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Perspectives on post-stroke care and outcomes

Analyses based on the 1-year follow-up from Riksstroke

TERESA ULLBERG

DEPARTMENT OF CLINICAL SCIENCES | NEUROLOGY | LUND UNIVERSITY 2016



Perspectives on post-stroke care and outcomes

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Analyses based on the 1-year follow-up from Riksstroke

Teresa Ullberg



LUND
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DOCTORAL DISSERTATION

With permission of the Faculty of Medicine at Lund University, Sweden,
to be defended at Kvinnokliniken aula, Skåne University Hospital in Malmö on
October 15th 2016, at 9.00 a.m.

Faculty opponent

Professor Grethe Andersen, Aarhus University

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	Author(s) Teresa Ullberg	
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Title and subtitle: Perspectives on post-stroke care and outcomes. Analyses based on the 1-year follow-up from Riksstroke		
<p>Abstract</p> <p>Aims: The present thesis focuses on post-stroke care and outcomes, and constitutes the first in-depth analysis of the 1-year follow-up from the Swedish Stroke Register (Riksstroke). The aims were to describe case-fatality and changes in functional outcome over the first year after stroke (Paper I), to analyze unmet rehabilitation needs and its associated factors (Paper II), to explore what proportions of patients received stroke follow-up after hospital discharge (Paper III), and to calculate primary adherence and 1-year persistence to secondary preventive drugs, as well as to investigate the associations between stroke follow-up, socio-economy and drug adherence (Paper IV).</p> <p>Methods: Paper I and II included nation-wide data from patients hospitalized with acute stroke and registered in Riksstroke from January 1, 2008 to December 31, 2010, and for paper III and IV, data on patients residing in the region of Skåne in southern Sweden were extracted and merged with other official registers.</p> <p>Results: Paper I included 64 746 patients and case-fatality was 13% at 3 months and 18% at 1 year. In 35 064 followed up 12-month survivors, functional dependency almost doubled (16 to 28%) between 3 and 12 months after stroke. One in 8 patients who lived independently at 3 months, deteriorated to functional dependency between 3 and 12 months. Older patients, and in particular older women, were susceptible for deterioration.</p> <p>Paper II included 37 383 patients. The study demonstrated that 1 in 5 previously independent 12-month stroke survivors reported unmet rehabilitation needs 1 year post-stroke. Patients reporting unmet rehabilitation needs also more often reported other unmet care needs, such as pain, depression and poor self-perceived health. Unmet rehabilitation needs were most common among older patients (>70 years).</p> <p>Paper III included 8 164 patients residing in Skåne. The probability of receiving a doctor's follow-up within 3 months after hospital discharge for stroke was 76%. Older patients, those with pre-stroke functional dependency, and those with previous or severe stroke, had lower probability of receiving a stroke follow-up within 3 months.</p> <p>Paper IV included 7 100 patients with ischemic stroke, residing in Skåne. The study showed that use of secondary preventive drugs decreased over the first year after stroke. One in 3 patients had stopped using at least one drug class at 1 year post-stroke. Stroke organizational factors such as discharge location and stroke unit care were associated with continued drug use. We found that a doctor's follow-up within 3 months was associated with drug adherence for antiplatelet and antihypertensive agents. High educational level was associated with continued use of warfarin.</p> <p>Conclusion: We identified disparities in Swedish post-stroke care, mainly affecting patients of old age and poor functional status. No structured follow-up service for stroke has been implemented in clinical routine, and this may affect the most vulnerable groups. We found that use of secondary prevention is suboptimal, and that rehabilitation and other care needs were unmet in a large proportion of patients at 1 year post-stroke. We also found that functional outcome after stroke is dynamic, and may change between 3 months and 1 year.</p>		
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2016-09-08

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Analyses based on the 1-year follow-up from Riksstroke

Teresa Ullberg



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To my family

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Original Papers

This thesis is based on the following papers referred to in the text by their Roman numerals. The four papers are appended at the end of the thesis. Permission for reprinting has been granted by the publishers.

- I. Ullberg T, Zia E, Petersson J, Norrving B. Changes in functional outcome over the first year after stroke. An observational study from the Swedish Stroke Register. *Stroke* 2015 Feb; 46(2): 389-94.
- II. Ullberg T, Zia E, Petersson J, Norrving B. Unmet rehabilitation needs one year after stroke. An observational study from the Swedish Stroke Register. *Stroke* 2016 Feb; 47 (2): 539-41.
- III. Ullberg T, Zia E, Petersson J, Norrving B. Doctor's follow-up after stroke in the south of Sweden. An observational study from the Swedish Stroke Register (Riksstroke). *European Stroke Journal* 2016, Vol. 1(2): 114-121.
- IV. Ullberg T, Glader E-L, Zia E, Petersson J, Eriksson M, Norrving B. Associations between stroke follow-up, socio-economy, and adherence to secondary preventive drugs in southern Sweden: Observations from the Swedish Stroke Register. Submitted manuscript.

Abbreviations

ACE	Angiotensin Converting Enzyme
ADL	Activities of Daily Living
ATC	Anatomical Therapeutic Chemical (drug classification system)
BI	Barthel Index
CI	Confidence Interval
DALY	Disability-Adjusted Life Years
ESD	Early Supported Discharge
ICD	International Classification of Diseases
ICF	International Classification of Function, Disability and Health
ICH	Intracerebral Hemorrhage
mRS	modified Rankin Scale
NIHSS	National Institute of Health Stroke Scale
NOAC	Novel Oral Anticoagulant
NPR	National Patient Register
OR	Odds Ratio
PAR	Population Attributable Risk
PIN	Personal Identification Number
PREM	Patient-Experienced Outcome Measure
PROM	Patient-Reported Outcome Measure
RCT	Randomized Clinical Study
RLS	Reaction Level Scale
RR	Relative Risk
TIA	Transient Ischemic Attack
TPR	Total Population Register
WHO	World Health Organization

Introduction

Despite important achievements within the acute stroke field during recent years¹⁻⁴, involving both new highly effective treatments and subsequent organizational changes, a majority of stroke patients experience residual neurological impairments or disabilities⁵, and carry a risk of stroke-related complications⁶. On a societal level, the burden of stroke has large implications, both economically and in terms of mortality and morbidity^{7, 8}. The present thesis focuses on stroke care and outcomes in the longer perspective, and constitutes the first in-depth analysis of the 1-year follow-up from the Swedish Stroke Register (Riksstroke).

Stroke definition and classification

The World Health Organization (WHO) definition of stroke originates from the 1976 publication by Hatano et al⁹:

“Rapidly developed 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 of vascular origin”

The definition includes ischemic stroke, intracerebral hemorrhage (ICH) and subarachnoid hemorrhage, but excludes transient ischemic attack (TIA). Stroke is a heterogeneous disorder caused by diverse pathological mechanisms. Ischemic stroke accounts for approximately 85% of stroke cases in developed countries¹⁰, and is caused by an interruption of a cerebral blood vessel. The most widely used classification system of ischemic stroke is the Trial of Org. 10172 in Acute Stroke Treatment (TOAST) classification system¹¹, which subdivides ischemic stroke causes into five core etiologies: large artery disease, small artery disease, cardiac embolism, other determined causes and cryptogenic stroke.

Large artery disease is a major cause (15–20%) of cerebral infarction in western populations¹². The main pathology is atherosclerosis. Approximately one quarter of ischemic strokes are caused by small vessel occlusion¹², characterized by single subcortical lacunar infarctions of less than 15–20 mm in size¹³. The mechanism behind small vessel disease is not entirely clear, but involves thickening of vessel walls,

with fibrosis and narrowing of the lumen¹⁴. Cardiac embolism accounts approximately 30% of ischemic strokes¹², and is most commonly caused by atrial fibrillation, but rare causes include emboli from patent foramen ovale and infective endocarditis. Approximately 5% of ischemic stroke cases are of other determined etiology¹⁵, such as arterial dissection, genetic or coagulation disorders or cerebral vasculitis. In the remaining 25–30% of ischemic strokes, the causal mechanism cannot be identified despite an extensive work-up, and these strokes are classified as cryptogenic (undetermined)¹⁶.

Intracerebral hemorrhage accounts for approximately 10% of stroke cases in western countries¹⁰, and is caused by the rupture of a cerebral blood vessel. Causes of ICH include small vessel disease, amyloid angiopathy, tumors and trauma, as well as venous disease and vascular malformations¹⁷.

Subarachnoid hemorrhage accounts for 5% of all stroke cases¹⁰. It is caused by the rupture of a meningeal vessel, and the majority (85%) are aneurysm ruptures¹⁸.

Stroke epidemiology in Sweden

Stroke is the second leading cause of death¹⁹, and the third leading cause of disability-adjusted life years (DALYs) worldwide²⁰. In the Global and Regional Burden of Stroke study, age-adjusted stroke incidence in high-income countries in 2010 was estimated at 139 (95% CI: 131–148) cases per 100 000 person-years in individuals <75 years, and 2 724 (95% CI: 2554–2900) per 100 000 person-years in individuals >75 years. The age-adjusted mortality rate was estimated at 24 (95% CI: 22–26) per 100 000 person-years in individuals <75 years, and 1 225 (95% CI: 1155–1394) per 100 000 person-years in individuals >75 years. Both incidence and mortality rates have decreased over the last decades, but the decrease in mortality rate is larger⁷.

In absolute numbers, there are approximately 25 000 stroke events registered in the National Patient Register (NPR) yearly in Sweden. There has been a decreasing trend over the last decade, except for ICH, which has remained stable (Figure 1). The prevalence of ischemic stroke in the Swedish population in 2010 (of approximately 9 million) was estimated at approximately 140 000 (1.8%)²¹.

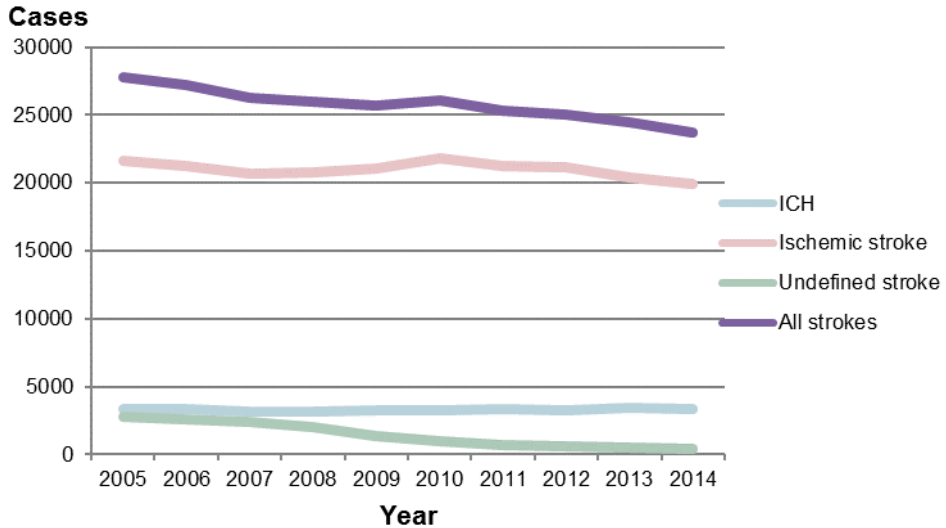


Figure 1. Diagram showing time trends for hospitalized stroke cases in Sweden from 2005-2014, for the diagnoses of ICH (I61), ischemic stroke (I63) and stroke not defined as ischemic or ICH (I64). Data from the Statistics Database of the National Board of Health and Welfare²².

Organization of stroke care in Sweden

The Ministry of Health and Social Affairs is responsible for issues concerning the healthcare and social system in Sweden. The National Board of Health and Welfare is a government agency under the ministry, which monitors, develops and evaluates social services, health and medical services, patient safety and epidemiology.

On a regional level, the county councils (n=20) and municipalities (n=290) run different parts of the healthcare and social sectors on separate budgets (Figure 2). The Health and Medical Service Act (Hälso- och sjukvårdslagen 1982:763) regulates the responsibilities of county councils that finance and run hospitals, primary care, and in part domiciliary care. Municipal services are regulated by both the Health and Medical Service Act and the Social Services Act (Socialtjänstlagen 2001:453), and the municipalities finance and run social services including institutional care, home care services, and domiciliary care. They also provide special accommodation for persons with physical disabilities, school health, as well as caregiver support. Rehabilitation services are provided both in-hospital, in primary care and in municipal care. For patients of employable age, the Swedish Social Insurance Agency (Försäkringskassan) and the Swedish Public Employment Service (Arbetsförmedlingen) also take active part in vocational rehabilitation.

Stroke care in Sweden involves all of the agencies and bodies above, which contributes to the complexity of managing this large group of patients. Recommendations for the management of stroke through the continuum of care are published in the Swedish National Guidelines for Stroke Care, by the National Board of Health and Welfare²³.

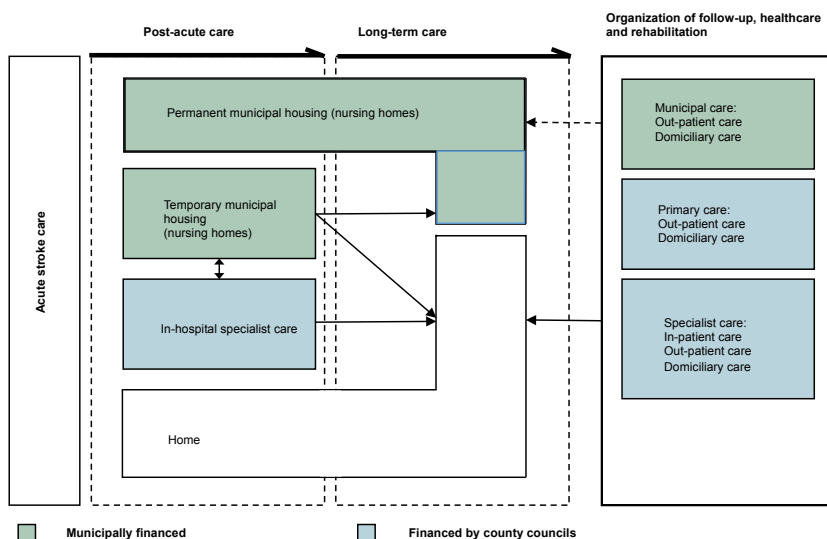


Figure 2. Overview over the organization and financing of stroke care, reconstructed from the Sveus report on stroke care²⁴.

In 2010, the mean hospital length of stay for ischemic stroke was 11 days for patients with ischemic stroke and 13 days for patients with ICH according to routine health statistics²².

Stroke outcomes

Stroke carries a high risk of death, which is an important hard clinical endpoint in stroke. Stroke case-fatality ratio refers to the proportion of patients with stroke who has died from any cause within a defined time interval. Figure 3 demonstrates the 90-day case-fatality in hospitalized first-ever stroke patients in Sweden registered in the NPR and in the Swedish Causes of Death Register²⁵. The 90-day case-fatality has decreased over the observed time period, but the change may be explained by variations in patient registration over time. In 2009, the 1-year case-fatality rate in patients hospitalized for stroke was 27% in Sweden²⁶. Stroke case-fatality rates at 1 year in other European countries show considerable variation (16–31%)^{27, 28}.

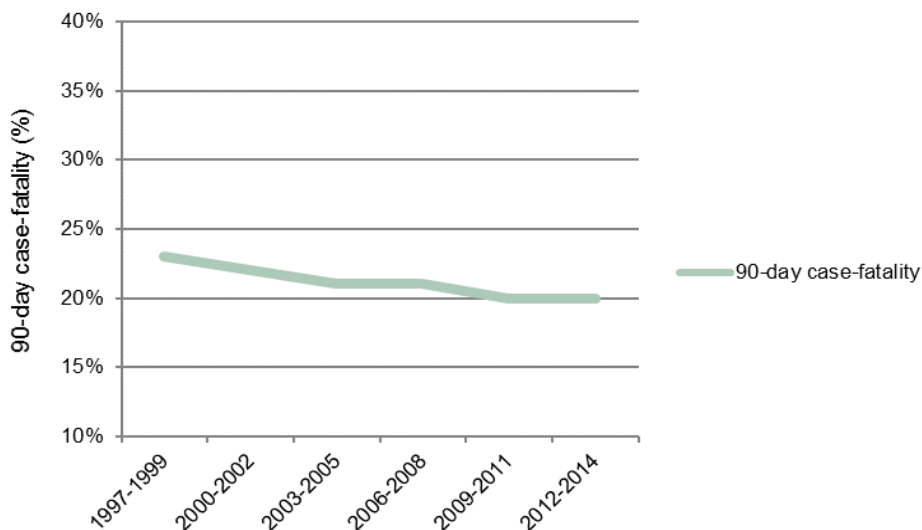


Figure 3. Case-fatality trend in patients hospitalized for first-ever stroke and registered in the NPR and the Swedish Causes of Death Register. Data from Open Comparisons²⁸.

Functional outcome aims to describe the ability of a patient to manage their daily life and activities of daily living (ADL) after stroke, and depends on motor and perceptual functions, as well as language and other cognitive functions²⁹. ADL can be divided into basic ADL functions (including activities like dressing, toileting, feeding and mobility) and instrumental ADL functions (including activities like shopping, housework, cooking and transportation). There are several scales to measure functional outcome after stroke, but the most widely used are the Barthel Index (BI)³⁰ and the modified Rankin Scale (mRS)³¹, both of which aim to distinguish functional dependence from independence. The BI covers only basic ADL functions and has a ceiling effect, while the mRS, which is a six-graded scale based on basic and instrumental ADL functions, covers the whole spectrum from no symptoms to severe disability (and death). The two scales correlate well³².

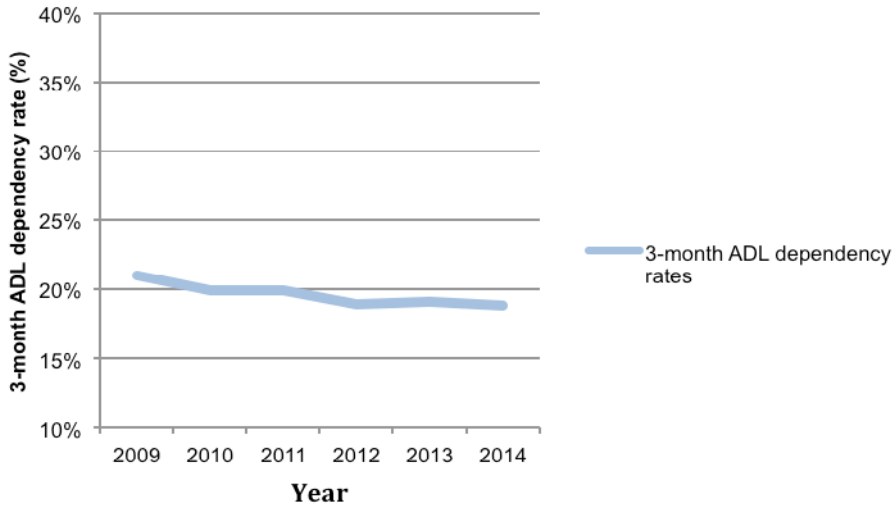


Figure 4. Diagram demonstrating ADL dependency proportions at 3 months post-stroke in the Swedish Stroke Register, adjusted for age, sex and consciousness level on hospital admission. Data from Open Comparisons²⁶.

The proportions of 3-month ADL dependency (based on dressing, toileting and mobility) captured from the Swedish Stroke Register have remained fairly stable at approximately 20% during recent years (Figure 4). Functional dependency rates 1 year after stroke in 2010 was 31% in the Swedish Stroke Register³³ and ranged from 20-37% in other studies³⁴⁻³⁷, but heterogeneous populations and measurement differences may partly explain the variation. Poor functional outcome after stroke is associated with high age³⁸⁻⁴⁰, severe stroke^{38, 40, 41}, female sex^{38, 41-46}, depression^{38, 47} and other comorbidities⁴⁸⁻⁵⁰. Poor outcome 3 months after stroke is highly predictive of death⁵¹.

Patient-reported outcome measures (PROMs) are standardized, validated questionnaires completed by patients to evaluate their perception of their own functional status and wellbeing, or their views of the outcome of a treatment. The PROMs are meant to represent the patients' perspective independent of the healthcare providers⁵². PROMs are used in >90% of Swedish National Quality Registers. PROMs concerning patient experiences (called PREMs; patient-reported experience measures) such as satisfaction are sensitive to expectations, preferences, personality and previous experiences. To reduce this influence, it is recommended to use specific experiences (such as met needs) rather than satisfaction only⁵³.

Rehabilitation after stroke

Stroke results in the death of functional neuronal tissue in the injured area. After stroke, the process known as spontaneous neurological recovery begins, involving molecular, cellular and behavioral changes in the brain, leading to some, or more rarely full recovery. Most spontaneous recovery is seen within the first three months after stroke. Cognitive deficits are more likely than motor deficits to show spontaneous gain beyond three months. Mild deficits recover more quickly than severe deficits⁵⁴.

Stroke rehabilitation aims to restore the patient's capacity to function normally or as close to normally as possible after stroke⁵⁵. Rehabilitation is a progressive, dynamic, and goal-oriented activity aimed at enabling a person to reach their optimal physical, cognitive, emotional, communicative and functional activity level⁵⁶. The foundation of rehabilitation is teamwork and the inter- or multidisciplinary team usually includes physicians, physical therapists, occupational therapists, speech and language therapists, psychologists and nurses. Rehabilitation is based on the individual's perceived inability, needs and interests, and goal setting is a tool for creating an individual, and realistic rehabilitation plan⁵⁵.

The rehabilitation process can start as soon as the patient is medically stable. It takes place in a variety of settings: the stroke unit, inpatient rehabilitation units, hospital outpatient clinics and primary care centers, as well as in the home setting with early supported discharge (ESD) teams. Most rehabilitation occurs during the first 3 months but it can also take place over an extended period⁵⁶.

There is some well-supported evidence for stroke rehabilitation. Complete multidisciplinary stroke unit care during the first days and weeks after stroke improves outcomes. Patients receiving stroke unit care are more likely to be alive, living independently, and at home 1 year after stroke¹. It is recommended that all patients admitted for acute stroke have an initial assessment to evaluate the need for early rehabilitation⁵⁶. Outpatient and community-based rehabilitation therapy also improves ADL outcomes, and reduces the odds of death and dependency⁵⁷. Physiotherapy improves motor and ADL function after stroke^{58, 59}. Group circuit and cardiorespiratory fitness training are safe and improve mobility^{60, 61}. Occupational therapy is beneficial for gaining and maintaining ADL function after stroke⁶².

ESD is designed to accelerate hospital discharge after stroke, and to provide multidisciplinary rehabilitation in the home environment in patients with mild to moderate disability after stroke. ESD has proven to shorten the length of hospital stay and to be safe. Patients receiving ESD are more likely ADL independent and living at home 6 months post-stroke. ESD is best completed by the same team that manages the patient in the hospital^{56, 63}.

In patients of employable age, vocational therapy is an important form of rehabilitation focusing on the patient's capacity to return to work. Other focuses of rehabilitation are on language and perceptual defects, dysphagia and nutrition, fall prevention, pain treatment, and leisure activities⁵⁶.

Previous studies have shown that older patients and patients with severe or prior stroke have less access to rehabilitation^{64, 65}.

The individual approach to rehabilitation plans and programs, and the wide variety of rehabilitation interventions available, make it difficult to measure rehabilitation received (both quantity and quality) in stroke registers. Rehabilitation services provided in municipal care are not registered in any official registers.

Long-term management of stroke

Long-term stroke care in Sweden is mainly managed within primary care, but there are examples of hospitals that have developed local follow-up routines for stroke. To this date, there is no stroke follow-up program implemented in clinical routine on a national level, but the Swedish National Guidelines for Stroke Care recommends a follow-up visit soon after hospital discharge in patients who have been admitted for stroke. The aim of the visit is to assess compliance and toleration to prescribed secondary preventive medication. In the longer perspective, long-term follow-up is recommended to manage secondary prevention, to follow up on functional level and rehabilitation, to detect stroke-related complications and to provide information and caregiver support. The guidelines also emphasize the need for equal care, without discrimination based on age, sex or other factors²³.

In 2012, a multidisciplinary stroke expert group developed the Post-stroke Checklist, in order to improve long-term stroke management across the continuum of stroke care. The Post-stroke Checklist is a practical tool for identifying stroke-related complications, and making adequate referrals (Table 1). A feasibility study found that the Post-stroke Checklist could identify a range of unmet needs, was feasible, useful and a relevant measure of post-stroke care⁶⁶.

Table 1.

Post-stroke Checklist below, is a tool for detecting, and making adequate referrals for common stroke-related problems.

Post-stroke Checklist	
<p>1. Secondary prevention Since your stroke or last assessment, have you received any advice on health-related lifestyle changes or medications for preventing another stroke?</p>	<p>No: Refer to a primary care physician or stroke neurologist for risk factor assessment and treatment if appropriate Yes: Observe progress</p>
<p>2. Activities of daily living Since your stroke or last assessment, are you finding it more difficult to take care of yourself?</p>	<p>No: Observe progress Yes: Do you have difficulty dressing or bathing? Do you have difficulty preparing hot meals? Do you have difficulty getting outside?</p>
<p>3. Mobility Since your stroke or last assessment, are you finding it more difficult to walk or move safely from bed to chair?</p>	<p>No: Observe progress Yes: Are you continuing to receive rehabilitation therapy? (If no, refer to a primary care physician, rehabilitation physician, or an appropriate therapist)</p>
<p>4. Spasticity Since your stroke or last assessment, do you have increasing stiffness in your arms/hands/legs?</p>	<p>No: Observe progress Yes: Is this interfering with ADL, sleep or causing pain? (If yes, refer to an appropriate physician)</p>
<p>5. Pain Since your stroke or last assessment, do you have any new pain?</p>	<p>No: Observe progress Yes: Refer to an appropriate physician</p>
<p>6. Incontinency Since your stroke or last assessment, are you having more of a problem controlling your bladder or bowels?</p>	<p>No: Observe progress Yes: Refer to an appropriate health care provider</p>
<p>7. Communication Since your stroke or last assessment, are you finding it more difficult to communicate with others?</p>	<p>No: Observe progress Yes: Refer to an appropriate health care provider</p>
<p>8. Mood Since your stroke or last assessment, do you feel more anxious or depressed?</p>	<p>No: Observe progress Yes: Refer to an appropriate physician</p>
<p>9. Cognition Since your stroke or last assessment, are you finding it more difficult to think, concentrate, or remember things?</p>	<p>No: Observe progress Yes: Does this interfere with activity or participation? If yes, refer to an appropriate physician</p>
<p>10. Life after stroke Since your stroke or last assessment, are you finding it more difficult to carry out leisure activities, hobbies or work?</p>	<p>No: Observe progress Yes: Refer to a local stroke group or organisation</p>
<p>11. Relationship with family Since your stroke or last assessment, has your relationship with your family become more difficult or stressed?</p>	<p>No: Observe progress Yes: Schedule next appointment together with patient and family member.</p>

Most outcomes in the longer term are affected by factors that are not under the control of the healthcare system⁶⁷. Therefore, the effect of stroke follow-up on outcomes can be difficult to estimate. Previous studies have shown that adherence to guidelines for post-stroke secondary prevention is poor^{68, 69}. A few studies have investigated the effect of comprehensive stroke follow-up compared with standard care. Results showed significantly less complications⁷⁰, better quality of life⁷⁰, and better risk factor control with respect to hypertension, cholesterol levels, smoking cessation or body mass index⁷⁰⁻⁷³. One study found significantly lower disability rates, stroke recurrence rates and lower vascular death rates at 1 year⁷². Other studies however, showed no benefit of intensified follow-up on risk factor control or functional outcome^{74, 75}.

Stroke risk factors

A patient characteristic that is independently associated with an increased risk of stroke is a stroke risk factor, but it does not necessarily reflect a causal relationship with a stroke event. To be identified as a stroke risk factor, a patient characteristic has to be present before the stroke event, and a prospective population based study approach is needed. Exceptions are patient characteristics that do not change over time, for example sex and genetics. The association between the risk factor and the outcome must be strong, consistent and biologically plausible. The stronger the association between the risk factor and the outcome (stroke), and the more prevalent the risk factor is, the more it will affect the incidence of stroke. Stroke risk factors can be described as non-modifiable or modifiable.

Non-modifiable stroke risk factors

Age is a strong stroke risk factor, and stroke incidence increases markedly with age in both men and women, and both for ischemic stroke and ICH⁷⁶. Male sex increases the age-adjusted risk of stroke⁷⁷⁻⁷⁹, except in the oldest age groups where the risk difference is attenuated⁷⁷. A hypothesis is that endogenous estrogen during the reproductive years is a stroke protective factor, but the mechanisms are not fully understood⁸⁰. After menopause, the prevalence of vascular risk factors increases in women⁸¹, and the stroke incidence doubles during the subsequent 10 years^{77, 79, 82}. However, so far studies on postmenopausal hormone replacement therapy with exogenous estrogen have however so far showed an increased stroke risk^{83, 84}. In absolute numbers, more strokes occur in women due to their longer life expectancy and the high stroke rates among the oldest.

Hereditary factors (polygenetic) may increase the risk of stroke, and several rare monogenetic stroke syndromes have also been identified⁸⁵.

Modifiable risk factors

Modifiable risk factors can be favorably changed with treatments or interventions. Vascular risk factors are common for all atherosclerotic disease: hypertension, diabetes mellitus, smoking and hypercholesterolemia, but they contribute differently to ischemic heart disease compared than to stroke^{86, 87}. Atrial fibrillation is an important stroke risk factor that does not cause atherosclerosis, but will for practical purposes be described as a vascular risk factor in this thesis.

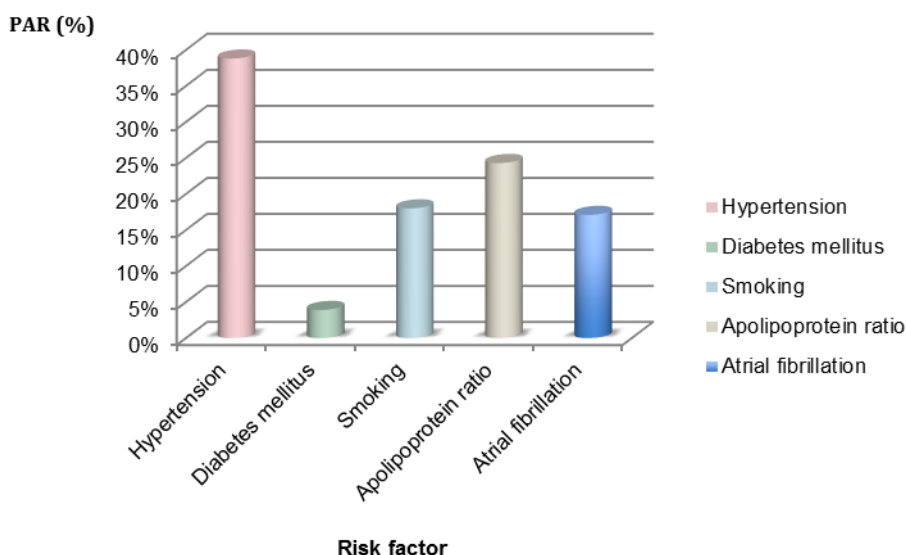


Figure 5.

Reconstruction from the 2016 INTERSTROKE study,⁸⁸ showing percentage population attributable risks (PAR) for main risk factors for stroke in Western Europe, North America and Australia. PAR is a theoretical measure estimating the proportion of a disease (stroke) that can be attributed to a specific risk factor.

Due to its high prevalence in the population, hypertension is the most important treatable risk factor for stroke⁸⁷. History of hypertension is associated with an increased Odds Ratio (OR) of ischemic stroke (OR=2.21, 95% CI: 1.66–2.94) and ICH (OR=1.61, 95% CI: 0.78–3.31), and is estimated to account for approximately 40% of strokes in western populations (Figure 5)^{88, 89}. The current definition of hypertension is a blood pressure above 140/90 mmHg, but the stroke risk also appears to be increased with blood pressure levels within the normal range and

without any evident threshold⁹⁰. Blood pressure variability, despite a controlled mean blood pressure is also a risk factor for stroke.⁹¹

While hypercholesterolemia is the most important risk factor for ischemic heart disease⁹², its role in ischemic stroke is less clear^{87, 93}. Elevated levels of total cholesterol or LDL has failed to show a strong association with unselected ischemic or fatal strokes^{94, 95}, but low HDL cholesterol, or elevated Apolipoprotein ratio B1 to A, is a known risk factor accounting for approximately 25% of all strokes (OR=1.83, 95% CI: 1.33–2.52) (Figure 5)^{88, 89, 96-98}. Since atherosclerotic stroke (large vessel disease) shares pathophysiological features with ischemic heart disease, the relation between plasma lipids and this stroke subtype may be stronger⁹³.

Diabetes mellitus increases the risk of stroke (OR 1.12, or relative risks (RR's) of 1.3–6 have been described) and accounts for approximately 5% of all strokes (Figure 5)^{88, 89, 99, 100}. The risk of stroke in women with diabetes is higher than in men (RR=1.27, 95% CI: 1.10–1.46) independent of sex differences in other major risk factors¹⁰¹. Diabetes may potentiate, or be potentiated by other risk factors.

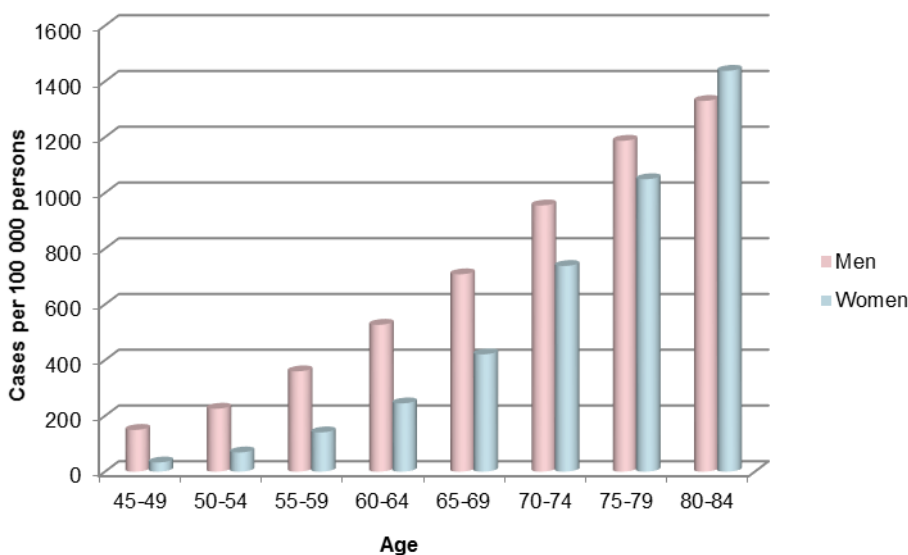


Figure 6. Age-specific prevalence (cases per 100 000 persons) of atrial fibrillation in hospital-treated patients in Sweden, in 2014, using data from the statistics database of the National Board of Health and Welfare²².

Atrial fibrillation is more prevalent with increasing age in both men and women (Figure 6), and is associated with an increased risk of stroke (OR=4.05, 95% CI: 2.74–5.98 for western Europe)⁸⁸. However, the risk of stroke in patients with atrial fibrillation depends on other stroke risk factors (age, sex, history of hypertension,

diabetes, vascular disease and congestive heart failure) and the individual stroke risk can be estimated using a risk scale. The most widely used scales are the CHADS2 and the CHA2DS2-VASc^{102, 103}. Women with atrial fibrillation are at higher risk than men of cardioembolic stroke¹⁰⁴, and cardioembolic stroke is associated with poor outcome¹⁰⁵.

Cigarette smoking is associated with an increased risk of atherosclerosis and increases the risk of ischemic stroke^{106, 107}. It accounts for approximately 20% of the PAR for stroke in Western Europe⁸⁸. Smoking cessation reduces the risk of stroke¹⁰⁸.

Other important modifiable risk factors for stroke are psychosocial factors (OR= 1.19, 95% CI: 0.72–1.96, although non-significant among western populations) and cardiac causes (OR=2.81, 95 % CI: 2.07–3.81). A healthy diet (measured by a health score index) is a stroke protective factor (OR=0.44, 95 % CI=0.33–0.60), as is exerting regular physical activity (OR=0.74, 95% CI=0.57–0.97). Altogether, the modifiable risk factors accounted for >90% of the PAR for stroke in the new INTERSTROKE study⁸⁸, and for >90% of the stroke burden (based on DALYs) in the Global Burden of Stroke study¹⁰⁹.

Secondary preventive measures in stroke

With the introduction of effective secondary preventive treatment and rapid assessment after minor stroke and TIA, stroke recurrence rates have decreased substantially over the last decades^{110, 111}.

Rapid assessment after TIA is recommended²³. The risk of early stroke after a TIA is high, but can be effectively lowered by 80% with rapid risk assessment including relevant diagnostic work-up (ABCD2 stroke risk score¹¹², carotid ultrasound and ECG monitoring) and initiation or optimizing of secondary preventive treatment^{113, 114}.

The benefit of carotid endarterectomy for symptomatic carotid stenosis (>70% stenosis) is well established, while the benefit of surgery for moderate stenosis (50–69%) is less clear¹¹⁵. The Swedish National Guidelines for Stroke Care recommends carotid endarterectomy for symptomatic carotid stenosis (>70%) within 2 weeks²³.

Antiplatelet agents are recommended for secondary prevention of non-cardioembolic stroke. Monotherapy with aspirin reduces the risk of recurrent stroke by 22%¹¹⁶. Aspirin in combination with dipyridamole is proven slightly more effective than aspirin alone^{117, 118}, but is poorly tolerated mainly due to headache¹¹⁸. Clopidogrel demonstrated a small reduction in overall recurrent vascular events compared with aspirin alone in the CAPRIE trial¹¹⁹. The recent SOCRATES trial failed to show

superiority of the newer antiplatelet agent ticagrelor to aspirin in preventing death or recurrent vascular events¹²⁰.

Anticoagulant agents are recommended for secondary prevention of cardioembolic stroke. The risk of cardioembolic stroke increases with age due to the increasing prevalence of atrial fibrillation in the population (Figure 6). Warfarin is effective in preventing stroke with non-valvular atrial fibrillation compared with placebo, aspirin or no treatment (64% risk reduction)¹²¹. In 2009, the first evidence for the benefit of novel oral anticoagulants (NOACs) compared to warfarin was published, and since then both dabigatran, rivaroxaban and apixaban are proven equal or superior to warfarin in preventing stroke, and have shown a more beneficial safety profile with respect to intracranial bleeds¹²²⁻¹²⁴.

Antihypertensive treatment is effective in secondary prevention of both ischemic stroke and ICH¹²⁵, and the risk reduction is proportional to the degree of blood pressure lowering¹²⁶. In most guidelines, antihypertensive treatment is recommended for all patients with ischemic stroke or ICH, to target normal blood pressure. In the Swedish National Guidelines for Stroke Care however, antihypertensive treatment is only recommended if severe hypertension is diagnosed (>180/110 mmHg)²³. Antihypertensive treatments include angiotensin converting enzyme (ACE) - inhibitors, angiotensin II-blockers, beta-blockers, diuretics, calcium channel blockers and alfa-blockers. Combination therapy was more effective than monotherapy in preventing stroke in the PROGRESS trial¹²⁶. A meta-analysis on blood pressure reduction with combination therapy versus monotherapy, demonstrated that the extra blood pressure reduction from adding a second antihypertensive agent was 5 times greater than doubling the dose of the first drug¹²⁷.

Lipid-lowering agents are recommended in patients with TIA and ischemic stroke. Statin use in patients with TIA or ischemic stroke is associated with a reduction in recurrent stroke^{128, 129}. In the SPARCL trial, a small increase in ICH was seen in the statin-arm compared to placebo¹²⁹. However, later studies demonstrate a reduction in all strokes and all-cause mortality with statin therapy¹³⁰. Use of other lipid-lowering agents appear less beneficial than statins for stroke risk reduction¹³¹.

From a global perspective, underuse of secondary prevention is most common in low- and middle-income countries, and country-level factors (economy) have larger impact than individual-level factors (sex, income and educational level, and risk factor status) on use of secondary preventive drugs. Europe and North America show the highest levels of secondary preventive drug use globally¹³². Despite that, medication adherence rates drop rapidly over the first 2 years after stroke in Sweden¹³³. Poor adherence to secondary preventive drugs is associated with unfavorable outcomes¹³⁴⁻¹³⁶. In a recent review, factors associated with adherence were patient-related (age and sex have shown conflicting results), socio-economic (high level of education was associated with improved adherence), therapy related (disability, reduced cognition, poor quality of

life, and low mood were associated with reduced adherence, while comorbidities were associated with improved adherence. Understanding of medication rationale, knowledge of how to refill prescriptions, and drug prescription and education at hospital discharge were associated with better adherence), factors related to stroke or general healthcare services (poor patient-care giver relations, inadequate continuity of care, and inadequate communication were associated with lower adherence rates, while stroke unit care, institutional living, care-giver support and accessible healthcare facilities were associated with better adherence), and stroke related (severe and previous stroke predicted non-adherence)¹³⁷.

Socio-economy and stroke

Socio-economic status aims to describe a composite measure of a person's income, education, employment, and social status¹³⁸. In practice, several different measures are used as markers for socio-economic status, making direct comparisons between studies and countries difficult.

The Global Burden of Stroke study in 2010 showed that while age-standardized stroke incidence is decreasing in high-income countries, it is increasing in low- and middle-income countries that currently hold 80% of all strokes globally. Stroke mortality has decreased in low- and middle-income countries in the last decades, but less than in high-income countries (20% versus 37%)⁷. In high-income countries, low socio-economic status is associated with both higher stroke incidence and stroke mortality, as well as worse functional outcome up to 1 year after stroke¹³⁹. Higher stroke rates are seen among ethnic minorities such as black versus white Americans^{79, 82, 140}. The ethnic and socio-economic disparities in stroke rates and outcomes may, at least in part, be explained by higher prevalence and poorer control of vascular risk factors^{139, 141}.

Low socio-economic status is associated with lower access to high-quality acute stroke care¹³⁹. In Sweden, socio-economic disparities (educational level, income level and country of origin) in stroke care have been explored within the Equal Stroke project. The studies found that university education was associated with stroke survival¹⁴², better access to stroke unit care and reperfusion treatment^{143, 144}, as well as higher probability of being prescribed secondary preventive drugs^{145, 146} but lower adherence to statin treatment¹⁴⁷. High income was associated with stroke survival¹⁴², and with prescription of secondary preventive medication^{145, 146}. Moreover, high income was associated with a lower risk of suicide¹⁴⁸. Non-European country of origin was associated with lower prescription of warfarin¹⁴⁵, and higher prescription¹⁴⁶ but lower adherence to statin treatment¹⁴⁷. Furthermore, non-European country of birth was associated with and lower risk of suicide¹⁴⁸.

Aim of the thesis

The overall aim of this thesis was to improve knowledge of different aspects of post-stroke care, rehabilitation and outcomes during the first year following stroke in a large unselected Swedish stroke cohort.

The specific aims were:

- I. Paper I: To describe case-fatality and functional outcome at 3 and 12 months post-stroke, to analyze changes in functional outcome between 3 and 12 months post-stroke, and to identify which factors were associated with functional decline.
- II. Paper II: To analyze what proportion of patients reported unmet rehabilitation needs 1 year after stroke, what characterized those who reported unmet rehabilitation needs, and which 12-month factors were associated with unmet rehabilitation needs.
- III. Paper III: To explore what proportion of patients received follow-up within 90, 120, 180 and 365 days after hospital discharge, and how patient characteristics were associated with stroke follow-up in patients living in the region of Skåne in southern Sweden.
- IV. Paper IV: To calculate adherence rates to secondary preventive medication at 4 months and 1 year after stroke, and to investigate the associations between stroke follow-up, socio-economy and adherence to treatment at 1 year post-stroke.

Subjects and methods

Study materials

This thesis consists of four observational cohort studies. Research materials are derived from data linkage between the Swedish Stroke Register, the Region Skåne patient administrative database, and population register data.

The Swedish Stroke Register: Riksstroke

Riksstroke is the Swedish national quality register for stroke care, and was founded in 1994³³. Since 1998, all Swedish hospitals treating acute stroke patients participate (presently 72). The main aims of Riksstroke are to support continuous quality improvement of Swedish stroke care, and to serve as a follow-up instrument for the Swedish National Guidelines for Stroke Care²³ issued by the National Board of Health and Welfare. New evidence-based practices can rapidly be introduced and evaluated through Riksstroke. Another aim of Riksstroke is to provide a research database on stroke management⁶⁷.

Riksstroke is funded by the National Board of Health and Welfare and the Federation of County Councils. The Riksstroke steering committee covers competence in all areas of stroke care, epidemiology and healthcare management, and runs the daily affairs together with the Riksstroke secretariat. All participating hospitals are members of a Riksstroke network. Hospitals receive yearly feedback reports, including comparisons to national data, but they also receive a statistics package for specific analyzes of own data. Riksstroke publishes publicly available annual reports comparing national data on process and outcome indicators on regional and hospital levels. All reports are available on the Riksstroke website³³.

Riksstroke is a hospital-based register, and data are collected at hospital discharge. Hospital personnel enter all items into the web-based register. Routines for registration vary between hospitals. Subjects for inclusion are all patients treated in-hospital for acute stroke. The register uses the WHO definition of stroke⁹. Subarachnoid hemorrhage, however, requires neurosurgical care, which is restricted to university clinics, and is not included in Riksstroke. Since 2010, TIA is registered in a

separate module within Riksstroke. Diagnoses eligible for inclusion are classified according to the International Classification of Diseases, 10th version (ICD-10)¹⁴⁹: ischemic stroke (I63), ICH (I61), and stroke not defined as ischemic or ICH (I64). The items entered into the register have shown >90% concordance with hospital records for most items in a validation study¹⁵⁰.

Riksstroke collects a combination of background, process and outcome data (Table 2). Background data (in the present thesis referred to as patient baseline characteristics) are routinely available from patient charts. Process indicators used in Riksstroke, such as stroke unit care, reperfusion therapy and secondary preventive treatment at discharge all have documented effect on outcome. Survival, ADL function and living conditions are outcome measures of direct importance for patients and their families, and no surrogate measures are used. Some PROM's have been introduced in the 3- and 12-month follow-ups⁶⁷.

Registration of stroke severity, measured by NIHSS (National Institute of Health Stroke Scale) was optional in 2008 to 2010, and only registered in a minority of cases. For the present thesis, consciousness level at admittance was used as a proxy for stroke severity. Consciousness level in Riksstroke is registered according to the RLS-85 (Reaction Level Scale)¹⁵¹, which is an eight-graded scale, with scores distributed on three levels: alert, drowsy and comatose. Consciousness level is equal to NIHSS in predicting mortality after stroke¹⁵².

Discharge destination and planned rehabilitation included three specified rehabilitation options in 2008–2010: ESD, inpatient geriatric rehabilitation or inpatient stroke rehabilitation. The wide variety of other rehabilitation options was not captured in the Swedish Stroke Register.

At 3 and 12 months after stroke, all patients registered in Riksstroke are contacted for a follow-up questionnaire. The 3-month follow-up was introduced in 1994. Depending on local resources, some patients are offered either a telephone interview or a personal interview with a nurse. The 12-month follow-up was first introduced in 2009. At 12 months, follow-up is per regular mail. The questions at 3 and 12 months are similar and the items include: living conditions, functional status (dressing, toileting and mobility items), needs of support and rehabilitation, presence of depressive symptoms, antidepressive medication, pain or fatigue and self-perceived health (Table 2). The patient, a next of kin or a caregiver fills out the questionnaire.

Table 2.

Patient baseline characteristics, process indicators, outcomes and PROM's collected in Riksstroke.

Patient baseline characteristics	Process indicators during hospital stay	Process indicators during follow-up	Outcomes	PROM's
Age	Length of stay	Access to doctor's follow-up	Functional status at 3 and 12 months	Met needs of help and support
Sex	Diagnostic work-up	Community support after discharge	Death	Satisfaction with care
Pre-stroke living conditions (at home /institution/ other) (living alone/co-living)	Stroke unit care	Access to speech therapist		Met needs of rehabilitation
Pre-stroke functional status (dressing/ toileting/mobility)	Acute treatment (reperfusion therapy or hemicraniectomy)	Access to rehabilitation		Self-perceived health
Vascular risk factors (diabetes mellitus/atrial fibrillation, hypertension, and smoking history)	Secondary preventive medication at discharge			Mood
Stroke Subtype (ischemic, primary ICH, stroke not defined)	Discharge destination			Satisfaction with information
Level of consciousness on admission (alert, drowsy, comatose)	Planned rehabilitation			
Prior stroke				
NIH Stroke Scale on admission (optional)				

The Swedish personal identification number

Since 1947, every Swedish individual has been assigned a unique, sex-specific 10-digit personal identification number (PIN), governed by the National Tax Board. The PIN is the unique identifier in the Total Population Register (TPR). The TPR includes data on name, age, sex, place of birth and residence, civil status, relations (spouse, child-parent, adoption), citizenship, immigration, emigration and death. Every birth

must be reported to the National Tax Board within one month. Immigrants with a residence permit, who intend to stay for more than one year receive a PIN from the National Tax Board, and those intending to stay for less than one year receive a coordination number. Immigrants without a residence permit receive a temporary PIN. The PIN can be changed when information on birth date or sex is incorrect, if an individual changes sex, or if an individual is under protected identity. Changes of the PIN are rare^{153, 154}. Jurisdiction of the PIN can be found in the Population Registration Act §18 (1991:481).

The Swedish Causes of Death Register

The Board of Health and Welfare regulates the Swedish Causes of Death Register since 1961. The register comprises all deaths among Swedish residents, both in Sweden and abroad, as well as underlying causes of death¹⁵⁵. The register was used for accurate date of death and mortality status in stroke patients in all four papers in this thesis.

The Region Skåne patient administrative database

The Region Skåne patient administrative database contains information (date, type of visit and ICD-10 codes) on all doctor's visits, nurse visits, hospitalizations, and consultant visits. For Paper III and IV, dates of post-stroke doctor's visits during the year following the stroke event were obtained from this database.

The Swedish Prescribed Drug Register

The Swedish Prescribed Drug Register was established in 2005, and is regulated by the Swedish government (legislation SFS 2005:363). Data is collected by the National Corporation of Swedish Pharmacies and transferred monthly to the Centre for Epidemiology, at the National Board of Health and Welfare. The register contains the following data: age, sex and PIN, dates of prescribing and dispensing, dispensed item, amount, dosage, expenditure, and reimbursement. Missing data are less than 0.3%¹⁵⁶.

All drugs are classified according to the Anatomical Therapeutic Chemical (ATC) classification system¹⁵⁷. For paper IV, data on ATC codes for warfarin and antiplatelet drugs (ATC B01), antihypertensive drugs (ATC C02, C03, C07, C08, C09), and statins (ATC C10) were obtained from the Swedish Prescribed Drug Register. Variables obtained were: substance name, formulation, package, dispensed amount and date of filling the prescription.

The Longitudinal Database of Health Insurance and Labour Market Studies (LISA by Swedish acronym)

Since 1990, this register run by Statistics Sweden holds all Swedish individuals from 16 years of age. The database integrates data from the labour market, educational and social sectors. It includes variables on employment, disposable income, country of birth, immigration and emigration, place of residence and employment, as well as highest level of education¹⁵⁸. For Paper IV, variables on highest level of education and country of birth were obtained.

Register linkage in Paper I-IV

The PIN is the key number for register linkage for research purposes. Register data used for this thesis were linked through the PIN, and the register linkage was performed by the Centre of Epidemiology at the National Board of Health and Welfare. Figure 7 shows the register linkage used in the four papers.

For Paper I and II, data on all stroke events registered in the Swedish Stroke Register from January 1, 2008 to December 31, 2010 were sent to the National Board of Health and Welfare. Data linkage to the Causes of Death Register was performed, adding data on date of death and mortality status. The PIN's were removed and replaced with a serial number to de-identify the patients. The National Board of Health and Welfare kept no key for the PIN.

For Paper III, data on all patients residing in the Region of Skåne, in Southern Sweden, were extracted from the Riksstroke data file and sent to the administrative department of Region Skåne. Data were linked with the PIN as key to data from the hospital and primary care administrative database of Region Skåne, and data were de-identified with replacement of the PIN with serial numbers. Region Skåne had prior to data linkage given a written consent to destroy Riksstroke data after linkage had been performed.

For Paper IV, the Riksstroke-Region Skåne data file was sent to Riksstroke and the PIN was added through a Riksstroke-specific serial number. The National Board of Health and welfare then added data on all filled prescriptions from 2008 to 2012 from the Swedish Prescribed Drug register, as well as data on socio-economy from the Longitudinal Database of Health Insurance and Labour Market Studies. The PINs linked the data, and were then removed together with the Riksstroke-specific serial number and replaced by new serial numbers. No key was kept.

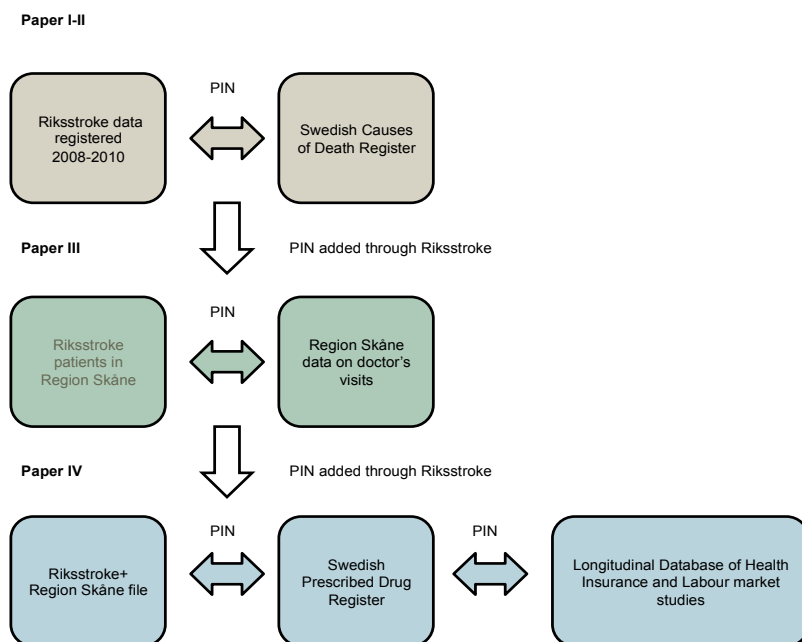


Figure 7. Data linkage in Paper I-IV
Register data linkage in Paper I-IV. PIN refers to the Swedish personal identification number.

Study subjects and outcome assessments

Paper I

Paper I included all patients >18 years of age, registered in Riksstroke from January 1, 2008, to December 31, 2010, with the diagnoses of ischemic stroke (I63), ICH (I61) and stroke not defined as ischemic or ICH (I64). Both first-ever and recurrent strokes were included but patients with pre-stroke disability were excluded. The reason for exclusion was that we aimed to assess changes in functional ability in previously independent patients.

The main study outcome variables were mortality status at 3 and 12 months (case-fatality), and functional status at 3 and 12 months. Case-fatality was defined as death by any cause within 3 and 12 months post-stroke, respectively. Data on mortality status and date of death were obtained from the Swedish Causes of Death Register

and are unambiguous¹⁵⁵. Functional status was defined as independency or dependency in activities of daily living (ADL) at 3 and 12 months. Patients were considered ADL independent if they managed dressing, toileting and indoor mobility independently. If they needed assistance to manage one or more activity, they were considered ADL dependent. The ADL items used were patient-reported and obtained through questionnaire follow-up at 3 and 12 months. Self-reported ADL items correlate well with modified Rankin Scale (mRS) grades at 3 months, and can be used as functional outcome assessments for stroke¹⁵⁹. We have assumed that self-reported data correlates equally to functional outcome at 12 months. The ADL outcome study assumed 1-year survival and follow-up at both 3 and 12 months, and analyses were only performed on those who received follow-up.

Paper II

Paper II also included all patients >18 years of age, registered in Riksstroke from January 1, 2008, to December 31, 2010, with the diagnoses of ischemic stroke (I63), primary ICH (I61) and stroke not defined as ischemic or ICH (I64). Both first-ever and recurrent strokes were included but patients with pre-stroke disability were excluded. Only those who survived 1 year and completed the 12-month follow-up were analyzed.

The main study outcome variable was the PROM “Unmet rehabilitation needs 12 months post-stroke”. Rehabilitation was defined in Riksstroke as:

Activities or training to improve or maintain mobility and the ability to cope with daily life

The register item read: “Have your needs of rehabilitation after stroke been met?” The response alternatives in the questionnaire were: “I had no need for rehabilitation”, “I have fulfilled needs”, “I have partly unmet needs”, “I have completely unmet needs” and “I don’t know”. Patients with partly and completely unmet needs were grouped as having unmet needs in the analyses.

In Paper II, the variable “Discharge destination after hospital stay” was used to describe which patients were discharged to a pre-specified rehabilitation program.

Paper III

Paper III included all patients >18 years of age residing in the Region of Skåne, in Southern Sweden, treated in-hospital for acute stroke and registered in Riksstroke from January 1, 2008, to January 31, 2010 with the diagnoses of ischemic stroke (I63) or ICH (I61). Data were linked to the patient administrative database of Region

Skåne, adding data on all doctor's visits the year following hospital discharge for a stroke event. Visits in primary care and hospital outpatient clinics were registered, as well as domiciliary visits to homebound patients or those in assisted living. The doctor's visits were not stroke-specific but included all-cause visits. Nurse's visits were not included.

The main study outcome variables were proportions that were followed up by a doctor within 90, 120, 180 and 365 days. Additional analyses were only performed on the 90-day follow-up variable.

Paper IV

For Paper IV, the database from Paper III was used, but we exclusively analyzed patients with ischemic stroke (I63). Exclusion of ICH was due to the different secondary preventive strategy for the two stroke subtypes. Data were added from the Swedish Prescribed Drug Register and the Longitudinal Database of Health Insurance and Labour Market Studies. The main aims of the study were to calculate adherence rates, and to investigate the associations between socio-economic status, doctors' follow-up after stroke and adherence to secondary preventive drugs 1 year post-stroke. Socio-economic status was defined by the highest level of education in the year before stroke (primary school (0–9 years), secondary school (10–12 years) and university education (>12 years)). Country of birth was divided into three categories: Sweden, Europe and Non-European. Primary drug adherence was defined as filling the first prescription within 120 days after hospital discharge. Drug persistence at 1 year was defined as filling a prescription between months 10–14. The four groups of drugs analyzed were antiplatelet drugs, warfarin, antihypertensive drugs, and statins. An assumption was made that a package contained 100 tablets, and that the dosage was 1 tablet a day. For patients on more than one anti-hypertensive drug, filling prescriptions for at least one of them qualified as primary adherent or persistent.

Statistical methods

SPSS versions 21.0, 22.0 and 23.0 were used for all statistical analyses. In all four studies, baseline data were analyzed calculating simple proportions (%), means and medians. Mean age was compared between groups using Student's t-test and Mann-Whitney U test was used to compare non-parametric data between groups. Chi square test was used to compare proportions.

A difference with a P-value of <0.05 was considered statistically significant in all studies.

In Paper I, Poisson regression was used as a multivariable model to analyze which baseline characteristics predicted ADL dependency at 12 months and which of these characteristics predicted deterioration from independent to dependent status between 3 and 12 months. ADL dependent (binary outcome: yes/no) was the dependent variable. Independent variables were the following baseline characteristics: age, sex, living alone, current smoking habit, atrial fibrillation, diabetes mellitus, hypertension, prior stroke, consciousness level at admittance and stroke subtype. Each background variable was first tested separately, adjusted for age. The analyses yielded age-adjusted relative risks for the effect of the variables on the outcome, and are presented with corresponding 95% confidence intervals. A Huber/White/Sandwich model was used to estimate covariance in the model.

In Paper II, logistic regression was used to model the associations between unmet rehabilitation needs (binary outcome: yes/no) and the following baseline characteristics were used as independent variables: sex, age, current smoking habit, atrial fibrillation, diabetes, hypertension, consciousness level at admittance, prior stroke, and stroke subtype. Each background variable was first tested separately, adjusted for age. The logistic regression yielded age-adjusted odds ratios (OR's) for the association between the inserted variables and the outcome, presented with corresponding 95% confidence intervals. Since the outcome was common (>20%), the OR should not be confused with relative risk but must be interpreted as odds.

In Paper III, a time to event variable was calculated starting from the date of discharge from hospital or in-patient rehabilitation. The event was defined as the first doctor's visit after discharge. Patients who died before the event were censored. A Kaplan-Meier function was used to estimate the probability of a doctor's follow-up within 90, 120, 180 and 365 days. Cox-regression was used to analyze the exposure effect (Hazard Ratio (HR)) of the independent variables (baseline characteristics) on the outcome (follow-up within 90 days). The HR, presented with a corresponding 95% confidence interval, tells us if the variables were associated with an increased or decreased probability of follow-up within 90-days. We introduced all variables with a P value of 0.2 or less in a univariate analysis: sex, age in groups: age <65, age 65–74, age 75–84, age 85+, pre-stroke ADL status, pre-stroke living conditions, diabetes mellitus, atrial fibrillation, prior stroke and consciousness level at admittance. A backwards elimination approach was used, with systematic removal of variables that were not statistically significant ($P < 0.05$).

In Paper IV, adherence rates were expressed as simple proportions (%). Logistic regression was used to model the probability of 90-day follow-up and drug adherence. Both proportions (%), and age-adjusted odds ratio (OR) with 95% confidence intervals (CI) were calculated to explore the associations between selected baseline and outcome variables, 90-day follow-up and drug adherence.

Ethical considerations

The studies of this thesis were approved by the Research Ethics Committee in Lund (No. 2012/453).

All patients and their next of kin are informed about registration in the quality register Riksstroke, and that data may be used for compiling statistics, for continuous quality monitoring of stroke care, and for research purposes. Patients can deny participation (opt-out consent). Consent is not collected for specific research projects. At 3 and 12 months follow-up, patients can choose not to participate (opt-in consent). Participation in Riksstroke involves no direct risk for patients.

Results

Follow-up rates in Riksstroke

The total number of stroke events registered in Riksstroke from January 1, 2008, to December 31, 2010, was 75 048, of whom 64 746 were ADL independent pre-stroke. The 3-month follow-up rate among 3-month survivors (n=62 773) was 87.4% (n=54 869). At 12 months, the number of 12-month survivors was 58 414. A total of 8 454 could not be found for 12-month follow-up, and 49 960 received the questionnaire. The follow-up rate at 12-months was 79.4% (n=39 686). A flowchart of survival and follow-up for the whole cohort is shown in Figure 8.

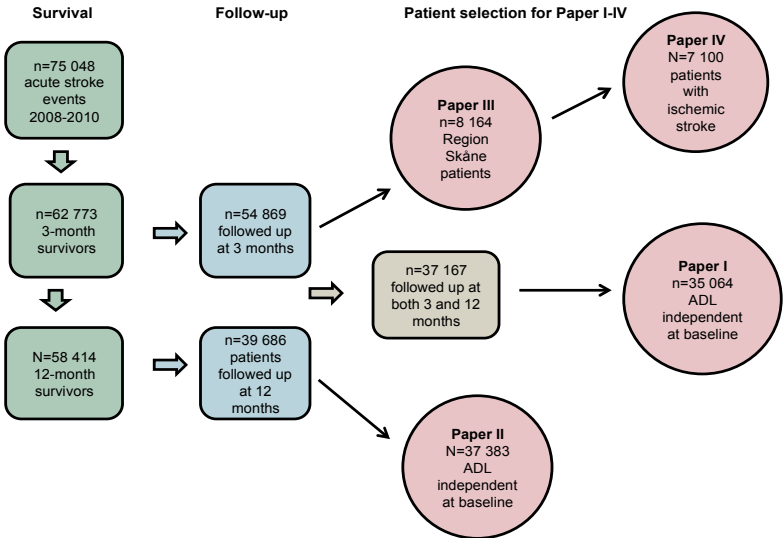


Figure 8. Flowchart of survival and follow-up for the whole Riksstroke cohort during the period 2008–2010.

Stroke case-fatality and functional outcome (Paper I)

Stroke case-fatality at 3 and 12 months

Paper I included 64 746 patients with first-ever or recurrent stroke. All patients were ADL independent pre-stroke.

Case-fatality at 3 months was 13.1% (n=8 483) at 3 months and 18.2% (n=11 779) at 12 months. There was a significant difference in 3 month-case fatality in women (14.8%, n=4 529) compared to men (11.6%, n=3954) ($p<0.0001$) in unadjusted data. The OR of death within 3 months in women was 1.32 (95% CI: 1.26-1.38) in an unadjusted logistic regression. With adjustment for age, no difference remained (OR 1.02 (95%CI: 0.98–1.07)). At 12 months, case-fatality in women was 20.2% (n=6 203) compared to 16.4% (n=5 576) in men ($p<0.0001$). The OR of death within 12 months in women was 1.29 (95%CI: 1.24–1.35), but the difference did not remain after adjustment for age (OR=0.98, 95% CI: 0.94–1.02).

In patients with pre-stroke ADL dependency (n=8 703), who were excluded from the study, case-fatality was considerable higher: 34.3% (n=2 983) at 3 months and 45.1% (n=3 923) at 12 months.

ADL outcomes at 3 and 12 months

The number of patients with pre-stroke ADL independency and first-ever or recurrent stroke, that were followed up at 3 and 12 months was 35 064.

ADL dependency rate at 3 months was 16.2% (n=5 663) and 28.3% (n=9 910) at 12 months. ADL dependency rates differed between men and women in unadjusted data at both 3 and 12 months. At 3 months, the ADL dependency rate was 14.6% (n=2 767) in men and 18.0% (n=2 896) in women ($p<0.0001$). At 12 months, the ADL dependency rate was 22.6% (n=4 290) in men and 34.9% (n=5 620) in women ($p<0.0001$)

With stratification for median age (75 years), results on ADL dependency rates are shown in Figure 9.

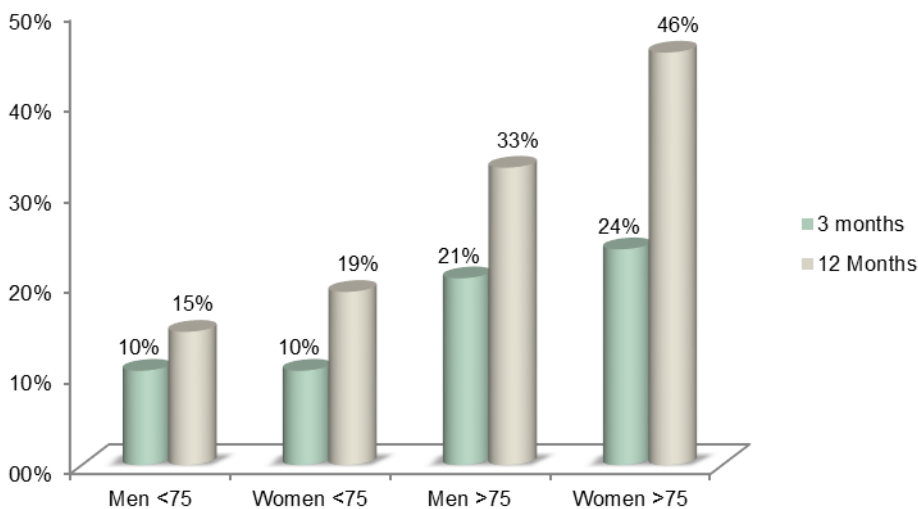


Figure 9. ADL dependency rates in men and women, over and under 75 years of age, at 3 and 12 months.

The OR for ADL dependency in women at 3 months was 1.29 (95% CI: 1.21–1.36) in unadjusted data. With adjustment for age, the OR for ADL dependency in women remained significantly higher than in men (OR=1.08 (95% CI=1.02–1.14)). At 12 months, the OR for ADL dependency in women was 1.83 (95% CI: 1.74–1.91) in unadjusted data. With adjustment for age, the OR for ADL dependency remained significantly higher than in men (OR=1.49, 95% CI=1.42–1.57).

Functional decline beyond 3 months after stroke

The number of patients who were ADL independent at 3 months was 28 683, and out of those, 4 544 (16%) declined to functional dependency between 3 and 12 months. As seen in Figure 9, decline was most pronounced in patients over 75 years of age.

Baseline characteristics in patients who declined versus remained stable in function over time, are shown in Table 3. Data were unadjusted. Patients with functional decline beyond 3 months were approximately eight years older, and had more often vascular risk factors: diabetes mellitus, atrial fibrillation and diabetes. Smoking pre-stroke, however, was more common among the functionally stable. Functional decline was more common in patients living in a single household pre-stroke (mostly women). Prior stroke or TIA were significantly more common among those with

functional decline. There was no association between stroke subtype and deterioration to ADL dependency in unadjusted data. Among those with functional decline, significantly lower proportions were discharged with warfarin and statins. In a subgroup analysis of patients with atrial fibrillation (n=5 989 of 28 683), a significantly lower proportion of patients were discharged with warfarin among those who deteriorated beyond 3 months post-stroke (35.7% compared to 58.5%, $p<0.0001$).

Table 3.

Table comparing baseline patient characteristics in those who remained functionally stable between 3 and 12 months and those with functional decline between 3 and 12 months. Data on smoking were missing in 6.2% of cases, and for the remaining variables data were missing in <0.7% of cases.

Variable	Functionally Stable (n=24 139)	Functionally declined (n=4544)
Mean age (SD)*	71.1 (SD=11.5)	79.0 (SD=9.7)
Female sex*	10 079 (41.8%)	2 792 (61.4%)
Living alone pre-stroke*	9 223 (38.2%)	2 490 (54.8%)
Assisted living pre-stroke*	164 (0.7%)	134 (2.9%)
Vascular risk factors		
Diabetes*	3 979 (16.5%)	1 041 (22.9%)
Atrial fibrillation*	4 691 (19.6%)	1 298 (28.6%)
Pre-stroke smoking*	3 812 (16.8%)	582 (13.8%)
Hypertension*	13 327 (55.6%)	2 924 (64.3%)
Prior stroke*	3 619 (15.1%)	1 175 (25.9%)
Prior TIA*	1 824 (7.6%)	410 (9%)
Stroke subtype**		
Ischemic stroke	21 709 (89.9%)	4 088 (90%)
ICH	1 958 (8.1%)	362 (8%)
Unspecified stroke	472 (2%)	94 (2%)
Level of consciousness on admission*		
Alert	23 125 (96.3%)	4 216 (92.8%)
Drowsy	798 (3.3%)	260 (5.7%)
Comatose	97 (0.4%)	43 (0.9%)
Medication at hospital discharge		
Warfarin*	3 665 (15.3%)	583 (12.8%)
Antiplatelet drugs**	18 242 (75.9%)	3 469 (76.7%)
Statins*	16 657 (69.3%)	2 476 (54.8%)

* $p<0.0001$, **ns (non-significant)

Risk of functional decline beyond 3 months post-stroke

Relative risks of functional decline to ADL dependency between 3 and 12 months post-stroke are shown in Table 4. All patients who were independent at 3 months (n=28 683) were analyzed. Patient baseline characteristics associated with an increased risk of functional decline between 3 and 12 months were female sex, current smoking habit, atrial fibrillation, diabetes mellitus, prior stroke, ICH or stroke not defined as ischemic or ICH, and severe stroke.

Table 4.

Table showing the relative risk (RR) of functional decline (presented with 95% CI) between 3 and 12 months post-stroke in patients (n=28 683) who were ADL independent 3 months post-stroke, in an age-adjusted Poisson regression model.

Variable	RR	95% CI Upper	Lower
Female sex*	1.60	1.50	1.70
Living alone pre-stroke**	1.04	0.98	1.11
Smoking habit*	1.43	1.31	1.55
Atrial fibrillation***	1.11	1.04	1.17
Diabetes mellitus*	1.50	1.41	1.60
Hypertension**	1.03	0.97	1.09
Prior stroke*	1.52	1.43	1.79
Level of consciousness*			
Drowsy	1.60	1.43	1.79
Comatose	2.34	1.79	3.05
ICH or undefined stroke****	1.14	1.05	1.25

*p<0.0001, **ns (non-significant), ***p=0.001, ****p=0.003

Unmet rehabilitation needs 1 year after stroke (Paper II)

Unmet rehabilitation needs in relation to age, sex and discharge destination

Paper II included 37 383 pre-stroke independent patients hospitalized with first-ever or recurrent stroke. The discharge destinations for all patients are shown in Figure 10. Approximately one third (28.8%) were discharged to a pre-specified rehabilitation program, consisting of ESD (n=4 425, 11.8%), inpatient geriatric rehabilitation (n=5 791, 15.5%), and inpatient stroke rehabilitation (n=638, 1.7%).

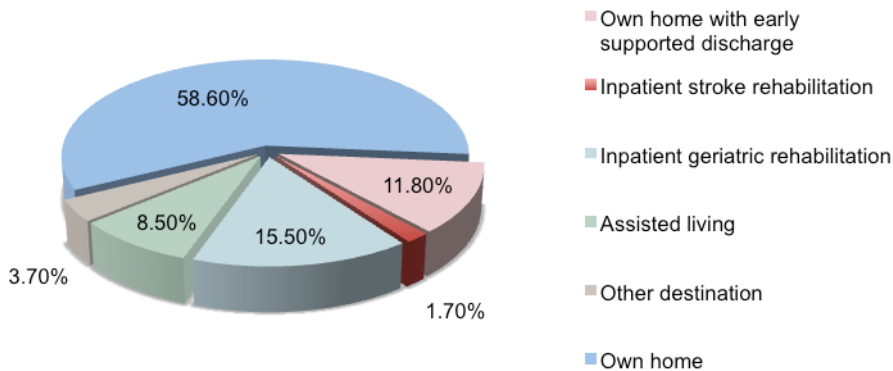


Figure 10. Planned discharge destination in 37 383 patients hospitalized for acute stroke. Data were missing in 0.2%.

One year post-stroke, 8 019 (21.5%) patients reported having unmet rehabilitation needs. The number of patients reporting not having had any rehabilitation needs were 15 623 (41.8%), 11 439 (30.5%) had met rehabilitation needs, and 1 277 (3.4%) did not know. Data were missing in 2.7% of patients. Of the 8 019 patients reporting unmet rehabilitation needs, 37.3% had been discharged to a pre-specified rehabilitation program: ESD (n=793, 9.9%), inpatient geriatric rehabilitation (n=1 944, 24.5%), and inpatient stroke rehabilitation (n=260, 3.2%).

Figure 11 describes unmet rehabilitation needs 1 year after stroke in relation to age. Unmet rehabilitation needs were most common among patients over 85 years of age (n=1 808, 31.8%), and least common in patients aged 55–64 (n=1 651, 16.7%). The proportion of men who reported unmet rehabilitation needs post-stroke was 21.1% (n=4 041), and 25% (n=3 978) of women reported unmet rehabilitation needs in unadjusted data (p<0.0001).

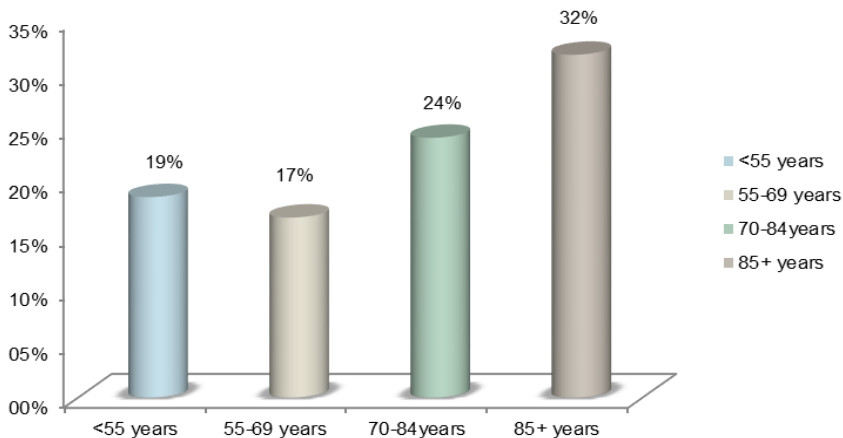


Figure 11. Proportions of stroke patients (n=37 383) divided into four age groups, reporting unmet rehabilitation needs 12 months post-stroke.

Baseline patient characteristics associated with unmet rehabilitation needs 1 year post-stroke

Patient baseline characteristics associated with unmet rehabilitation needs 1 year post-stroke were female sex, living alone pre-stroke, smoking, atrial fibrillation, diabetes mellitus, severe stroke, and ICH or stroke not defined as ischemic or ICH (Table 5).

Table 5. Age-adjusted multivariable logistic regression analysis showing OR's with corresponding 95% CI, for unmet needs of rehabilitation 1 year post-stroke in 37 383 patients.

Variable	OR	95%CI Lower	Upper
Female sex*	1.14	1.07	1.20
Living alone pre-stroke*	1.02	1.02	1.03
Smoking habit*	1.24	1.14	1.34
Atrial fibrillation*	1.19	1.12	1.27
Diabetes mellitus*	1.24	1.15	1.32
Hypertension**	0.95	0.90	1.01
Prior stroke*	1.63	1.53	1.75
Level of consciousness*			
Drowsy	2.32	2.10	2.60
Comatose	3.04	2.39	3.87
ICH or undefined stroke*	1.26	1.20	1.32

*p<0.0001, **ns (non-significant)

12-month factors associated with unmet rehabilitation needs 1 year post-stroke

Table 6 compares 12-month social and medical characteristics in patients with met rehabilitation needs (n=11 439) 1 year post-stroke with patients with unmet needs (n=8 019) at 1 year post-stroke. Patients answering: “do not know” were not analyzed. Data are unadjusted. Patients reporting unmet rehabilitation needs were approximately 3 years older, and presented with a considerably poorer overall health status. Patients who reported not having had any rehabilitation needs, presented with a more favorable health status than those declaring needs (Paper II, online Supplemental Table II).

Table 6.

Table comparing 12-month health and social status in patients with met needs versus unmet needs of rehabilitation at 1 year post-stroke. Data are unadjusted.

Variable	Met needs (n=11 439) n (%)	Unmet needs (n=8 019) N (%)
Mean age (SD)*	72.4 (SD=12.3)	75.4 (SD=11.4)
Female sex**	5 238 (45.8)	3 978 (49.6)
ADL dependency at 12 months**	3 650 (31.9)	4 732 (59.0)
Living conditions at 12 months**		
Own home without community support	7 298 (64.8)	3 406 (43.5)
Own home with community support	2 682 (23.8)	2 503 (31.9)
Assisted living	1 263 (11.2)	1 905 (24.3)
Partly / fully dependent on next of kin**	7 299 (64.4)	6 856 (86.4)
Antidepressant medication**	2 781 (24.9)	2 526 (32.2)
Pain**		
Occasionally	4 467 (39.6)	3 153 (40.0)
Often / always	2 289 (20.3)	2 783 (35.4)
Non-sufficient pain medication**	3 601 (32.3)	4 253 (54.5)
Low / very low self-perceived health	2 003 (17.8)	3 769 (48.1)

*p=0.01, **p<0.0001

Doctor's follow-up after stroke (Paper III)

Paper III included 8 164 patients with acute ischemic stroke or ICH, living in southern Sweden. The proportion of women was 49.2% (n=4 013), and mean age was 75.3 (SD=12.4) years (77.9 (SD=12.1) years in women and 72.6 (SD=12.1) years in men).

The cumulative probability of receiving a doctor's follow-up

The cumulative probability of receiving the first doctor's follow-up within 90 days after hospital discharge was 76.3%. The cumulative probability of a doctor's follow-up was 83.6% within 120 days, 88.7% within 180 days, and 93.1% within 365 days after hospital discharge (Figure 12).

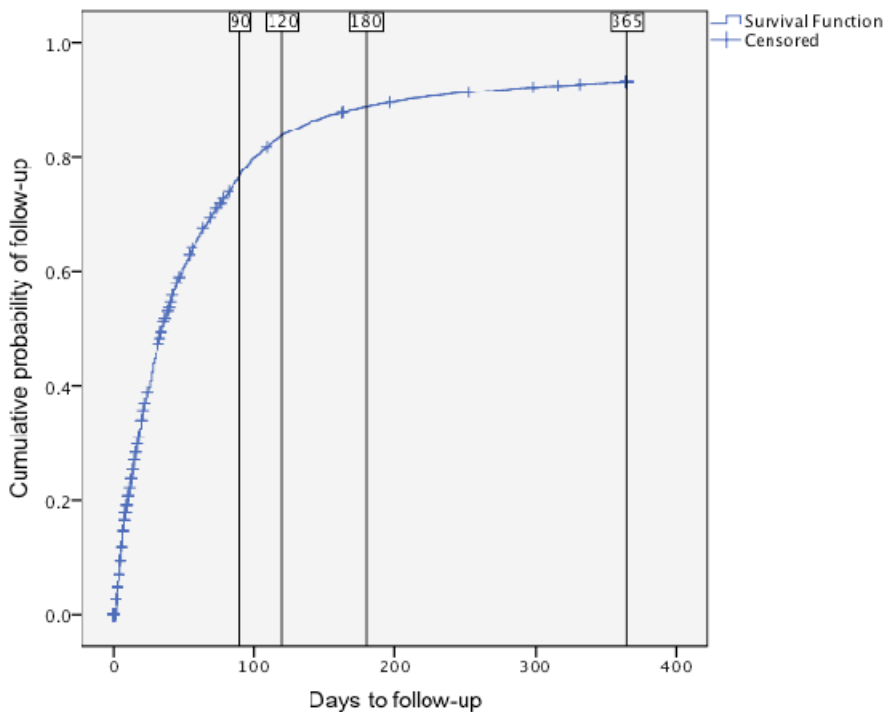


Figure 12. Kaplan-Meier 1-survival plot showing the cumulative probability of receiving the first doctor's follow-up within 90, 120, 180 and 365 days (vertical lines) after hospital discharge in 8164 patients with acute stroke.

Associations between patient characteristics and 90-day follow-up using unadjusted data

Table 7 shows the associations between patient baseline characteristics and 90-day follow-up in 90-day survivors (n=6 771). We found an age gradient, where higher age was associated with lower follow-up rates. Also, living in a single household, having pre-stroke dependency and prior stroke, as well as presenting with severe stroke were associated with significantly lower 90-day follow-up rates. We found no differences in 90-day follow-up rates between sexes, or between stroke subtypes. Follow-up proportions did not differ in patients with diabetes mellitus or hypertension, compared to patients without those diagnoses. Atrial fibrillation was associated with a lower follow-up rate at 90 days, but patients on warfarin may have had other healthcare interactions.

Table 7.

Associations between patient characteristics recorded during the hospital stay, and a 90-day doctor's visit in 6 771 90-day stroke survivors. Data are unadjusted.

Variable	Follow-up within 90-days N(%)	Chi square test (two-sided) p-value
Age		<0.0001
Ages <65	1 182 / 1 441 (82.0)	
Ages 65-74	1 298 / 1 669 (77.8)	
Ages 75-84	1 680 / 2 234 (75.2)	
Ages 85+	975 / 1 427 (68.3)	
Sex		0.191
Female	2 425 / 3 228 (75.1)	
Male	2 710 / 3 543 (76.5)	
Pre-stroke living conditions		<0.0001
Living alone	2 300 / 3 124 (73.6)	
Co-living	2 820 / 3 624 (77.8)	
Pre-stroke functional status		<0.0001
ADL independent	4 771 / 6 199 (77.0)	
ADL dependent	307 / 488 (62.9)	
Prior stroke		<0.0001
Yes	923 / 1 333 (69.2)	
No	4 198 / 5 417 (77.5)	
Stroke subtype		0.963
Ichemic stroke	4 611 / 6 081 (75.8)	
Primary ICH	524 / 690 (75.9)	
Level of consciousness on admission		<0.0001
Alert	4 664 / 6 108 (76.4)	
Drowsy	378 / 503 (75.1)	
Comatose	66 / 124 (53.2)	
Hypertension		0.885
Yes	2 977 / 3 929 (75.8)	
No	2 139 / 2 817 (75.9)	
Diabetes mellitus		0.202
Yes	976 / 1 263 (77.3)	
No	4 154 / 5 499 (75.5)	
Atrial fibrillation		0.001
Yes	1 168 / 1 604 (72.8)	
No	3 952 / 5 147 (76.8)	

Associations between patient characteristics and the probability of receiving a 90-day follow-up in a multivariable model

In Table 8, associations between patient baseline characteristics and the probability of receiving a follow-up visit within 90 days post-stroke in 8 164 patients are shown. High age was associated with lower probability of receiving a doctor's follow-up within 90 days, as was pre-stroke dependency, prior stroke, and severe stroke. Female sex and diabetes mellitus were positively associated with the probability of follow-up.

Table 8.

Cox regression multivariable analysis showing the association, expressed as HR's with corresponding 95% CI, between patient baseline factors and the probability of a 90-day follow-up in 8 164 stroke patients. Ref. refers to reference category.

Variable	HR	95% CI		p-value
		Lower	Upper	
Age (<65 ref.)	1			
Ages 65-74	0.93	0.86	1.00	0.047
Ages 75-84	0.94	0.88	1.01	0.099
Age 85+	0.84	0.77	0.90	<0.0001
Sex (male ref.)	1.07	1.01	1.12	0.013
Pre-stroke ADL dependency	0.90	0.82	0.99	0.04
Prior stroke	0.82	0.76	0.87	<0.0001
Level of consciousness on admission (alert ref.)	1			
Drowsy	1.06	0.97	1.17	0.187
Comatose	0.51	0.41	0.63	<0.0001
Diabetes mellitus	1.10	1.03	1.17	0.003

Adherence to secondary preventive drugs after stroke (Paper IV)

Drugs at discharge, primary adherence and drug persistence

Of the 7 100 patients with acute ischemic stroke that lived in Region Skåne and were registered in Riksstroke from 2008 to 2010, 5 602 were alive by the end of follow-up (14 months post-stroke). Baseline data are shown in Table 1, Paper IV. We studied the following four drug classes: warfarin, statins, antihypertensive and antiplatelet drugs. At hospital discharge, 5 454 / 5 602 (97.4%) of patients were discharged with one or more of the four drug classes. Drugs at discharge, primary adherence and drug persistence at 1 year are summarized in Table 9.

Table 9.

Table summarizing drugs at discharge, primary adherence and drug persistence in 5 602 patients with ischemic stroke.

Drug class	Drug at discharge N (%)	Primary adherence n (%)	Drug persistence n (%)
Antiplatelet	4 523 (80.7)	4 302 (95.1)	3 771 (83.4)
Warfarin	805 (14.4)	721 (89.6)	559 (69.4)
Antihypertensive	4 111 (73.4)	3 914 (95.2)	3 614 (87.9)
Statin	3 902 (69.7)	3 640 (93.3)	2 960 (75.9)

The set of drugs that the patients were discharged with was defined as the discharge drug regimen. By the end of follow-up, 3 706 / 5 454 (68%) continued filling prescriptions of all discharge drug classes (discharge drug regimen persistent), and 1 748 / 5 454 (32%) were non-persistent to their discharge drug regimen. Patients who were non-persistent to discharge drug regimen did not differ by age, sex, educational level or country of birth, to those who were persistent (Table 3, Paper IV). ADL dependency at 3 months was negatively associated with persistence to discharge drug regimen (age-adjusted OR=0.63 (95%CI: 0.57–0.92)). Patients who did not receive stroke unit care had lower OR of persistent drug use (age-adjusted OR=0.84, 95%CI: 0.70–0.99). Follow-up within 90 days was not associated with overall regimen persistence. However, when analyzing the four drug classes separately, the odds of drug persistence was lower in patients who had not received a follow-up visit within 90 days after hospital discharge for antihypertensive drugs (age-adjusted OR=0.74 (95%CI: 0.60–0.91) and antiplatelet drugs (age-adjusted OR=0.80, 95%CI: 0.69–0.98), and as a trend for statins (age-adjusted OR=0.85, 95%CI: 0.85–1.01), but not for warfarin. Also, on a drug class level, university education was associated with persistent use of warfarin (age-adjusted OR=1.61, 95%CI: 1.01–2.57), and non-European country of birth was negatively associated with persistent use of antihypertensive drugs (OR=0.53, 95%CI: 0.30–0.92).

90-day doctor's follow-up in relation to age, sex, socio-economy and medication at discharge

Of the 5 602 patients who were alive by the end of follow-up, 4 177 (74.6%) received a doctor's follow-up within 90 days from hospital discharge. Associations between 90-day follow-up and age, sex, socio-economy and secondary preventive drugs at discharge are shown in Table 10. Patients >75 years and patients discharged without secondary preventive medication had lower OR of receiving a 90-day follow-up visit. Patients with university education also had lower OR of receiving a follow-up visit. Sex and country of birth showed no associations with 90-day follow-up.

Table 10.

Associations between 90-day follow-up and age, sex, socio-economy and drugs at discharge in 5 602 patients with ischemic stroke, using 90-day follow up as the dependent variable. Proportions (%), and odds ratio (OR) with 95% confidence intervals (CI), from a logistic regression modeling are shown, with 90-day visit as the dependent variable and adjusted for age (Ref. = reference category).

Variable	90-day follow-up n (%)	P-value	OR (95% CI) (Age-adjusted)	P-value
Age (un-adjusted)				
<=75	2 104 (78.6)	<0.0001	Ref.	
>75	2 073 (70.9)		0.67 (0.59-0.75)	<0.0001
Sex				
Men	2 218 (75.2)	0.282	Ref.	
Women	1 959 (73.9)		1.03 (0.91-1.17)	0.627
Education				
Primary school	1 857 (75.5)	0.041	0.95 (0.82-1.09)	0.470
Secondary school	1 551 (78.0)		Ref.	
University education	619 (74.0)		0.79 (0.67-0.95)	0.012
Country of birth				
Sweden	3 570 (75.1)	0.323	Ref.	
Europe	512 (75.2)		0.93 (0.77-1.12)	0.452
Non-European	95 (81.2)		1.18 (0.73-1.89)	0.506
Secondary preventive drugs at discharge				
Yes	4 117 (75.5)	<0.0001	Ref.	
No	60 (40.5)		0.23 (0.16-0.32)	<0.0001

Discussion

Methodological considerations

The strengths of quality register-based research are that it contributes with large size study materials, and that inclusion is generally not restricted by age, functional status or co-morbidity, producing an unselected cohort with generalizable results. However, coverage may be prioritized over detail. Detailed information can be limited in quality registers compared to randomized controlled trials (RCT's) and epidemiological registers, for both economic and practical reasons. On the other hand, performing register-based research is usually less expensive. In observational studies, causality cannot be proven, although associations can be found. Riksstroke provides a large number of study subjects. With large research materials, even small differences between groups are detected with high statistical significance. However, most small differences may be of limited clinical relevance.

Bias is defined as a systematic error in the design, conduct, or analysis of a study that results in a mistaken estimate of an exposure's effect on the risk of the disease. Bias threatens the validity of study results. Internal validity reflects the extent to which a causal conclusion based on a study is warranted, and external validity reflects to which extent the results of a study can be generalized to a population at large. Bias can be divided into selection bias, information bias and confounding.

Selection bias

Selection bias refers to a statistical error caused by an un-representable sample; hence the selection of study subjects does not represent the population that it aims to describe.

Selection bias at inclusion in Riksstroke

Case ascertainment reflects the finding of all true stroke events. The true number of stroke events in Sweden is uncertain¹⁶⁰⁻¹⁶². The gold standard of estimating stroke incidence is through population-based epidemiological registries. The incidence of first-ever stroke by the start of this century was estimated to 144/100 000 person-

years¹⁶³. Combined approaches using the National Patient Register (NPR) and the Causes of Death Register have been validated to a high-standard epidemiological database (MONICA)¹⁶⁰. The positive predictive value for first-ever stroke events in the two registers together was 93.6% when compared with first-ever events in the MONICA register. Compared to previous validations, results have improved¹⁶⁴⁻¹⁶⁶. In a recent case completeness validation study by Riksstroke, cases registered in Riksstroke were compared with cases registered in the NPR. Riksstroke covered 89.5% of cases registered in the NPR, or cases registered only in Riksstroke (but not in the NPR)¹⁶⁷. Incomplete case ascertainment introduces selection bias and skewed results affecting both process indicators (such as stroke-unit care) and outcome indicators (such as case-fatality)¹⁶⁸.

Riksstroke is a hospital-based register and stroke patients that are not treated in-hospital are not registered. It has been estimated that approximately 84%–92% of patients with first-ever strokes are treated in-hospital^{162, 168}. A study showed that patients sent home from the emergency room were more often male, had mild strokes and low 28-day case-fatality. Patients managed solely in primary care were older, in assisted living, and had a high 28-day case fatality¹⁶².

Coverage rate refers to the proportion of first-ever strokes from the NPR that is registered in Riksstroke. In 2008, the coverage rate was 83%, in 2009 it was 85% and in 2010 it was 88%³³. Under-coverage occurs when some members of a population are inadequately represented in the study sample. In admitted patients, fatal strokes are less likely reported, as well as patients treated outside the stroke-unit¹⁶¹. First-ever stroke is slightly over-diagnosed in the NPR, and recurrent stroke to a higher extent because ICD classification of stroke sequelae and recurrent stroke are less precise¹⁶⁰. According to the ICD-10 manual, an acute stroke diagnosis may remain for 12 months after stroke. Therefore, first-ever stroke is used for measuring coverage in Riksstroke.

Selection bias at follow-up

Attrition Bias is a type of selection bias caused by loss of study participants. Attrition may significantly influence study results, and in controlled clinical trials it has been shown to give considerably larger treatment effects¹⁶⁹. In quality register observational studies, loss to follow-up is a common problem. Patients who were alive at 3 and 12 months but did not provide follow-up information to Riksstroke were lost to follow-up. Lost to follow-up consisted both of those who chose not to participate, and those who could not be found because of emigration, protected identity or invalid address. In Table 11, baseline data in patients lost to follow-up are described in relation to the whole cohort, to patients who died before follow-up, and to patients who were followed up. Lost to follow-up in the table was defined as those who survived 12 months and had incomplete or no follow-up (n=21 247). Patients with complete follow-up had an overall better medical status than those who were lost to follow-up.

Previous analyses of non-responders in Riksstroke have shown that they are more often women, older, living alone and pre-stroke ADL dependent¹⁷⁰. In this material, patients who were lost to follow-up did not differ much by sex and age from those who were followed up, but they were more likely to live alone, to be pre-stroke ADL dependent, to have vascular risk factors and to have severe stroke (Table 11). Selecting patients with better prognosis from Riksstroke in the present thesis most likely leads to more favorable outcome results than would be seen in the complete cohort.

Table 11.

Baseline characteristics in patients lost to follow-up in Riksstroke. Data were missing in <1.3%, except for smoking (10%).

Variable	Total cohort (n=75 048)	Death within 12 months (n=16 634)	Complete follow-up (n=37 167)	Lost to follow- up (n=21 247)
Proportion of women	49.1%	55.7%	49.1%	48.4%
Mean Age (SD)	75.2 (SD=12.2)	81.2 (SD=9.8)	73.7 (SD=11.6)	74.4 (SD=13.2)
Living alone pre-stroke	50.6%	63.4%	43.0%	54.1%
Pre-stroke ADL dependency	11.8%	25.0%	5.0%	14.1%
Prior stroke	25.9%	24.8%	19.6%	37.6%
Vascular risk factors				
Diabetes mellitus	20.3%	21.7%	18.7%	22.1%
Hypertension	59.2%	61.2%	58.2%	59.5%
Atrial fibrillation	28.9%	41.8%	23.0%	28.8%
Smoking	14.2%	9.0%	15.2%	16.3%
Stroke subtype				
Ischemic stroke	85.7%	78.1%	89.0%	85.8%
Primary ICH	11.8%	18.0%	9.1%	11.6%
Undefined stroke	2.6%	3.9%	2.0%	2.6%
Level of consciousness on admission				
Alert	82.0%	55.4%	92.5%	84.2%
Drowsy / comatose	18.0%	44.5%	7.5%	15.8%
Stroke unit care	77.3%	69.0%	81.1%	77.0%

Survivorship bias is a systematic error caused by exclusion of those who died before follow-up, in this case 3- or 12-month follow-up. Survivorship bias is closely related to attrition bias. Both are relevant in Paper I, II and IV. By excluding patients who died within 12 months or were lost-to follow-up we introduced a selection bias. In study I, we excluded patients with pre-stroke disability, which affected analyses on case-fatality. Patients with pre-stroke ADL dependency had higher case-fatality (Results section). In study IV, we only analyzed survivors for drug adherence. If

continued drug use had an impact on survival, persistence may have been over-estimated.

In Paper III (and partly IV), which was based on time to an event, all patients were included until an event occurred, and this lowered the risk of introducing selection bias.

Confounding

Confounding is a systematic error that occurs when an exposure-outcome association is affected by other factors also affecting the outcome. This can be illustrated with an example using data from Paper I. The ADL dependency proportion at 12 months post-stroke was 28.3%, 22.6% in men and 34.9% in women. The OR of being ADL dependent at 12 months post-stroke was 1.83 (95% CI: 1.74–1.92) for women. Mean age in women with stroke in Sweden is approximately four years older than in men. This means that age may be a confounding factor for the association between female sex and ADL dependency at 12 months. The simplest way to control for age as a confounder is to stratify the study material by age. The proportions of ADL dependency differed with stratification for age (Figure 13). When adjusting for age in a logistic regression model with ADL dependency as dependent variable and sex and age as independent variables, the OR of ADL dependency for women compared to men was lowered to 1.49 (95%CI: 1.42–1.57). There may be other confounding factors influencing the association between female sex and ADL dependency, such as co-morbidity and initial stroke severity. In Riksstroke it is possible to adjust for presence of diabetes, hypertension, atrial fibrillation, and consciousness level on admission. When adjusted for these factors, the OR of ADL dependency in women was 1.54 (95%CI: 1.46–1.61). However, Riksstroke does not collect information on for example dementia, which may also contribute to functional decline after stroke. Factors that are of importance, but that we cannot control for, can be described as residual confounders. It cannot be concluded from these results, whether the poorer prognosis in women is a real association or a result of residual confounding.

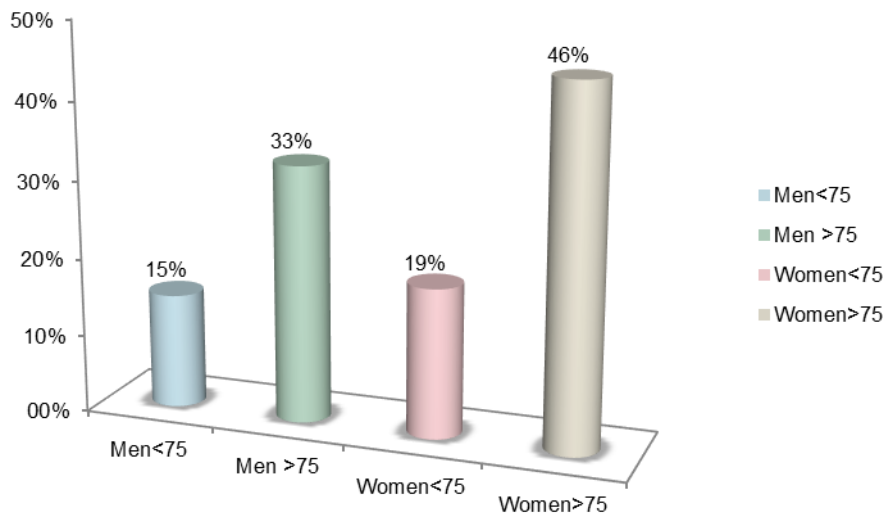


Figure 13.

Proportions of men and women over and under 75 years of age that were ADL dependent at 12 months. ADL dependency is unevenly distributed in the to age groups, and age confounds the association between sex and ADL outcome at 12 months.

Confounding is also of importance in Paper III, where we explored the probability of stroke follow-up within 90 days, and which factors affected the probability of doctor's follow-up within 90 days after stroke. For practical reasons, we studied all-cause visits and not only stroke-specific visits. Attendance for other conditions that we did not have information on from Riksstroke, may have confounded the association between the exposure (stroke) and the outcome (follow-up). The probability of follow-up within 90 days is therefore likely to be over-estimated in the study.

Outcomes are what really matter for patients and families, but most outcomes in the longer term are affected by factors that are outside the control of health-care systems. The longer the follow-up, the more other factors than medical have an impact. Therefore, the associations between patient baseline characteristics or process indicators, and outcomes may be affected by residual confounding.

The register item of unmet rehabilitation needs at 12 months (Paper II) has not been validated in Riksstroke, and may not correlate to actual rehabilitation received. It may be confounded by other conditions leading to unmet needs, and could therefore be prone to confounding. In a Riksstroke validation study from 2012–2013, the similar item “are your needs for help and support met?” from the 3-month follow-up showed low test-retest-reliability¹⁷¹. Patient-experienced outcome measures are important, but may be affected by expectations, previous healthcare experiences, and personality.

Information bias

Information bias refers to bias that arise from measurement errors. Riksstroke data have shown >90% concordance with information from patients charts for most variables¹⁵⁰. In a recent validation of the acute form, content validity as well as inter-hospital reliability was high¹⁶⁷. The questions assessing ADL outcome at 3 months show good agreement with the Barthel Index (BI) and the mRS, and can be used as a measure of basic ADL function^{150, 159}. However, self-reported ADLs are not gold standard in functional outcome assessment due to the presumed higher risk of misclassification (Paper I).

There were different modes of responding to the 3- and 12-month survey. The patients could fill out the questionnaire independently or with help, or a next of kin or caregiver could fill out the questionnaire. At 3 months, some patients were offered a telephone interview or a personal interview with a nurse.

At 3 months, 39.1% (n=21 468) of those who completed follow-up (n=62 773) filled out the questionnaire independently, and 26.8% (n=14 712) filled out the questionnaire with assistance. A telephone interview was performed in 12.1% (n=6651) of cases, and a personal interview was held in 3.4% (n=1870) of cases. A next of kin filled out the questionnaire in 7.9% (n=4343) of cases and a caregiver in 9.2% (n=5044) of cases, and in the remaining 1.1% (n=616), another person filled out the questionnaire. Data were missing in 0.3%.

At 12 months, 58.8% (n=23 350) of those who completed follow-up (n=39 686), filled out the questionnaire independently, and 26.1% (n=10 731) filled it out with assistance. A caregiver filled out the questionnaire in 0.4% (n=151) of cases, a next of kin in 10.2% (n=4033) of cases and another person in the remaining 1.7% (n=686) of cases. Data were missing in 2.8%.

The person filling out the questionnaire may have influenced responses (information bias), but it is not likely that dependency rates and rehabilitation needs were underestimated.

Generalizability

The high case ascertainment and coverage rate in Riksstroke is important for the generalizability of the results. Results are generalizable to the Swedish stroke population, and results on outcomes such as ADL dependency and case-fatality are thought to be generalizable to other western populations. However, traditions of rehabilitation and stroke follow-up show considerable difference between regions and countries and results must be interpreted bearing that in mind.

Strengthening the Reporting of Observational Studies in Epidemiology (STROBE)

STROBE¹⁷² is an initiative from epidemiological researchers to strengthen the reporting of observational, epidemiological studies. The initiative recommends transparency in what was planned, done, found and what conclusions were drawn. Moreover, the STROBE Statement is a checklist of 22 items that should be addressed in articles of analytical epidemiology¹⁷³. We attempted to follow the STROBE Statement checklist for cohort studies in all four papers.

General discussion

The present thesis constitutes the first in-depth analyses of the 1-year follow-up from Riksstroke, providing longitudinal data on hard clinical endpoints, as well as patient-experienced outcomes from a large, unselected stroke cohort. Moreover, we present Riksstroke data in relation to doctor's follow-up after stroke, in relation to socio-economy and in relation to adherence to secondary preventive medication, captured from other official registers.

With decreased stroke mortality that is not yet matched by a proportional decrease in stroke incidence, the absolute number of stroke survivors increases⁷. This implicates the need for long-term, and in particular longitudinal data, on stroke outcomes and process indicators, as well as the patient perspective on the continuum of stroke care and outcomes. Riksstroke is unique in providing nation-wide long-term, and longitudinal data with both high validity and coverage.

Changes in functional outcome

In this nation-wide longitudinal study (Paper I) of ADL outcome at 3 and 12 months post-stroke, we found that ADL dependency rates increased from 16 to 28% between 3 and 12 months after stroke in previously independent individuals, and that a substantial proportion (16%) of patients who were ADL independent at 3 months, transitioned to ADL dependency between 3 and 12 months.

The substantial increase in ADL dependency shown in our study, differs from previous studies that have shown more stable dependency proportions over time^{38, 174-177}. This can be exemplified in the Riksstroke 1-year follow-up report from 2009³³, in which all patients were analyzed, and functional outcome remained fairly stable between 3 and 12 months (19% versus 22% dependency proportions). This difference may be explained by the longitudinal design of our study, which only

included followed up survivors. It is likely that a substantial proportion of the most disabled at 3 months die before 12 months, masking the real number of patients who deteriorate over this period. Dependency proportions may thus appear stable over time, which was also previously described in the OXVASC group¹⁷⁴. Changes in ADL or mobility (using a longitudinal approach) between 3 and 12 months post-stroke have been assessed only in few studies^{177, 178}, and these reported functional decline in 21–40%. Patients >80 years were susceptible to deterioration¹⁷⁸, which is consistent with our finding that patients who deteriorated were approximately 8 years older than those who remained functionally stable. Other studies on functional decline after stroke using different follow-up intervals, found depression, cognitive impairment and physical inactivity to predict decline^{179, 180}.

Female sex, severe and previous stroke as well as presence of vascular risk factors were associated with ADL dependency at 12 months, as well as with functional decline between 3 and 12 months in our study. Predictors of functional decline are not previously well studied outside of rehabilitation settings, but predictors of poor functional outcome found in previous studies included high age³⁸⁻⁴⁰, female sex⁴¹⁻⁴⁶, severe stroke^{38, 40, 41} and presence of comorbidities⁴⁸⁻⁵⁰, correlating well with our findings.

Even though we found associations, based on the study design, we cannot draw any causal conclusions. We lack information on factors that may be of importance for decline: subsequent stroke events and hospitalizations for other reasons between 3 and 12 months, as well as presence of cognitive impairment. Attrition bias, in terms of a more favorable health status in responders, may have led to an underestimation of disability levels.

Of the factors associated with poor outcome or decline, only comorbidities, and in particular vascular risk factors, are modifiable. This highlights the importance for timely secondary preventive measures to prevent recurrent and disabling stroke¹⁸¹.

Perceived unmet rehabilitation needs

This study (Paper II) reflects the patient perspective of post-stroke rehabilitation. We found that 22% of previously independent 12-month survivors reported unmet rehabilitation needs 1 year post-stroke. Higher proportions of unmet needs were reported in two Swedish studies: 29% and 33% respectively^{182, 183}. However, the numbers of participants were lower (175 and 86 respectively) and study settings differed compared to our nation-wide study with a majority of minor strokes, which could contribute to the lower proportion of unmet rehabilitation needs in our study.

In Sweden, there is currently no national guideline for patient selection for rehabilitation. Furthermore, there are large regional variations in both patient

selection and rehabilitation services available. Unmet rehabilitation needs were most commonly reported (32%) in the very old (>85 years), and in patients between 70 and 84 years (24%). Previous studies have shown that older patients have less access to post-stroke rehabilitation^{64, 65}. White matter disease and silent infarcts increase with age, and are associated with worse rehabilitation outcomes, but not age per se^{184, 185}. We argue that age alone should not be a restricting factor for rehabilitation particularly in previously independent subjects.

Severe stroke was strongly associated with unmet rehabilitation needs (OR=3). Like high age, severe stroke is associated with less access to post-stroke rehabilitation⁶⁴. Patients with severe stroke have the largest benefit of comprehensive stroke unit care¹⁸⁶, but initial stroke severity and extent of improvement over the first days or weeks are highly predictive for long-term outcome¹⁸⁷. Therefore, presumed lack of rehabilitation potential may explain why the most severe strokes have less access to inpatient rehabilitation units. Moreover, shorter lengths of hospital stay for stroke may require early prognostication.

In our study, use of antidepressant medication was more commonly reported in patients with unmet rehabilitation needs. The causality of this association remains unclear, but one study has reported associations between depression and unmet needs after stroke¹⁸⁸. Post-stroke depression is common, affecting 30% of stroke-survivors, and is associated with poor functional status and functional decline after stroke^{179, 180}. Increased mortality and disability are independent outcomes of post-stroke depression¹⁸⁹. Diagnosing and intervening on post-stroke depression is of importance.

Patient-perceived outcomes can be influenced by other patient factors, such as expectations and previous healthcare experiences, which makes the outcome measure less reliable⁵³. This is the main limitation of the study. Furthermore, the variable is difficult to validate due to the challenge of capturing the quantity and quality of rehabilitation received. Goals in rehabilitation are individual and need to be realistic, but rehabilitation goal-achievement was not assessed in this study. Despite these limitations, our results are consistent with the findings from previous studies.

The large group of previously independent 12-month stroke survivors with unmet rehabilitation needs signals an overall poor health situation, with higher dependency rates, and insufficient pain medication, depression, and low or very low self-perceived health. Our results emphasize the importance of a comprehensive stroke follow-up, addressing multiple stroke-related domains.

Doctor's follow-up after stroke

The study of doctor's follow-up after stroke (Paper III) showed that 25% of 3-month survivors were not attended by a doctor within 3 months after hospitalization for acute stroke. Patients of old age, with pre-existing or severe stroke, or ADL dependency had less chance of receiving a doctor's follow-up within 3 months. We included all-cause visits, and not only stroke-specific doctor's visits, and therefore follow-up rates may be over-estimated in this study. Patients may have had nurse visits or other healthcare interactions, and these were not captured in the present study.

Only a few studies have assessed follow-up proportions after stroke. One study from the UK (from 2002) showed that 14% of patients were not seen by a doctor within 3 months post-stroke. Severe disability (OR=0.17), age >80 years (OR=0.55), and living in a nursing home (OR=0.19), were associated with lower odds of a primary care visit after stroke¹⁹⁰. Another study (also from the UK) found that 25% had not been seen by a doctor 3 months after hospital discharge, and non-treatment with secondary prevention was more common among those not followed up¹⁹¹.

Our findings of (1) insufficient follow-up rates, and (2) inequalities in post-stroke care are contrary to the recommendations in the Swedish National Guidelines for stroke care regarding a timely stroke follow-up in primary care after discharge from hospital and equality of stroke care²³. In the National Clinical Guidelines for Stroke Care from the UK, a compulsory routine assessment in primary care has been introduced at 6 months, and yearly thereafter. Patients with any disability by the end of the first rehabilitation period should be reassessed every six months. Risk factor treatment is to be revised yearly, with verbal and written information on all medicines^{192, 193}. The effect of the 6-month follow-up is yet to be evaluated.

We argue that a compulsory and comprehensive stroke follow-up in primary care or in a hospital outpatient clinic appears appealing and justified, and should improve both follow-up rates and equality of care.

Adherence to secondary preventive drugs

This longitudinal study on adherence to secondary preventive drugs after stroke (Paper IV) showed that hospital initiation (or continuance) of secondary prevention was 95% for antithrombotic drugs (aggregated), 73% for antihypertensive drugs, and 70% for statins, but that large proportions of patients discontinued their treatments during the first year. Adherence rates at 1 year were 69% for warfarin, 76% for statins, 88% for antihypertensive agents, and 83% for antiplatelet drugs. The rapid decrease in secondary preventive drug use over time has previously been described in Riksstroke¹³³.

We analyzed the association between 1-year drug persistence and stroke follow-up within 90 days, and found that patients who did not receive follow-up had lower odds of persistent treatment with antihypertensive, and antiplatelet drugs. The association between stroke follow-up and drug treatment has previously been shown in one study¹⁹¹. Drug prescriptions only last for 3 months in Sweden, and therefore, a follow-up within 3 months may be crucial for refilling prescriptions but also for assessing tolerance and primary drug adherence.

University education was associated with persistent use of warfarin, and the relation between educational level and adherence is previously described¹³⁷, but was not found for the other drug classes in our study.

At 1 year post-stroke, we found that 32% were non-persistent to the set of drugs that they had been discharged with (discharge drug regimen), correlating well with a recent review and meta-analysis on non-adherence to secondary prevention after stroke, showing 30% non-adherence¹³⁷. Patients who had received stroke unit care, and had followed the general paths at discharge from hospital had higher odds of continuing with their discharge drugs in our study, indicating that organizational factors may play a part in long-term adherence^{133, 137, 194}. Non-persistence to discharge regimen was associated with ADL dependency at 3 months, but the causality remains unclear.

The study design used objective data on adherence, but our measures of primary adherence and persistence may be prone to measurement errors (information bias). Accumulation of pills could have led to delayed prescription filling. Drug discontinuance may have been initiated by a healthcare provider and adequate in some cases. Moreover, we only included patients who were alive by the end of follow-up (14 months post-stroke), and adherence may have been over-estimated if it increased survival. Educational level is only one of many markers of socio-economic status.

Given the large risk reduction of adequate secondary prevention on recurrent vascular events, improved medication adherence should be a key target in secondary preventive strategies. However, non-adherence to medication is complex and multi-factorial involving individual, stroke related, healthcare related and socio-economic factors¹³⁷. The interventions needed to improve long-term adherence may have to include improved hospital routines for prescriptions and patient education as well as clear instructions at transition of care from hospital to outpatient care¹⁹⁴. Our results imply that continued use of secondary preventive drugs 1 year after stroke remains sub-optimal. Routine assessments of secondary prevention during the subsequent year after stroke may improve adherence rates.

Summary

The main findings of this thesis implicate that the framework for an effective and equal post-stroke care in Sweden is weak, which primarily affects vulnerable groups of old and disabled patients. We found an inverse relation between care needs and care received. The implementation of a comprehensive multiple-domain follow-up after stroke in clinical routine appears justified and may result in higher follow-up rates, and improved equality of care, but may also improve patient-experienced outcomes. A routine assessment using simple checklists may improve the detection and adequate referral for common stroke-related problems. Risk factor management and secondary preventive drug adherence remains suboptimal in Sweden, and even though adherence is complex and multi-factorial, regular assessments of tolerance and compliance may improve adherence rates.

Conclusions

The main aim of the present thesis was to improve knowledge of post-stroke care and outcomes over the first year after stroke, using data from the Swedish Stroke Register, as well as other official registers. Our conclusions are:

- I. Functional outcome after stroke is dynamic, and even though a majority of patients remain stable between 3 and 12 months, a substantial proportion of patients deteriorate. Patients >75 years, and in particular older women are vulnerable to functional decline.
- II. Unmet needs of rehabilitation are commonly reported in 12-month stroke survivors (1 in 5). Unfulfilled rehabilitation needs are most commonly reported among older patients, and in particular among the very old (>85 years). Other unmet needs, such as pain, depression and poor self-perceived health are more common among patients with unmet rehabilitation needs.
- III. One in four patients with stroke does not receive a doctor's follow-up within 3 months after hospital discharge. Vulnerable groups of patients with old age, functional dependency, and prior or severe stroke have lower probability of receiving follow-up.
- IV. The use of secondary preventive drugs decreases after stroke, and 1 in 3 patients discontinues treatment with one more drug class during the first year after hospitalization for acute stroke. A doctor's follow-up within 3 months may be of importance for drug adherence. High educational level was associated with adherent warfarin use, but apart from that, we did not find any associations between adherent drug use and age, sex or educational status.

Future perspectives

Merging of quality register data with routine administrative data, and data from other official registers is an effective approach to capture a larger perspective of the disease studied, in this case stroke. For this thesis, it was not possible to achieve nation-wide routine administrative data due to the use of different computer systems and local regulations. Administrative data are key to analyzing and understanding of processes in healthcare. A challenge for the future is to capture hospital and primary care, as well as municipal care routine administrative data in communicating registers on a national level. An initiative within register-based research has recently been implemented to facilitate the merging of quality register data with other official registers (registerforskning.se). Register-based Randomized Controlled Trials (RRCT's) in stroke care will be an important way to combine the benefits of long-term observational designs with the possibility to prove causality in RCT's in the near future.

We found that some patients deteriorated in functional status over time, but we lack information on important patient factors that may be associated with functional decline, such as recurrent stroke events and hospitalizations for other reasons. Data could be captured from the National Patient Register and studied further in the future.

Capturing the amount and type of rehabilitation received remains a challenge. The large variety in rehabilitation services and settings on regional and national levels is one of the reasons, and rehabilitation provided in municipal care has until now not been registered in any official registers. The poor access to data on rehabilitation makes systematic improvements difficult. We found that older and disabled patients reported unmet rehabilitation needs, but we cannot correlate that finding to quantity or quality of rehabilitation received. Access to rehabilitation, and quantification of rehabilitation received are research areas requiring further study. The International Classification of Function, Disability and Health (ICF) is a supplement to the ICD-10¹⁹⁵. Two individuals with the same disease can have completely different functional abilities, which the ICF, but not the ICD-10 can capture. ICF can be used as a clinical tool to describe functional level and disability in relation to health in a standardized manner, but also for standardized administrative coding, and for comparisons between regions or countries, as well as for comparisons over time.

We have argued that a comprehensive and compulsory stroke follow-up could be beneficial both to improve equality of care and follow-up rates. This should however be tested systematically in a trial.

Swedish summary

Svensk sammanfattning

Bakgrund

Stroke är den andra vanligaste dödsorsaken, och den tredje vanligaste orsaken till funktionsnedsättning på världsplan. Varje år insjuknar ca 25 000 personer i stroke i Sverige, och för cirka två tredjedelar rör det sig om det första strokeinsjuknandet. Man beräknar att minst 140 000 personer lever med följderna av stroke i Sverige.

Stroke är ett samlingsbegrepp för en rad tillstånd. Hjärninfarkter utgör den största delen (85 %). Mindre vanligt är intracerebral blödning (utgör ca 10 %) som uppstår när ett kärl i hjärnan brister spontant, eller subarachnoidalblödning (utgör ca 5 %) som uppstår när ett av kärlen på hjärnans yta brister spontant. I Riksstroke, som är det svenska kvalitetsregistret för strokesjukvård, registreras hjärninfarkter och intracerebrala blödningar.

Man har under senare år gjort stora landvinningar inom akut strokebehandling, och upptäckt flera nya effektiva behandlingar som minskar risken för död eller hjälpberoende efter stroke. I korta drag finns trombolysbehandling sedan mitten av 90-talet, en kraftigt blodförtunnande behandling som har god effekt hos utvalda patienter om given inom 4,5 timmar. Under 2015 publicerades inte mindre än fem kontrollerade, randomiserade studier som alla påvisade en tydlig behandlingstvinst vid endovaskulär behandling av stroke orsakade av kärlocklusion. Hemikraniektomi är ytterligare en behandling för de mest allvarliga strokefallen, där man sett att dödligheten minskar. Emellertid hjälper dessa behandlingar bara hos en mindre, utvald grupp av patienter med akut stroke. Vård på strokeenhet minskar risk för död och hjälpberoende och ska komma så många patienter som möjligt till godo.

Trots stora framgångar inom akut strokebehandling får majoriteten av strokepatienterna kvarvarande symtom av motorisk eller kognitiv art. Rehabiliteringsinsatser är aktuella för det stora flertalet. Stroke innebär i det längre perspektivet stora insatser från vården och kommunerna. De ekonomiska konsekvenserna av stroke på samhällsnivå är stora, och utgörs bland annat av förlorade arbetsaktiva år, särskilda boenden, vård och omsorg.

Jämfört med det stora fokus som lagts på akut strokevård, har betydligt mindre intresse ägnats åt stroke i det längre perspektivet. Det finns idag inget strukturerat uppföljningssystem för den stora patientgruppen (aktuellt minst 140 000 individer) som har haft stroke. Personer som haft stroke har 15 gånger ökad risk för en ny stroke eller annan kardiovaskulär händelse, och behandling av riskfaktorer minskar risken för nya insjuknanden. Därför är det av stor vikt att de vaskulära riskfaktorerna (rökning, diabetes mellitus, hypertoni och förmaksflimmer) identifieras och behandlas, ett arbete som till största delen äger rum i primärvården. Riskfaktorer behandlas både med livsstilsinterventioner så som kost och motion, men också med läkemedel.

Utöver att minska risken för återinsjuknanden, så kallad sekundärprevention, är strokeuppföljning också viktigt för att identifiera komplikationer till stroke. Depression drabbar en tredjedel av personer med stroke, och demens drabbar en av tio med förstagångsstroke och en av tre med återinsjuknande. Utöver det är det vanligt förekommande att utveckla venösa blodproppar, spasticitet, samlivsproblem, urininkontinens eller smärta. En internationell expertgrupp inom stroke har utvecklat en checklista som kallas Poststroke Checklist. Den har framtagits för att hjälpa vårdgivaren att identifiera ovanstående, behandlingsbara följder till stroke. Den har nyligen översatts till svenska, men används ännu inte rutinmässigt.

Riksstroke registrerar varje år cirka 25 000 strokepatienter som varit inlagda på sjukhus för stroke. Patienterna följs upp vid 3 och 12 månader via en enkät som besvaras av patienten själv, en anhörig eller en vårdgivare. Till denna avhandling har vi använt data från patienter registrerade i Riksstroke år 2008–2010. Riksstrokedata har även sammanslagits med data från flera statliga och administrativa register.

Målsättning

Målsättningen med avhandlingsarbetet var att undersöka andelen avlidna, och andelen hjälpberoende individer vid 3 och 12 månader efter stroke, att undersöka förekomsten av otillfredsställda rehabiliteringsbehov 1 år efter stroke, att studera uppföljande återbesök hos läkare det första året efter stroke, och slutligen att analysera associationer mellan uppföljning, följsamhet till sekundärpreventiv behandling och socio-ekonomi hos individer med stroke.

Resultat

Avhandlingen är baserad på fyra delarbeten (Arbete I–IV). Kvinnor hade sämre funktionsnivå än män vid både 3 och 12 månader. Funktionsnivån försämrades mellan 3 och 12 månader efter insjuknandet, speciellt hos äldre över 75, och i synnerhet hos kvinnor (Arbete I). Ett år efter stroke, ansåg sig en av fem patienter ha

otillfredsställda rehabiliteringsbehov. Otillfredsställda rehabiliteringsbehov var vanligast förekommande hos de äldsta patienterna (>85 år), och hos de med allvarligt stroke. Patienter med otillfredsställda rehabiliteringsbehov vid 1 år hade också ökad förekomst av smärta, depression och låg självskattad hälsa vid 1 år (Arbete II). En av tre patienter bedömdes inte av en läkare inom 3 månader efter utskrivning från sjukhus. Avsaknad av uppföljning var vanligast hos äldre och hos de med funktionsnedsättning (Arbete III). Behandling med strokeförebyggande läkemedel minskade snabbt under det första året efter stroke (Arbete IV). En av tre hade slutat med minst en strokeförebyggande läkemedelstyp vid ett år. Återbesök hos läkare inom 3 månader var associerat med fortsatt läkemedelsbehandling med blodtrycksmedel och blodförtunnande medel. Högutbildade var mer följsamma till behandling med antikoagulantia (blodförtunnande) men i övrigt hittades inga samband mellan socioekonomi och följsamhet till behandling (Arbete IV).

Diskussion

Avhandlingen avspeglar omhändertagandet av strokepatienter i det längre perspektivet, ett område som fått betydligt mindre fokus än det akuta omhändertagandet. Idag finns ingen på nationell nivå tydlig uppföljningsstruktur för strokepatienter som skrivits ut från sjukhus, även om enskilda sjukhus har etablerat en struktur för uppföljning. Avsaknaden av struktur i den långsiktiga strokevården speglas i de resultat som kommit fram i avhandlingsarbetet, och som påvisar ojämlikheter i vården. Speciellt identifieras de vulnerabla patientgrupperna av äldre och funktionsnedsatta där lägre andelar får återbesök och högre andelar har kvarvarande rehabiliteringsbehov vid 1 år. Vi fann samband mellan återbesök inom 3 månader, och följsamhet till sekundärpreventiva läkemedel, även om orsakssambandet är ovisst. Generellt minskar läkemedelsbehandlingen snabbt under det första året efter utskrivning, men orsakerna till det behöver studeras ytterligare. När de gäller kvinnors sämre funktion efter stroke, och ökade benägenhet till försämring över tid, så kan man utifrån den här studien inte dra slutsatser om det är uttryck för ojämlikhet i vården eller om det förklaras av förväxlingseffekter från faktorer vi inte har tillgång till i Riksstroke. Det är också ett område som behöver studeras mer ingående. Avhandlingen styrker vikten av införandet av en strukturerad uppföljning för att säkra en god och jämlik vård.

Riksstroke 1-årsuppföljning som infördes 2009, har inte tidigare blivit analyserad så djupgående. Den longitudinella aspekten, där man följer samma individ från akutskedet, till 3 och sedan 12 månader efter stroke, har bidragit med ny viktig kunskap om förändringar i sjukdomen över tid. 1-årsuppföljningen har bidragit med ny information om det sammantagna hälsotillståndet 1 år efter stroke, som på så vis kan återkopplas till vården och dess beslutsfattare.

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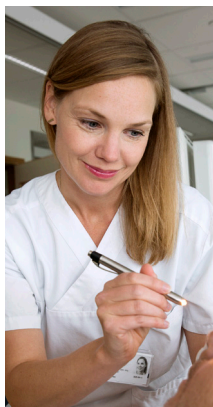
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Teresa Ullberg is a senior resident in neurology at Skåne University Hospital in Sweden. In the picture, she is examining a patient in the stroke unit. In recent years, important achievements within acute stroke treatment have improved patient outcomes, but less focus has been on long-term care. This thesis focuses on stroke care and outcomes in the longer perspective and is the first in-depth analysis of the Riksstroke 1-year follow-up.

