2005-2006, with regards to better general aphasia knowledge.

The scoring rules of item 9 may influence the detection of aphasia, where there may be an allowance for an incorrect response, provided all other domains of language function are normal.[116,171]

Another aspect of using NIHSS item 9 to detect aphasia is that comatose patients automatically receive a score of 3 on item 9. In paper II, 28 patients had a score of 3, global aphasia, and 7 of these patients had a decreased level of consciousness according to the Reaction Level Scale 85 (RLS 85).[152] According to additional medical chart review and assessment at follow-up in the present thesis, only 3 comatose patients may have been incorrectly diagnosed with aphasia. This may pose a bias of the incidence rate of aphasia.

In paper III, NIHSS was used to monitor recovery. Studies of NIHSS have previously established the reliability and validity for using NIHSS to measure stroke outcome.[117,173,174] The objective of paper III was to include comparisons of aphasia short-term outcome, and the same aphasia assessment method that had been used in the initial phase of stroke (NIHSS) was therefore applied. Nonetheless, the use of stroke scales as a measure of outcome can be questioned. Even though NIHSS can allow for serial monitoring and detecting a difference in status, limitations of the NIHSS must be considered. The detected prevalence of aphasia may have been affected, misclassifying patients as having aphasia or not having aphasia (false-positives and false-negatives).

Additionally, NIHSS was administered by different health professionals in different hospital settings (acute and subacute phase) which may have affected the results of the NIHSS evaluation. However, as mentioned above, reliability of NIHSS when performed by a person certified to assess NIHSS, has been shown to be excellent regarding all health care professionals even with limited clinical experience.

The NIHSS is poorly associated with the impact a neurological deficit may have on the specific individual, with no attention to e.g. the ability a patient has to compensate for symptoms, or patients´ perspectives. For these reasons, more standardized comprehensive aphasia assessments are used in paper IV to elucidate more accurate information on aphasia recovery.

To summarize, NIHSS has important value in the studies in this thesis, with a strength of feasibility within acute phase stroke research. Nonetheless, understanding the limitations of stroke scales is central and the use of such scales to describe longer-term recovery and disability, without incorporating patients´ perspectives, are at least in part limited.

All measurements at baseline were collected by SLT, research nurses or physicians at LSR adhering to clearly defined protocols, and information was validated by the thesis author.

Paper IV

At the 1 year follow-up, patients were assessed with a standardized, detailed, aphasia test, the Comprehensive Aphasia Test (CAT),[175] and a patient reported outcome measure, the Aphasia Impact Questionnaire (AIQ).[140] All patients were assessed by the same SLT and the standardized CAT protocol was administered with clearly defined instructions[138] to mitigate the risk of information bias.

AIQ is a self-reported measurement, and thereby a subjective assessment in measuring an individual´s self-perception of degree of language ability and the impact it has on everyday life. This has become a ´gold standard´ method for assessing health-related quality of life in adults with aphasia.[176] However, a challenge in the assessment, is its subjectivity, and items of the AIQ may not have the same salience to different persons with aphasia, including that questions may have varying meanings for different individuals.[177] Subjectivity can be influenced by age, gender, socioeconomic status and culture, making it more difficult to make comparisons between individuals, affecting the generalizability of the results.[177] Patients' ability to adapt to their illness and alter their perspective on severity also need to be considered. However, assessing PWA. and their experience of having aphasia, provide a comprehensive understanding of the health status of PWA and incorporating HRQoL aspects are essential in the measurement of overall health outcome.[178]

CAT has previously been validated in the stroke population with aphasia[136,179-181] and has been translated and adapted into Swedish, with ongoing studies of psychometric properties.[135] There may be a ceiling effect in CAT for those persons with very mild aphasia,[175] which may introduce a bias when interpretating the results of recovery of aphasia. Further, the lengthy administration time of CAT may affect the result of tested language functions due to e.g. poststroke fatigue.

Likewise, there may be risk of bias when interpreting the results of health-related quality of life, using the Aphasia Impact Questionnaire (AIQ), when PWA receive support from a SLT or next of kin in completing the form. Using a proxy causes less well-known psychometric properties. However, instructions for the administration of AIQ is to give as much support, encouragement and feedback as possible,[140] with directions to modify the questioning to make it accessible to someone with aphasia.[140]

Confounding

Confounding refers to an inaccuracy in the estimated measure of association and occurs when a variable is associated with both the primary exposure of interest and the measured outcome.[182] Bias due to confounding can distort associations that are essentially caused by a confounder variable. Minimizing confounding bias was done by measuring and adjusting for potential confounding variables.

Paper II

Incidence rates of aphasia were standardized to the updated European Standard Population (ESP) of 2013 and sex- and age adjusted to the Swedish population of 2017. Standardization to a common population is important to accurately compare incidence rates. Potential confounders when comparing incidence rates from different demographic and geographical areas include differences in the population composition, regarding e.g. age and sex. Standardization to the World Standard Population yielded a lower incidence rate than that of the ESP or Swedish population due to a higher proportion of young people, since stroke more often occurs among older individuals. The incidence rate of aphasia adjusted to the ESP and the Swedish population were similar (31 per 100 000 person-years vs 35 per 100 000 person-years), inferring a similar population distribution.

Paper III

Paper III examined several baseline measures and their association with aphasia outcome, with multivariable regression analysis. Several associations were affected by confounding factors. For example, when examining associations between increased mortality for patients with aphasia, both age and stroke severity could potentially have caused bias if not adjusted for, since both age and stroke severity likely influence both the exposure and outcome measures. Likewise, associations between TOAST subtypes, risk factors and aphasia were considered and adjusted for confounding when examining these associations.

Paper IV

Similarly, as described above, regression models were used to assess the relation between baseline and follow-up variables, aphasia outcome and HRQoL. Variables considered for confounding were stroke severity, age, gender, level of education and the effect of cognitive impairment on HRQoL for aphasia. Variables separate from stroke and aphasia, can also impact HRQoL regardless of a diagnosis of aphasia.[28]

Other statistical calculations were also considered. In Paper IV, more complex statistical models such as ANOVA or mixed models could have been plausible choices, however due to the limited number of participants included in the study these were not used.

The generalizability of the results depends on the population studied. The population cohort studied is likely representative, not only for Sweden but also for other high-income countries. Even though the municipality of Lund has one of the highest rates of higher level education compared to other Swedish municipalities,[150] the catchment area of SUS (with an additional 7 municipalities) comprises of educational levels similar to that of the total Swedish population.[150] In the future, the population composition may change in Sweden concerning monolingualism vs bilingualism and language acquisition due to changes in demographics.

General Discussion

Aphasia Diagnosis

In paper I, the widespread and globally used NIHSS item 9, was validated for its use to diagnose aphasia after ischemic stroke. Despite that NIHSS has become the standard for routine assessment of neurological deficits in the acute phase of stroke,[116] NIHSS item 9 had not been explicitly validated to detect aphasia. NIHSS is routinely included in the acute neurological examination and, therefore, a potentially useful tool for first identification of aphasia and to monitor progress. Examining NIHSS' accuracy in diagnostic precision of aphasia, was therefore vital and has considerable implications for stroke care.

The major finding of paper I was that all patients with severe to global aphasia were correctly diagnosed with NIHSS, however, people with mild aphasia risked being misclassified.

NIHSS has excellent specificity of 95%, however the sensitivity of 72% raises concerns, since the absence of aphasia upon a NIHSS item 9 examination does not necessarily eliminate language impairment. Similar tendencies have been reported with other screening tests being adequate instruments to diagnose severe impairments, yet mild symptoms have been difficult to differentiate from normal functions.[1] Even though only correctly diagnosing 70% of people with mild to moderate aphasia (positive predictive value), prior studies and other language tests have demonstrated similar results,[6,183] NIHSS item 9 can be regarded as an acceptable tool considering its widespread clinical implementation. This emphasizes the need to consider the underlying reasons for an incorrect diagnosis, where the conclusions from paper I shows that it may be difficult to differentiate between aphasia and motor speech disorders, as well as identifying persons with cognitive or predominately comprehension deficits. Since even mild aphasia may have great impact on the individual patient, accurate diagnosis is imperative.

Additionally, studies in language proficiency have reported that language barriers can affect length of hospital stay,[184] the likelihood of follow-up appointments,[185] and patient treatment.[186] These findings may extend to the aphasia population, particularly since communication is a fundamental task needed in all aspects of participation and activities, among those being health care access.

Altogether, dedicated focus on improving diagnosis of aphasia is warranted and essential for assuring the quality of health care for this patient group. Routine, structured screening and assessment for aphasia will not only permit more accurate detection of its presence, but also facilitate interdisciplinary management.

Aphasia Incidence

The main finding in paper II was that despite a decrease in stroke incidence, the proportion of ischemic stroke patients who have aphasia in the acute phase remains stable at approximately 30%. This suggests that recent advances in stroke prevention have not affected the incidence of aphasia after first-ever ischemic stroke.

The overall absolute number of PWA after ischemic stroke decreased accordingly with the decrease of stroke incidence rates. There was a trend towards a larger decrease among men having aphasia in comparison to women, this could however, be due to the small sample size or that stroke severity was higher for women in 2017-2018.

Even though a high proportion of patients with aphasia present with a cardioembolic stroke, the risk of aphasia is most importantly related to stroke severity. Age was also associated with higher risk of more severe strokes.

There was no temporal difference of aphasia severity. This is of grave concern since initial severity is an important prognostic factor for recovery.[103,187] Similar severities of aphasia have been reported in the 1990s and in the beginning of the 21st century,[79,82,83] warranting higher focus on future possibilities of reducing the risk of aphasia, perhaps by continued focus on the reduction of stroke severity and risk factors effecting severity of stroke, i.e. atrial fibrillation.

Short-term and Long-term Prevalence of Aphasia

Paper III reports up-to-date short-term prevalence of aphasia. At median day 5 (≤15 days post stroke) 15% of all living stroke patients have aphasia. Even though the proportion of patients with aphasia depends on methodological aspects concerning the timing and type of language assessment, the results suggest a decrease in prevalence of aphasia compared to earlier decades.[82,87,188,189]

According to the Swedish Stroke Register (Riksstroke) there have been considerable changes in acute stroke care in Sweden with an increase of recanalization treatment from 3% in 2005 to 15% in 2017.[190] Advanced acute stroke treatment may therefore have affected the outcome of aphasia after stroke and reduced the proportion of people with aphasia at median day 5. This adheres to other research showing improvement of aphasia and an increase in recovery after acute stroke treatment,[191,192] with positive effects on independency in activities of daily living (ADL) after stroke.[190]

In the long-term perspective, paper IV, reports a continued prevalence of aphasia of 15% of all living stroke patients at 1 year. This may suggest that the majority of aphasia recovery takes place early after onset, a finding that is consistent with previous studies.[83]

This thesis does not report on timing or percentage of PWA receiving speech and language therapy, which potentially has enhanced aphasia recovery[37] and may have affected the overall prevalence. Also, patients with other neurogenic communication disorders, due to e.g. cognition deficits, may have been included in the cohort of patients with aphasia, since cognitive disorders and aphasia partially have similar symptoms. Additionally, distinguishing language deficits from mild cognitive symptoms may be clinically difficult since language is not possible without supportive cognitive processes of e.g. short-term memory and executive function.[193]

Short-term Prognosis of Aphasia

Paper III also demonstrated that a majority, approximately 57%, of stroke patients with aphasia had favorable short-term aphasia outcome. Full aphasia recovery was observed in 39% of people with aphasia. The results are corroborated by other recent studies that have reported similar findings regarding aphasia recovery after ischemic stroke.[87] Even though direct comparisons are difficult to perform, due to differences in for example methodology and stroke management, previous studies from the 1990s reported higher proportions of aphasia and a larger proportion of patients with more severe aphasia than that of today.[82] This can be interpretated as an improvement in functional outcome of aphasia, most likely owing to the decrease of stroke severity over the past 20 years,[194] as well as to the progress of acute recanalization therapy.[195]

Case Fatality

Stroke patients have relatively high mortality[196] and this was also observed in the studied cohort of PWA, where the in-hospital mortality was 18%.[197] PWA have a significantly higher mortality rate than stroke patients without aphasia, most likely due to stroke severity. For a number of patients, stroke is still fatal, nevertheless, mortality rates have decreased significantly over the years[198] with previous studies of PWA reporting a mortality rate over 30%.[82]

Continued stroke prevention and focus on treating stroke risk factors to reduce stroke severity are further warranted. Further improved diagnosis and treatment of risk factors, for example atrial fibrillation, is likely to have substantial impact on stroke.[199]

Long-term Aphasia Recovery

The results in paper IV showed that most of aphasia recovery occurred during the first months after stroke, adhering to recent studies suggesting that after 6 months, aphasia is considered a chronic condition with a plateau of language improvement after this point in time.[105] Significant aphasia improvement was seen between 1 month and 12 months post stroke, and rates of language recovery was slower after 3-6 months post-stroke, which is supported by previous work.[92]

Nevertheless, the findings in e.g. Figure 22 illustrate a high variability in outcome of aphasia among individual patients, suggesting that inter-individual language recovery exists, and that later recovery, although perhaps slower, is still possible. Improvement was also numerically observed across all severities of aphasia and within all language domains, however only statistically significant improvement was noted regarding naming, repetition, and comprehension of written language. Favorable aphasia outcome declined with relation to aphasia severity; 41% of people with mild aphasia, 37% with severe aphasia and 22% of global aphasia showed improvement. Even though overall language recovery have been observed across all types of aphasia, different aphasia syndromes have demonstrated to recover to different degrees.[20] Initial aphasia severity seems to be the best predictor of recovery.[103]

Considering the total cohort of patients, 61% of patients with initial aphasia after ischemic stroke have chronic aphasia (as assessed at 12 months). That almost 6 out of 10 will have long-lasting language impairment, most likely accompanied by other symptoms effecting overall psychological health, is of considerable concern.

Health-Related Quality of Life for People with Aphasia

Paper IV detected that the HRQoL was negatively affected for a majority of PWA. PWA reported that aphasia affected communication, participation as well as their emotional well-being. These findings are consistent with previous studies reporting negative effects and poor HRQoL for PWA.[27,31,200] In addition, the findings of paper IV showed that there was no significant temporal difference in HRQoL between 3- and 12 months post stroke. This emphasizes the necessity of including HRQoL-assessments early and incorporating this aspect in the treatment of aphasia. Understanding what aspects of peoples' lives that are most affected after aphasia can help guide clinicians in intervention,[31,54] with person-centered rehabilitation relevant to the individual, for example patient targeted naming therapy or communication partner training. HRQoL measures have not been systematically incorporated in clinical practice of speech and language therapy[201,202] and are seldomly used as an outcome measure.[37] PWA in our cohort have therefore not received SLP therapy with focus on HRQoL, which may have contributed to the non-significant change of HRQoL reported by the participants in the study.

Paper IV also reports on factors related to HRQoL for PWA. Language comprehension and expressive language functions were both associated with HRQoL, with the strongest correlation seen for writing. PWA have previously been shown to have difficulties with technology-based written communication[203] and writing has become increasingly important with text-based communication having a central role in how people communicate.[204] The increased significance of literacy and importance of writing skills in the social environment[204] corroborates our results of the impact of writing deficits on HRQoL for PWA.

Previous studies reported an association between aphasia severity and quality of life,[27] but these studies did not consider overall stroke severity.[27] The results of paper IV confirm that HRQoL is affected by aphasia severity, however, in addition, HRQoL is significantly negatively affected for PWA regardless of stroke severity and age. This finding is important to consider in the management of people with aphasia.

Although the degree of aphasia impairment and severity of stroke are important aspects of HRQoL for PWA, there may also be other variables that influence the self-perceived impact aphasia has on an individual. Factors such as age, gender, social support, mood, and a person´s ability to compensate for their disability, may all affect HRQoL.[205-207] Furthermore, participating in a study, and receiving adequate and early SLT consultation, in comparison to standard care, may have affected the results of HRQoL for PWA in our study. Additional rehabilitation early after stroke has been seen to increase self-reported HRQoL among stroke patients.[208] Though it is not clear to what degree and how long a potentially positive affect on HRQoL would last, effects of having a SLT accessible, including scheduled appointments (sometimes via home visits), should be considered when interpretating HRQoL outcomes.

Several variables have been suggested to be related to good HRQoL after stroke, particularly having social support[206] and participating in social activities.[209] Taking this into consideration, it is not surprising, that PWA with diminished social networks[7] and support of others, report significantly worse HRQoL compared to stroke patients without aphasia.[27,31] Other personal factors may also affect self-perception of HRQoL for PWA, these include premorbid language function and communication skills, as well as how a person relates to the importance of communicating with the environment.[210] Communication is used in various ways and with different intents,[210] and the needs and purpose for communication may vary between people, thus affecting the impact aphasia may have on the individual.

Our results emphasize the importance of incorporating HRQoL in aphasia assessments and capturing the patients´ perspective on the impact of aphasia. Aphasia rehabilitation programs can then specifically aim to improve symptoms of the language disorder as well as improve the patient´s overall well-being, through incorporation of the patient in the rehabilitation process.

Ethical Considerations in Aphasia Research

With the loss of language and communicative abilities, people with aphasia may be unable to provide their views and input concerning decisions regarding their care and complying to participate in research. Difficulties can arise in deficits of comprehending research information or expressing the decision option they prefer.[211] There are no agreed-upon guidelines for the decision-making ability of people with aphasia,[212] special focus on this topic therefore needs to be considered.

Decision-making involves multiple cognitive and linguistic abilities and even though PWA may have preserved abilities to make an informed decision, they do not always have access to the language required to understand or express their opinions. Since the adequacy of information given to a patient can influence a persons´ decision-making, it is important to provide correct and sufficient information regarding a research study.[5] The present study therefore provided participants with aphasia friendly-material, as well as involved the patients´ next of kin in the study inclusion process when needed, ultimately aiming at increasing the patients´ own informed decision-making. Specialist training within communication disorders, like that of a SLT, have been seen to help identify and support patients with deficits and thereby gain informed consent.[5]

Furthermore, since symptoms and ability to make decisions can fluctuate throughout recovery, consenting to a longitudinal study can be extra difficult for PWA. Evidence show that persons with communications deficits do not always receive the support they require,[213] therefore, information about the study was provided at every follow-up appointment to ensure that PWA had sufficient means to comprehend information and strategies to facilitate the communication of their decision.[214] The SLT was also receptive to non-verbal cues of consent or decline.

Making assumptions for people with aphasia without providing communicational support may pose ethical consequences with risk that the decision goes against patient autonomy.[215] On the other hand communication barriers have in prior studies led to the exclusion of PWA from clinical trials,[216] due to difficulties in the consent process.

In conclusion, this thesis has used methods for supporting and adapting communication to PWA to try to facilitate communication and ensuring that the decision reflects PWA´s choice. Making PWA ineligible to be included in research due to difficulties in obtaining consent, would have substantial impact on future management and rehabilitation of people with aphasia after ischemic stroke.

Conclusions

- NIHSS may be used to diagnose patients with aphasia in acute stroke care, however, caution should be taken when patients have speech motor deficits, difficulties with cognition or predominately symptoms of language comprehension. PWA with mild aphasia symptoms risks being misdiagnosed.
- The initial incidence of aphasia in first-ever ischemic stroke remains stable at approximately 30%, with no significant temporal change between 2005-2066 and 2017-2018, despite changes in stroke prevention.
- The age- and sex-standardized incidence rate of aphasia after first-ever ischemic stroke adjusted to the Swedish populations amounts to 35 per 100 000 person-years.
- Stroke severity (according to NIHSS excluding the aphasia component) is independently and significantly associated with aphasia and aphasia outcome.
- Patients with aphasia have significantly more severe strokes, longer hospital stays, are more often discharged to short-term care facilities and have higher mortality compared to stroke patients without aphasia.
- Short-term aphasia outcome is favorable for a majority of patients (57%) with 39% experiencing complete recovery.
- Long-term aphasia outcome shows that 61% have persisting aphasia and are in need of rehabilitation. Of the group with persisting aphasia, 52% experience mild to moderate aphasia, whereas 48% have severe to global aphasia.
- HRQoL is affected for PWA. Aphasia negatively impacts communication, participation as well as emotional well-being, and is strongly related to aphasia severity.
- HRQoL for PWA is stable from 3 months to 12 months post stroke, however individual variations are seen. There is need for further research on how to improve aphasia outcome and incorporate HRQoL measures in SLT intervention.

Future Perspectives

Stroke is the disease that causes the most physical disability among the adult population[39,40] and aphasia after stroke continues to be a common symptom with consequential disabling outcomes for individuals. Despite preventative efforts and advanced stroke treatment, aphasia management and treatment need to be emphasized within stroke care and rehabilitation. Improved disease prevention with effects on aphasia is needed, as well as further development of the care for PWA to reduce the devastating consequences of language impairment.

The WHO has emphasized rehabilitation after stroke, focusing not only on the impairment of bodily function, but also on the impact and effect stroke has on patients´ quality of life.[54,108,109] Important topics within aphasiology that need further focus include a holistic approach to rehabilitation with impairment-based therapy and functional communication therapy in relation to the general environment. Future treatment-based studies need to fill large knowledge gaps within aphasiology, such as answering questions concerning how patients may benefit from therapy, when to treat patients, and what type of intervention PWA need. This is important to provide additional knowledge that may lead to new evidence-based therapies for PWA. Other aspects in need of further study are how treatment can aim at overall communication ability for PWA, translating into real-life communication effects.

Incorporating aspects of cognition and fatigue in research of aphasia therapy may also support new knowledge of how other factors than language affect treatment results for PWA. The interaction of cognition and cognitive abilities important for the re-learning of language, needs to be assessed and explored in future treatment studies.

This thesis demonstrates the dynamics of aphasia outcome after stroke. Aspects concerning the neural plasticity and neuroanatomy of language disabilities and recovery, regarding the timing of intervention, are still unclear. Research within these areas, including neuroimaging, can give a clearer understanding into the recovery process of aphasia and how treatment affects the neurobiology of recovery.

Paper I reports the importance of diagnostic accuracy of language assessments. However, validated aphasia measures within aphasiology remain scarce and a focus on standardizing and validating aphasia evaluations is required. The comprehensive aphasia test (CAT) has recently been translated and adapted into Swedish and in an international collaboration chosen as an outcome measure within aphasiology.[137] Continued studies collecting normative data on normal language function in the Swedish population, as well as standardizing performance of PWA, are needed to confirm the test´s validity and its use in clinical care and research.

Qualitative studies may provide improved insights into the views of PWA which have been insufficiently studied to date. This thesis confirms poor HRQoL for PWA, however future qualitative methods may increase the understanding of factors that may contribute to poor HRQoL, providing a more comprehensive perspective of this patient group. Understanding the individual's concepts and experiences among PWA may provide more in-depth insights of what aspects to target in intervention.

Qualitative research also provides data collection from a real-world context and a better understanding of the effect aphasia has on communication in the environment, as compared to the quantitative communication measures used today. Open-ended responses may have an important role in this context. Perception and an understanding of an individual's premorbid cognitive function and language and communication skills, including how the specific person values communication, may also be enhanced through qualitative research. Factors of how a person communicated prior to the stroke and incorporating ICFs perspective on intervention is also of importance for patient-centered health care.

Society today is rapidly and vastly changing, with high proportions of individuals with higher education and bilingualism being common in the Swedish population.[150] The effect of aphasia on first and second language acquisition and potential restorative components of being multilingual should also be subjects for future research.

This thesis with current epidemiological data of aphasia in Sweden, contributes to a foundation for the future management of this patient group. The need for routine screening and assessment of aphasia after ischemic stroke should be highlighted and will not only allow for more accurate detection of the presence of aphasia, but also facilitate interdisciplinary management. Accurate evaluation of aphasia may facilitate differentiating related and confounding diagnoses, such as the presence of other cognitive impairments or depression. Future perspectives also include planning for health care resources, assessing societal costs of aphasia e.g. the impending increase in retirement age, and initiating work on how health care better can adhere to clinical aphasia and stroke guidelines.

To conclude, further research is needed in all aspects of aphasiology, though management and rehabilitation of aphasia should be prioritized. Research should include treatment options to improve language impairment and health-related quality of life, and incorporation of the patients´ perspective and their self-perceptions regarding their language impairment. In-depth knowledge and heightened awareness on aphasia after ischemic stroke, are essential to mitigate the potentially severe consequences aphasia.

Populärvetenskaplig Sammanfattning

Stroke är en av våra stora folksjukdomar och är den vanligaste orsaken till funktionsnedsättning bland vuxna. Afasi är en språkstörning till följd av en hjärnskada och ett vanligt symtom vid stroke. Av alla personer som får afasi har 85% haft stroke. I dagsläget finns få aktuella studier som kartlagt hur många som insjuknar varje år med afasi efter en förstagångsstroke i Sverige (även kallat incidens) och det är svårt att prognosticera återhämtning av afasi vid stroke.

Afasi påverkar en persons förmåga att prata, förstå tal, läsa och/eller skriva. Symtomen kan variera i omfattning och svårighetsgrad; från en total oförmåga att kommunicera genom tal eller skrift, till lindriga symtom inom en specifik språklig funktion.

Förmågan att prata och kommunicera är något som vi använder oss av dagligen och en språkstörning som afasi får därför stora konsekvenser för den enskilde individen och deras närstående. Afasi påverkar förmågan att uttrycka ens känslor, tankar, och att ställa och svara på frågor. Vidare behövs språk för inlärning och för att vi ska känna oss delaktiga i samhället och de allra flesta aktiviteter som vi ägnar oss åt inbegriper någon form av kommunikation. På individnivå kan därför afasi vara förödande med stora negativa konsekvenser för en persons livskvalitet och psykosociala välbefinnande.

De senaste decennierna har strokesjukvården gjort stora framsteg i arbetet att förebygga stroke genom att till exempel behandla riskfaktorer för stroke (högt blodtryck, diabetes, hjärtsjukdom etc.), samtidigt som det har kommit nya behandlingsmetoder för stroke i akutskedet. Detta kan ha påverkat hur många personer som insjuknar i afasi och vilka typer av språkliga symtom patienterna får. Kunskap om hur många som insjuknar, vad som påverkar återhämtning och hur det går för patienterna, är av stor vikt för att kunna planera sjukvård och rehabilitering för patientgruppen.

Avhandlingen består av fyra delarbeten där följande studeras: 1) metod för diagnosticering av afasi i akutskedet, 2) förekomsten av nyinsjuknanden i afasi efter förstagångsstroke, 3) korttidsprognos av afasi och faktorer som kan påverka återhämtning 4) långtidsprognos av afasi och hur personer med afasi själva upplever sina svårigheter och hur det påverkar deras livskvalitet.

Lund Stroke Register är en pågående sjukhusbaserad studie vid Skånes Universitetssjukhus i Lund som kontinuerligt inkluderar patienter som har diagnosticerats med en förstagångsstroke.

Delarbete I syftade till att säkerställa hur personer med afasi på ett pålitligt sätt kan diagnosticeras i akutskedet av stroke. National Institutes of Health Stroke Scale (NIHSS) är ett bedömningsinstrument, en så kallad strokeskala, som används globalt för att mäta symtom och svårighetsgrad av stroke. Skalan utvärderar och bedömer flertal olika strokesymtom, däribland afasi. Trots att skalan är mycket välkänd och används som klinisk praxis, har man tidigare inte verifierat att skalan kan användas för att diagnosticera afasi.

I delarbete I bedömdes totalt 221 patienter med NIHSS språkdel och sedan bedömdes patienterna med ett språkligt test som heter Language Screening Test (LAST) som utfördes av logoped. Resultaten av dessa två test har sedan jämförts sinsemellan för att studera hur väl NIHSS kan hitta patienter med afasi.

Resultaten visar att NIHSS har en specificitet på 95%, detta betyder att patienter som *inte* har afasi med mycket hög sannolikhet får ett negativt testresultat. Sensitiviteten av NIHSS, dvs sannolikheten att personer blir korrekt diagnosticerade med afasi när de faktiskt har afasi, var 72%. Alla patienter som hade svår afasi blev korrekt diagnosticerade, men testet hade ibland svårt att hitta de med lättare afasi.

Faktorer som påverkade NIHSS-metodens förmåga att diagnosticera afasi var andra strokesymtom såsom övriga talsvårigheter (till exempel sluddrigt tal pga. försämrad motorisk funktion) eller kognitiva (intellektuella) nedsättningar. Även personer som primärt hade afasi med språkliga symtom av typen svårt att *förstå* när någon talar, feldiagnosticerades oftare. Resultaten visade också att personer med hög ålder och lägre utbildning oftare får fel diagnos. Resultaten i delarbete I har viktig klinisk betydelse för de som arbetar med strokepatienter och visar att screening med NIHSS i akutskedet kan användas för att diagnosticera afasi, men att försiktighet bör iakttas vid testning av de med lättare språkliga symtom. Detta eftersom ett negativt test (dvs att man blir godkänd på testet NIHSS) inte alltid innebär att personen i fråga *inte* har afasi.

Delarbete II kartlägger antalet nyinsjuknanden i afasi efter en stroke. Mellan mars 2017 och februari 2018 insjuknade totalt 338 personer i Skånes Universitetssjukhus Lund (SUHL) upptagningsområde med en förstagångsstroke på grund av hjärninfarkt (blodpropp i hjärnan). Av dessa var 308 personer med i studien och 30% (dvs 91 patienter) hade afasi. Vid jämförelser av hur många som insjuknade med afasi i samma område år 2005–2006, var andelen 27%, vilket betyder att proportionen av personer som får afasi har legat på ungefär samma nivå mellan år 2005–2006 och år 2017–2018. Svårighetsgraden av afasi hade inte heller förändrats mellan 2005–2006 och 2017–2018 och 6 av 10 personer med afasi hade en svår eller global afasi. Svår afasi innebär att all kommunikation sker genom fragmentariska uttryck och att gissningar utgör huvuddelen av kommunikationen mellan individer, medan global afasi innebär att personen inte har något användbart språk alls.

Justerar man antalet personer med afasi till befolkningsstorleken i Sverige och till ålder- och könsammansättningen i samhället (även kallat ålder- och könstandardiserad incidens) så innebär detta att totalt 35 personer per 100 000 invånare insjuknar i afasi efter att ha fått en förstagångsstroke i Sverige varje år.

Många strokepatienter med afasi, får en stroke på grund av att en blodpropp har bildats i hjärtat som sedan stiger mot hjärnan. Detta är ofta en svår form av stroke och en anledning till att personer med afasi oftare har en svårare stroke jämfört med strokepatienter som inte har afasi. En svårare stroke kan vara en bidragande orsak till att patienter med afasi också kan ha efterföljande negativa konsekvenser av sin stroke. De har högre dödlighet jämfört med strokepatienter utan afasi och 18% av alla med afasi avlider på sjukhuset, jämfört med 2% av strokepatienter utan afasi. Personer med afasi skrivs också oftare ut till korttidsboende (jämfört med att få åka hem) och har längre vårdtider. Svårighetsgraden av stroke (mätt med testet NIHSS enligt ovan) och stigande ålder ökar risken för att få afasi.

Sammanfattningsvis är andelen av strokepatienter som får afasi hög (omkring 27–30%) och har inte förbättrats jämfört med år 2005–2006. Ökat fokus på åtgärder för att förebygga afasi efter stroke är därför indicerat. Vetskapen om hur många som insjuknar och vilken svårighetsgrad av afasi de har, är av stort värde för att beräkna och planera framtida sjukvårdsresurser för personer med afasi.

I delarbete III genomgick patienterna med afasi ytterligare en uppföljning, i genomsnitt dag 5 efter insjuknandet (alla bedömdes ≤15 dagar efter insjuknandet), för att kartlägga hur många som hade kvarstående afasi. Mellan mars 2017 till maj 2018 hade totalt 107 (av totalt 391 strokepatienter) afasi vid insjuknandet. Vid dag 5 var 89 av dessa 107 patienter fortfarande vid liv och av dem hade 61% kvarstående afasi. Ungefär hälften av dem hade lätt afasi och den andra hälften svår eller global afasi (som beskrivet ovan). Lättare stroke var oftare associerat med god återhämtning, och de med lätt afasi hade större chans att bli förbättrade jämfört med de med svår afasi, även om förbättringsgraden varierade på individnivå.

Faktorer som mest påverkade återhämtningen av afasi var den initiala svårighetsgraden av stroke, där svårare stroke innebar sämre återhämtning. Även tidigare funktionsbortfall, dvs att patienten redan före sitt insjuknande i stroke hade en funktionsnedsättning som innebar svårigheter att klara av att utföra alla vardagliga aktiviteter, ökade risken för sämre återhämtning. Antalet strokeriskfaktorer en patient hade före sin stroke, så som högt blodtryck, diabetes, hjärtsjukdom och rökning, hade också en negativ påverkan på chansen till återhämtning från afasi.

Sammanfattningsvis förbättrades majoriteten av personer som fått afasi (totalt 57% hade förbättrats) redan i genomsnitt dag 5 efter sin stroke. Av dessa var det 39%

vars språkliga förmåga helt återställdes. Detta innebär att korttidsprognosen av afasi nu har förbättrats jämfört med tidigare decennier. Trots detta är det många patienter som har kvarstående afasi och är i behov av rehabilitering.

Slutligen, i delarbete IV, så undersöktes alla överlevande strokepatienter med afasi ingående, både gällande afasi och deras livskvalitet vid 1-, 3- och 12-månader efter insjuknande (samma deltagare som i delstudie I). I studien bedömdes hur många som förbättrades i sin afasi och vilka kvarstående symtom patienterna hade. Patienterna fick också själva fylla i ett livskvalitetformulär för att beskriva hur afasin påverkade dem i vardagen.

Av totalt 60 patienter som hade afasi enligt logopedbedömning i akutskedet av stroke, var det 74% som hade kvarstående svårigheter efter 1 månad (4 patienter hade avlidit innan bedömning och ytterligare 2 var för sjuka för att genomföra undersökningen). Vid 3 månader efter strokeinsjuknandet var det 67% av de överlevande som hade kvarstående afasi (ytterligare 2 hade avlidit, 1 avböjde deltagande). Vid 6–12 månader bedöms afasi vara kronisk och vid sista uppföljningen vid 12 månader var det totalt 61% som hade kvarstående afasi (ytterligare 2 hade avlidit). De allra flesta (87%) uppvisade någon form av språklig förbättring mellan 1 och 12 månader, dock var den av varierande grad. Patienterna hade språkliga symtom av olika grad inom samtliga språkliga funktioner, dvs både svårt att prata, förstå språk, läsa och/eller skriva.

I ett självskattningsformulär rapporterade majoriteten av patienterna att afasi påverkade både deras förmåga att kommunicera med omgivningen, deras delaktighet i aktiviteter samt deras känslomässiga välbefinnande till hög grad. Livskvalitet var relaterat till svårighetgrad av afasi samt även patienters kognition (intellektuella funktioner) och språkförståelse, där sämre förmåga var relaterad till sämre livskvalitet. Även om individuella variationer fanns, rapporterade personerna med afasi i genomsnitt ingen betydande förbättring mellan 3- och 12 månader vilket innebär att deras afasi fortsatte ha stor negativ påverkan på vardagssituationer.

Sammantaget visar denna avhandling att andelen som får afasi efter stroke är fortsatt hög men att den tidiga återhämtningen av afasi är relativt god. Trots framsteg inom strokesjukvården är det många patienter som har kvarstående afasi efter stroke och som upplever stora begränsningar i deras vardag, med stor inverkan på deras självupplevda hälsa. Med hjälp av aktuella data kring antalet som får afasi efter stroke i Sverige, kan behovet av vårdresurser beräknas, med ett ökat fokus på att förbättra rehabiliteringen av både språkliga symtom och afasins påverkan på individens livskvalitet.

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