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Stroke in the Long Term

Prognosis, comorbidity, disability, readmission, and the caregiver perspective

STEFAN SENNFÄLT

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This is a comprehensive description of long-term prognosis after stroke in over 20 000 individuals followed for up to five years. The thesis describes key factors affecting mortality and functional outcome such as type of stroke, comorbidity, and pre-stroke functional status. It also explores readmission patterns and addresses the situation of informal caregivers such as spouses or children.

Stefan Sennfält is a Doctor of Medicine at Lund University Hospital and a member of the Stroke Policy and Quality Register Research Group at Lund University.

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Abstract

Background: Stroke is a major cause of mortality and disability. Prognosis is constantly evolving and is affected by multiple factors, many of which have not previously been thoroughly analyzed. This thesis aims to provide an updated and comprehensive description of long-term prognosis after stroke, specifically exploring key factors such as comorbidity (Study II), pre-stroke functional dependency (Study III), readmission patterns (Study IV), and strain and well-being in informal caregivers (Study V).

Method: The thesis describes patients registered in the Swedish Stroke Register (Riksstroke) in 2011 and 2013. Beyond Riksstroke's regular follow-up surveys at three and 12 months, additional long-term surveys were conducted at three years (2013 cohort) and at five years (2011 cohort), which also enquired about the situation of informal caregivers.

Data on comorbidity were obtained from the Swedish National Patient Register and the Swedish Prescribed Drug Register. The Charlson Comorbidity Index was used to guide selection of which chronic conditions to include. The Swedish National Patient Register also provided data on hospital readmissions.

The modified Drug Rankin Scale was used to classify dependency level, and dependency was defined as a score of >3.

Bivariate, multivariable, and hierarchical cluster analyses were performed and multiple imputation was used to minimize bias from loss to follow-up.

Results: The common thesis cohort comprised 22 905 patients, and different subgroups were included in the individual studies. Total loss to follow-up was 12.7% at three months, 21.2% at 12 months, 20.3% at three years, and 16.9% at five years.

Study I included the whole common cohort and provides a prognostic overview of both ischemic stroke (IS) and intracerebral haemorrhage (ICH). At five years after stroke, over two out of three patients with IS, and over three out of four patients with ICH, were either deceased or functionally dependent. The less favourable prognosis for ICH was largely explained by a higher early mortality.

Study II included 11 775 pre-stroke independent IS patients. Comorbidity was common and had strong implications for long-term survival and functional outcome in all age groups. The largest effects were found for dementia, kidney and heart failure.

Study III showed great heterogeneity among 5899 pre-stroke dependent IS patients. In those of severe pre-stroke dependency, comorbidity burden was higher, drug prescription was lower, and prognosis less favourable.

Study IV included 10 092 pre-stroke dependent and independent IS patients. Readmission was common, particularly in the early phase after stroke, and a small group of patients with high comorbidity burden accounted for the majority of readmissions. The dominating cause was circulatory conditions.

Study V explored the situation of 5063 informal caregivers to stroke patients. Life impact, need of support, and poor psychological well-being increased with degree of dependency of the stroke survivor. In caregivers to completely dependent survivors, 51.4% reported poor psychological well-being.

Conclusions: The thesis describes substantial heterogeneity among stroke patients which is reflected in great variations in long-term prognosis, readmission patterns, and caregiver strain. This warrants a stratified and comprehensive approach to long-term support, healthcare, and research, which should also include informal caregivers.

Key words Ischemic stroke, intracerebral haemorrhage, long-term, prognosis, survival, functional status, comorbidity, disability, informal caregiver

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Five years ago, I suffered a stroke.
This thesis is dedicated to my family
who supported me through this difficult time.

Contents

Preface

Stroke has traditionally been viewed as having a grim outcome. In the late 18th century, the British physician Richard Pew noted: *"the patient, having recovered more or less the use of the other side, does in some instances drag on a miserable existence for a considerable length of time; but very rarely indeed recovers his former intellectual or bodily health"*.[1]

To this day, while there have been major advances in acute treatment, once the damage is done, there are few treatment options. Instead, the stroke survivor must learn to overcome various functional deficits affecting speech, limb strength, or cognitive abilities. However, quality of life can be far from the "miserable existence" described above and can even return to pre-stroke levels. This thesis aims to provide data that may contribute to the development of long-term healthcare and support after stroke, allowing more patients to live life to the fullest.

Abstract

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List of publications

I Sennfält S, Norrving B, Petersson J, Ullberg T. Long-Term Survival and Function After Stroke. Stroke. 2019;50(1):53–61.

II Sennfält S, Pihlsgård M, Petersson J, Norrving B, Ullberg T. Long-term outcome after ischemic stroke in relation to comorbidity – An observational study from the Swedish Stroke Register (Riksstroke). European Stroke Journal. 2020;5(1):36–46.

III Sennfält S, Pihlsgård M, Norrving B, Ullberg T, Petersson J. Ischemic stroke patients with pre-stroke dependency: characteristics and long-term prognosis. Acta Neurologica Scandinavica. 2020;Published online August 1, 2020.

IV Sennfält S, Petersson J, Ullberg T, Norrving B. Patterns in hospital readmissions after ischemic stroke - an observational study from the Swedish stroke register (Riksstroke). European Stroke Journal. 2020;Published online June 15, 2020.

V Sennfält S, Ullberg T. Informal caregivers in stroke: Life impact, support, and psychological well-being - A Swedish Stroke Register (Riksstroke) study. Int J Stroke. 2020;15(2):197–205.

Abbreviations

ADL	Activities of daily living
AF	Atrial fibrillation
AIDS	Acquired immune deficiency syndrome
ATC	Anatomical Therapeutic Chemical Classification System
CADASIL	Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy
CCI	Charlson Comorbidity Index
$CHADS^2$	Score for atrial fibrillation stroke risk (congestive heart failure, hypertension, age over 75, diabetes, previous stroke)
CI	Confidence interval
CKF	Chronic kidney failure
COPD	Chronic obstructive pulmonary disease
CT	Computed tomography
HDL	High density lipoprotein
HR	Hazard ratio
ICD-10	Statistical Classification of Diseases and Health Related Problems, tenth revision
ICH	Intracerebral haemorrhage
IQR	Interquartile range
IS	Ischemic stroke
LAD	Large artery disease
LDL	Low density lipoprotein
LISA	Longitudinal Integrated Database for Health Insurance and Labor Market Studies
MDS	Multidimensional scaling
MI	Multiple imputation
MI	Myocardial infarction
MRI	Magnetic resonance imaging
mRS	Modified Rankin Scale

NMDA	N-Methyl-D-aspartic acid
NOAC	Non-vitamin K oral anticoagulant
OAC	Oral anticoagulant
OR	Odds ratio
PAR	Population attributable risk
PIN	Personal identification number
PH	Proportional hazards
PVD	Peripheral vascular disease
RA	Rheumatoid arthritis
RLS-85	Reaction Level Scale 85
SAD	Small artery disease
SAH	Subarachnoid hemorrhage
SCDR	Swedish Cause of Death Register
SD	Standard deviation
SF-36	Short Form (36) Health Survey
SHARE	Survey of Health, Ageing and Retirement in Europe
SNBHW	Swedish National Board of Health and Welfare
SNPR	Swedish National Patient Register
SPDR	Swedish Prescribed Drug Register
TIA	Transient ischemic attack
TOAST	Trial of ORG 10172 in Acute Stroke Treatment
WHO	World Health Organization

1.
Introduction

1.1 Definition

Stroke is defined as *"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".*[2] This differentiates stroke from transient ischemic attack (TIA), where there is a resolution of symptoms within 24 hours, and also from conditions that mimic stroke such as seizures, migraines, or psychiatric disorders.[3]

1.2 Epidemiology

The absolute number of new stroke cases is increasing, now approaching 15 million per year globally.[4] One in four people over the age of 25 can be expected to have a stroke in their lifetime.[4,5] However, in high-income countries, age-adjusted incidence and mortality rates have decreased over the last few decades, largely due to better control of risk factors such as smoking, atrial fibrillation, and blood pressure.[6,7] In Sweden, age-adjusted incidence and mortality have decreased by approximately 40% in both men and women during the last 15 years (2004-2018) (Figure 1.1),[8] and in 2018 there were approximately 25 500 new cases.[8]

There are currently about 80 million stroke survivors in the world,[4] and the number of Swedish people living with varying degrees of disability as a consequence of stroke has been estimated to be at least 140 000.[9]

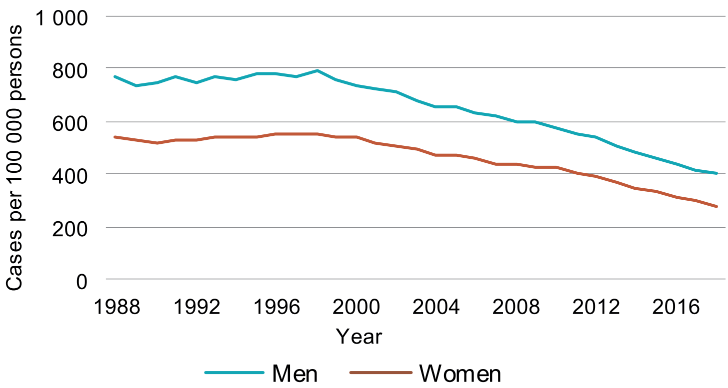


Figure 1.1 Age-standardized stroke incidence rates for Swedish men and women, 1988–2018.

1.3 Pathophysiology

Stroke is classified as either ischemic (≈85% of cases) or haemorrhagic (≈15%).[10,11] Clinical manifestations overlap and neuroimaging, such as computed tomography (CT) and/or magnetic resonance imaging (MRI), is used to distinguish between them.

Ischemic stroke

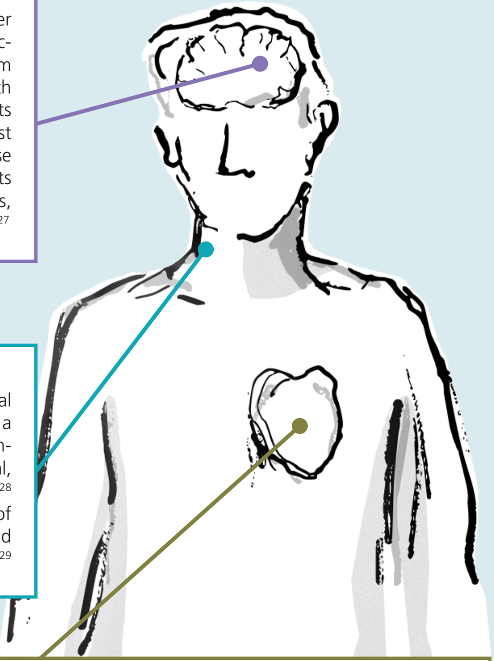
Ischemic stroke (IS) is usually the result of cerebral blood vessel occlusion and is classified according to the mechanism by which this occurs. The TOAST (Trial of ORG 10172 in Acute Stroke Treatment) classification scheme is widely used and denotes five major subtypes:[12]

1) Cardioembolic
2) Large artery disease (LAD)
3) Small artery disease (SAD)
4) Stroke of other determined aetiology (including rare causes)
5) Stroke of undetermined aetiology

The most common cause of IS is cardiac embolism (20–30%) followed by SAD (15–25%) and LAD (10–20%).[13-18] The proportion of cardioembolic stroke is especially high in the elderly, whereas rare causes and stroke of undetermined aetiology are more common in younger patients.[19] See Figure 1.2 for a detailed description of the subtypes.

Haemorrhagic stroke

Approximately 15% of all strokes are primarily haemorrhagic. At least two thirds of these are intracerebral haemorrhages (ICH) and a small proportion are subarachnoid haemorrhages (SAH).[10,11] ICH is typically caused by the spontaneous rupture of small penetrating arteries in deep structures of the brain such as the basal ganglia, the thalamus, the brain stem (predominantly the pons), and the cerebellum.[20] Chronic hypertension is thought to be an important cause, rendering blood vessels brittle and prone to the formation of aneurysms that eventually burst.[21] A particular type of ICH occurs in cerebral amyloid angiopathy, where the haemorrhage is located in the cerebral lobes and caused by vessel wall deposition of amyloid beta.[22]



Small artery disease (15–25%)
Several mechanisms, such as blood–brain barrier dysfunction and vessel stiffening, cause defections in small penetrating arteries, leaving them unable to supply the brain parenchyma with blood.[23,24] This results in single subcortical infarcts less than 15-20 mm in size called lacunae,[25] most often located in deep brain structures.[23] These small, localized lesions commonly produce deficits of a specific modality without cortical symptoms, e.g. pure motor stroke or pure sensory stroke.[26,27]

Large artery disease (10–20%)
Atherosclerosis is the key pathophysiological mechanism behind large artery disease. This is a complex process where vessel wall injury and inflammation leads to the accumulation of material, such as lipids, and the formation of an atheroma.[28] These lesions are more likely to form in areas of high turbulence, e.g. the carotid bifurcation, and may generate emboli to the cerebral vasculature.[29]

Cardioembolic stroke (20–30%)
Blood clots may form in the heart and embolize to the cerebral vasculature. This most often occurs in a diseased heart, which constitutes a favourable milieu for clot formation, e.g. in atrial fibrillation. Due to their relatively large size, cardiac emboli frequently cause extensive lesions with poor prognosis.[15]

Rare causes (≈5%)
A small proportion of cases are due to rare causes such as coagulopathy, vasculitis, or arterial dissection, and are proportionally more common in younger patients. For instance, arterial dissection occurs in 1-2% of strokes in all age groups but may be involved in up to 10-25% of cases in younger patients.[33]

Undetermined aetiology (≈20%)
In a substantial proportion of cases, most commonly in young patients, no single cause can be determined. However, as diagnostic tools have become more refined, the proportion of strokes of unknown cause has decreased: from 30-40% in the late 1980s[30] to less than 20% at the turn of the 21st century.[31,32]

Figure 1.2 Pathophysiology of ischemic stroke. Description of the five major subtypes of the TOAST classification.

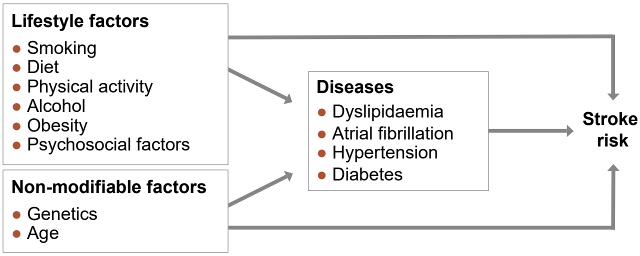


Figure 1.3 Modifiable and non-modifiable risk factors in stroke.

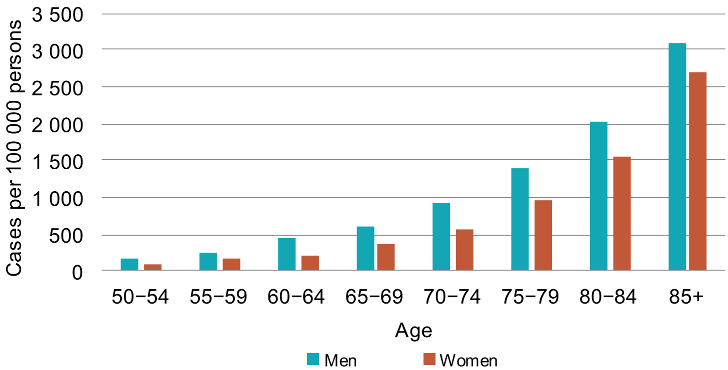


Figure 1.4 Stroke incidence in Swedish men and women in 2018 in relation to age.

1.4 Risk factors

Risk factors are traditionally classified as either modifiable or non-modifiable (Figure 1.3). Examples of important non-modifiable risk factors for stroke include age and genetic makeup. Modifiable risk is heavily influenced by lifestyle and cardiovascular diseases such as hypertension and diabetes.

Non-modifiable risk factors

The incidence of most vascular events, including both IS and ICH, increases dramatically with age[34] (Figure 1.4).[8] In 2018, 0.2% of Swedes aged 50–54 years suffered a stroke compared to 3.5% of those aged 80–84 years.[8] The mean age of stroke patients registered in the Swedish national stroke register (Riksstroke) in 2018 was 75 years.[35]

The total heritability of IS has been estimated to approximately 38%. Specifically, this proportion was 40% for LAD, 33% for cardioembolic stroke, and 16%

for SAD.[36] There are several genetic conditions conferring substantial increase in risk, such as cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), and cerebral amyloid angiopathy.[22, 37] However, for the vast majority of patients, genetic risk is primarily attributable to multiple polygenic factors, each with a small individual contribution. In addition, many genetic variations increase the risk for vascular conditions such as diabetes, hypertension, or atrial fibrillation (AF), thus indirectly increasing stroke risk.[38]

Modifiable risk factors

The INTERSTROKE study, including over 25 000 patients from 32 countries, estimated the collective contribution to stroke risk of the ten strongest modifiable risk factors to over 90%.[39] These risk factors were: hypertension (population attributable risk [PAR] 47.9%), physical activity (35.8%), dyslipidaemia: LDL/HDL ratio (26.8%), diet (23.2%), obesity: waist-to-hip ratio (18.6%), psychosocial factors (17.4%), smoking (12.4%), cardiac causes including AF (9.1%), alcohol (5.8%), and diabetes (3.9%)[39] (Figure 1.5). In addition, previous stroke/TIA was found to predispose individuals to recurrent stroke.

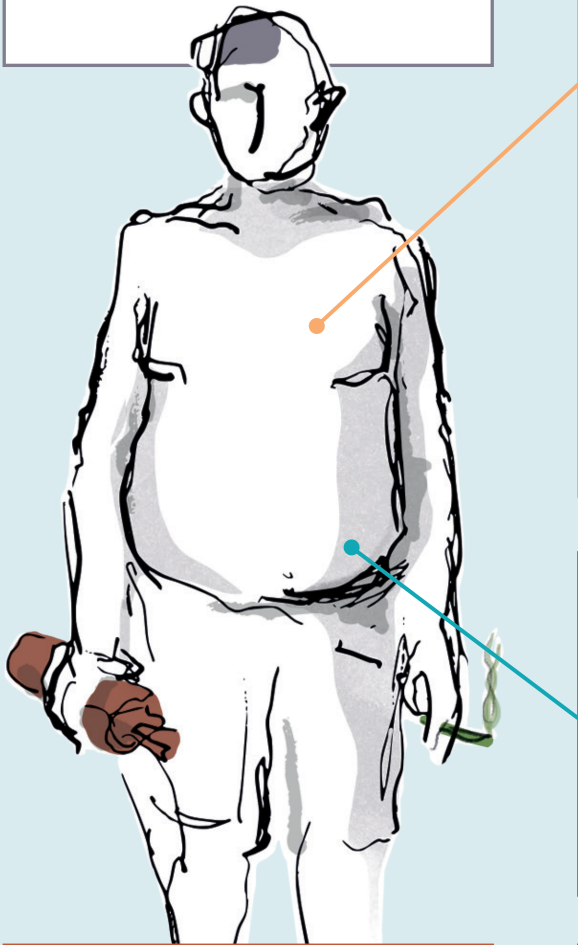
Importantly, comorbidity, i.e. the existence of other chronic medical conditions,[40] is common in stroke patients[41] and diseases sharing a common aetiology, such as combinations of cardiovascular and metabolic conditions tend to co-occur,[42, 43] resulting in a considerable cumulative increase in risk.

Strategies for risk factor management are similar for primary and secondary prevention. In addition to lifestyle changes, several risk-lowering medications are prescribed in clinical practice such as antihypertensive, anticoagulant, and lipid-lowering agents. Combining lifestyle changes and pharmacological therapy may reduce the long-term risk of recurrent vascular events by as much as 80% in stroke and TIA patients.[44]

Previous stroke/transient ischemic attack
Risk of recurrent stroke is highest soon after index stroke/transient ischemic attack,[54-58] and particularly elevated after a large artery disease stroke.[59] Antiplatelet drugs such as Aspirin are recommended after stroke of presumed arterial origin and have been found to prevent an estimated 13% of vascular events.[60] Dual antiplatelet therapy gives additional benefits in selected patients.[61]

Hypertension
This is overall the most important treatable risk factor for stroke,[39] and causes a large increase in risk for both young[45] and elderly.[46, 47] Many studies have demonstrated a substantial risk reduction by lowering blood pressure,[48] and the effect of treating high systolic pressure seems to be of particular importance.[46] European guidelines recommend lowering systolic pressure to <140 mmHg for all patients, with a target of 120–130 in those who can tolerate it,[49] as evidence suggests there are additional benefits to a more aggressive approach.[50, 51]

Atrial fibrillation
The prevalence of atrial fibrillation increases dramatically with age.[62] Untreated, it is associated with a five-fold increase in stroke risk.[63] The risk is further exacerbated by cardiovascular comorbidity, the risk increasing by a factor of 1.5 for every point increase on the CHADS^2 score.[64] Anticoagulant medication is recommended for stroke prevention,[65] but many patients do not receive adequate treatment.[66] Warfarin was the first anticoagulant medication used in clinical practice and has been shown to reduce stroke risk by two-thirds compared with Aspirin or no therapy.[67] In recent years, new oral anticoagulant drugs have been developed and large randomized controlled trials have demonstrated similar or superior risk-benefit profiles compared to warfarin.[68] Therefore, several recent guidelines now recommend these drugs as first-line therapy.[69]



Physical activity, diet and obesity
Regular physical activity and a healthy diet (including reducing salt[76] and eating fish,[77] fruit and vegetables[78]) are associated with reduced risk of stroke.[79] Conversely, obesity, particularly waist-to-hip ratio, is associated with increased risk.[79]

Diabetes
The increased risk of stroke in diabetics is thought to occur via several mechanisms including vascular endothelial dysfunction and accelerated atherosclerosis.[52] However, strict glycaemic control has not consistently been shown to reduce risk.[53]

Alcohol
Interestingly, light to moderate alcohol consumption is associated with decreased risk of cardiovascular events,[72] including stroke.[73] This effect is thought to be mediated by reduced atherosclerosis/inflammation.[74, 75] However, higher consumption confers an increased risk.

Smoking
There is a strong dose-response relationship between smoking and stroke.[70] In addition, smoking is associated with multiple vascular diseases, which are independent risk factors for stroke.[71]

Figure 1.5 The strongest modifiable risk factors for stroke.

1.5 Acute symptoms of stroke

The symptoms of stroke are extremely variable. Due to the topographical organization of the brain, specific symptoms are seen depending on which cerebral vessel (and region) is affected (Figure 1.6). There are four major cerebral artery pairs supplying the brain: the anterior cerebral, middle cerebral, posterior cerebral, and the vertebral arteries.

The anterior cerebral arteries primarily supply the most medial portions of the frontal and parietal lobes.[80] Characteristic symptoms of a lesion in this region include weakness or sensory loss of the contralateral lower extremity and behavioural changes.[81, 82]

The middle cerebral arteries are the largest of the cerebral arteries. They supply two-thirds of the lateral surface of the hemispheres, the most common site of cerebral ischemia.[80] Symptoms may include weakness and sensory loss in the contralateral arm and side of the face, speech impairment, apraxia, and neglect.[80]

The posterior cerebral arteries constitute the main source of blood to the occipital lobe.[80] The most common clinical features of lesions here are visual defects along with cognitive impairment and confusion.[83]

The vertebral arteries supply the brain stem and cerebellum via several smaller branches.[80] A stroke affecting this area commonly causes ataxia or vertigo but may, if the brainstem is severely affected, produce serious manifestations involving arousal and global motor activity.[84]

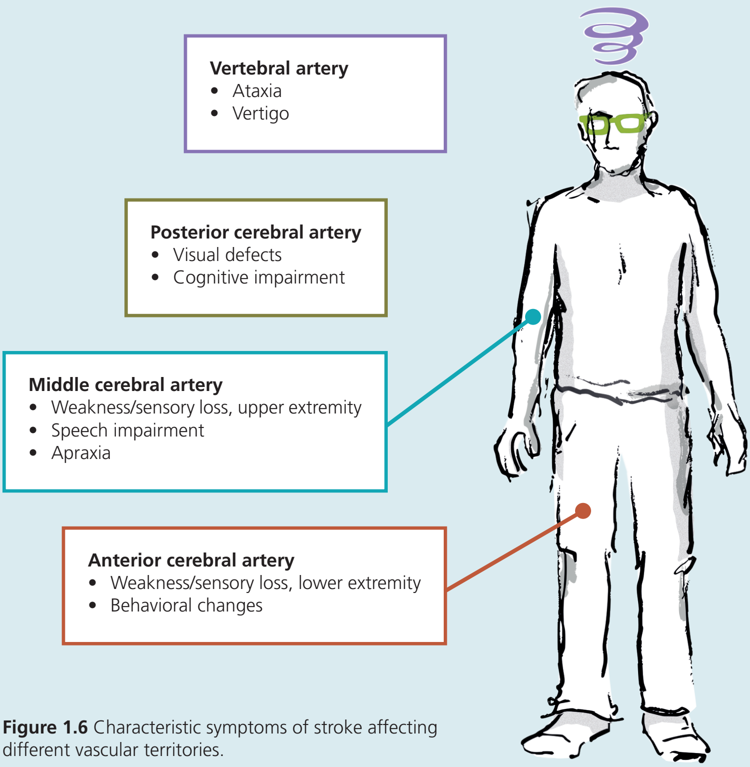


Figure 1.6 Characteristic symptoms of stroke affecting different vascular territories.

1.6 Outcome after stroke

The sections below describe some of the major outcomes of stroke, such as survival, functional outcome, neuropsychiatric outcome, and hospital readmission. In addition, since friends and family of the stroke survivor are secondarily affected, the caregiver perspective is also adressed.

Survival

Stroke is the second leading cause of death globally.[85] Early mortality is substantial: at 30 days, all-stroke survival is approximately 72–85%,[86-95] at twelve months 43–69%,[86, 88, 90, 92-96] and at five years it decreases to 40%–65%.[86, 88-90, 97, 98] However, there is great prognostic variation according to stroke severity and subtype. Survival for ICH is significantly lower than for IS, particularly in the short term. After 30 days, only 41–76% of ICH patients are alive[90-95, 99-102] compared to 79–95% of IS patients.[86, 90-93, 95,103-105] At five years, the corresponding proportions are 27–32%[90, 106-108] and 48–61%, respectively[89, 90, 103, 105] (Figure 1.7, see appendix I for a detailed table of papers included in the compilation). In addition, prognosis in IS varies according to the pathophysiological mechanism. Mortality is highest for LAD[109] and cardioembolic stroke.[15, 110]

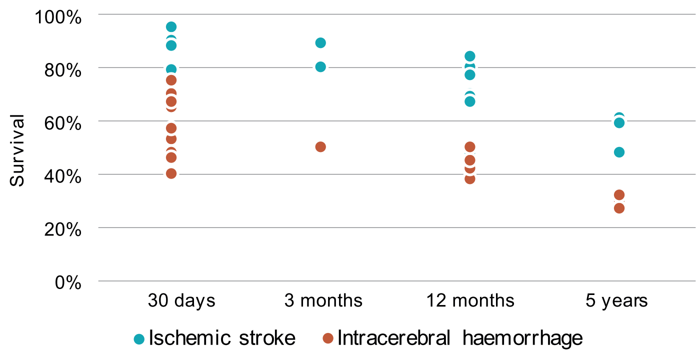


Figure 1.7 Distribution of reported survival for ischemic stroke and intracerebral haemorrhage . Each dot represents reported survival in individual studies (See appendix I for details).

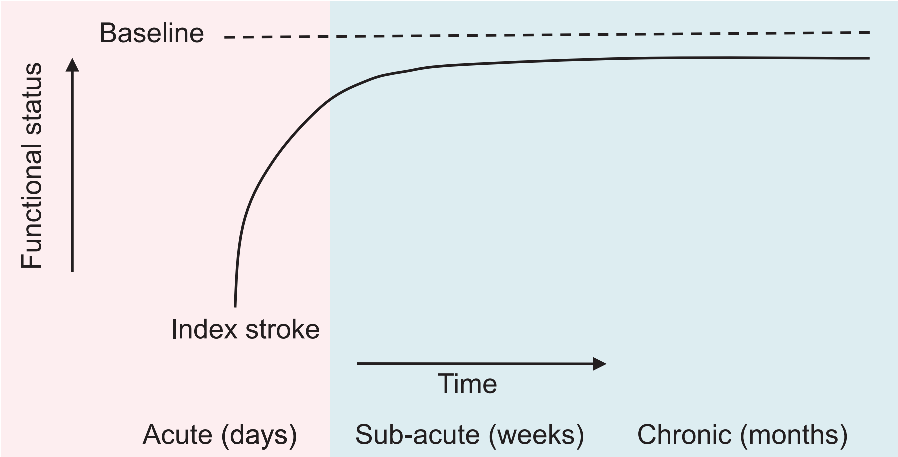


Figure 1.8 Phases of functional recovery after stroke.
The solid line illustrates rapid early functional improvement.

Functional outcome

Stroke typically causes acute onset functional impairment, but most patients regain some function over time. This is due to neuroplasticity, the ability of the brain to reorganize and, to a lesser degree, repair itself.[111, 112] There are essentially three phases of stroke recovery: acute (within seven days), sub-acute (between seven days and six months), and chronic (beyond six months)[113] (Figure 1.8). Recovery is rapid during the first few days after stroke, but clinically meaningful improvement is typically only seen within the first few months.[111, 112]

Large studies on long-term functional outcome after stroke are sparse and methodologies (e.g. outcome measures and inclusion criteria) are inconsistent. What is clear however is that the aggregate functional impairment as a result of stroke is substantial.[114] Specifically, there are reports of unfavourable functional outcome in 37% of survivors at 12 months,[96] in 31.4–50% of survivors at five years,[97, 98, 115] and in 29% at 10 years.[116] Note that these studies only include survivors, which might explain why the proportion seems to decrease over time (functionally dependent patients are more likely to die).

Neuropsychiatric outcome

The most common neuropsychiatric morbidities as a consequence of stroke are depression, anxiety, fatigue, and apathy, each of which are seen in up to 30% of patients.[117] Of particular importance is the close association of stroke to cognitive impairment and dementia. The prevalence of dementia at the time of stroke has been estimated to be approximately 10%, with an additional 10% of patients developing the disease soon after their first stroke. After recurrent stroke, the prevalence is more than 30%.[118]

Readmission

Post-stroke readmission rates are high. All-cause readmission has been reported in 39%–49% of patients within one year,[119-121] and 68–83% within five years.[120-122] This compares to 20% and 63%, respectively, during the same time period in a similar-aged non-stroke population.[120] Cardiac disease, recurrent stroke, infection, and falls are cited as common causes for readmission after stroke, with recurrent stroke being particularly common in the first few months.[119-124] Stroke-related complications such as pneumonia, venous thromboembolism, dysphagia, incontinence, and depression are also common readmission causes, particularly in the short-term.[121, 125] Not surprisingly, high comorbidity burden is predictive of readmission.[41, 126]

The caregiver perspective

Informal caregivers provide the lion's share of daily assistance and in many high-income countries (e.g. Sweden), recent institutional changes have put greater emphasis on informal caregiving.[127] It is difficult to estimate the extent of such assistance, which varies from case to case. Tentative estimations range from about nine to 17 hours per week on average in the first year after stroke.[128, 129]

The caregiving role has a substantial life impact. For instance, one study showed that 24% of informal caregivers in paid employment quit their job or took leave, while an additional 22% rearranged their work schedule or reduced their working hours.[129] In another study, 40% of caregivers reported a significant reduction in their ability to perform vocational work and 47% reported a reduction in their leisure activities.[130]

Informal caregivers commonly report positive experiences such as increased self-esteem, strengthened relationships, and feeling appreciated.[131, 132] However, caring for a stroke survivor might also be associated with significant strain. The proportion of caregivers under strain during the first six months after stroke has been estimated to 25–37%, with higher proportions at later time points.[133, 134] In a systematic review of studies with a longer follow-up period of up to three years after stroke, 25–54% of informal caregivers reported strain, a proportion that remained elevated over time.[135]

A high degree of strain is associated with poor physiological well-being,[131, 133, 134, 136-139] and the prevalence of depression in caregivers has been estimated to be around 30–52%.[131, 138] Moreover, there are reports of increased long-term mortality in caregivers experiencing strain.[140]

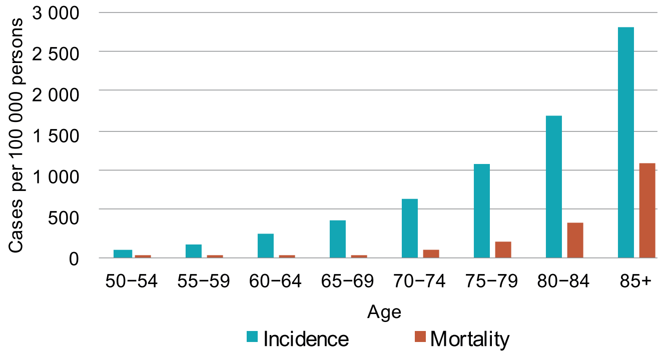


Figure 1.9 Stroke mortality in relation to incidence for different age groups in Sweden 2018.

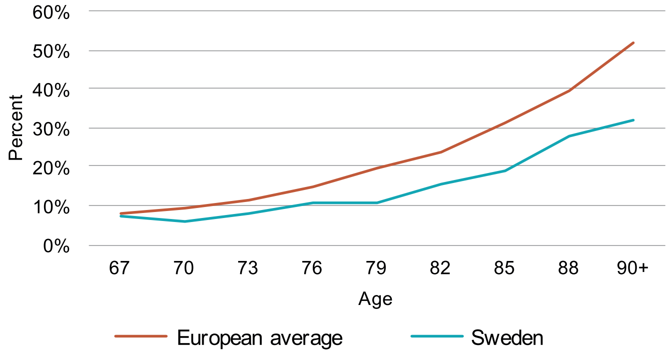


Figure 1.10 The proportion of functionally dependent individuals in Sweden In relation to age and compared to the European average.

1.7 Patient factors affecting long-term outcome

Not surprisingly, age is strongly correlated with poor outcome. The ratio of stroke mortality to incidence increases dramatically in older persons[8] (Figure 1.9). Other key factors associated with poor prognosis are disability[141-144] and high comorbidity burden.[145-147, 39-143] The sections below elaborate on these two factors and describe the related clinical concept of frailty.

Disability

The proportion of individuals in the general population that are dependent on help for activities of daily living (ADL) increases steadily with age. Interestingly, while this increase is large between the ages of 50–70 years in southern European countries, it is somewhat delayed in Sweden.[148] In the 2017 Survey of Health, Ageing and Retirement in Europe (SHARE), the proportion of persons over 65 years of age dependent on help in least one ADL domain was 11.1% in the Swedish general population, compared to an European average of 16.4%[149] (Figure 1.10). The corresponding proportions among those over 80 years of age were 21.6% and 32.7%, respectively.

A large proportion of stroke patients (11-20%) are already functionally dependent prior to stroke.[141, 142, 150] However, this proportion differs depending on the definition used, e.g. different cut-off points on the modified Rankin Scale (mRS). Physical disability is associated with poor prognosis after stroke. For instance, Kwok et al. have reported a linear relationship between pre-stroke mRS score and probability for in-patient death,[142] and Ganesh et al. have shown a strong relationship between early functional deterioration and long-term death or institutionalization.[141]

Comorbidity and multimorbidity

Comorbidity describes the co-occurrence of other conditions alongside a primary condition, while the related term *multimorbidity* simply refers to the existence of multiple medical conditions in a single individual.[40] Multimorbidity is present in the majority of individuals over 65 years of age,[42, 151] and is more common in stroke patients[41] where it has a large impact on prognosis. A large Danish study described a five-year survival of only 20.5% in stroke patients with high comorbidity versus 60.3% in those without comorbidity.[89] Specific conditions such as dementia, kidney and heart failure are particularly strong predictors of poor outcome.[89, 145, 152, 153] What is more, conditions sharing common pathophysiological mechanisms tend to co-occur in clusters in the same individual, leading to a substantial total increase in risk of poor outcome. A common clustering pattern is cardiovascular/metabolic diseases. In a systematic review of studies investigating multimorbidity patterns in the general population, a prominent cardiovascular cluster was found in ten out of 14 studies.[43] Among the ten most frequently identified conditions,-four could be classified as cardiovascular and four were established independent stroke risk factors.

In relation to its fundamental clinical and economic impact, multimorbidity has received little attention.[154] Also, scientific reporting is heterogeneous, largely due to methodological differences, making it difficult to correctly gauge and address the issue.[42]

Frailty

Frailty is the result of cumulative decline in many physiological systems during a lifetime, leading to increased vulnerability to stressors.[155] This leads to an increased risk for adverse events such as falls, hospitalization, and death, as well as a host of different diseases and impaired quality of life.[156-159] The development of frailty is multifactorial[160] and closely linked to age[161] and multimorbidity.[162] Frailty is more common in certain settings, such as nursing homes[163] and importantly, in stroke patients. In one study, frank frailty (as defined by a frailty index score) was present in around 25% of acute stroke patients and pre-frailty, was present in an additional 50%.[164]

The concept of frailty is frequently used in the geriatric setting and it has been suggested that frailty assessment should be integrated into the care of all patients over 70 years of age.[165] However, definitions and reporting practices vary,[166] and reported prevalence ranges between 4–59% in older persons.[167]

1.8 Stroke management and support

The post-stroke period can be divided into an acute, sub-acute and chronic phase, each with its unique set of challenges and needs (Figure 1.11). In the acute phase, the patient is admitted to hospital (preferably to a stroke unit) and interventions such as thrombolysis and/or thrombectomy may be performed. Having survived the immediate aftermath of stroke, most patients can be sent home (with or without home care service), but those with additional needs are transferred to in-patient rehabilitation, a short-term care facility, or to permanent residency in assisted living.[168]

In the sub-acute/chronic phase, the survivor begins to adjust and reintegrate into society. This process is as much psychological as it is physical; the challenges of adapting to post-stroke life and identity may have a profound impact on well-being.[169] An important goal of post-stroke support is to assist in the reorientation to new standards and expectations. In Sweden, long-term medical follow-up and care is usually the responsibility of primary care centres, with a select few patients followed at hospital clinics. In addition, the municipality provides home care service, rehabilitation, and caregiver support.

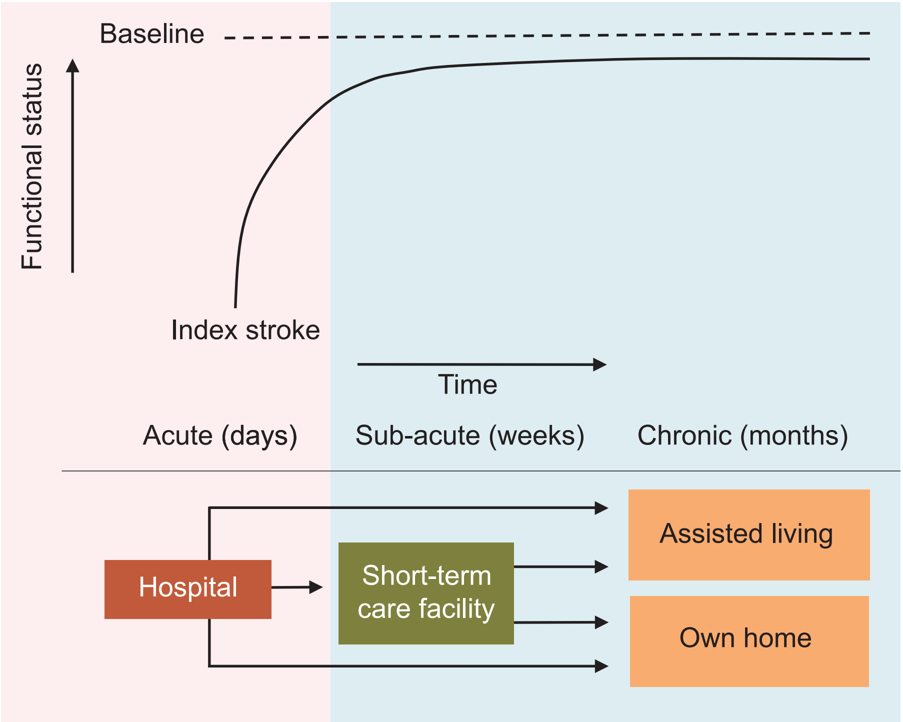


Figure 1.11 Simplified illustration of the stroke care chain in relation to the phases of recovery.

Routine monitoring of all stages in the stroke care chain is paramount for improving care and outcome. Such monitoring ideally leads to information about the structure of stroke services, process of care, outcome, and patient experience of care.[170] In Sweden, this information, where available, is entered in a national database known as Riksstroke which is the world's longest-running national stroke quality register (established in 1994).[171] There are now national registers in at least 26 countries,[172] but due to local conditions and priorities, reporting practices vary.[172]

The sections below elaborate on key interventions in the acute phase (stroke unit care and acute treatment) and the sub-acute/chronic phase (early follow-up, rehabilitation, and caregiver support).

The stroke unit

In a stroke unit, organized care is provided by multidisciplinary teams specialized in the care and rehabilitation of stroke patients. These teams are able to effectively address stroke-specific concerns and have access to specialized equipment, such as heart monitors to identify AF. Stroke unit care is associated with improved outcome independent of patient age, sex, initial stroke severity, or stroke subtype,[173] and is recommended as the first unit of admission by the Swedish National Board of Health and Welfare (SNBHW).[174] However, currently almost one in seven patients is not admitted to a stroke unit within 24 hours of stroke, most often due to logistical reasons or lack of hospital beds.[175]

Acute treatment

In IS, there is typically a central core of irreversibly damaged tissue and a surrounding area of *penumbra*, which is supplied with blood from surrounding vessels. Penumbra tissue is initially viable and can regain function if reperfused within a certain timeframe,[176] which is the goal of acute interventions such as thrombolytic therapy and thrombectomy.[177] However, these interventions are associated with significant risks (such as major bleed in thrombolysis) and therefore, certain high-risk patients such as the functionally dependent or very old are often exempt from therapy.[178] Recent evidence, though, supports the effectiveness and safety of thrombolytic therapy in these high-risk groups[179-181] and fewer patients are now being excluded from treatment.

Early follow-up

A key component in Swedish stroke follow-up recommendations is a structured follow-up visit three to six months after stroke.[174] The purpose is to evaluate secondary prevention, to identify new symptoms or needs, and to offer intervention or referral. To this end, post-stroke checklists have proven feasible and useful[182, 183] and are recommended for identifying unmet needs.[174] However, in a recent Swedish study, 23.7% and 11.3% of patients had not received follow-up within three and six months, respectively.[184]

Rehabilitation

There is strong evidence for the effectiveness of organized goal-oriented rehabilitation, e.g. structured physical and speech therapy,[185, 186] to facilitate recovery after stroke. This is ideally a sustained and coordinated effort involving a team of physicians, nurses, nutritionists, social workers, and occupational therapists, and can be initiated at the stroke unit.[187] A comprehensive approach is crucial since difficulties after stroke can involve a number of different areas. Some patients require continuous multidisciplinary rehabilitation after discharge, while for others, specific occasional interventions are sufficient. The SNBHW recommends structured inpatient rehabilitation for those with moderate to severe stroke, which is estimated to comprise approximately 20% of patients.[175]

After discharge, Swedish municipalities assume responsibility for long-term rehabilitation and continuous physical and speech therapy. ADL training is recommended on an as-needed basis.[174] However, there are no specific recommendations for multidisciplinary teams and evaluation has shown that these are used in only 110 of 235 municipalities.[175] Moreover, these teams commonly only include a few selected professions and the availability of speech rehabilitation and psychological support is limited. Overall, Swedish post-stroke support and rehabilitation is unevenly distributed with respect to geography, but also age, since rehabilitation is more often offered to younger individuals, particularly those of working age.[175]

Caregiver support

Informal caregiving requires significant commitment and may be stressful and time-consuming.[128, 129, 133, 188] Support programmes aimed specifically at informal caregivers are often poorly developed and vary between comparable high-income countries.[189, 190] In 2009, there was an amendment to the Swedish Social Services Act (5 ch. 10 § [2001:453]) stating that municipalities were now obligated to offer support to informal caregivers of a next of kin with a chronic, persistent disease or physical disability. However, caregivers need to specifically apply for this support and few take advantage, often because they are simply unaware it exists, or believe the services available are not adapted to their needs.[191] Overall, there is a lack of adequate informal caregiver support and it varies greatly in availability and extent across Sweden.[192]

1.9 Knowledge gaps and study aims

Study	Knowledge gaps	Aim
I	While there have been major advances in stroke care and rehabilitation, recent long-term studies describing both survival and functional outcome are sparse, particularly those comparing ICH and IS.	To describe survival and functional outcome after IS or ICH for up to five years post-stroke.
II	Multimorbidity has received little attention despite its fundamental clinical and economic impact.[154] In stroke, comprehensive reports on long-term outcome relative to comorbidity are sparse.[193]	To explore the prevalence and clustering of chronic conditions, as well as survival and functional outcome in relation to comorbidity burden, in IS patients.
III	There are few comprehensive descriptions of pre-stroke dependent patients, which are often lumped together into one single group.	To describe characteristics and prognosis of IS patients stratified by level of pre-stroke functional dependency.

IV	Hospital readmission after stroke is common, which puts a strain on hospital-based healthcare.[194, 195] However, there are few in-depth, stratified descriptions of long-term readmission patterns.	To explore readmission patterns in the first five years following IS, and to characterize groups of patients based on readmission frequency.
V	Informal caregivers are crucial for recovery and adaptation after stroke. Caregiver support is identified as an important area of research and development,[170] but efforts are hampered by lack of extensive long-term caregiver follow-up studies.	To provide an account of the caregiver situation, including life impact, unmet needs of support and psychological well-being, in relation to degree of functional dependency of the stroke survivor.

2.
Method

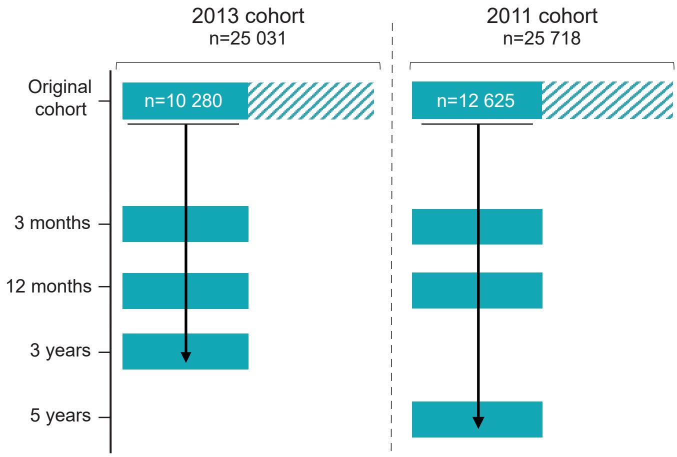


Figure 2.1 Overview of the follow-up schemes in the 2013 and 2011 cohorts.

Table 2.1 Comparison of baseline characteristics and outcomes at 3 and 12-month follow-up in the 2011 and 2013 cohorts.

Presented as number (%). There were no statistically significant differences between cohorts.

SD=standard deviation.

	2011 cohort n=12 625	**2013 cohort** n=10 280
Sex (male)	6617 (52.4)	5389 (52.4)
Age (mean ± SD)	76.0 ± 12.0	76.1 ± 12.2
Diagnosis (ischemic stroke)	11 092 (87.9)	8955 (87.1)
Level of consciousness at admission		
Alert	10 303 (82.6)	8411 (82.8)
Drowsy	1504 (12.1)	1233 (12.1)
Comatose	661 (5.3)	512 (5.0)
Independent before stroke	8906 (70.5)	7303 (71.0)
Independent at 3 months	4530 (40.7)	3648 (41.2)
Independent at 12 months	3832 (39.3)	3243 (39.1)
Alive at 3 months	10 372 (82.2)	8376 (81.5)
Alive at 12 months	9346 (74.0)	7561 (73.6)

2.1 Study design and cohort

The studies in this thesis were all longitudinal observational cohort studies based on the Riksstroke year cohorts of 2013 and 2011 (Figure 2.1).[196, 197] Approximately 25 000 stroke cases were registered in each of these years. About half of these (n=10 280 and n=12 625, respectively) were randomly selected for long-term follow-up and are described in the thesis.

All patients were followed up at three months and 12 months after stroke by paper-based questionnaires. Additionally, the 2011 cohort was followed up at five years and the 2013 cohort was followed up at three years. A questionnaire filled out by the primary informal caregiver was included in the three and five-year follow-up.

Patients <18 years of age, those diagnosed with unspecified stroke, and those with unknown pre-stroke functional status were excluded. Subarachnoid haemorrhage was not registered in Riksstroke in 2011 or 2013 and was thus not included.

As baseline characteristics and outcomes at three and 12-month follow-up did not differ significantly between the year cohorts (Table 2.1), the two cohorts were merged. This resulted in a large common cohort of 22 905 patients. Studies I–IV included different combinations of subgroups based on diagnosis (intracerebral haemorrhage [ICH] or ischemic stroke [IS]), pre-stroke functional status (dependent or independent), year cohort (2011 or 2013), and recurrent stroke (yes or no) (Table 2.2). Studies I and IV included both pre-stroke independent and dependent patients, whereas Study II only included independents, and Study III only included dependents (Figure 2.2). Study V primarily described informal caregivers.

Table 2.2 Subgroups included in each of the individual studies in the thesis.
Dep=pre-stroke dependent, ICH=Intracerebral haemorrhage, Indep= pre-stroke independent, IS=ischemic stroke.

		Year cohort		Pre-stroke functional status		Stroke subtype		Recurrent stroke	Caregivers
	n=	2011	2013	Dep	Indep	ICH	IS		
Study I	22 929 *	■	■	■	■	■	■	■	
Study II	11 775	■	■		■		■		
Study III	5899 **	■	■	■			■	■	
Study IV	10 092 ***	■		■	■		■	■	
Study V	5063	■	■						■

*Including 24 additional cases as compared to the common cohort. These cases were duplicates and were excluded from subsequent studies. ** Pre-stroke independent patients were included as a reference group (n= 14 148) *** Only patients from the 2011 cohort that were alive at hospital discharge were included.

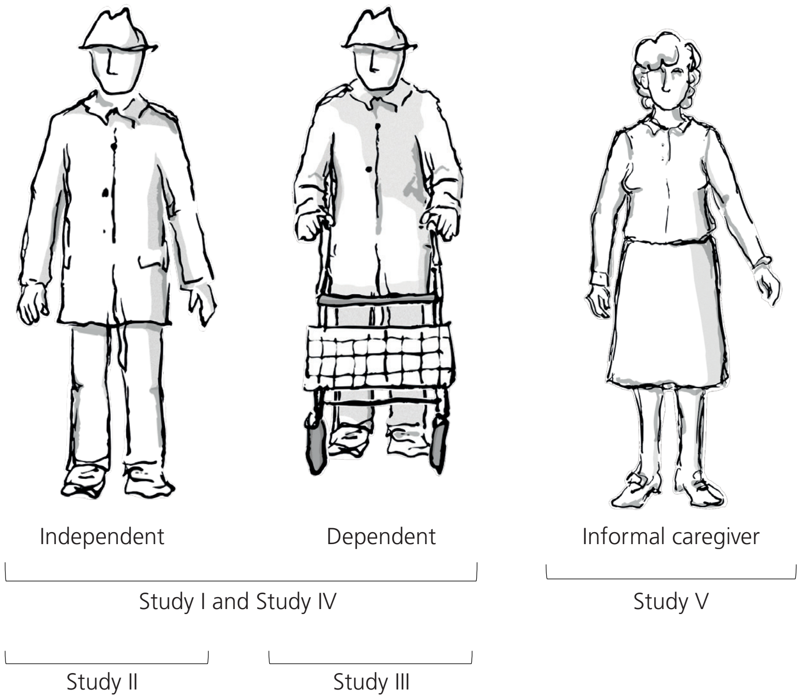


Figure 2.2 Illustration of inclusion in each study in relation to pre-stroke functional status (dependent vs independent).

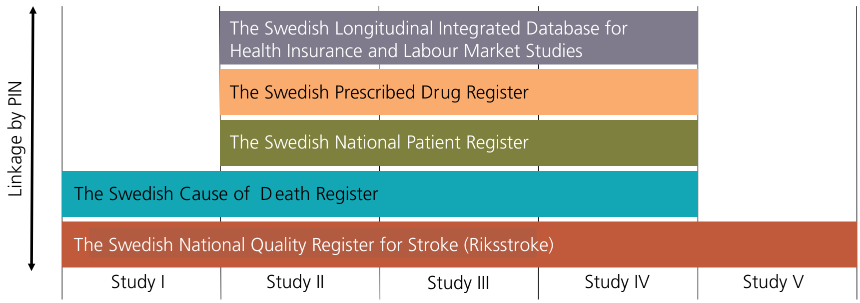


Figure 2.3 Overview of the main registers used in each of the studies.
PIN=personal identification number.

2.2 Data sources

The thesis includes data from several large registers (Figure 2.3). Since 1947, all persons residing in Sweden are assigned a ten-digit personal identity number (PIN) by the Swedish Tax Agency which allows data on each individual to be found in different databases and registers. This number was used for data-linkage. The following sections describe the five main registers used in the thesis. In addition, Statistics Sweden and the Swedish National Board of Health and Welfare (SNBHW) were important sources for supporting data.

The Swedish National Quality Register for Stroke (Riksstroke)

Riksstroke is the Swedish national quality register for data on stroke care. All 72 Swedish acute care hospitals contribute information about their stroke patients and in 2011 and 2013, it was estimated that >90% of hospital admitted stroke cases were included.[196, 197] The register contains data collected during index stroke hospital stay as well as survey data from paper-based follow-up questionnaires routinely distributed to all registered patients at three and 12 months after stroke and on occation at additional time points. Evaluation has shown >90% accuracy for medical record information entered into Riksstroke.[198]

Baseline data were obtained on demographics, risk factors, comorbidity, treatment parameters, pre-stroke functional status, and living conditions. Data on post-stroke functional status and living conditions were obtained from follow-up surveys conducted at three months, 12 months, three years and five years. Data on caregiver burden, support, well-being, and unmet needs were obtained from a caregiver long-term follow-up questionnaire.

The Swedish Cause of Death Register

Data on mortality status and date of death were obtained from the Swedish Cause of Death Register (SCDR), which has an almost complete coverage of all Swedish citizens.[199, 200]

The Swedish National Patient Register

Data on comorbidity and hospital readmission were primarily obtained from the Swedish National Patient Register (SPNR), which contains data from outpatient and inpatient healthcare contacts (excluding primary care). More than 99% of all hospital discharges are registered, and an estimated 85-95% of all inpatient diagnoses are valid.[201] Diagnoses are registered using the Statistical Classification of Diseases and Health Related Problems, tenth revision (ICD-10).[202]

To identify comorbidities for each patient, data on all diagnoses (primary and secondary) for all outpatient and inpatient health contacts five years prior to index stroke were obtained.

Also, data on primary diagnoses and dates of admission and discharge were obtained for all readmissions after index stroke (in 2011 since only the 2011 cohort was included for readmission analysis) until the end of 2016.

The Swedish Prescribed Drug Register

Data from the Swedish Prescribed Drug Register (SPDR) were used to identify additional cases of dementia. The SPDR covers all prescriptions made and filled by Swedish pharmacies, and patient identity data is missing for less than 0.3% of all dispensed drugs.[203] Data are registered using the Anatomical Therapeutic Chemical Classification System (ATC).

Data were obtained on prescription-only drugs specific to dementia (ATC N06D). These include anticholinesterases, e.g. Donepezil, and NMDA antagonists, e.g. Memantine.

The Swedish Longitudinal Integrated Database for Health Insurance and Labour Market Studies

Data on highest level of education were obtained from the The Swedish Longitudinal Integrated Database for Health Insurance and Labour Market Studies (LISA) register, which contains data for almost all Swedish citizens with an estimated accuracy of 85%.[204]

Statistics Sweden

Statistics Sweden is the Swedish government agency responsible for official statistics. Data were obtained on demographic projections and survival in the general population.

The Swedish National Board of Health and Welfare

The SNBHW is a Swedish government agency tasked with various duties within the fields of social and medical services, patient safety, and epidemiology. The agency provided data on hospital admissions in the general population as well as stroke incidence, mortality, and care.

2.3 Measures and definitions

Comorbidity

Patients were considered to have a specific chronic condition if the diagnosis was registered in the SNPR at any time five years prior to index stroke. Prevalence data registered at index stroke admission were obtained from Riksstroke on a few conditions. Also, patients who had filled their prescriptions for drugs specific to dementia (ATC N06D) at any time from 2005 to index stroke were considered to have dementia. The Charlson Comorbidity Index (CCI) was used to guide selection of which conditions to be included.[205] The original CCI includes 19 chronic conditions and has previously been used for predicting mortality and functional outcome in stroke.[146, 147] In contrast to the CCI, ulcer disease, hemiplegia, and AIDS were not included in the thesis studies, and liver disease and diabetes were not subdivided. Also, angina pectoris, atrial fibrillation, and hypertension, which are not featured in the CCI, were added. This resulted in a list of 17 conditions (Table 2.3).

Table 2.3 List of the 17 included chronic conditions and corresponding ICD-10 codes. CCI=Charlson Comorbidity Index, COPD=chronic obstructive pulmonary disease.

	ICD-10 code
CCI conditions included	
Solid tumour, non-metastatic	C00–76
Solid tumour, metastatic	C77–79
Leukaemia/myeloma	C88–96
Lymphoma	C81–86
Chronic liver disease	B18, K70, K72, K73, K74
Chronic kidney failure	N18
COPD	J44
Rheumatoid arthritis	M04, M05
Peripheral vascular disease	I73
Congestive heart failure	I50
Myocardial infarction	I21, I22
Diabetes	Riksstroke data
Dementia	F00–03
Previous stroke	Riksstroke data
CCI conditions not included	
Ulcer disease	-
Hemiplegia	-
AIDS	-
Non-CCI conditions included	
Atrial fibrillation/flutter	Riksstroke data
Angina pectoris	I20
Hypertension	Riksstroke data

Table 2.4 The modified Rankin Scale.

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

Functional status

Functional status was described using the modified Rankin Scale (mRS)[206] (Table 2.4, adapted from Banks et al.[206]). Scores were estimated from information on dependency in specified activities of daily living (ADL) domains (toileting, dressing, mobility), living conditions, and need of support from next of kin, using a validated and previously specified translation algorithm.[207] Independency was defined as mRS≤2. The mRS score was used consistently throughout the thesis except in study V where survivor functional status was reported subjectively by the caregiver as either independent, partially dependent, or completely dependent.

Loss to follow-up

Loss to follow-up was defined as those not returning the follow-up questionnaire or with incomplete information on any of the variables needed for estimating the mRS-score. Deceased individuals were considered followed up.

Stroke severity

Level of consciousness at admission was used as a proxy marker for stroke severity[208] and was registered using the Reactions Level Scale 85 (RLS).[209] This scale consists of the categories alert (RLS 1), drowsy (RLS 2–3), and comatose (RLS 4–8).

Socioeconomic sttus

Highest level of education was used as a proxy marker for socioeconomic status.

Caregiver assistance to stroke survivors

Caregivers reported frequency of assistance on a four-graded scale: never, sometimes, often, or always, in multiple personal ADL domains: dressing, toileting, bath/shower, indoor and outdoor mobility. Additionally, assistance (yes/no) in several instrumental ADL domains was reported: contact with health services, medication, rehabilitation, and chores previously handled by the stroke survivor.

Caregiver support

Caregiver support was defined as services aimed specifically at relieving informal caregivers in their caregiving role.

Caregiver psychological well-being

Caregiver psychological well-being was quantified using a score analogous to the 36-item Short-Form Health Survey (SF-36)[210] mental health component. The SF-36 includes five items that are used to construct a "mental health score", ranging from one to 100, where a low score indicates poor psychological well-being. Several items in the Riksstroke caregiver questionnaire overlap with those in the SF-36, but only two items have been adopted without modification (Appendix II), precluding the calculation of a complete SF-36 mental health score using Riksstroke data. However, according to the SF-36 reference material, these two items display the strongest correlation with the total SF-36 "mental health score".[210] The two items were used to calculate an analogous caregiver psychological well-being score. This score was then compared to the SF-36 normative reference values for the Swedish population.[210] The normative mean value for the age group 55-74 years (score 81) minus one standard deviation (20) was used as a cut-off value (61) for poor psychological well-being.

Readmission rate

Readmission rate was reported per live person-years. It was calculated by dividing the total number of readmissions during each three-month period by the number of patients alive at the beginning of this interval. The quotient was then multiplied by four.

2.4 Statistical methods

The following statistical methods were included in the thesis:

- The chi-squared test (for categorical variables) and the student's t-test (for normally distributed quantitative variables) were used to analyze differences in baseline characteristics.
- Hierarchical cluster analysis was used to explore comorbidity clustering.
- Two methods were employed to deal with loss to follow-up: simple omission and multiple imputation (MI).
- Time-to-event analyses (Kaplan-Meier and Cox proportional hazards [PH] regression models) were used to estimate probability/hazard for death and hospital readmission.
- Binary outcomes were analyzed using logistic regression.

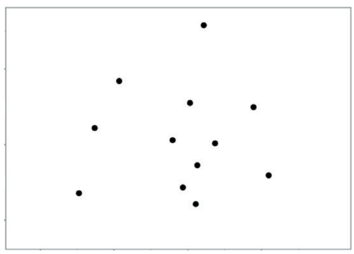
For all analyses, the level of significance was set to 5%. The sections below describe key statistical methods and their implementation in the thesis.

Hierarchical cluster analysis

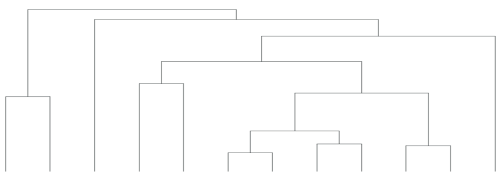
Hierarchical cluster analysis[211] was used in Study II to explore co-occurrence of chronic conditions. Pairwise correlation was performed using the Yule's Q formula (Appendix III), yielding a value from -1 to 1 (Figure 2.4). The "distance" between conditions was defined as 1- Yule's Q. These values were used to construct a hierarchical cluster dendrogram where clusters were identified by visual

Dementia	-											
Malignancy	0.05	-										
Diabetes	-0.01	0.01	-									
HT	0.23	0.11	0.58	-								
Angina	0.34	0.16	0.43	0.62	-							
MI	0.53	0.15	0.47	0.63	0.88	-						
HF	0.45	0.36	0.45	0.61	0.77	0.85	-					
AF	0.49	0.16	0.09	0.31	0.37	0.35	0.66	-				
PVD	-1.00	0.14	0.54	0.43	0.69	0.77	0.63	0.20	-			
COPD	0.66	0.43	0.24	0.31	0.63	0.63	0.72	0.23	0.71	-		
RA	-1.00	0.26	-0.02	0.12	0.34	0.50	-0.22	0.08	0.20	0.52	-	
CKF	0.37	0.41	0.71	0.60	0.61	0.61	0.80	0.29	0.80	0.40	0.07	-
	Dementia	**Malignancy**	**Diabetes**	**HT**	**Angina**	**MI**	**HF**	**AF**	**PVD**	**COPD**	**RA**	**CKF**

Yule's Q value grid



Multidimensional scaling



Dendrogram

Figure 2.4 Three different ways of illustrating comorbidity clustering.

inspection. Multidimensional scaling (MDS)[211] was used to further illustrate the results. Each condition was assigned two-dimensional coordinates in such a way as to make distances in the abstract two-dimensional space as close to corresponding values of 1-Yule's Q as possible. Note that a priori the dimensions lack clinical meaning.

Omission of missing cases

In Study II, missing cases were simply omitted. Data on mortality status were almost complete, and thus, patients lost to follow-up were alive but were of unknown functional status. The distribution of functional outcome in followed up survivors was extrapolated to survivors lost to follow-up. This method works best when attrition is minimal or if there are no systematic differences in patient characteristics affecting the outcome of interest. It was considered appropriate for Study II since loss to follow-up was relatively low in pre-stroke independent survivors (the participants in Study II).

Multiple imputation

In MI, missing information on patients lost to follow-up is inferred by using data from other patients.[212] Figure 2.5 shows an illustration of the methodology. In this example, there is missing information on variable 1 for patient D (Figure 2.5A). Values in the other variables (2–4) are compared to corresponding values in patients A–C. Patient D most resembles patients A and B and thus is most likely to also have the same variable 1 value, i.e. turquoise (Figure 2.5B).

For this technique to work, there needs to be a large number of variables available to make a reasonable estimation, and there has to be an association between predictor variables and the variables to be imputed.

MI was used for Studies I and III, which included pre-stroke dependent patients, in whom there was a greater proportion of non-responders (thus making simple omission more likely to cause significant bias). A large number of baseline characteristics were used as predictor variables: sex, age, diagnosis, living condi-

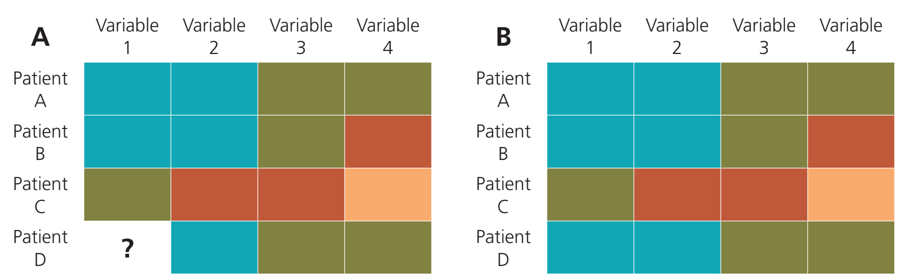


Figure 2.5A–B. Illustration of the multiple imputation method.
The missing value in patient D is inferred by information in patients A–C.

tions before stroke, previous stroke, smoking, previous transient ischemic attack/amaurosis fugax, atrial fibrillation, diabetes, hypertension, level of consciousness at admission, and functional status prior to stroke. Functional ability in toileting, dressing, mobility, living conditions and need of support from next of kin were used both as predictors and variables to be imputed. Since a large number of predictor variables likely associated with functional outcome were used, it seemed reasonable to assume that missing values could be inferred by observed values. Five imputations were conducted, each based on ten iterations of the underlying Markov chain. The five resulting data sets were then used to calculate an average, limiting the effect of variation in individual imputations. The mean and spread is presented in Appendix IV.

Time-to-event analyses

Time-to-event analyses are frequently used to estimate the probability/hazard of experiencing a (binary) event (e.g. death or readmission) within a certain time interval. Subjects are followed until they experience the event of interest, until the end of the study period, or until loss to follow-up.[213]

Two closely related statistical approaches were employed: Kaplan-Meier survival analysis and Cox proportional hazards (PH) regression modelling.

The Kaplan-Meier survival curve displays the estimated cumulative occurrence of the event against time. Different groups can be compared by hypothesis testing, e.g. by using the log-rank test.[214] Kaplan-Meier analyses were conducted to estimate the probability of death (Study I, III) or readmission (Study IV). Beyond three years, survival data were only available for the 2011 cohort and thus, the 2013 cohort was censored at three years in survival analyses.

While the Kaplan-Meier method is essentially a univariate approach, the Cox PH method allows for assessing the effect of multiple covariates.[215] While it does not directly model survival probabilities, it yields a single hazard ratio (HR) for the whole study period. The model is based on the proportional hazards assumption. This means that the effect of a covariate cannot vary over time. Cox PH modelling was used to analyze the effect of multiple variables on the probability of death (Study I, III) or readmission (Study IV).

Logistic regression

Logistic regression is used to estimate the effect of multiple covariates on a binary outcome. In contrast to time-to-event analyses, logistic regression does not take into account the relative time to occurrence of an event.

In Study I, the effects of several variables on the functional status of survivors at three or five years was estimated in separate models adjusted for sex, age, prestroke functional dependency and level of consciousness at admission.

In Study II, the prognostic impact of the total comorbidity burden and individual chronic conditions was analyzed in separate models adjusted for age, sex, level of consciousness at admission, and highest level of education. Due to its disproportional impact on outcome, patients with known metastatic malignancy (0.9%) were not included.

In Study V, the effect of several patient and caregiver characteristics on caregiver psychological well-being was investigated using a model adjusted for caregiver age and general health.

3. Results

3.1 Characteristics of the common cohort

The total number of included patients was 22 905; 20 047 (87.5%) with ischemic stroke (IS), and 2858 (12.5%) with intracerebral haemorrhage (ICH) (Table 3.1). There was comorbidity in 82.5% of patients, 20.0% had high comorbidity, i.e. at least four additional chronic conditions, and 29.2% were functionally dependent before stroke. The proportion of pre-stroke dependents increased with age (Figure 3.1): 34% in those over 65 of age and 50% in those over 80. However, when excluding those that received home care service but were independent in activities of daily living (ADL), these proportions decreased to 21.5% and 31.0%, respectively. The corresponding proportions in the Swedish general population have been estimated to 11.1% and 21.6%, respectively (dependent in at least one ADL domain).[149]

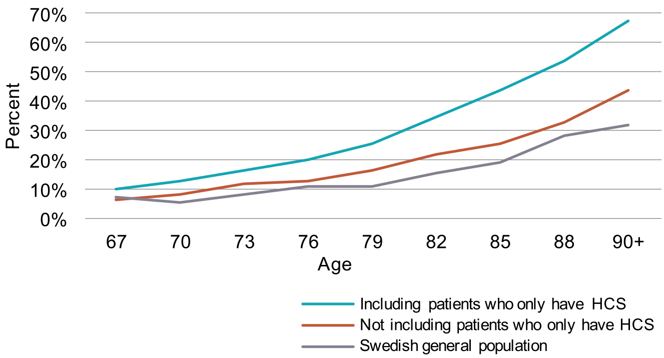


Figure 3.1 The pre-stroke proportion of dependents in activities of daily living in this thesis versus in the Swedish general population.

HCS=home care service.

Table 3.1 Patient characteristics in the common cohort.
Presented as number (%).
IQR=Interquartile range, mRS=modified Rankin Scale, SD=Standard deviation, TIA=transient ischemic attack.

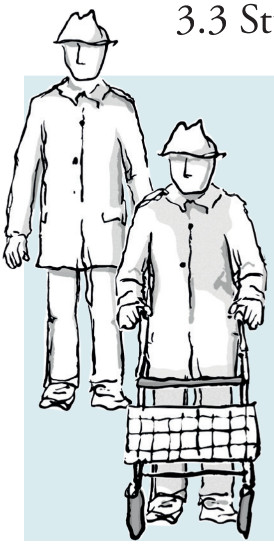
	n=22 905
Year cohort	
2011	12 625 (55.1)
2013	10 280 (44.9)
Sex (male)	12 006 (52.4)
Age	
Mean ± SD	76.0 ± 12.1
Median (IQR)	78 (16)
Diagnosis	
Ischemic stroke	20 047 (87.5)
Intracerebral haemorrhage	2858 (12.5)
Pre-stroke functional status	
mRS ≤2 (independent)	16 209 (70.8)
mRS 3	3747 (16.4)
mRS 4	2135 (9.3)
mRS 5	814 (3.6)
Level of consciousness at admission	
Alert	18 714 (82.7)
Drowsy	2737 (11.9)
Comatose	1173 (5.2)
Living conditions before stroke	
At home without home care service	16 770 (73.2)
At home with home care service	3919 (17.1)
Assisted living	2102 (9.2)
Other	111 (0.5)
Risk factors	
Previous stroke	4969 (21.8)
Previous TIA/amaurosis fugax	1911 (8.5)
Atrial fibrillation	6745 (29.6)
Hypertension	14 417 (63.3)
Smoking	2802 (12.2)
Diabetes	4877 (21.4)
Dementia	1129 (4.9)
Total comorbidity burden	
None	4001 (17.5)
Low (1 condition)	5688 (24.8)
Moderate (2–3 conditions)	8626 (37.7)
High (≥4 conditions)	4590 (20.0)

3.2 Loss to follow-up and missing data

Loss to follow-up in the common cohort was 12.7% at three months, 21.2% at 12 months, 20.3% at three years, and 16.9% at five years (Figure 3.2). The total response rate in the caregiver questionnaire was 53%. However, in dyads with responding stroke survivors the caregiver response rate was higher, at 71.8%.

Missing data in baseline variables was less than 1%, except for previous transient ischemic attack (TIA)/amaurosis fugax (1.8%), level of consciousness at admission (1.2%), and smoking (6.9%).

3.3 Study I



Study population
22 929 pre-stroke dependent and independent patients with first-ever, or recurrent ICH or IS.

Main results

- Overall prognosis was poor: at five years, 79.0% and 70.6% of patients were either deceased or functionally dependent in ICH and IS, respectively.
- The prognostic difference was largely explained by a higher early mortality in ICH. In the long term, mortality rate was similar.
- Among survivors, long-term functional outcome was less favourable in ICH.

Overall prognosis

Long-term prognosis was generally poor, particularly in ICH. At five years, 79.0% of patients with ICH were either deceased or functionally dependent compared to 70.6% in IS (p<0.01) Figure 3.3).

Survival

Most of the difference in prognosis between IS and ICH was explained by higher early mortality in ICH. At 30 days, only 69.3% of patients diagnosed with ICH were alive compared to 88.9% in IS (p<0.01) (Figure 3.4). However, among 30-day survivors, long-term survival was almost identical in ICH and IS (p=0.858). Cumulative survival at five years was 48% for all patients; 49.4% for IS and 37.8% for ICH (p<0.01). This compares to 64.6% in a reference cohort from the Swedish general population.

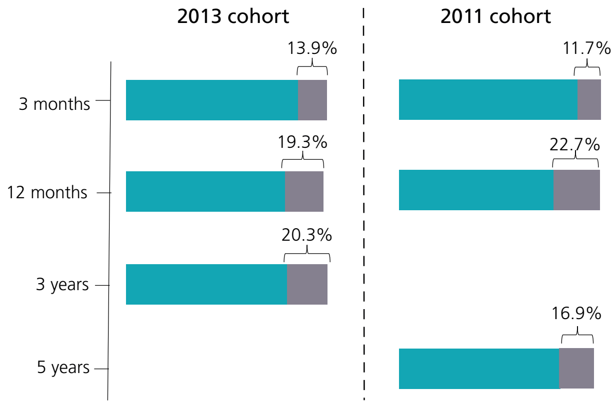


Figure 3.2 Loss to follow up at different time points.
Gray=loss to follow-up.

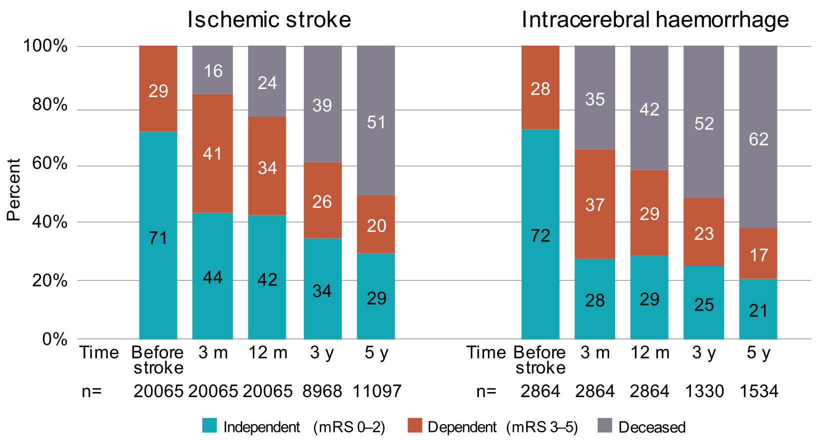


Figure 3.3 Overall five-year prognosis in ischemic stroke and intracerebral haemorrhage.
Imputed values were used in patients lost to follow-up.
m=months, y=years.

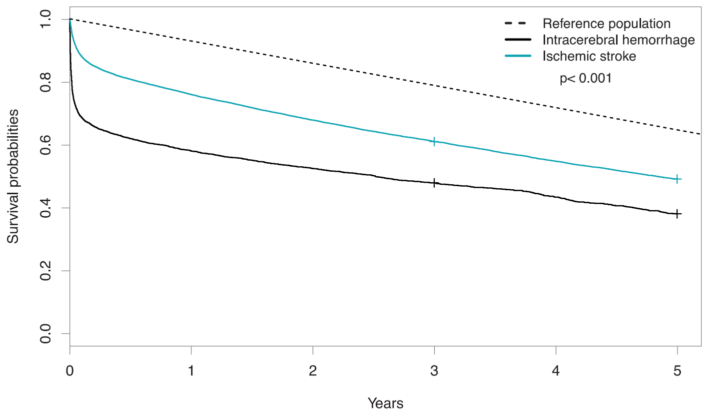


Figure 3.4 Five-year survival in ischemic stroke and intracerebral haemorrhage.
The dashed line shows survival in a reference cohort from the Swedish general population.

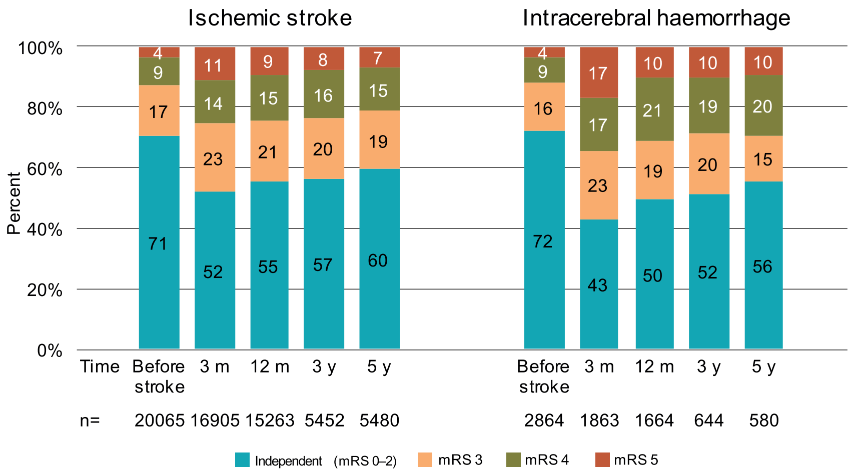


Figure 3.5 Functional outcome in survivors at different time points.
Imputed values were used in patients lost to follow-up.
m=months, y=years.

Table 3.2 Prevalence of comorbidity stratified by age.
Presented as number (%).

	Total n=11 775	**≤64** n=2544	**65–74** n=3412	**75–84** n=3833	**≥85** n=1986
Selected comorbidities					
Solid tumour, non-metastatic	1285 (10.9)	98 (3.9)	354 (10.4)	552 (14.4)	281 (14.1)
Congestive heart failure	817 (6.9)	79 (3.1)	175 (5.1)	322 (8.4)	241 (12.1)
Diabetes	2331 (19.8)	479 (18.5)	778 (22.8)	778 (20.3)	305 (15.4)
Atrial fibrillation	2871 (24.4)	241 (9.5)	679 (19.9)	1129 (29.5)	822 (41.4)
Angina pectoris	885 (7.5)	93 (3.7)	226 (6.6)	367 (9.6)	199 (10.0)
Hypertension	6875 (58.4)	1031 (40.5)	1996 (58.5)	2493 (65.1)	1355 (68.3)
Total comorbidity burden					
None	2919 (24.8)	1143 (44.9)	853 (25.0)	650 (17.5)	253 (12.7)
Low (1 condition)	3739 (31.8)	773 (30.4)	1157 (33.9)	1208 (31.5)	601 (30.3)
Moderate (2–3 conditions)	3948 (33.5)	537 (21.1)	1112 (32.6)	1474 (38.5)	825 (41.6)
High (≥4 conditions)	1162 (9.9)	91 (3.6)	289 (8.5)	477 (12.5)	305 (15.4)

Functional outcome

The overall proportion of functional dependency in survivors was seen to decrease over time, possibly because of higher mortality in dependent patients. Even though the largest part of the aggregated difference (IS vs ICH) in outcome was explained by higher early mortality, analysis of survivors at different time points revealed that the proportion of functional dependency was consistently higher for ICH (Figure 3.5).

3.4 Study II

Study population
11 775 pre-stroke independent patients with first-ever IS.

Main results
- Comorbidity was common: present in 75.2% of patients, and conditions tended to co-occur in distinct clusters.
- There was less favourable outcome with increasing comorbidity in all age groups.
- The largest individual effects were found for dementia, kidney and heart failure.

Prevalence of chronic conditions

In all patients, 24.8% had no comorbidity, 31.8% had low comorbidity (1 condition), 33.5% moderate comorbidity (2–3 conditions), and 9.9% had high comorbidity (≥4 conditions). The prevalence of most conditions increased with age. Six of the 16 included conditions (one less condition as compared to 17 in the common thesis cohort since patients with previous stroke where not included) had a prevalence higher than 5%. These were, in descending order of prevalence: hypertension, atrial fibrillation (AF), diabetes, non-metastatic solid tumour, angina pectoris, and congestive heart failure (Table 3.2).

Clustering of conditions

The study cohort was stratified by median age (74) and the two age groups were analyzed separately for co-occurrence of conditions (Figure 3.6 shows results for the older group). Several distinct clusters were identified that were similar in both groups. There was a large cluster of cardiovascular conditions (angina, chronic kidney failure, heart failure, myocardial infarction, and peripheral vascular disease) that contained several sub-clusters (Figure 3.6A). In older patients, this large cluster also included chronic obstructive pulmonary disease (COPD).

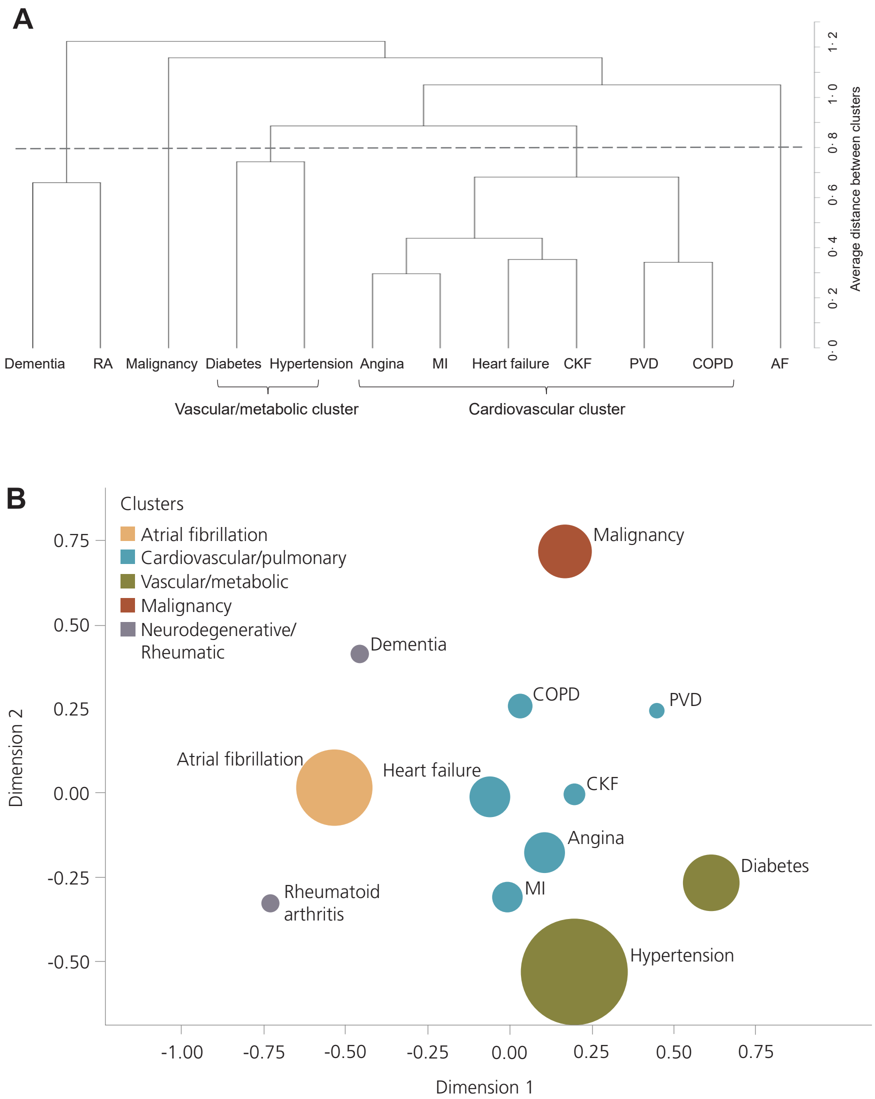


Figure 3.6A–B Comorbidity clusters in patients ≥75 of age (n = 5819).

Figure A shows a dendrogram where a high degree of co-occurrence is shown as late divergence and the dashed line indicates the cut-off point for separating clusters. The clustering pattern was further illustrated by multidimensional scaling (B) where each condition was assigned to a specific location in a two-dimensional space and distinct clusters were labelled in different colors. A short distance represents a high degree of co-occurrence and circle size represents relative prevalence.

AF=atrial fibrillation, COPD=chronic obstructive pulmonary disease, CKF=chronic kidney failure, MI=myocardial infarction, PVD=peripheral vascular disease, RA=rheumatoid arthritis.

Two other vascular conditions: hypertension and diabetes, formed a separate vascular/metabolic cluster. Both malignancy and AF occurred separately and did not cluster with any other condition. The clustering pattern of dementia was inconsistent between age groups, possibly because of low prevalence. The results were further illustrated using multidimensional scaling (MDS) (Figure 3.6B).

Survival and functional outcome

A higher comorbidity burden increased the risk of poor outcome considerably, both in respect to mortality (Figure 3.7A) and functional outcome (Figure 3.7B). This effect was proportionally larger in younger patients. In patients under 65 of age, mortality at 12 months was over six times as high in those with high comorbidity versus those with no comorbidity. In patients over 84 years of age, the corresponding difference was only two-fold.

Multivariable analyses showed that dementia, kidney and heart failure were the strongest predictors of poor outcome (deceased or dependent) at three months and three/five years after stroke (Table 3.3).

A Mortality at 12 months

Comorbidity burden	**Age group** <65	65–74	75–84	≥85
None (n=2889)	2.6%	6.6%	9.9%	24.8%
Low (n=3705)	4.7%	7.6%	12.2%	23.7%
Moderate (n=3913)	8.6%	11.1%	16.0%	33.0%
High (n=1150)	16.9%	19.2%	26.7%	38.7%

B Poor functional outcome at 12 months in survivors

Comorbidity burden	**Age group** <65	65–74	75–84	≥85
None (n=2022)	10.2%	13.0%	30.9%	60.2%
Low (n=2611)	14.4%	16.2%	29.4%	65.5%
Moderate (n=2477)	13.0%	22.3%	38.2%	63.6%
High (n=601)	28.9%	28.9%	48.4%	61.6%

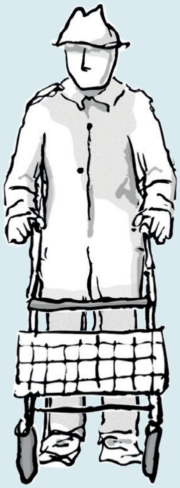
Figure 3.7A–B Twelve-month mortality (A) and functional outcome in survivors (B), stratified by age and comorbidity burden.

Low=1 condition, moderate=2–3 conditions, high≥4 conditions.

Table 3.3 Prognostic impact of individual chronic conditions on risk of poor outcome (deceased or dependent). Adjusted for age, sex, level of consciousness at admission, and educational level.
CI=confidence interval, COPD=chronic obstructive pulmonary disease, OR=odds ratio.

	3 months n=10 012 OR (95% CI)	**3/5 years** n=8939 OR (95% CI)
Heart failure	1.70 (1.42–2.05)	2.53 (1.99–3.22)
COPD	1.26 (0.98–1.62)	2.18 (1.62–2.93)
Kidney failure	1.83 (1.34–2.51)	3.54 (2.25–5.55)
Hypertension	1.04 (0.94–1.15)	1.13 (1.02–1.26)
Dementia	2.79 (1.83–4.28)	6.64 (3.08–14.33)
Malignancy	1.03 (0.90–1.18)	1.34 (1.14–1.56)
Diabetes	1.45 (1.29–1.64)	1.71 (1.52–1.98)

3.5 Study III



Study population
5899 pre-stroke dependent patients with first ever or recurrent IS, plus a reference cohort of 14 148 pre-stroke independents.

Main results

- Pre-stroke dependent patients differed significantly from independents in key characteristics, most notably age and comorbidity burden.
- With increasing pre-stroke dependency level, comorbidity burden was higher, drug prescription (including anticoagulants) was lower, and prognosis less favourable.
- In the moderate dependency group (the lowest level of dependency), a relatively large proportion survived and maintained their pre-stroke functional level.

Patient characteristics

Pre-stroke dependent patients differed significantly from independents in several key parameters (Table 3.4). They were on average ten years older (median age 85 versus 75 years) and comorbidity burden was greater. Dependent patients were split into three groups based on pre-stroke level of dependency: moderate (mRS 3, 55.9%), moderately severe (mRS 4, 32.0%), and severe (mRS 5, 12.2%). Age distribution was similar between these groups, but comorbidity burden increased with dependency level. There was high comorbidity (≥4 conditions) in 32.7%, 37.9%, and 42.1% in moderate, moderately severe, and severe dependency, respectively. This was partly explained by the increasing proportion of previous stroke (30.0% to 45.7%) and dementia (7.8% to 26.5%).

Medication and care parameters

A small proportion (4.2%) of pre-stroke dependent patients received thrombolytic therapy. This proportion was seen to decrease significantly with increasing dependency level (Figure 3.8). Also, there was significantly lower prescription of stroke-specific drugs such as statins, antihypertensive, antiplatelet, and oral anticoagulant (OAC) drugs with increasing level of pre-stroke dependency. In those without AF (presumed non-cardioembolic stroke), 74.4% of severe dependency patients were prescribed antiplatelet drugs at discharge compared to 91.5% in independent patients of comparable age (≥78). Similarly, in patients with AF (presumed cardioembolic stroke), OAC prescription at discharge was 15.6% versus 55.1%.

Table 3.4 Patient characteristics and comorbidity in pre-stroke dependents, stratified by degree of dependency. Including a reference cohort of pre-stroke independents. Data presented as number (%) if not indicated otherwise. Differences between groups were statistically significant for all variables ($p<0.05$).

IQR=interquartile range, mRS=modified Rankin Scale.

	Pre-stroke independent	**Pre-stroke dependent**		
	Total n=14148	**Moderate (mRS 3)** n=3300	**Moderately severe (mRS 4)** n=1889	**Severe (mRS 5)** n=710
Age, median (IQR), years	75 (16)	86 (10)	85 (11)	85 (11)
Male sex	8167 (57.7)	1228 (37.2)	803 (42.5)	252 (35.5)
Total comorbidity burden				
None	209 (20.6)	254 (7.7)	122 (6.5)	36 (5.1)
Low (1 condition)	4014 (28.4)	581 (17.6)	261 (13.8)	111 (15.6)
Moderate (2–3 conditions)	5241 (37.0)	1385 (42.0)	790 (41.8)	264 (37.2)
High (≥4 conditions)	1984 (14.0)	1080 (32.7)	790 (37.9)	299 (42.1)
Selected comorbidities				
Atrial fibrillation	3564 (25.2)	1410 (42.7)	781 (41.3)	318 (44.8)
Congestive heart failure	1059 (7.5)	648 (19.6)	448 (23.7)	160 (22.5)
Dementia	206 (1.5)	256 (7.8)	316 (16.7)	188 (26.5)
Diabetes	2925 (20.7)	739 (22.4)	512 (27.1)	203 (28.6)
Hypertension	8680 (61.4)	2340 (70.9)	1329 (70.4)	453 (63.8)
Myocardial infarction	709 (5.0)	269 (8.2)	172 (9.1)	53 (7.5)
Previous stroke	2310 (16.4)	984 (30.0)	764 (40.8)	323 (45.7)

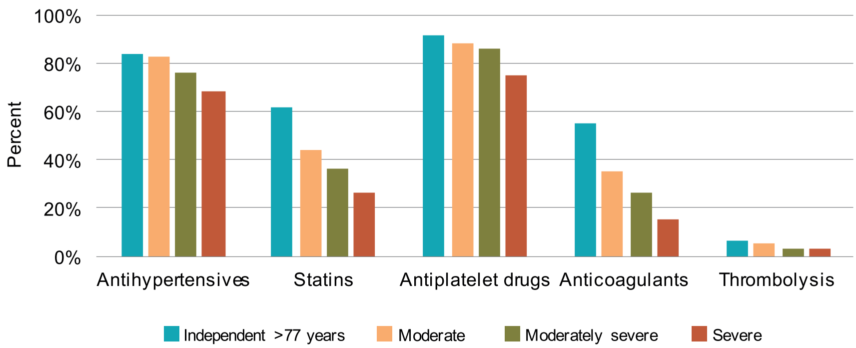


Figure 3.8 Thrombolysis and stroke-specific drug prescription at discharge in relation to pre-stroke dependency level.

Antiplatelet drug prescription is shown for presumed non-cardioembolic stroke only and prescription of anticoagulants for presumed cardioembolic stroke only.

Survival and functional outcome

Prognosis varied substantially between patients of different pre-stroke dependency level. Three-month mortality was 49.6% in severe dependency (mRS 5), 37.3% in moderately severe dependency (mRS 4), 25.3% in moderate dependency (mRS 3), and 14.0% in independent (mRS 0–2) patients of comparable age (≥78) (Figure 3.10A). Between three and 12 months, more pre-stroke independent survivors improved in functional status than died or deteriorated, while the inverse relationship was seen in pre-stroke dependent patients: 10.9% improvement versus 31.7% poor outcome in the moderate dependency group and 9.4% versus 38.1% in the moderately severe group (Figure 3.9A). At three-year follow-up, the proportion that had died or deteriorated was 86.3% in severe dependency, 87.5% in moderately severe dependency, 82.6% in moderate dependency, and 75.1% in independent patients ≥78 years (Figure 3.10B). Multivariable analyses showed that a high level of pre-stroke dependency and comorbidity were significantly associated with poor outcome adjusted for age, sex, stroke severity, and socioeconomic status.

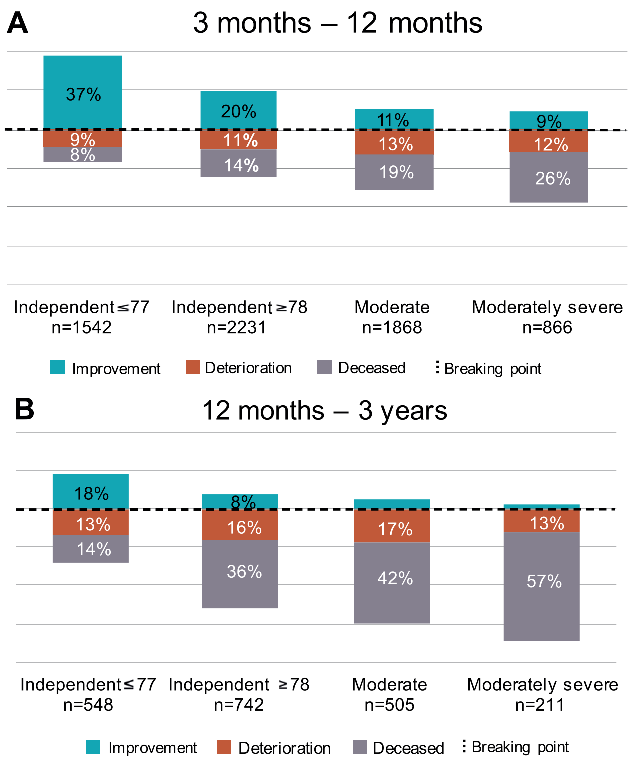


Figure 3.9A–B Change in functional status between 3 and 12 months (A) and between 12 months and 3 years (B) in 3-month and 12-month survivors, respectively.

Differences in overall outcome between groups were statistically significant ($p<0.05$) at all follow-up time points.

Moderate pre-stroke dependency=mRS 3, moderately severe pre-stroke dependency=mRS 4, severe pre-stroke dependency=mRS 5. Percentages ≤3 were not labelled.

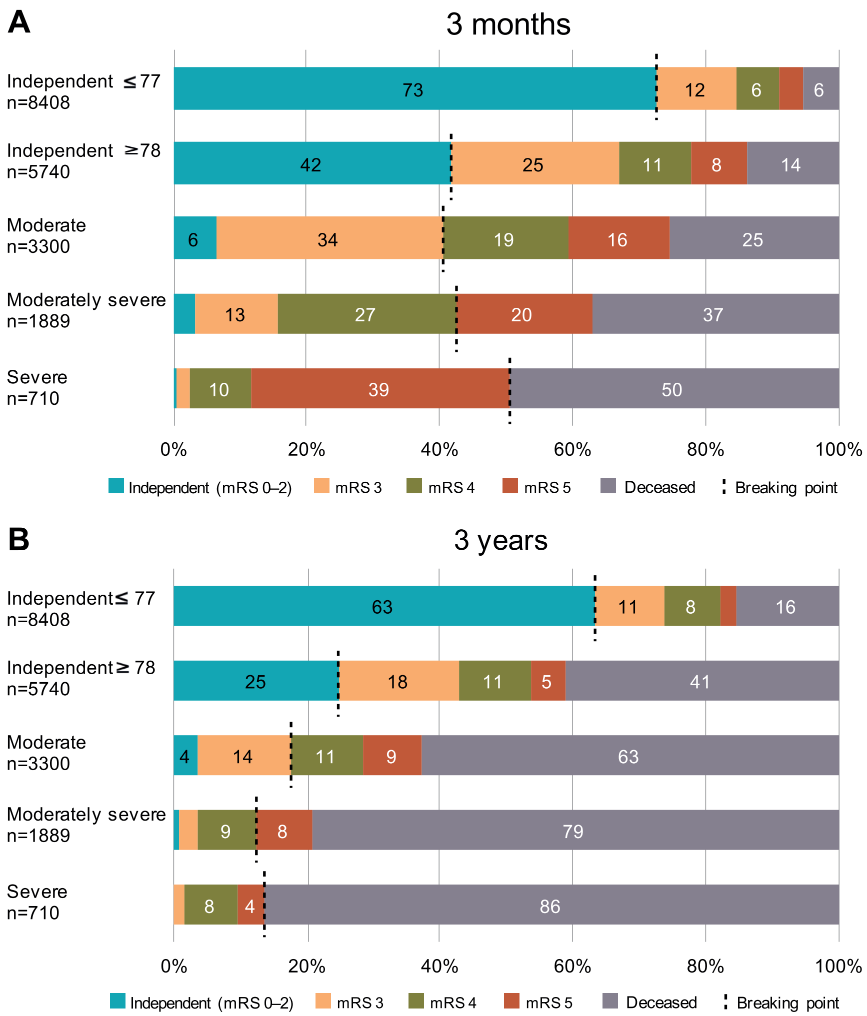
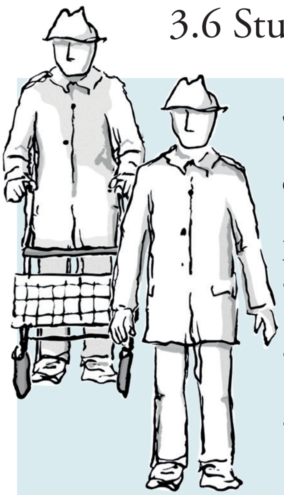


Figure 3.10A–B Functional status at 3 months (A) and 3 years (B) in relation to pre-stroke dependency level.

Groups of different pre-stroke dependency levels are shown as separate bars. The breaking point in each bar separates those who maintained pre-stroke functional status (to the left) and those who had died or deteriorated in functional status (to the right). Differences in overall outcome between groups were statistically significant ($p<0.05$) at all follow-up time points.

Moderate pre-stroke dependency=mRS 3, moderately severe pre-stroke dependency=mRS 4, severe pre-stroke dependency=mRS 5. Percentages ≤3 were not labelled.

3.6 Study IV



Study population
10 092 pre-stroke dependent or independent patients with first-ever or recurrent IS.

Main results
- Readmission after stroke was common, particularly in the early phase and in those with high comorbidity burden.
- Approximately 20% of patients accounted for 60% of readmissions and 5% of patients accounted for 25%.
- Patients of few versus many readmissions differed substantially in characteristics and, to a lesser degree, in causes of readmission.

Readmission rate

The probability of readmission in all patients was 0.46 within 12 months and 0.81 within five years after index stroke. When stratifying by comorbidity burden, the probability curves diverged substantially (p<001) (Figure 3.11). The probability of readmission within 12 months for none, low (1 condition), moderate (2–3 conditions), and high comorbidity burden (≥4 conditions) was 0.36, 0.39, 0.49, and 0.61, respectively. Readmission rate in all patients varied over time: 1.42 per live person-years between one and four months, declining during the first year to stabilize at 0.66–0.87 throughout the remaining follow-up period (Figure 3.12).

Distribution of readmissions

The total number of readmissions was unevenly distributed between individuals: 45.2% had 0–1 readmissions but only accounted for 6.4% of the total number of readmissions (Figure 3.13). Conversely, 22.7% of patients had ≥5 readmissions, which accounted for 63.8% of the total number, and a small group (5.7%) had ≥10 readmissions, which accounted for 27.4%.

Patients alive at 12 months were grouped based on number of readmissions: low (0–1, 40.8%), intermediate (2–4, 33.2%), high (5–9, 19.2%), and very high (≥10, 6.8%) (Table 3.5). The proportion of high comorbidity burden (≥4 conditions) was 10.5% in those with a low number of readmissions compared to 32.9% in those with a very high number. Individual comorbidities with the largest relative differences in prevalence between these groups were chronic kidney failure (1.1% versus 7.2%), COPD (1.8% versus 9.3%), myocardial infarction

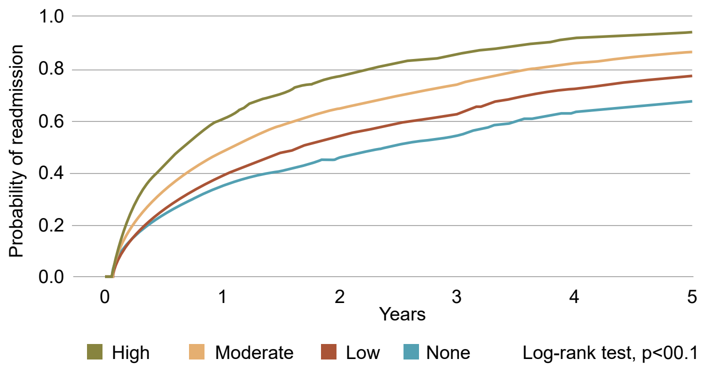


Figure 3.11 Kaplan–Meier curves describing the probability of readmission within five years after stroke in patients of different level of comorbidity burden.

Low=1 condition, moderate=2–3 conditions, high≥4 conditions.

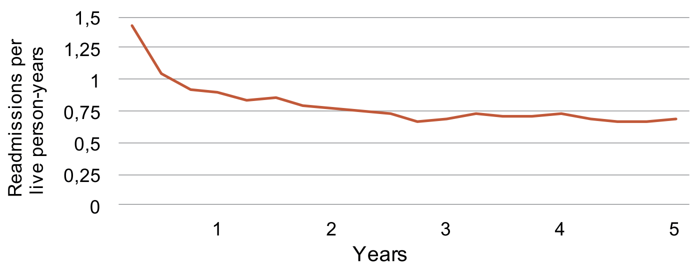


Figure 3.12 Variation in readmission rate in all patients up to five years after stroke.

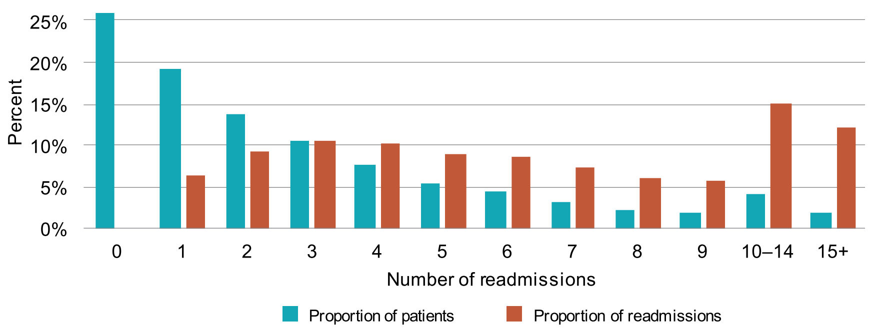


Figure 3.13 Distribution of number of readmissions among patients.

For example, 19% of patients had 1 readmission, which represented 6% of the total number of readmissions.

Table 3.5 Patient characteristics, stratified based on number of readmissions.
Presented as number (%) unless otherwise stated. Only patients alive at 12 months were included.
COPD=chronic obstructive pulmonary disease, IQR=interquartile range.

	Total n=8450	Low (0-1) n= 3449	Intermediate (2-4) n=2806	High (5-9) n=1624	Very high (≥10) n=571
Age (median [IQR])	76 (16)	73 (18)	78 (16)	78 (13)	74 (14)
Male sex	4578 (54.2)	1876 (54.4)	1489 (53.1)	895 (55.1)	318 (55.7)
Total comorbidity burden					
None	1691 (20.0)	950 (27.5)	473 (16.9)	206 (12.7)	62 (10.9)
Low (1 condition)	2269 (26.9)	1042 (30.2)	786 (28.0)	352 (21.7)	89 (15.6)
Moderate (2–3 conditions)	3144 (37.2)	1094 (31.7)	1109 (39.5)	709 (43.7)	232 (40.6)
High (>4 conditions)	1346 (15.9)	363 (10.5)	438 (15.6)	357 (22.0)	188 (32.9)
Selected comorbidities					
Atrial fibrillation	2129 (25.2)	726 (21.0)	743 (26.5)	478 (29.4)	182 (31.9)
Chronic kidney failure	181 (2.1)	38 (1.1)	48 (1.7)	54 (3.3)	41 (7.2)
Congestive heart failure	700 (8.3)	167 (4.8)	235 (8.4)	195 (12.0)	103 (18.9)
COPD	313 (3.7)	61 (1.8)	105 (3.7)	94 (5.8)	53 (9.3)
Diabetes	1696 (20.1)	579 (16.8)	524 (18.7)	403 (24.8)	190 (33.3)
Hypertension	5152 (61.0)	1884 (54.6)	1787 (63.7)	1091 (67.2)	390 (68.3)
Myocardial infarction	433 (5.1)	107 (3.1)	146 (5.2)	114 (7.0)	66 (11.6)
Previous stroke	1725 (20.6)	556 (16.2)	602 (21.6)	410 (25.5)	157 (27.8)

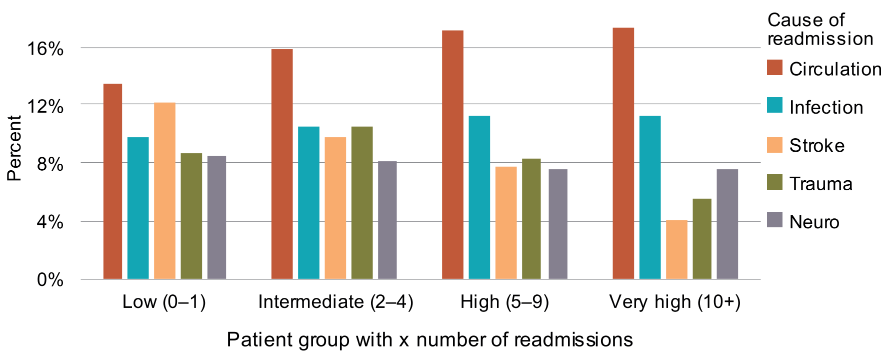


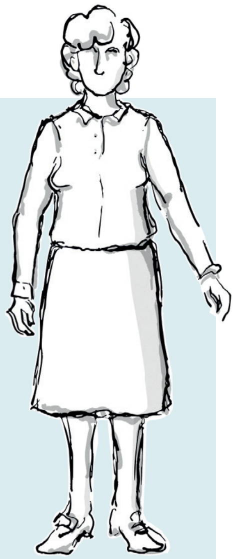
Figure 3.14 Distribution of causes of readmission in patients with different number of readmissions.

(3.1% versus 11.6%), and congestive heart failure (4.8% versus 18.0%). The relative distribution of causes of readmission varied slightly between groups of different number of readmissions (Figure 3.14). The proportion of readmissions due to stroke was 12.1% in patients with a low number of readmissions compared to 4.1% in those with a very high number. Similarly, the proportion of readmissions due to trauma was 8.6% in patients with a low number of readmissions compared to 5.5% in those with a very high number. The proportion of readmissions due to circulatory conditions was larger in patients with a higher total number of readmissions.

3.7 Study V

Study population
5063 informal caregivers (such as spouses or children) to stroke survivors.

Main results
- Caregiver life impact, need of support, and poor psychological well-being increased with degree of dependency of the stroke survivor.
- In caregivers to completely dependent survivors:
  - 41.1% were unable to leave the survivor for more than one hour.
  - 23.7% expressed unmet need of caregiver support.
  - 51.4% reported poor psychological well-being.



Amount of assistance provided to survivors

The study population of 5063 informal caregivers was divided into three groups based on the level of dependency of "their" stroke survivor: independent (n=2860), partial dependency (n=1691), and complete dependency (n=512) as defined subjectively by the caregiver. The amount of assistance provided by caregivers increased with survivor degree of dependency. The proportion of caregivers of completely dependent survivors always providing assistance was 33.6% in dressing, 28.1% in toileting, 46.2% in bath/shower, 23.6% in indoor mobility and 51.3% in outdoor mobility (figure 3.15A). These proportions were much lower in the partially dependent group (figure 3.15B).

Degree of survivor dependency had a fundamental life impact: 41.1% of caregivers to completely dependent survivors were not able to leave the survivor alone for more than one hour at a time. In the partially dependent group, this proportion was only 11% (Figure 3.16).

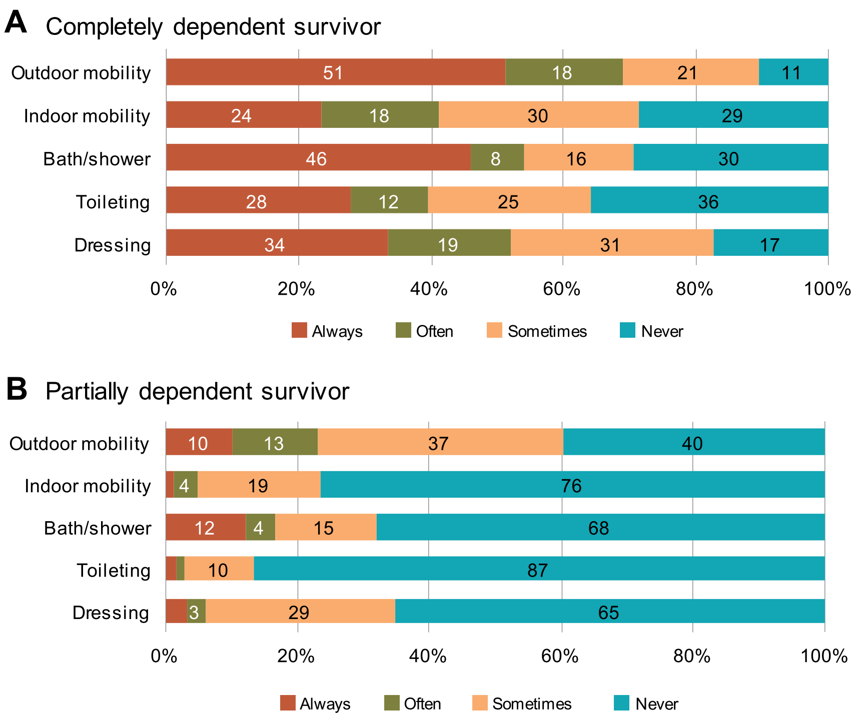


Figure 3.15A–B Frequency of assistance provided by informal caregivers to completely dependent (A) and partially dependent (B) survivors in various domains of activities of daily living.

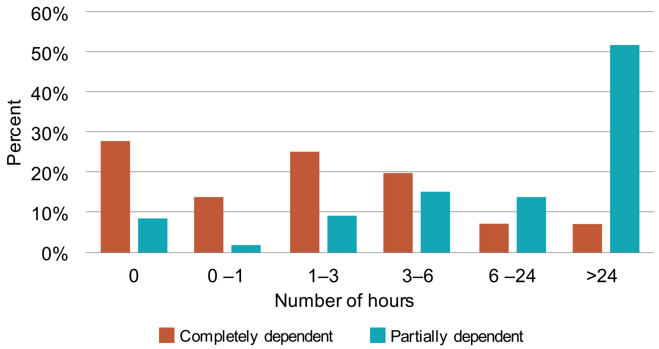


Figure 3.16 Proportion of caregivers to completely and partially dependent survivors able to leave the survivor alone for x amount of hours.

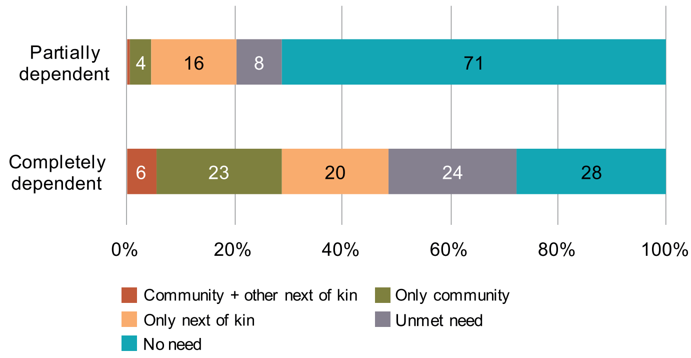


Figure 3.17 Support received by informal caregivers to completely and partially dependent survivors from other next of kin and/or the community.

Caregiver support

In the completely dependent group, 48.6% of caregivers received support in their caregiving role. However, over one third of these, 19.8%, only received support from other next of kin. Moreover, 23.7% expressed unmet need of support (Figure 3.17). In the partially dependent group, caregiver support was mainly provided by other next of kin (16.7%), the proportion receiving community support was small (4.6%), and only 8.4% expressed unmet need.

In addition, few caregivers had contact with local patient associations: only 4% in the partially and 9.3% in the completely dependent group, and almost half in both groups reported insufficient knowledge about stroke.

Caregiver psychological well-being

There was a significant increase in caregiver feelings of frustration, fatigue, sadness, and anxiety with degree of survivor dependency. In the independent group, the proportion of poor psychological well-being was 19.3% compared to 34,7% in the partially dependent group and 51.4% in the completely dependent group (Figure 3.18).

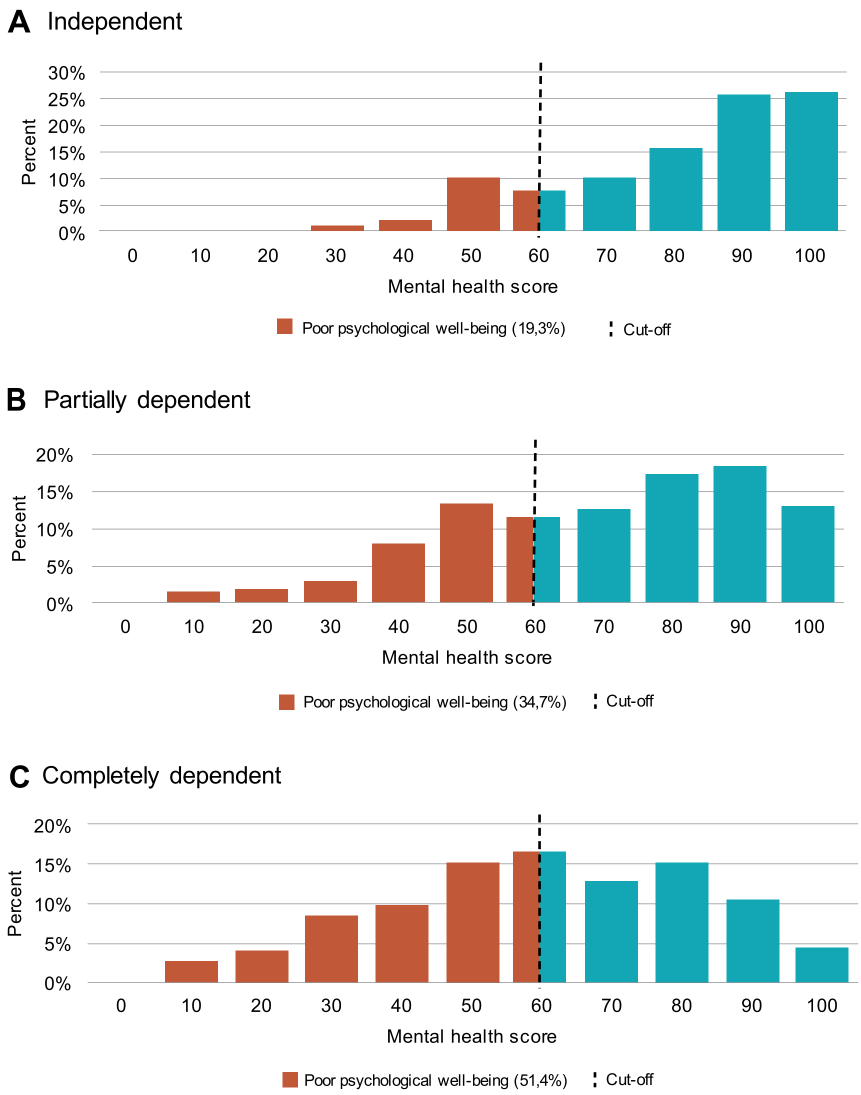


Figure 3.18A–C Psychological well-being in informal caregivers to independent (A), partially (B), and completely dependent (C) survivors.

Expressed using a score analogous to the SF-36 mental health component. A score below 61 was defined as poor psychological well-being.

4. Methodological considerations

4.1 Study design

The studies were all registry-based observational cohort studies.

The Swedish healthcare system is well suited to registry-based research. There is a multitude of high quality registers, and each patient can be easily found in multiple databases using their personal identification number (PIN). However, in registry-based research, while data are often available for a large number of individuals, they may lack detail. Also, it is difficult to adapt data collection to answer specific research questions as registry data are usually collected for purposes other than research.

Since the aim of this thesis was to study the natural history of a disease in a large number of patients rather than to investigate a specific controllable exposure or intervention, an observational cohort approach was reasonable.

While a cohort study can be used to examine multiple outcomes and exposures, there is an inherent risk of selection bias in both the initial stages and during follow-up.

4.2 Bias

There are many potential sources of bias at various stages of the research process.[216] Several examples pertinent to this thesis are discussed below. These are presented with respect to the chronology of the research process: the set-up stage, the follow-up period, the analysis stage, and putting results into context (Figure 4.1).

Selection bias at inclusion

This type of bias occurs when the initial study sample is not representative of the target population.

Only patients admitted to hospital are registered in Riksstroke. The proportion of Swedish stroke patients admitted has been estimated to be around 86–92% of all cases.[217, 218] Those not admitted are primarily patients with mild strokes sent home from the emergency department, or patients of advanced age residing in nursing homes whose strokes are solely managed in primary care.[218] The resulting bias is difficult to estimate as these two groups have very different prognoses.

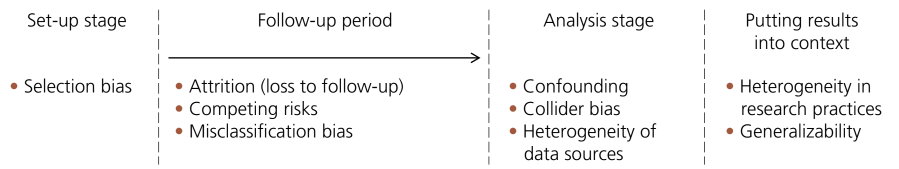


Figure 4.1 Potential sources of bias at various stages during the research process.

Also, some cases that are admitted fail to be registered. The Riksstroke reports from 2011 and 2013 estimate this proportion to be less than 10%,[196, 197] and it is uncertain whether there is any systematic pattern as to which patients are not registered.

Attrition bias (loss to follow-up)

The risk of attrition bias depends on whether or not the reason for loss to follow-up is associated with the outcome of interest. If, for example, participants drop out of a study investigating functional status because of difficulty getting to the follow-up facility, results will clearly be biased since only physically fit individuals would be included. The biasing effect of attrition can be appreciated by comparing those lost to follow-up to those who completed follow-up with respect to baseline characteristics or follow-up data collected from other registers.

Analysis of the common cohort revealed that among patients lost to follow-up, there was a higher proportion of factors associated with poor prognosis such as pre-stroke functional dependency and decreased level of consciousness at presentation (Table 4.1), likely resulting in bias. To address this problem, we used multiple imputation (MI). On comparing the data set that included imputed data to a data set where cases lost to follow-up were simply omitted, we see that loss to follow-up was indeed likely associated with an underestimation in functional dependency (Figure 4.2).

Table 4.1 Comparison of selected baseline characteristics in respondents at all time points, and patients lost to follow-up on at least one occasion.

Presented as number (%) unless otherwise stated. Only patients alive at 3/5 years were included (n=11 591). Differences between groups were statistically significant for all variables (p<0.05).

SD=standard deviation.

	Respondents (n=6429)	**Lost to follow-up** (n=5162)
Sex (male)	3721 (57.9)	2802 (54.3)
Age (mean ± SD)	71 ± 11	70.4 ± 13
Diagnosis (ischemic stroke)	5827 (90.6)	4588 (88.9)
Independent before stroke	5964 (92.8)	4361 (84.5)
Living alone before stroke	2187 (34)	2412 (46.7)
Previous stroke	924 (14.4)	990 (19.3)
Level of consciousness at admission		
Alert	6017 (94.5)	4654 (91.2)
Drowsy	303 (4.8)	373 (7.3)
Comatose	44 (0.7)	75 (1.5)

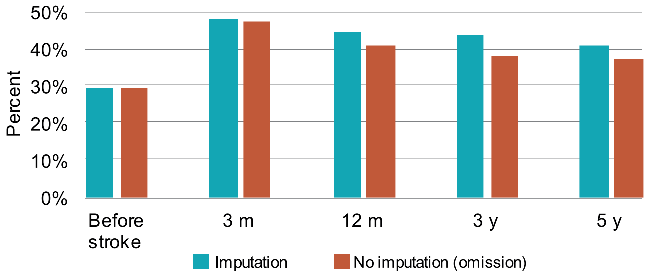


Figure 4.2 Comparison of the estimated proportion of dependency in ischemic stroke survivors at various time points using either multiple imputation or omission to handle loss to follow-up.
m=months, y=years.

Competing risks

This may occur when two events (one of which is the event of interest) are mutually exclusive. For example, when studying stroke-related death, death by other causes is a competing risk since it is not possible to have a stroke if already deceased.[219] In Kaplan-Meier survival analysis, cases are censored upon loss to follow-up for any cause and the assumption is that censoring is independent, i.e. that there are no systematic differences between those censored and those remaining in the study.

In Study IV, the probability of hospital readmission was estimated using the Kaplan-Maier method, and those that died without being readmitted were censored. Should they have lived, would the probability of them being readmitted be greater than in the remaining cohort? This is likely since these individuals were older and had a greater comorbidity burden. However, the proportion of patients that died without being readmitted was relatively small: 10.5% within five years post stroke compared to 74.0% that had been readmitted within the same period.

Misclassification bias

This occurs when the procedure to determine exposure or outcome is flawed, producing erroneous results.[216]

The modified Rankin Scale (mRS) was a key outcome measure in this thesis (used both for pre-stroke and post-stroke functional status) and there are several important potential sources of bias related to its use.

First, mRS scores were estimated from self-reported information rather than based on a standardized clinical assessment, which might have introduced reporting bias.

Secondly, the mRS was originally conceived for assessing post-stroke functional status only. Although the reliability of pre-stroke mRS has been shown to be comparable with standard mRS, there may be poor correlation with certain markers of function, suggesting limited validity.[220]

Thirdly, mRS was used to describe change in functional status over time. However, this scale is unable to capture subtle changes that may still be clinically important. Moreover, there were likely significant floor and ceiling effects: the algorithm used to calculate mRS scores does not differentiate between mRS 0–2 and consequently, all of these patients were lumped together into one single category of independents. Also, for severely dependent patients (mRS 5), any further deterioration cannot be accounted for using mRS.

An additional major potential for misclassification bias was the quantification of psychological well-being in Study V. Using a score analogous to the Short Form (36) Health Survey, the proportion of caregiver poor psychological well-being was estimated to be between 19.3 and 51.4%, depending on the pre-stroke functional status of the stroke survivor. The similarity of these results to the previously reported prevalence of depression of 30–52% in caregivers[131, 138] attests to the validity of this methodology.

Confounding

Confounding occurs when a perceived exposure-outcome relationship is actually caused by an additional factor that correlates with both exposure and outcome.[216]

Several adjustment variables were included to avoid confounding in multivariable analyses. For instance, all models were adjusted for age, which may otherwise have generated a perceived relationship between various covariates and the outcome of interest, e.g. between mortality and dementia, which are both associated with advanced age (Figure 4.3).

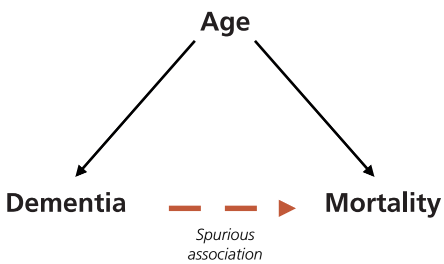


Figure 4.3 Illustration of confounding.

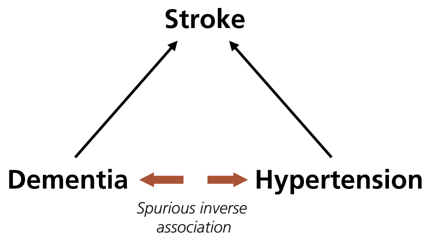


Figure 4.4 Illustration of collider bias.

Collider bias

This may occur when conditioning on an outcome (e.g. selecting only patients with stroke) induces dependence between risk factors, even when no actual association exists.[221, 222] For example, because dementia is a strong risk factor by itself, patients with this condition may require less of a contribution of risk from other factors (e.g. hypertension) compared with those without dementia, introducing a spurious inverse association (Figure 4.4).

Heterogeneity of data sources

When integrating data from multiple sources, differences in methodology, data quality, or coverage may result in misleading conclusions.

The Swedish National Patient Register (SNPR), our main source of data on comorbidity and hospital readmission, lacks data from primary care and thus the prevalence of conditions not requiring specialist or hospital care may have been underestimated. An important example is dementia, which is often diagnosed and managed solely in primary care. To remedy the potential for underestimation, data was also obtained from the Swedish Prescribed Drug Register on dementia-specific drug prescription. However, despite these efforts, the data included in this thesis shows a prevalence of only 6.3% in 75–84 year olds, and 8.0% in ≥85 year olds. The Swedish National Board of Health and Welfare has estimated the prevalence of dementia to be approximately 6% at ages 75–79 years, 13% at 80–84 years, 24% at 85–89 years, 34% at 90–94 years and 45% at 95 years and over.[223] Thus there was likely a considerable underestimation of prevalence of dementia, particularly in older individuals. This is supported by data from the Swedish Dementia Registry showing that patients diagnosed in primary care are older than those diagnosed at a specialist clinic.[224]

In Study III, information on post-stroke functional status was provided by the patient, whereas information on pre-stroke status was reported by hospital personnel. The use of multiple sources may explain why a small proportion of patients seemed to improve in functional status relative to their pre-stroke status.

Table 4.2 Survivor/caregiver agreement with respect to level of survivor dependency level. Cohen Kappa analysis.

Total per cent of complete agreement: 77.4%. Measure of agreement (kappa): 0.622 (p<0.001)

		Caregiver		
		Completely dependent	Partially dependent	Independent
Survivor	**Completely dependent**			
	Count (expected)	439 (77.8)	285 (253.7)	24 (416.5)
	Percentage of total	9.1%	5.9%	0.5%
	Partially dependent			
	Count (expected)	54 (196.3)	1233 (639.6)	599 (1050.1)
	Percentage of total	1.1%	25.5%	12.4%
	Independent			
	Count (expected)	10 (228.9)	121 (745.7)	2068 (1224.4)
	Percentage of total	0.2%	2.5%	42.8%

In Study V, data from both caregiver and survivor follow-up questionnaires were used. This allowed for a comprehensive assessment of the survivor/caregiver situation but was also a potential source of bias since caregivers and survivors may answer differently (reporting bias). Some items overlapped, and one such item, degree of survivor dependency, was used to test for survivor/caregiver responder agreement. A Cohen Kappa analysis gave a kappa-value of 0.622 indicating moderate to substantial agreement.[225] The percentage of complete agreement was 77.4% (Table 4.2).

Heterogeneity in research practices and reporting

In multimorbidity research, there is considerable heterogeneity in reporting practices. A review of comorbidity literature found a total of 150 included conditions in 39 different combinations.[226] Also, comorbidity index weights are dictated by the outcome variable of interest and there is no single gold standard index for studying both mortality and functional outcome.[146, 147, 152, 227] In this thesis, comorbidity burden was estimated based on number of conditions rather than a weighted index in order to make the results as generalizable as possible. However, this approach does not account for the varying severity of different conditions.

Another major issue relates to the definition of functional dependency, which may differ between studies. In the common cohort of this thesis, the proportion of pre-stroke dependent patients increased with age: 34% of those over 65 years and 50% of those over 80 years were pre-stroke dependent. Individuals receiving home care service, but not reporting need for help in specific domains of activities of daily living (ADL), were classified as functionally dependent. The Riksstroke surveys only include a limited set of ADL parameters and by including home care service, global functional impairment not otherwise identified could be captured. However, this substantially increased the proportion of dependent patients, particularly those of slight dependency. When only including individuals reporting dependency in a specific ADL domain, the proportion of dependent patients decreased to 21.5% and 31.0% in those over 65 and 80 years, respectively (Figure 3.1).

Generalizability of study results (external validity)

Generalizability (external validity) largely depends on the study setting since population characteristics and other factors may vary. For instance, there are significant geographical differences in the relative proportions of stroke subtypes. In East Asian countries there is a higher incidence of intracerebral haemorrhage,[228] and both atherosclerotic stroke and small vessel disease stroke are more common compared to other parts of the world.[229] Also, North American studies have reported increased incidence of stroke, particularly of atherosclerotic aetiology, among Hispanics and African-Americans compared to Caucasians.[230] Importantly, low to middle income countries differ from high-income countries in terms of healthcare resources and consequently, prognosis.[231] However, overall health status has also been shown to differ between high-income countries, and a recent study reported great variability in stroke services between European high-income countries, further complicating comparison.[232] For example, as illustrated in Figure 1.10, the proportion of functionally dependent elderly individuals is lower in the Swedish population than in other European countries.

The studies in this thesis were conducted in Sweden, a high-income country with a relatively universal social security system and a demographic composition dominated by persons of Scandinavian ethnicity. Consequently, the results are not generalizable to low and middle income countries and those with significantly different demographics.

4.3 Summary of the main strengths and weaknesses of the thesis

Strengths

- A comprehensive approach including comorbidity, pre-stroke functional status, readmissions, and the caregiver perspective.
- The recency of the data.
- A large patient material from an unselected national cohort (n=22 905).
- An extended follow-up period of up to five years.
- Reliable data sources with good coverage.
- Relatively low loss to follow-up of 12.7–21.2%.

Weaknesses

- No clinical assessment was made to determine functional status.
- No comorbidity data were available from primary care, which may have disproportionately affected the estimated prevalence of certain conditions.
- Results are not generalizable to low-to middle income countries.
- No in-depth sex-disaggregated analyses were performed.

5. General discussion

5.1 Main findings

This thesis demonstrates the serious nature of stroke. Despite major advances in management, a large number of people are severely affected both short-term and long-term. At five years post stroke, of all the patients studied in the thesis, 79.0% (intracerebral haemorrhage [ICH]), and 70.6% (ischemic stroke [IS]) were either deceased or functionally dependent (Study I). However, in ICH patients, there was a relatively high survival rate compared to previous research (Figure 5.1). This difference may be due to improved medical care over the last few decades. An increasing number of stroke patients are being treated at stroke units (in Sweden the proportion was 53.9% in 1995 compared to 87.5% in 2010[233]), and more people are receiving adequate primary and secondary prevention.

Secondly, the thesis illustrates the heterogeneity and complexity of stroke. The variation in patient characteristics and prognosis was thoroughly described in Studies I–III, each focusing on different key factors such as type of stroke, age, comorbidity, and disability. A high degree of pre-stroke disability (mRS 4–5), high comorbidity burden, and advanced age had a particularly large (negative) impact on prognosis. In addition to prognosis, healthcare utilization and the situation of informal caregivers was also investigated in the thesis. Study IV showed that a small proportion of patients with a high degree of comorbidity accounted for the majority of readmissions: approximately 20% of patients were responsible for 60% of readmissions, and 5% of patients were responsible for 25%. In Study V, substantial amounts of strain and unmet needs of support were reported by informal caregivers.

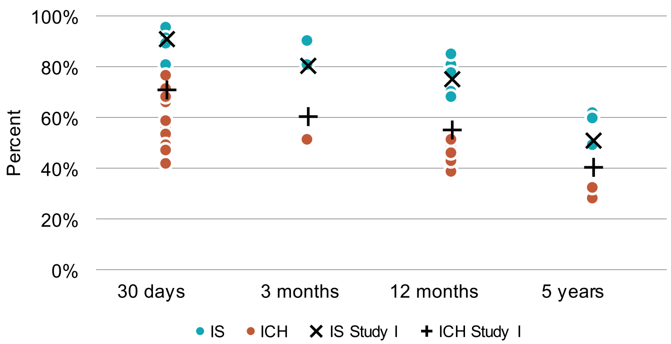


Figure 5.1 Survival in Study I compared to previous research.
Each dot denotes reported survival in individual previous studies (See appendix I for details).
ICH=intracerebral haemorrhage, IS=ischemic stroke.

5.2 Implication for care and policy

The thesis findings tie in to a wider discussion of healthcare organization and optimal use of resources. Such considerations are likely to increase in importance, partly due to demographic change. In 1950, the probability of an 80-year-old surviving to experience their 90-year birthday was on average 15–16% for women and 12% for men. In 2002, this probability had increased to 37% and 25%, respectively.[234] Figure 5.2 shows the projected proportion of Swedish citizens over 75 years of age until the year 2050,[235] with a large increase in the very old (over 90 years of age).

The aggregate effect on demand for healthcare and support is difficult to estimate, as there are a multitude of factors at play with opposing effects. For instance, whereas research has suggested a development towards a reduction in disability in the elderly, likely due to advances in medical care and changes in socioeconomic factors,[236, 237] a simultaneous increase in chronic disease has been observed.[238, 239] Importantly, age-adjusted stroke incidence and mortality is decreasing in many high-income countries, which may be sufficient to out-pace the growth and ageing of the population.[6, 7, 240] But as the risk of dying following a stroke is decreasing, there is an increase in the number of survivors with varying degrees of functional impairment.[241]

What is clear however is that continued improvement in prevention and long-term management, particularly in those of advanced age, with disability, and/or other chronic conditions, will continue to be important for reducing stroke morbidity.

Below, four major topics (multimorbidity, functional dependency, complex needs, and informal caregiving) are elaborated upon in the context of healthcare development and research. Additional research priorities are also suggested.

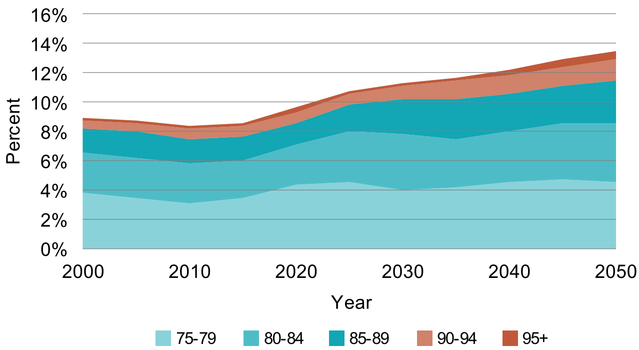


Figure 5.2 Projected proportion of Swedish citizens 75 years of age or older, 2000–2050.

Multimorbidity

Multimorbidity has received little attention despite its fundamental clinical and economic impact,[154] and current literature is sparse. Also, scientific reporting is heterogeneous, largely due to methodological differences, making it difficult to correctly gauge and address the issue.[42] Stratification and prognostication in stroke have mainly relied on clinical variables from the acute setting and a few other known risk factors, but important intrinsic factors such as comorbidity have largely been overlooked.[242] Study II and III highlights the ubiquity and prognostic importance of comorbidity in stroke patients, who are often high healthcare consumers (as shown in Study IV). The care of multimorbid patients is complex and multiple services are frequently involved, each with separate management plans, which increases the risk of fragmentation, dilution of responsibility, polypharmacy and increasing costs.[154, 243] Most healthcare systems are designed around the treatment of single conditions and simply adhering to the guidelines for every condition in patients with complex multimorbidity is often unmanageable.[244] A gravitation towards a patient-centred approach that takes into account all medical and non-medical factors to tailor care to the patient has been suggested.[245] This will likely require healthcare structural changes, which may include strengthening primary care. Further, there is a known tendency for conditions sharing a common aetiology, such as combinations of cardiovascular and metabolic conditions, to co-occur[42, 43] which was shown specifically in stroke patients in Study II. This further highlights the potential benefit for coordinating care across medical services.

Pre-stroke functional dependency

In the common cohort of this thesis, there was a high proportion of pre-stroke dependency, which increased with age: 34% of those over 65 years and 50% of those over 80 years were pre-stroke dependent. This included patients that received home care service but did not report dependency in a specific ADL domain. When excluding these particular individuals, the numbers decreased to 21.5% and 31.0% in those over 65 and 80 years, respectively. However, these proportions were still substantially higher compared to the general Swedish population where corresponding proportions have been estimated to be 11.1% and 21.6%, respectively (defined as dependent in at least one ADL domain).[149]

Study III demonstrated substantial differences within the large group of patients with pre-stroke dependency, both in characteristics and prognosis. In those of severe dependency, comorbidity burden was higher, drug prescription was lower, and prognosis less favourable, whereas in those with moderate pre-stroke dependency, a relatively large proportion survived and maintained their pre-stroke functional level. Also, the results of this study suggest that pre-stroke dependents might be under-treated, for example that oral anticoagulants (OAC) may be under-prescribed, which has also been suggested by previous research.[246] However, since treatment is affected by many factors such as risk versus benefit considerations, no such conclusions can be drawn with certainty based on the data presented in this thesis. Moreover, in the most recent Riksstroke data, the prescription of OAC has increased substantially, particularly for non-vitamin K antagonist oral anticoagulants (NOAC),[35] which in this thesis comprised a very modest proportion of total OAC prescriptions.

A relatively small proportion (4.2%) of pre-stroke dependents received thrombolytic therapy. However, acute interventional therapy in stroke is in rapid development and the patients studied in this thesis had their index stroke before major revisions of the Swedish national guidelines in 2014. Thrombolysis rates have now increased substantially in the elderly, reaching 12% in those >80 of age in 2018[35] compared to 4.6% in the thesis cohort. But while several studies support the effectiveness of thrombolytic therapy in those with pre-stroke disability,[179-181] evidence is limited regarding efficacy and safety in particular subgroups (e.g. those with dementia or severe disability). European guidelines state that acute intervention should primarily be reserved for those without pre-stroke disability, pointing to an absence of evidence to support specific recommendations in those with pre-stroke mRS ≥2.[247]

The findings in this thesis highlight the need for stratification in both clinical management and research with respect to dependency level in stroke patients with pre-existing disability.

Complex needs

Many stroke patients are frail, some already prior to their stroke and many as a consequence of it. Important factors associated with frailty are disability, comorbidity, and advanced age. Frailty leads to increased vulnerability to the effects of physiological stressors such as stroke. These individuals tend to have lower baseline functional status and are left with greater residual impairment as a consequence of stroke (illustrated in Figure 5.3). The needs of this group are highly variable and often complex, which warrants a structured and comprehensive approach. This might include frailty assessment, post-stroke checklists, community-based multidisciplinary teams, and continuous contact with the same healthcare provider.

Routine frailty assessment in selected patients has proven useful in identifying high-risk individuals.[165] Frailty is a dynamic condition and can be prevented or at least slowed by interventions,[248] and as a consequence stroke incidence can also be reduced.[249] Although evidence is sparse,[250] several interventions in the primary care setting have been shown to be effective.[251, 252]

Post-stroke checklists, which can be modified for long-term care,[253] are feasible and useful,[182, 183] but are not yet widely implemented in clinical practice.

Multidisciplinary teams are now considered standard of care in the inpatient

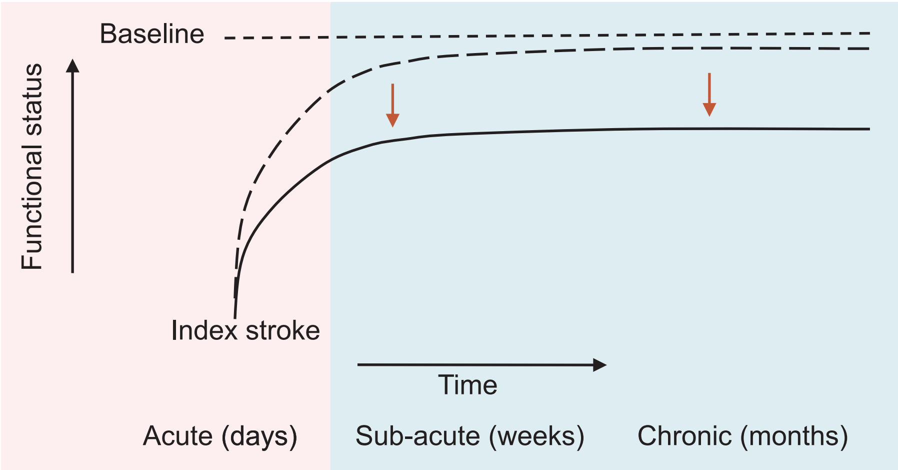


Figure 5.3 Illustration of functional status after stroke in frail individuals (solid line) as compared to those without frailty (dashed line).

setting, but are not well implemented in community-based care.[175] Also, continuous contact with the same heathcare provider allows for a sense of stability, improves patient satisfaction, particularly in patients with complex medical needs,[254] and reduces the number of visits at the emergency department.[255]

Informal caregivers

While informal caregivers are instrumental in post-stroke care and recovery, it is not uncommon for them to feel marginalized and disconnected from the care process.[256] Study V demonstrated significant strain and poor psychological wellbeing in this group but only 20.8% of caregivers of completely dependent survivors received formal caregiver support, and 18.1% were unaware of the existence of such a support program. This is not unique for Sweden; caregiver support programs are poorly developed in many comparable high-income countries.[189]

Informal caregivers constitute an enormous hidden workforce, and the cost of effective support programs is likely low compared to the potential cost of caregiver burnout (the opportunity costs of informal caregiving has been shown to be high[188]). Caregiver support has been recognized as an important area for research and development,[170] and efforts to integrate and support informal caregivers needs to be accelerated. Furthermore, in this thesis, only 4% and 9.3% of caregivers of partially and completely dependent survivors, respectively, were in contact with patient associations. Initiatives from civil society need to be encouraged and better integrated as a complement to formal care.

5.3 Additional suggestions for future research priorities

First, stroke prognosis is a moving target and there is need for continuous epidemiologic surveillance and updated reports.

Second, while the implementation of OAC and thrombolytic therapy has greatly improved prognosis in IS, there are currently few treatment options for ICH patients, who have a less favourable prognosis.

Third, the needs of stroke patients and caregivers change over time and providing adequate support across the care continuum is important.[257] In the acute and sub-acute phases, needs are largely stroke-specific and patients are often managed at specialized neurology clinics. In the longer term however, the responsibly for care and support is gradually transitioned to other providers, often primary care and local municipalities. This is the period where multimorbidity and complex needs (some of which are stroke-related and others are not) may become more apparent. Longitudinal research describing long-term needs is sparse and there is a need for evidence supporting providers and decision-makers.

Fourth, while stroke incidence and mortality is decreasing in many high-income countries, the impact of stroke in low and middle income countries is likely to increase dramatically in the near future. The population ≥60 years of age in less developed regions is projected to increase to almost 1.6 billion in 2050 from 554 million in 2013, and there is uncertainty as to how changes in lifestyle and prevalence of chronic diseases will affect risk and dynamics of stroke.[148] There is need for further research describing prognosis in different countries and exploring potential long-term management strategies adapted to local conditions.

Last, in-depth sex-disaggregated analyses were outside the scope of this thesis. However, this perspective needs to be explored further, particularly differences in comorbidity patterns.

6.
Conclusions

6.1 Study I

At five years after stroke, more than two out of three patients with ischemic stroke and more than three out of four patients with intracerebral haemorrhage were either deceased or functionally dependent. Although there have been major advances in short-term and long-term stroke care in recent decades, further improvement is needed, particularly in intracerebral haemorrhage where there are currently few therapeutic options available.

6.2 Study II

Comorbidity was common in stroke and had strong prognostic implications both for mortality and function at all ages. A comprehensive approach to stroke care that includes comorbidity as a key component is warranted.

6.3 Study III

There was great heterogeneity among pre-stroke dependent patients. In those of severe dependency, comorbidity burden was higher, drug prescription was lower and prognosis less favourable. Research efforts and treatment strategies needs to address patients of different pre-stroke levels of dependency separately.

6.4 Study IV

Approximately 20% of patients were responsible for 60% of readmissions, and 5% of patients for 25%. Patients with a greater number of readmissions had more comorbidity and displayed a somewhat different pattern of readmission causes. There is a need for better support for comorbid stroke patients in the community setting, and further research describing healthcare utilization patterns in this group.

6.5 Study V

A higher degree of dependency in the stroke survivor was associated with caregiver strain and poor psychological well-being. The study results emphasize the need for integrating support aimed specifically at informal caregivers, preferably at an early stage, to avoid preventable caregiver strain and to optimize survivor care.

6.6 The thesis in two sentences

A large degree of heterogeneity among stroke patients was reflected in substantial variation in prognosis and needs. This warrants a stratified and comprehensive approach to long-term support, healthcare, and research, which should include not only stroke patients but also their informal caregivers.

Sammanfattning på Svenska

Stroke är en mycket vanlig sjukdom och idag räknar man med att det finns över 140 000 drabbade i Sverige som lever med varierande grad av funktionell nedsättning. Prognosen efter stroke påverkas av många olika faktorer varav flera tidigare inte fått så mycket uppmärksamhet. Den här avhandlingen ämnar ge en heltäckande bild av långtidsprognosen och varje delarbete fokuserar på olika viktiga aspekter såsom samsjuklighet, funktionsnedsättning innan stroke, återinläggningar samt de anhörigas situation.

Projektet bygger på data från Riksstroke, det svenska kvalitetsregistret för strokesjukvård, och mer specifikt en långtidsuppföljning som genomfördes år 2016 av patienter som insjuknat tre eller fem år tidigare (över 22 000 inkluderade patienter) och deras anhöriga. Data har även inhämtats från bland annat Patientregistret, SCBs befolkningsregister samt Läkemedelsregistret.

Delarbete 1 beskriver överlevnad och funktionsförmåga upp till fem år efter ischemisk stroke respektive hjärnblödning (vilket också räknas som en typ av stroke). Både överlevnad och funktionsförmåga var lägre för hjärnblödning vid samtliga uppföljningstillfällen. Efter fem år var hela 79 % av dessa patienter avlidna eller beroende av hjälp i vardagen jämfört med 70,6 % av de som drabbats av ischemisk stroke.

Delprojekt 2 fokuserar på samsjuklighet vid stroke och den prognostiska betydelsen av detta. Samsjuklighet definieras som de kroniska tillstånd patienter har utöver att ha drabbats av en stroke. Ca 75% av alla patienter i studien hade någon form av samsjuklighet och andelen döda eller funktionellt beroende steg kraftigt med grad av sjukdomsbörda. Bland enskilda sjukdomar var demens starkast associerad med dålig prognos följt av njur- och hjärtsvikt.

Delprojekt 3 beskriver karaktäristika, behandling och prognos för strokepatienter som redan innan insjuknandet var beroende av hjälp och stöd i vardagen. Arbetet visade på stora olikheter inom den här gruppen: sämre funktionsförmåga innan stroke var associerat med mer samsjuklighet, mindre medicinering och sämre prognos.

Delprojekt 4 kartlägger återinläggningar på sjukhus under de fem första åren efter stroke. Återinläggning var mycket vanligt, i synnerhet under de första sex månaderna, och en liten grupp individer med hög grad av samsjuklighet stod för den allra största delen. Ungefär 20% av patienterna visade sig stå för 60% av återinläggningarna. Den totalt sett dominerande orsaken till återinläggning var kardiovaskulära sjukdomar men orsaker varierade över tid och mellan patienter med få respektive många återinläggningar.

Delprojekt 5 beskriver de anhörigas situation. Den stora mängden hjälp och stöd de gav den strokedrabbade var associerat med påtagliga begränsningar och psykisk ohälsa. I gruppen anhöriga till drabbade med mycket stora behov kunde över 40 % inte lämna den drabbade längre än en timme i taget, 23 % hade behov av mer stöd för egen del och över hälften uppgav psykisk ohälsa.

Sammanfattningsvis beskriver avhandlingen långtidsprognos efter stroke ur många olika perspektiv utifrån ett stort och tillförlitligt material. Resultaten understryker komplexiteten och variabiliteten hos strokepatienter vilket kommer till uttryck i stora skillnader i prognos, återinläggningsmönster, och påverkan på anhöriga. Ett gott omhändertagande i det längre perspektivet kräver därför ett stratifierat tillvägagångssätt där patienter med olika egenskaper och förutsättningar hanteras olika. Det är också nödvändigt med en helhetssyn där många olika faktorer (såsom funktionsnedsättning och samsjuklighet) tas i beaktan. Dessutom visar resultaten på betydelsen av att även stödja anhöriga som ofta står för den allra största vårdinsatsen.

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As a young medical doctor, the first years of practicing medicine are crucial. During my internship I spent six months working at the primary care clinic Kärråkra in Eslöv, a small rural community outside of Lund. This has been the most rewarding experience of my career so far. I thank the senior physicians and the other staff members for their willingness to share their knowledge, and for their concern for providing quality healthcare. Also, I thank my colleagues at various clinics at Lund University Hospital, particularly at the Neurology clinic, for their support and guidance.

I like numbers and it has been fantastic to have had access to an accomplished statistician such as Mats Pihlsgård. He has enthusiastically shared his expertise and helped me understand how to best approach my data.

It is essential that a thesis looks good. I want to thank Gunilla Albertén for her help in typesetting and overall design, and Frida Nilsson for illustrations, both at Media-Tryck, Lund University. You have done an amazing job in making my vision a reality. Also, I am grateful to Annika Carlsson, the artist behind the beautiful cover illustrations.

It is also important that the text flows nicely without the occasional errors of a non-native English speaker such as myself. Without the help of the excellent proof-reader Lee Nolan, this thesis would be a far less appetizing read.

I also want to thank the staff at Riksstroke, in particular statistician Fredrik Jonsson, for preparing the data from Riksstroke, Professor Sölve Elmståhl, Lund University, for comments on well-being measures, and Professor Jonas Björk, Lund University, for comments on my text describing bias.

Finally, this thesis includes data from the Survey of Health, Ageing and Retirement in Europe. See Börsch-Supan et al. and Bergmann et al. for details.[258, 259]

Appendix

Appendix I Compilation of community-based studies reporting short and long-term stroke mortality. Percent was presented as integers. Only studies from 1990 forward with at least a no. of 40 were included. d=days, m=months, y=years.

					Survival at different time points			
	Author	**Country**	**no.**	**Year**	**30 d**	**3 m**	**12 m**	**5 y**
All stroke	Brønnum-Hansen et al.[86]	Denmark	4162	2001	72%		59%	40%
	Appelros et al.[96]	Sweden	377	2003			67%	
	Feigin et al.[97]	New Zeeland	1938	2010				51%
	Wolfe et al.[88]	USA	3373	2011	72%		64%	43%
	Hankey et al.[98]	Australia	370	2002	77%			65%
	Corraini et al.[89]	Denmark	201 691	2018	85%			52%
	Dennis et al.[90]	UK	675	1993	81%		69%	55%
	Anderson et al.[91]	Australia	536	1993	76%			
	Kolominsky-Rabas et al.[92]	Germany	354	1998	81%	72%	63%	
	Thrift et al.[93]	Australia	276	2001	80%		63%	
	Vemmos et al.[94]	Greece	555	2000	74%		43%	
	Carolei et al.[95]	Italy	819	1997	74%		63%	
Ischemic stroke	Ganesh et al.[105]	UK	1606	2017	89%		80%	61%
	Brønnum-Hansen et al.[86]	Denmark	4162	2001	79%			
	Corraini et al.[89]	Denmark	201 691	2018				59%
	Andersen et al.[104]	Denmark	251 23	2009	95%	89%		
	Hartmann et al.[103]	USA	980	2001	95%		84%	59%
	Dennis et al.[90]	UK	545	1993	90%		77%	48%
	Anderson et al.[91]	Australia	380	1993	88%			
	Kolominsky-Rabas et al.[92]	Germany	278	1998	89%	80%	70%	
	Thrift et al.[93]	Australia	200	2001	88%		69%	
	Vemmos et al.[94]	Greece	447	2000			49%	
	Carolei et al.[95]	Italy	656	1997	80%		68%	
Intracerebral hemorrhage	Dennis et al.[90]	UK	66	1993	48%		38%	30%
	Fogelholm et al.[107]	Finland	411	2005			42%	27%
	Jakovljevic et al.[260]	Finland	909	2001			45%	
	Hillen et al.[108]	UK	222	2003			50%	32%
	Thrift et al.[93]	Australia	40	2001	55%		50%	
	Anderson et al.[91]	Australia	59	1993	70%			
	Kolominsky-Rabas et al.[92]	Germany	48	1998	58%	50%	42%	
	Labovitz et al.[101]	USA	155	2005	65%			
	Khan et al.[100]	Sweden	699	2005	67%			
	Vemmos et al.[94]	Greece	77	2000	53%		47%	
	Carolei et al.[95]	Italy	122	1997	48%		42%	
	Bejot et al.[99] 1	France	87	1989	57%			
	Bejot et al.[99] 2	France	94	1994	41%			
	Bejot et al.[99] 3	France	97	1999	46%			
	Bejot et al.[99] 4	France	102	2004	76%			

Appendix II Overview of corresponding items on psychological well-being in the Short Form (36) Health Survey (SF-36) mental health component versus the Riksstroke caregiver questionnaire.

In SF-36, five items are used to construct a mental health score. Those items that correspond completely with items in the Riksstroke caregiver questionnaire are highlighted turquoise. All questions begin with the phrase "How much of the time in the past 4 weeks have you felt…". The Riksstroke items were translated into English by the authors of paper V.

SF-36 mental health component	Riksstroke caregiver questionnaire
Have you been a very nervous person?	Anxious and worried?
So down in the dumps that nothing could cheer you up?	-
Calm and peaceful?	Calm and peaceful?
Downhearted and blue?	Downhearted and blue?
Have you been a happy person?	-

Appendix III The Yule's Q formula.

V denotes presence of condition 1 (0=no, 1=yes) and U denotes presence of condition 2 (0=no, 1=yes).

	V=0	V=1
U=0	a	b
U=1	c	d

$$Q = \frac{ad - bc}{ad + bc}$$

Appendix IV Proportion of mRS scores in survivors at different time points, in original versus imputed data sets.

In the original data sets, cases lost to follow-up were omitted. In the imputed data sets, missing data were replaced with imputed values. Five imputations were performed and a mean was calculated. The mean, lowest, and highest scores in the five individual imputations are presented.

mRS=modified Rankin Scale.

		Original data	Imputed data		
			Mean	**Lowest**	**Highest**
3 months	Independent (mRS 0–2)	51.7%	51%	50.8%	51.2%
	mRS 3	22.2%	22.7%	22.6%	22.8%
	mRS 4	14.3%	14.2%	14.1%	14.4%
	mRS 5	11.8%	12%	11.9%	12.1%
12 months	Independent (mRS 0–2)	58.7%	54.7%	54.6%	54.9%
	mRS 3	18.7%	20.4%	20.3%	20.5%
	mRS 4	14.9%	15.6%	15.4%	15.8%
	mRS 5	7.6%	9.2%	9.1%	9.4%
3 years	Independent (mRS 0–2)	61%	56.1%	55.1%	57.1%
	mRS 3	18.8%	19.8%	19.2%	20.6%
	mRS 4	14%	16%	15.3%	16.7%
	mRS 5	6.2%	8.1%	7.9%	8.3%
5 years	Independent (mRS 0–2)	62.2%	59.1%	58%	60.5%
	mRS 3	17.6%	18.7%	18.3%	19.1%
	mRS 4	14.4%	15.1%	14.4%	15.7%
	mRS 5	5.8%	7%	6.7%	7.3%

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