Aspects on Stroke Outcome

Survival, functional status, depression and sex differences in Riks-Stroke, the National Quality Register for Stroke Care

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Umeå 2008
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Abstract

Stroke is a major cause of death and disability worldwide. In Sweden, about 30,000 strokes occur each year. The aim of this thesis was to analyse survival, functional outcome and self-reported depression after stroke, and to explore possible differences between men and women in stroke care and outcome.

These studies were based on Riks-Stroke, the Swedish national quality register for stroke care. Information on background variables and treatment were collected during the hospital stay. The patient’s situation and outcome after stroke were followed-up after 3 months. Long term survival was retrieved from the Swedish Population Register (Folkbokföringen).

Possible sex-differences in stroke care and outcome 3 months after stroke were explored in 24,633 strokes, registered during 2006. In conscious patients, the proportions treated at stroke units were similar for men and women. Men and women had equal chance to receive thrombolytic therapy or secondary prevention with oral anticoagulants. Compared to men, women were less likely to develop pneumonia, but more likely to experience deep venous thromboses and fractures during hospital stay. Women had worse 3-month survival and functional outcome, differences that were explained by their higher age and impaired level of consciousness on admission. Women felt more depressed and perceived their health as worse than men did. Women were also less satisfied with the care they had received in the hospital.

The agreement between self-reported functional outcome 3 months after stroke and the commonly used modified Rankin Scale (mRS) was explored in 555 stroke survivors from 4 hospitals during May-September 2005. Riks-Stroke’s self-reported questions classified 76% of the patients into correct mRS grade.

The association between functional outcome 3 months after stroke and 3-year survival was assessed in 15,959 men and women who had had a stroke during 2001-2002. Patients with estimated mRS grades 3, 4 and 5 had hazard ratios for death of 1.7, 2.5 and 3.8, respectively, as compared with patients with lower grades, 0-2. Depressed mood, male sex, high age, diabetes, smoking, antihypertensive therapy at onset and atrial fibrillation were also identified as predictors of poor survival.

Self-reported depression 3 months after stroke and use of antidepressants were analysed in 15,747 stroke survivors from 2002. Fourteen percent felt depressed 3 months after stroke. Female sex, age <65, previous stroke, living alone or in institution, or being dependent in activities of daily living (ADL) were factors associated with self-reported depression. At the follow-up, 22% of the men and 28% of the women were using antidepressant medication, which were approximately twice as many as in the general population. Still, 8% of all patients in Riks-Stroke reported depressive mood but no treatment with antidepressants.

In conclusion, men and women with stroke in Sweden experience similar treatment and outcome in most aspects. Patient-reported functional outcome can be reliably transformed to a standard disability scale. Impaired functional outcome three months after stroke is an independent predictor of poor long-term survival. Depressive mood is common after stroke and is associated with poor survival and impaired functional outcome.

Key words: stroke, stroke outcome, registry, sex differences, case fatality, functional recovery, depression
Sammanfattning på svenska  
(Swedish summary)

Stroke är en av de vanligaste orsakerna till död och funktionshinder i världen. Bara i Sverige inträffar varje år ca 30 000 insjuknanden i stroke. Målet med den här avhandlingen var att undersöka överlevnad, funktionshinder och nedstämdhet efter stroke, samt att undersöka skillnader i behandling och utfall mellan män och kvinnor.

Dessa undersökningar är baserade på material från Riks-Stroke, som är kvalitetsregistret för strokesjukvård i Sverige. I registret samlades information om bakgrundvariabler och behandling under sjukhusvistelsen. Patienternas situation och utfall följdes sedan upp efter 3 månader. Information om överlevnad på lång sikt inhämtades från folkbokföringen.


Överensstämmelsen mellan patienternas självrapporterade funktionsstatus 3 månader efter stroke och en skala som ofta används för att fastställa funktionsgrad, modified Rankin Scale (mRS), analyserades i 555 individer. De kom från 4 sjukhus och insjuknade under perioden maj-september 2005. De egenrapporterade frågorna från Riks-Stroke klassificerade 76% av patienterna till korrekt mRS-grad.

Sambandet mellan funktionsförmåga 3 månader efter stroke och överlevnad upp till 3 år efter insjuknandet undersöktes i 15 959 kvinnor och män som fick stroke under 2001-2002. Patienter med måttliga till allvarliga funktionshinder (mRS 3, 4 eller 5) hade sämre överlevnad än patienter med inga eller lättare funktionshinder (motsvarande 1.7, 2.5, respektive 3.8 gånger ökad risk jämfört med patienter med mRS 0-2). Nedstämdhet, manligt kön, hög ålder, diabetes, rökning, behandling för högt blodtryck före insjuknandet och förmaksliminer var också relaterade till sämre överlevnad.

Nedstämdhet och användning av antidepressiva preparat 3 månader efter stroke analyserades i 15 747 individer som drabbades av stroke under 2002 och överlevde. Fjorton procent kände sig nedstämda 3 månader efter stroke. Kvinnligt kön, ålder under 65 år, tidigare stroke, boende ensam eller på institution, eller beroende av hjälp för att utföra aktiviteter som rör det dagliga livet var också kopplade till nedstämdhet. Vid uppföljningen rapporterade 28% av kvinnorna och 22% av männen...
att de använde antidepressiva preparat, vilket är ungefär dubbelt så många som
generellt i Sveriges befolkningen i samma åldersgrupp. Trots det så kände sig 8% av
alla patienter i Riks-Stroke ofta eller ständigt nedstämda utan att ha någon behand-
ling för depression.

Sammanfattningsvis så visade studierna att män och kvinnor får liknande vård och
har liknande utfall i de flesta avseenden. Patientens rapportering av funktionsför-
måga går att översätta till en standard-skala för skattning av funktionsstatus. Ned-
satt funktionsförmåga 3 månader efter stroke är en oberoende prediktor för sämre
långtidsöverlevnad. Nedstämdhet efter stroke är vanligt förekommande och är rela-
terad till sämre överlevnad och nedsatt funktionsförmåga.
# List of abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>ADL</td>
<td>Activities of Daily Living</td>
</tr>
<tr>
<td>AF</td>
<td>Atrial Fibrillation</td>
</tr>
<tr>
<td>ASA</td>
<td>Acetyl Salicylic Acid</td>
</tr>
<tr>
<td>ATC</td>
<td>Anatomical Therapeutic Chemical</td>
</tr>
<tr>
<td>BI</td>
<td>Barthel Index</td>
</tr>
<tr>
<td>CES-D</td>
<td>Center for Epidemiologic Studies-Depression short form</td>
</tr>
<tr>
<td>CF</td>
<td>Case Fatality</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence Interval</td>
</tr>
<tr>
<td>CT</td>
<td>Computerized Tomography</td>
</tr>
<tr>
<td>DDD</td>
<td>Defined Daily Doses</td>
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<tr>
<td>DSM</td>
<td>The Diagnostic and Statistical Manual of Mental Disorders</td>
</tr>
<tr>
<td>ESD</td>
<td>Early Supported Discharge</td>
</tr>
<tr>
<td>HR</td>
<td>Hazard Ratio</td>
</tr>
<tr>
<td>ICD</td>
<td>International Classification of Diseases</td>
</tr>
<tr>
<td>ICF</td>
<td>International Classification of Functioning, Disability and Health</td>
</tr>
<tr>
<td>ICH</td>
<td>Intracerebral Haemorrhage</td>
</tr>
<tr>
<td>IS</td>
<td>Ischaemic Stroke</td>
</tr>
<tr>
<td>MADRS</td>
<td>Montgomery Åsberg Depression Rating Scale</td>
</tr>
<tr>
<td>mRS</td>
<td>modified Rankin Scale</td>
</tr>
<tr>
<td>OR</td>
<td>Odds Ratio</td>
</tr>
<tr>
<td>Prime-MD</td>
<td>Primary Care Evaluation of Mental Disorders</td>
</tr>
<tr>
<td>RLS</td>
<td>Reaction Level Scale</td>
</tr>
<tr>
<td>SAH</td>
<td>Subarachnoidal Haemorrhage</td>
</tr>
<tr>
<td>SIGH-D</td>
<td>Structured Interview Guide for the Hamilton Depression Rating Scale</td>
</tr>
<tr>
<td>TIA</td>
<td>Transient Ischaemic Attack</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organisation</td>
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</tbody>
</table>
Original papers

This thesis is based upon the following papers:


Original papers have been reproduced with permissions from Lippincott Williams & Wilkins, Baltimore (Papers II and IV) and S. Karger AG, Basel (Paper III).
1 Introduction

More than five million people died from stroke in 2001, which was a tenth of all deaths worldwide. In high-income countries, stroke is the third most common cause of death after ischemic heart disease and cancer. It is also the second most common cause of disability. In Sweden, about 30 000 strokes occur each year of which three quarters affect men and women with no previous stroke. The outcome is often severe. Three months after stroke one in five patients has died and a third of the surviving patients are dependent in primary activities of daily living.

Stroke

The World Health Organization (WHO) defines stroke as rapidly developing clinical signs of focal (or global) disturbance of cerebral function, with symptoms lasting 24 hours or longer or leading to death, with no apparent cause other than of vascular origin. This definition excludes patients with transient ischemic attack (TIA), and patients with cerebral symptoms from subdural haemorrhage, trauma or tumours.

Stroke results from an interruption of the brain perfusion causing damage to the brain tissue. The majority of strokes are ischaemic and account for about 80% of all strokes whereas intracerebral and subarachnoidal bleedings account for about 20% of all strokes. Ischaemic strokes may be caused by thrombi, a local clot of blood blocking a brain-artery, or by emboli, most frequently originating from the heart or the carotid arteries, obstructing blood flow to parts of the brain. An intracerebral haemorrhage occurs when an artery, within the brain parenchyma, ruptures. Subarachnoidal haemorrhages are most commonly caused by the rupture of an aneurysm or a vascular malformation. Subarachnoidal haemorrhage differs with respect to pathogenesis and epidemiology and has not been considered in this thesis.

Stroke epidemiology

Women, on average, are older than men when they have their strokes (Figure 1). The mean age was 77.8 years in female and 73.2 in male stroke patients in Sweden 2001. This difference is in accordance with that in a review by Feigin et al., where the mean age at stroke onset was 74.8 years among women and 69.8 among men. The same study estimated the stroke prevalence, i.e. the number of people who had had a stroke, to 5-10 per 1000 individuals in different populations, increasing with age.

Studies from different populations show inconsistent time trends regarding stroke incidence and case fatality. In Finland, the case fatality did not change significantly while the incidence decreased. A decrease in incidence has also been observed in New Zealand. Stable incidence as well as stable case fatality have been reported in the USA while studies from France, Lithuania and Sweden suggest a stable stroke incidence and a decreasing case fatality. All together, when the ageing of populations leading to more people entering more stroke-prone age-groups is taken...
into consideration, the disease-burden of stroke is likely to increase rather than decrease in several countries around the world. That includes Sweden.

![Figure 1. The age distribution of stroke patients in Riks-Stroke 2006](image)

**Major risk factors for stroke**

Risk factors for stroke may be divided into modifiable and non-modifiable. Non-modifiable risk factors for stroke include age, sex, ethnicity, low birth weight and heredity. Hypertension, smoking, cardiovascular disease, diabetes, asymptomatic carotid stenosis, atrial fibrillation, dyslipidemia, unhealthy diet, obesity, physical inactivity and postmenopausal hormone therapy are established modifiable risk factors for stroke. The Swedish national guidelines for stroke care recognized the first two, hypertension and smoking, as the most important modifiable risk factors since they are associated with a clearly increased risk, are common in the population, and intervention is known to decrease the risk. The risk for stroke increases approximately 30% per 10 mm increment in systolic blood pressure, while smoking nearly doubles the risk for stroke. Approximate relative risk of stroke for an individual, and the estimated number of strokes in the population attributable to each factor are presented for a selection of risk factors in Figure 2.
Several of the risk factors have synergistic effects that may further enhance the risk of cardiovascular death. The SCORE-system\textsuperscript{19} was developed to help identify people with high risk of cardiovascular death (stroke or myocardial infarction) within 10 years. It combines the factors age, sex, smoking, blood pressure and total cholesterol.

The risk factors for stroke are essentially the same for men and women.\textsuperscript{23} Of those who have had a stroke, men are at higher risk of having a recurrent stroke.\textsuperscript{24} Women with diabetes have a worse prognosis after stroke than men with diabetes\textsuperscript{23} and the impact of smoking is also higher in women.\textsuperscript{21, 26}

**Fundamentals of stroke prevention and treatment**

**Primary prevention**

Everybody benefits from positive life-style changes such as reduced or cessation of smoking, increased physical activity, weight-reduction if overweight and introduc-
tion of a more healthy diet. People with previous cardiovascular disease, several risk factors, one or more highly elevated risk factor or diabetes are at high risk of stroke. In those individuals, medical treatment with lipid- and blood pressure-lowering drugs are motivated.\textsuperscript{15, 16} In general, treatment with antiplatelets or oral anticoagulants are recommended for patients with atrial fibrillation.\textsuperscript{15, 16} Surgery is indicated for a selection of patients with asymptomatic carotid artery stenosis.\textsuperscript{17}

**Acute treatment**

*Medical management*

It is important to minimize the delay from stroke onset to hospital arrival and diagnosis. Routine acute assessments include medical history, neurological examination, laboratory tests, ECG, and computerized tomography (CT). MRI may be preferred for those patients who have symptoms from cerebellum or the brain stem (posterior fossa). In patients diagnosed with acute ischaemic stroke, thrombolytic therapy within three hours from onset has been shown to improve outcome.\textsuperscript{19} Currently, only 4\% of the patients with ischemic stroke in Sweden receive thrombolytic therapy. As many as a quarter of all patients may be eligible for thrombolytic treatment if they arrive to hospital without delay.\textsuperscript{20} Antiplatelet therapy with ASA is recommended for patients with ischaemic stroke,\textsuperscript{22} and has a small but clinically relevant effect in reducing the risk of recurrent ischaemic stroke and improving long-term outcome.\textsuperscript{30}

*Stroke unit care*

Organized stroke unit care has been shown to improve survival, reduce dependency and reduce the need for institutional care.\textsuperscript{31-33} It includes several components and may be defined as care in a dedicated ward provided by a multidisciplinary team of stroke specialists caring exclusively for stroke patients.\textsuperscript{32} Stroke unit care can be characterised by:

- An area of the hospital dedicated to stroke patient care
- A multidisciplinary team including medical, nursing, physiotherapy, occupational therapy and speech therapy staff with regular meetings at least once per week
- Educational program for staff, and medical and nursing staff specialised in stroke and/or rehabilitation
- Detailed information on stroke disease, rehabilitation and recovery to patients and care-givers
- Early mobilisation and rehabilitation of the patient
- Comprehensive assessment of common problems to prevent and to attend to possible complications

*Secondary prevention*

The principle for secondary prevention is in many aspects similar to that of primary prevention. In addition, beneficial effects of antihypertensive treatment\textsuperscript{35} and lipid-lowering drugs\textsuperscript{36} have been shown, and these drugs are also recommended in patients whose initial blood-pressure and cholesterol levels are normal.\textsuperscript{16} Patients with ischaemic strokes benefit from antiplatelet treatment in order to prevent new cardiovascular events.\textsuperscript{37} Treatment with oral anticoagulants further reduces the risk
of a new stroke in ischemic stroke patients with atrial fibrillation. Patients with 50-99% carotid stenosis benefit from surgery, preferably within 2 weeks after the stroke.

Rehabilitation
Conventionally, stroke patients receive a substantial part of their rehabilitation in hospital. New services have been developed with emphasis on rehabilitation at home, with early supported discharge from hospital (ESD). ESD has not only been shown to reduce the length of hospital stay, but also to reduce death and dependency after stroke. Rehabilitation

Treatment of post-stroke depression
Treatments with tricyclic antidepressants and selective serotonin reuptake inhibitors (SSRIs) have been shown to reduce depressive symptoms after stroke. However, it is not evident whether pharmacological agents improve recovery or prevent depression after stroke. Due to the adverse reaction profile of tricyclic agents, SSRI agents are recommended as the primary choice for treatment of depression in stroke patients.

Sex differences in prevention and treatment
The current Swedish national guidelines for stroke care conclude that there is no scientific evidence supporting different medical management for men and women. However, men and women may have different needs for help and support after stroke depending on differences in social factors and functional ability and this should be considered. In patients with ischaemic strokes, women have been shown to benefit more from thrombolytic therapy. Hence, sex may be a factor to consider when balancing risks and benefits with this type of treatment in the future.

Stroke outcome
Stroke is a common disease with severe implications for the patient as well as his or her family. Besides reduced survival and physical impairments after stroke, it may also affect cognitive functions and quality of life. This thesis is focussing on survival, functional outcome and post-stroke depression. A selection of recent observational studies on the subject is presented in Table 1.

Survival
Survival and predictors of poor survival following stroke have been investigated in several studies. Advanced age, diabetes, hypertension, physical inactivity, cardiac disease, recurrent stroke, stroke subtype, no stroke unit care, depression and stroke severity have all been associated with poor survival. The risk of dying is highest early after stroke. Approximately 60% of all deaths during the first year after stroke occur within the first month, and more than three quarters occur within the first 3 months. The case fatality of stroke patients treated in hospital in Sweden is estimated to be 7% within the first week, 13% within the first 28 days and 19% within 3 months after stroke. Two years after stroke, 37% have died.
Table 1. A selection of observational studies published since 2000 on survival, functional outcome and depression after stroke, identifying independent predictors of poor outcome

<table>
<thead>
<tr>
<th>Study</th>
<th>Location</th>
<th>N</th>
<th>Selection</th>
<th>Follow-up</th>
<th>Outcome</th>
<th>Predictors (identified in multiple regression)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anderson 2004</td>
<td>Auckland, NZ</td>
<td>680</td>
<td>Stroke</td>
<td>21 years</td>
<td>Death</td>
<td>Age, prestroke dependency, non-smoker, diabetes, stroke type, previous stroke, loss of consciousness, speech defect, weakness/plegia. NB univariate analysis</td>
</tr>
<tr>
<td>Appelros 2002</td>
<td>Örebro, Sweden</td>
<td>377</td>
<td>First stroke</td>
<td>1 year</td>
<td>Death</td>
<td>Age, prestroke dementia, atrial fibrillation, stroke severity, stroke severity</td>
</tr>
<tr>
<td>Appelros 2004</td>
<td>Örebro, Sweden</td>
<td>251</td>
<td>First stroke</td>
<td>1 year</td>
<td>Depression (mRS ≥3)</td>
<td>Age, heart failure, stroke severity</td>
</tr>
<tr>
<td>Desmond 2003</td>
<td>Columbia, USA</td>
<td>421</td>
<td>Ischaemic stroke, age ≥60</td>
<td>3 months</td>
<td>Depression (DSM-IV)</td>
<td>mRS at 1 year, ischemic heart disease</td>
</tr>
<tr>
<td>Di Carlo 2003</td>
<td>Europe</td>
<td>4534</td>
<td>First stroke</td>
<td>3 months</td>
<td>Death</td>
<td>Female sex, dementia, lesion location, major hemisphere stroke syndrome</td>
</tr>
<tr>
<td>Gargano 2007</td>
<td>Michigan, USA</td>
<td>373</td>
<td>Stroke</td>
<td>3 months</td>
<td>Dependency (BI&lt;95)</td>
<td>Age, female sex, discharge mRS ≥3, previous stroke</td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>Study</th>
<th>Location</th>
<th>N</th>
<th>Selection</th>
<th>Follow-up</th>
<th>Outcome</th>
<th>Predictors (identified in multiple regression)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hanley 2000</td>
<td>Perth, Australia</td>
<td>370</td>
<td>First stroke</td>
<td>5 years</td>
<td>Death</td>
<td>Age, intermittent claudication, TIA, pre-stroke dependency, smoke status, level of consciousness, urinary incontinence</td>
</tr>
<tr>
<td>Hanley 2002</td>
<td>Perth, Australia</td>
<td>254</td>
<td>First stroke,</td>
<td>5 years</td>
<td>Death or dependency</td>
<td>Age, hemiparesis, pre-stroke dependency, recurrent stroke during follow-up</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>30-days survivors</td>
<td></td>
<td>(mRS ≥3)</td>
<td></td>
</tr>
<tr>
<td>de Jong 2002</td>
<td>Maastricht, NL</td>
<td>998</td>
<td>First ischaemic stroke</td>
<td>2 years</td>
<td>Death</td>
<td>Age, diabetes</td>
</tr>
<tr>
<td>Kammersgaard</td>
<td>Copenhagen,</td>
<td>905</td>
<td>Ischaemic stroke</td>
<td>5 years</td>
<td>Death</td>
<td>Age, stroke severity, atrial fibrillation, diabetes, smoking, previous stroke</td>
</tr>
<tr>
<td>Lai 2005</td>
<td>Denmark, Kansas,</td>
<td>459</td>
<td>Stroke</td>
<td>6 months</td>
<td>Dependency (BI)</td>
<td>Age, stroke severity, pre-stroke physical function, depressive status</td>
</tr>
<tr>
<td></td>
<td>USA</td>
<td></td>
<td></td>
<td></td>
<td>Death</td>
<td></td>
</tr>
<tr>
<td>Petty 2000</td>
<td>Rochester, USA</td>
<td>454</td>
<td>First ischaemic stroke</td>
<td>5 years</td>
<td>Death</td>
<td>Age, heart failure, ischaemic heart disease, mRS&gt;3</td>
</tr>
<tr>
<td>Slot 2008</td>
<td>Edinburgh, UK</td>
<td>2054</td>
<td>Ischaemic stroke,</td>
<td>7 years</td>
<td>Death</td>
<td>Age, male sex, atrial fibrillation, anti-platelet use prior to stroke, functionally dependent at 6-month (mRS ≥2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>6-months survivors,</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>(Lothian cohort)</td>
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</tr>
<tr>
<td>Weimar 2002</td>
<td>Germany</td>
<td>1963</td>
<td>Ischaemic stroke</td>
<td>1 year</td>
<td>Dependency (mRS ≥2)</td>
<td>Age, diabetes, previous stroke, prestroke mRS, living alone, stroke severity (NIHSS)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Depression (CES-D≥10)</td>
<td>Female sex, cardiovascular disease, prestroke mRS, living alone, sensory deficit</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Age, male sex, history of myocardial infarction, intermittent claudiation, diabetes or peripheral vascular surgery, mRS≥2, CT and ECG findings</td>
</tr>
<tr>
<td>van Wijk 2005</td>
<td>NL</td>
<td>2473</td>
<td>TIA or minor ischaemic</td>
<td>10 years</td>
<td>Death</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>stroke</td>
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</tbody>
</table>
Function and disability

Functional outcome after stroke

Table 2. The modified Rankin Scale (mRS)
Post-stroke depression
Depression is another frequent complication after stroke. According to pooled estimates from two reviews,74,75 about one third of stroke survivors are expected to have depressive symptoms at any time during follow-up. However, reported prevalence from individual studies varies widely.60,76-79 Depression after stroke may be a direct effect of the brain lesion or it may be a reaction on inevitable changes in life caused by the stroke. Post-stroke depression is associated with increased mortality,80,81 poor functional recovery82,83 and reduced quality of life.84,85

Different methods are used to diagnose depression such as The Diagnostic and Statistical Manual of Mental Disorders (DSM), the Montgomery Åsberg Depression Rating Scale (MADRS)86 or the Primary Care Evaluation of Mental Disorders (Prime-MD)87 which is based on the DSM criteria. Depressive symptoms may also be assessed by the patients, using a single item question.88

Sex differences in stroke outcome
A previous Swedish study based on data from 20013 observed no difference in case fatality between men and women. Among survivors, women were more likely to be dependent in ADL or live in an institution 3 months after stroke. At the follow-up, women were also more likely to feel depressed.

National quality registers
In 2007, there were 56 national quality health registers on various items in Sweden supported by the government, and more were being built up.89 All registers collect individual information on diagnosis, treatment and outcome to be used to monitor and follow-up the quality and results of care on a national as well as regional level. In addition, the registers have become valuable assets for research.

The Swedish quality register for stroke care, Riks-Stroke, was established in 199490 and will be described in Section 3. It was the first register, with national coverage, to monitor stroke care. Some countries have established, and others have started to establish, similar systems. The Danish National Indicator Project (DNIP)91 began in 2000 and monitors the quality of care for several diseases including stroke. The Registry of the Canadian Stroke Network (RCSN)92 was established in 2001. In Norway a national stroke register is currently being established, and in Finland all stroke patients are included in the register of the National Research and Development Centre for Welfare and Health. The Paul Coverdell National Acute Stroke Registry was initiated in 2001 and covers several states in the USA.93 Other countries have other systems to monitor the quality of stroke care. Those include the UK National Sentinel Audit for Stroke94, the Scottish Stroke Services Audit,95 the National Stroke Audit in Australia and the German Stroke Data Bank96.
2 Objectives

The overall objective of this thesis was to study different aspects of outcome after stroke. This included an analysis of survival, functional outcome, self-reported depression and possible differences in management and outcome between men and women. The specific aims of each paper were:

I. to explore possible differences related to sex in baseline characteristics, stroke management and stroke outcome in Sweden

II. to investigate if functional outcome after stroke, as assessed in a quality register, can be transformed into a standard assessment of functional outcome

III. to determine to what extent functional outcome three months after stroke is associated with long-term survival

IV. to describe and analyse
   - the prevalence of self-reported depression following stroke
   - risk factors associated with depression after stroke
   - treatment with antidepressant drugs after stroke
3 Material and methods

The Riks-Stroke register

Riks-Stroke is the national quality register for stroke care in Sweden. It was initiated in 1994 to monitor and improve the quality of stroke care. Since 1998 the register includes all hospitals, which admit patients with acute stroke in Sweden.

The register records information on baseline characteristics including living arrangement and dependency in primary ADL prior to stroke. Risk factors for stroke, level of consciousness on admission, medical treatment, admission to stroke unit and secondary complications during the hospital stay are also registered. Three months after stroke, the patients are contacted for a follow-up. They are asked to answer a questionnaire either by telephone or mail. The patients’ living arrangement, dependency in primary ADL, satisfaction with hospital care, need for support, perceived support, problems with speech, self-reported depression and patient-perceived general health are recorded.

Patients diagnosed with ischemic stroke (ICD-10 I63), intracerebral haemorrhage (ICD-10 I61) or unspecified acute cerebrovascular event (ICD-10 I64) are eligible for registration. Individual hospitals can also choose to register additional stroke diagnoses (ICD-10 I60-I69) and transitory ischemic attacks (ICD-10 G45) but these are not included in the yearly feedback to the hospitals or in this thesis.

The proportion of acute stroke patients treated in hospital in Sweden is estimated to lie between 84% and 92%. Between 21 000 - 25 000 stroke events have been recorded in the register annually (Figure 3). Based on epidemiologic calculations Riks-Stroke has an approximate coverage of 90% of all ischemic and intracerebral haemorrhages in all ages. The follow-up frequency is also high, reaching 89% in 2006 (Figure 3).

Ethical considerations

All included patients have been informed about the registration in Riks-Stroke. Participation in Riks-Stroke is voluntary and patients can deny participation or can ask that their data be withdrawn at any time. Riks-Stroke has been approved by the Regional Ethical Review Board at Umeå University, and the corresponding data-handling procedures have been approved by the National Computer Data Inspection Board. The validation of Riks-Stroke’s questions on functional outcome (Paper II) and depression (included in Paper IV) has separate approvals from the Regional Ethical Review Board.
Variable assessment

Survival
The exact date of death was recorded in Riks-Stroke until three months after the stroke. Later dates of death, used in Paper III, were retrieved from the Swedish Population Register (Folkbokföringen).

Function and disability
Riks-Stroke included questions on mobility and if the patients managed toilet visits and dressing/undressing without assistance from another person. Patients who managed those tasks without assistance were defined to be independent in primary ADL. A previous study has shown that this measure of primary ADL is strongly correlated with the Barthel index. Moreover, those three questions together with information on whether the patient lived in his/her own home with/without community support, and if he/she was dependent on a family member/next-of-kin for help and support was used to estimate the functional outcome according to the modified Rankin Scale in Paper II. The corresponding translation was used in the subsequent Paper III.

Self-reported depression and use of antidepressant medication
At the follow-up, three months after stroke, the patients were asked whether or not they felt depressed. They were given five fixed response alternatives: “never/almost never”, “sometimes”, “often”, “all the time” and “do not know”. Patients who answered “often” or “all the time” were considered to have self-reported depression. The patients were also asked if they took medicine against depression and the response alternatives were: “yes”, “no” and “do not know”. The alternative “do not know” was handled as missing value.
Self-reported depression assessed in Riks-Stroke has been compared with the Prime-MD instrument, an established instrument to screen for depression, in a separate study managed by Eva-Lotta Glader (data not published). Thirty-six patients (one third each with mild, moderate and severe neurological deficits) were interviewed approximately 3 months after they had had their stroke. None of the 22 patients without depression according to Prime-MD reported depressive symptoms in Riks-Stroke (100% specificity). The Riks-Stroke question detected 5 of the 13 patients with mild or severe depression according to Prime-MD (38% sensitivity) (Table 3).

Table 3. Validation of self-reported depression in Riks-Stroke vs. Prime-MD, 3 months after stroke

<table>
<thead>
<tr>
<th>Prime-MD</th>
<th>Do you feel depressed?</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Never</td>
<td>Sometimes</td>
</tr>
<tr>
<td>No depression</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>Mild</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Severe</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Total</td>
<td>11</td>
<td>19</td>
</tr>
</tbody>
</table>

* Information was missing for one person

Other

Level of consciousness on admission was recorded using three levels based on the Reaction Level Scale (RLS 85). Patients with RLS 1 were defined as alert, RLS 2-3 as drowsy and RLS 4-8 as unconscious.

Additional features of outcome were addressed in Paper I. Patients were asked to rate their general health using the alternatives: "very good", "fairly good", "fairly bad", "very bad" and "do not know". Patients were defined to perceive their general health as good when they responded using either of the first two alternatives. Difficulties with speech were assessed by asking the patients a simple yes/no-question.

Statistical methods

Details of the statistical analyses are presented for each individual paper in a separate section. The general structure of the statistical analyses has been:

1. Descriptive statistics (e.g. mean values, proportions and graphs)
2. Univariate analysis (e.g. Student’s t-test, Pearson χ²-test, simple regression)
3. Methods controlling for confounding (e.g. multiple regression, stratified analysis, and/or subgroup analysis)

Results from the statistical analyses have been presented with mean values, proportions, correlations, hazard ratios and odds ratios with corresponding 95% confidence intervals or p-values. Two-sided tests have been used and the level of significance
has been set to 0.05. Presented p-values and confidence intervals have not been corrected for multiple testing.

Kappa statistic
The Cohen’s Kappa statistic was one of several measures used to describe the level of agreement between two measurements of mRS in Paper II. The simple kappa statistic is based on the difference between the observed proportion of agreement (p) and the proportion of agreement that would be expected simply by chance (p_e) and is defined as $\kappa = (p - p_e) / (1 - p_e)$. This statistic does not consider the magnitude of misclassification. Therefore, a weighted version with Fleiss Cohen type of weights quadratic weights was used.

Logistic regression
The logistic regression model was used to examine the association between binary outcome variables, e.g. feeling depressed (yes/no), and one or several explanatory/independent variables (e.g. age or sex). It can be thought of as an extension of the chi-square test, but in which both multiple and continuous explanatory variables may be included. The general form of the logistic model is $\text{logit}(p) = \ln\left(\frac{p}{1-p}\right) = \beta_0 + \beta_1 x_1 + \ldots + \beta_n x_n$, where $p$ is the probability of being depressed, $\beta_i (i=0,\ldots,n)$, are the regression coefficients and $x_i (i=1,\ldots,n)$, are the values of the explanatory variables. From this formula, the estimated odds ratio for a 1-unit increment in $x_i$ can be derived as $e^{\beta_i}$.

Cox proportional hazard regression
When the outcome of interest was time to event, i.e. survival time, the Cox proportional Hazard model was used. The model is described by the hazard at time $t$, $h(t, x)$, including one or more explanatory factors $x$. The model, $h(t, x) = h_0(t) \exp(\beta_1 x_1 + \ldots + \beta_n x_n)$, involves a baseline hazard, $h_0(t)$, that does not depend on the explanatory factors, together with the exponential of a linear combination of the explanatory variables. The hazard ratio (HR), can be expressed as $h(t, x') / h(t, x) = \exp[\beta_1 (x_1 - x_1') + \ldots + \beta_n (x_n - x_n')]$, where $x'$ and $x$ denote different values of the explanatory factors. Hence, HR does not depend on the baseline hazard. The HR for a 1-unit increment in $x_i$ can then be derived as $e^{\beta_i}$ and is independent of time. This is the underlying assumption of a proportional hazard, which means that the hazard ratio is constant over time.

Missing values
Modelling was performed both by excluding missing values and by including them as a separate category. When the two alternative methods did not differ substantially only results from the first were presented.

Individual material and methods

Paper I
Sex differences in stroke care and outcome were analysed in 24 633 stroke events registered in Riks-Stroke during 2006. Background variables, other than sex, that were considered were age, living arrangement, ADL-dependency, previous stroke, atrial fibrillation, diabetes, treatment for hypertension and smoking status. Other
variables which were also investigated were: level of consciousness on admission, type of stroke, CT, stroke unit care, thrombolytic therapy, secondary complications during hospital stay and secondary prevention. Analysis of outcome included the following: 90-day case fatality, institutional living, ADL-dependency, speech-difficulties, self-reported depression and self-perceived general state of health three months after stroke. Patients' satisfaction with hospital care was also explored.

Statistical methods
Categorical variables were summarized by proportions. Age was summarized by mean values. Differences between men and women were tested using Student’s t-test for age and Pearson \( \chi^2 \)-test for proportions. Multiple logistic regressions, including sex and age as independent covariates, were used to adjust for women’s higher age at stroke onset. The corresponding results are presented by age-adjusted odds ratios (OR) and 95% confidence intervals of OR. Possible sex differences were further explored in more consistent subgroups of patients and by adjustments for additional confounding factors. SAS version 9.1.3 was used for statistical analyses.

Paper II
The assessment of functional outcome in Riks-Stroke was explored using 555 stroke survivors who were admitted to one of the hospitals in Lund, Uppsala, Örebro or Umeå between May 1 and September 30, 2005 and who were registered in Riks-Stroke.

A telephone-interview was performed by an experienced nurse three months after the stroke. The interview began with the Riks-Stroke standard follow-up questionnaire and ended with additional questions to assess the patient’s mRS-grade.

A group consisting of physicians specialised in stroke, an epidemiologist and a statistician specified an algorithm for translation of the Riks-Stroke questions into mRS-grades. Based on the information available in Riks-Stroke, it was not feasible to distinguish between the mRS-grades 0, 1 and 2, and therefore those grades were merged and no effort was made to separate them. The translation was based on five of the Riks-Stroke follow-up questions:

1. Are you, today dependent on a family member/next-of-kin for help/support (1=partly dependent, 2=entirely dependent, 3=no, not at all)?
2. Where are you staying now (1=in own home without community support, 2=in own home with community support, 3=living in community facility, 5=in acute care hospital, 6=other, 7=in a geriatric/rehabilitation unit)?
3. How mobile are you (1=I can move around without help both indoors and outdoors, 2=I can move around without help indoors but not outdoors, 3=I need another person’s help to move)?
4. Do you receive help from anybody to go to the toilet (1=I can manage toilet visits without assistance, 2=I need help to go to the toilet)?
5. Do you receive help with dressing/undressing (1=I can manage dressing/undressing without help, 2=I need help dressing/undressing)?
The specification of the algorithm for translation was done after the assessment of mRS but prior to data-extraction. Minor adjustments of the pre-specified translation were made after initial analyses.

**Statistical methods**
The agreement between the actual mRS and mRS as translated from Riks-Stroke’s questions was summarized by frequency tables. Proportion of agreement, Spearman’s correlation and Cohen’s kappa with Fleiss-Cohen type of weights were also calculated. SAS version 9.1 was used for statistical analysis.

**Paper III**
The study on survival based on functional outcome three months after stroke included 17,755 stroke events registered in Riks-Stroke during the period 2001-2002. In addition to information from the Riks-Stroke register, survival status and date of death were collected from the Swedish Population Register (Folkbokföringen) as of May 4, 2006. Of the 84 hospitals in Sweden, which admitted patients with acute stroke during this period, all data were excluded from the 11 hospitals, which lacked 3-month follow-up data from more than 25% of their stroke patients. Patients who were independent in primary ADL before stroke (toilet, dressing and mobility), had suffered an ischaemic stroke or an intracerebral haemorrhage and reported no previous stroke were included in the study population. The translation algorithm defined in Paper II was used to specify each patient’s mRS grade.

**Statistical methods**
Survival curves, stratified by age group and sex or mRS score, were computed using the Kaplan-Meier product limit method. Cox proportional hazard regression was used to simultaneously adjust for other possible predictors. Survival times were censored three years after the 3-month follow-up. Age was included as a continuous covariate and other variables were categorical. The results are presented as hazard ratios (HR) and corresponding 95% confidence intervals (CI). Statistical analysis was carried out using SAS version 9.1 and SPSS version 15.

**Paper IV**
Information from Riks-Stroke was used to investigate self-reported depression and use of antidepressant medication in stroke patients 2002. In total, 15,747 patients were alive and followed up three months after stroke.

Information on the sale of antidepressants (ATC code N06A) in the general Swedish population during year 2002 was obtained from the Swedish pharmacy chain, which had exclusive rights to sell drugs prescribed by a physician, Apoteket AB, Stockholm. Defined Daily Doses (DDD) per 1000 inhabitants were used to express the sales. DDDs for antidepressant agents were those defined by the WHO Collaborating Centre for Drug Statistics Methodology (available at website http://www.whocc.no/atcddd). The point prevalence (%) of antidepressant use was then estimated as DDD/1000x100.

**Statistical methods**
The association between self-reported depression and other factors under investigation (sex, age, stroke subtype, level of consciousness on admission, recurrent stroke, living situation and ADL function 3 months after stroke) was analysed by
univariate and multiple logistic regression. Corresponding odds ratios were presented together with 95% confidence intervals. The use of antidepressant medication was analysed similarly. Statistical analyses were carried out using SAS version 8.2
4 Summary of results

Sex differences (Paper I)

During 2006, 12,283 (49.9%) women and 12,350 (51.1%) men were registered in Riks-Stroke. Women had a less favourable pre-stroke situation than men had on several aspects. They were older at stroke onset (mean age 78.4 vs. 73.6 years), they were more often living alone (64.6% vs. 35.3%) or in institution (12.6% vs. 6.5%) and were more often dependent in ADL (13.9% vs. 9.3%) prior to stroke. Women were less often fully conscious on admission to hospital (77.3% vs. 84.9%). Women were less likely to receive care at a stroke-unit (80.2% vs. 83.0%), but the difference was no longer present after adjustments for level of consciousness on admission.

Women were more likely to experience deep venous thromboses (1.2% vs. 0.7%) and fractures (0.8% vs. 0.5%), while men were more likely to develop pneumonia during their hospital stay (4.5% vs. 3.7%). There were no sex-related differences in thrombolytic therapy in patients under 80 year of age with ischaemic stroke. Men and women under 80 years of age with atrial fibrillation and ischaemic stroke had equal probability to receive secondary prevention with oral anticoagulants. There were no sex-related differences in secondary prevention with other antithrombotic therapy or antihypertensive treatment. Women were less likely to receive lipid-lowering drugs at discharge from hospital (35.0% vs. 45.2%).

Women had poorer 3-month survival (79.8% vs. 84.8%). More women than men were dependent in ADL at the follow-up (14.5% vs. 11.6% of the patients who were independent in ADL prior to stroke). However, after adjustments for age and level of consciousness on admission, women had, on average, slightly better survival than men (Figure 4) and similar ADL proficiency (Figure 5) as men had.

![Figure 4. 90-day case fatality (%) stratified by sex, age group and level of consciousness on admission to hospital](image-url)
Among patients living at home without community support prior to stroke, women were less often living at home three months after stroke as compared with men (85.5% vs. 88.4%). The difference in residency was not present in patients under 85 years of age or in older patients who were living alone (Figure 6).

Figure 5. ADL-dependency 3 moths after stroke in stroke survivors who were independent prior to stroke, stratified by sex, age group and level of consciousness on admission to hospital.

Figure 6. Institutional living 3 months after stroke in stroke survivors who were living at home without community support prior to stroke and were fully conscious on admission to hospital, stratified by sex, age group and living situation prior to stroke.
At the follow-up, women were more likely to perceive their general state of health as bad than were men (21.9 vs. 18.0). Women were also more likely to report that they felt depressed (15.4% vs. 11.0%). Perceived difficulties with speech did not differ between men and women. Independently of age, women were less satisfied with the care they had received in hospital on all measured aspects.

Assessment of functional outcome (Paper II)

During the study period, 783 patients were registered at the four hospitals, which participated in the study. At the time of follow-up, 132 patients had died and 23 could not be reached or chose not to participate. Of the remaining 628 patients, 37 could not be classified into mRS grades during the interview. Reasons for failures were non-Swedish speaking patients, unwillingness to answer some of the questions, aphasia, dementia or other severe concomitant diseases. Thirty-six patients did not answer one or more of the Riks-Stroke questions used for translation, leaving a total of 555 patients with valid data.

Table 4. Translation of Riks-Stroke questions into mRS grades (Q1-Q5 refer to questions number 1-5)

<table>
<thead>
<tr>
<th>mRS grade</th>
<th>Definition of the translation using Riks-Stroke questions (all criteria should be fulfilled)</th>
</tr>
</thead>
</table>
| 0-2       | - Q1: not, or only partly, dependent of next of kin for help/support  
|           | - Q2: living in own home without community support  
|           | - Q3: can move around without help both indoors and outdoors  
|           | - Q4: can manage toilet visits without assistance  
|           | - Q5: can manage to dress/undress without help  |
| 3         | - Q1: entirely dependent on next of kin for help/support  
|           | or  
|           | - Q2: not living in own home without community support  
|           | or  
|           | - Q3: cannot move around without help outdoors  |
|           | - Q3: can move around without help at least indoors  
|           | - Q4: can manage toilet visits without assistance  
|           | - Q5: can manage to dress/undress without help  |
| 4         | - Q3: unable to move around without help indoors  
|           | or  
|           | - Q4: needs help to go to the toilet  
|           | or  
|           | - Q5: needs help dressing/undressing  |
| 5         | - Q2: not living at home  
|           | - Q3: needs another person’s help to move  
|           | - Q4: needs help to go to the toilet  
|           | - Q5: needs help dressing/undressing  |
The translation (Table 4), which used five of the questions from Riks-Stroke, classified 76% of the patients into correct mRS scores (Table 5). The correlation between the translated scores and the actual mRS was 0.821 and Cohen’s Kappa (weighted) was 0.853. Men and women had similar correlation and Kappa values.

Table 5. Frequency table of the actual mRS grade vs. mRS translated from Riks-Stroke questions. Frequencies are presented separately for women and men (women/men)

<table>
<thead>
<tr>
<th>mRS grade</th>
<th>0-2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-2</td>
<td>109/175</td>
<td>22/13</td>
<td>5/7</td>
<td>0/0</td>
<td>136/195</td>
</tr>
<tr>
<td>3</td>
<td>12/15</td>
<td>28/13</td>
<td>2/5</td>
<td>0/0</td>
<td>42/33</td>
</tr>
<tr>
<td>4</td>
<td>0/1</td>
<td>6/12</td>
<td>29/35</td>
<td>16/9</td>
<td>51/57</td>
</tr>
<tr>
<td>5</td>
<td>0/0</td>
<td>0/1</td>
<td>1/5</td>
<td>20/14</td>
<td>21/20</td>
</tr>
<tr>
<td>Total</td>
<td>121/191</td>
<td>56/39</td>
<td>37/52</td>
<td>36/23</td>
<td>250/305</td>
</tr>
</tbody>
</table>
Functional outcome and long-term survival (Paper III)

Of 19 804 stroke survivors who experienced an ischaemic or a haemorrhagic stroke during 2001-2002, who were independent in ADL before stroke, with no previous stroke and were admitted to hospitals with follow-up frequency above 75%, 17 755 (89.7%) were followed-up after three months. However, 1 796 patients did not answer one or more of the Riks-Stroke questions used to assess mRS. Hence, the main analysis was based on 15 959 stroke patients.

Three months after stroke 8 811 (55.2%) had mRS 0-2, 3966 (24.8%) had mRS 3, 1742 (10.9%) had mRS 4 and 1440 (9.0%) had mRS 5. Patients with different mRS grades differed with respect to sex, age, stroke subtype, consciousness on admission, atrial fibrillation, smoking status and antihypertensive therapy prior to stroke and self-reported depression at the follow-up (Table 6).

Table 6. Mean and proportions (95% confidence interval) of basic characteristics for each mRS grade 3 months after stroke (n=15 959)

<table>
<thead>
<tr>
<th>Variable</th>
<th>mRS 0-2 (n=8811)</th>
<th>mRS 3 (n=3966)</th>
<th>mRS 4 (n=1742)</th>
<th>mRS 5 (n=1440)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demography</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean age (yrs)</td>
<td>69.6 (69.3-69.8)</td>
<td>77.6 (77.3-77.9)</td>
<td>76.3 (75.9-76.8)</td>
<td>78.7 (78.3-79.2)</td>
</tr>
<tr>
<td>Men, %</td>
<td>60.5 (59.5-61.5)</td>
<td>38.0 (36.5-39.6)</td>
<td>52.8 (50.4-55.1)</td>
<td>41.4 (38.8-43.9)</td>
</tr>
<tr>
<td>Stroke onset/admission</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haemorrhagic stroke, %</td>
<td>10.0 (9.4-10.7)</td>
<td>9.4 (8.4-10.3)</td>
<td>14.6 (12.9-16.2)</td>
<td>16.9 (14.9-18.8)</td>
</tr>
<tr>
<td>Fully conscious, %</td>
<td>95.7 (95.3-96.1)</td>
<td>91.3 (90.5-92.2)</td>
<td>81.1 (79.2-82.9)</td>
<td>67.6 (65.2-70.1)</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>17.2 (16.4-18.0)</td>
<td>19.9 (18.6-21.1)</td>
<td>22.2 (20.2-24.1)</td>
<td>22.3 (20.2-24.5)</td>
</tr>
<tr>
<td>Antihypertensive therapy, %</td>
<td>43.2 (42.1-44.2)</td>
<td>49.3 (47.7-50.9)</td>
<td>46.3 (43.9-48.7)</td>
<td>47.5 (44.9-50.1)</td>
</tr>
<tr>
<td>Atrial fibrillation, %</td>
<td>16.4 (15.6-17.2)</td>
<td>24.7 (23.3-26.0)</td>
<td>25.7 (23.7-27.8)</td>
<td>30.8 (28.4-33.3)</td>
</tr>
<tr>
<td>Smoker, %</td>
<td>21.3 (17.6-20.3)</td>
<td>14.9 (13.7-16.1)</td>
<td>14.4 (12.6-16.2)</td>
<td>10.8 (9.1-12.6)</td>
</tr>
<tr>
<td>Stroke-unit care, %</td>
<td>78.5 (77.7-79.4)</td>
<td>75.6 (74.2-76.9)</td>
<td>78.2 (76.2-80.1)</td>
<td>77.3 (75.1-79.5)</td>
</tr>
<tr>
<td>3-month follow-up</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Feeling depressed, %</td>
<td>7.9 (7.3-8.5)</td>
<td>14.9 (13.8-16.1)</td>
<td>19.5 (17.6-21.4)</td>
<td>29.2 (26.6-31.8)</td>
</tr>
</tbody>
</table>
Impaired functional outcome 3 months after stroke was an independent predictor of poor survival (Figure 7). Patients with mRS grades 3, 4 and 5 had hazard ratios of 1.7 (95% CI: 1.6-1.9), 2.5 (95% CI: 2.2-2.9) and 3.8 (95% CI: 3.4-4.3), respectively, as compared with patients with lower mRS grades. In addition to high mRS, male sex, advanced age, diabetes, smoking, antihypertensive therapy before stroke onset, atrial fibrillation and depressed mood were also recognized as significant predictors of poorer survival using a multiple Cox regression model.

Figure 7. Kaplan-Meier survival curves, survival since the 3-month follow-up. Separate lines for each mRS score
Self-reported depression and use of antidepressants (Paper IV)

Of 22,530 stroke events in 2002, 3,980 died during the first three months and 2,803 were lost to follow-up. Of the remaining 15,747 patients, data on depressive mood were missing for 1,748. Different subsets of patients have been used in the different analyses (Figure 8).

![Diagram showing patient subsets and data collection]
At the follow-up, 3 months after stroke, 16.4% of the female and 12.4% of the male stroke survivors reported that they always or often felt depressed, (Figure 9). Female sex, age below 65 years, living alone, having had a recurrent stroke, being dependent on others and institutional living 3 months after stroke were identified as independent predictors of self-reported depression using a multiple logistic regression model. Of the stroke patients, 28.1% of the women and 22.5% of the men reported use of antidepressants at the follow-up. Of the 2806 patients using antidepressant drugs, 1895 (67.5%) did not report depressive mood (Table 7). On the other hand, 943 patients of the entire cohort reported depressive mood but no treatment with antidepressants (8.4%). When compared with the general population, about twice as many stroke patients were treated with antidepressants (Figure 9).

Figure 9. Proportion of patients who reported that they often or always felt depressed 3 months after stroke, use of antidepressants 3 months after stroke (stroke) and use of antidepressants in the general population in Sweden (SWE)

Table 7. Frequency table of self-reported depression and use of antidepressants 3 months after stroke

<table>
<thead>
<tr>
<th></th>
<th>Reporting depression</th>
<th>Not reporting depression</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Using antidepressants</td>
<td>911</td>
<td>1895</td>
<td>2806</td>
</tr>
<tr>
<td>Not using antidepressants</td>
<td>943</td>
<td>7543</td>
<td>8486</td>
</tr>
<tr>
<td>Total</td>
<td>1854</td>
<td>9438</td>
<td>11292</td>
</tr>
</tbody>
</table>
5 Discussion

In this thesis, different aspects on outcome after stroke and differences between men and women concerning stroke management and outcome were investigated. The results were based on data from a nation-wide quality register for stroke care, Riks-Stroke. All Swedish hospitals that admitted patients with acute stroke participated. The register covered a majority of all acute strokes treated in hospital and the proportion of patients lost to follow-up after three months was low. Hence, the patient selection bias is expected to be low and unlikely to have had any substantial effect on the results.

Are there sex differences in stroke management and outcome?

In Paper I, we found that women’s worse outcome regarding case fatality and functional ability 3 months after stroke was explained by their higher age and lower level of consciousness at admission to hospital. When age and level of consciousness were adjusted for, our data, on the contrary, suggested that women have a better chance to survive 3 months after stroke and have a similar functional outcome as men have. Our result on functional ability supports the finding of Lai et al. concerning basic activities of daily living. In general, women’s spouses are older than men’s spouses. This is likely to explain why women were at higher risk than men of being institutionalized three months after stroke, in the group of patients ≥85 years who were living with a spouse prior to stroke.

Men and women were managed similarly in hospital with respect to stroke thrombolysis, stroke unit care and antithrombotic medication. Other studies have found differences related to sex in thrombolytic therapy, while yet other studies have shown similar results as we did. Our finding, that women were less likely to receive lipid-lowering drugs at discharge from hospital, have also been reported from Scotland. Several studies have shown that more men with stroke have a history of myocardial infarction which may explain this difference.

We observed that women were more likely to experience deep venous thromboses and fractures, while men were more likely to develop pneumonia during their hospital stay. Secondary complications have previously been shown to be more common in women, but few studies have explored sex-related differences in specific secondary complications. Gargano et al. studied deep venous thromboses and pneumonia, but did not observe the same differences. Other studies support our finding on pneumonia. Women’s higher risk of fractures after stroke is compatible with their higher risk of fractures in the general Swedish population above 60 years of age and women’s higher risk of osteoporotic fractures.

In Paper I and IV, we observed that women were more likely to feel depressed 3 months after stroke than were men. Women were also more likely to perceive their general health as bad. Female patients were less satisfied with the care, rehabilitation, dialogue and information they had received during the hospital stay than were male patients. Women’s lower satisfaction rate is in accordance with a survey of
5857 patients admitted to hospitals in the USA. A study on stroke care decision-making has suggested that women worry more about risks and want more information before they make decisions about their stroke care than do men. It may be that female stroke patients need a different type of information or that the information should be presented in a different way than for men.

**Transforming patient-reported functional outcome into mRS**

A successful translation from the self-reported Riks-Stroke outcome questions into mRS-grades was derived in Paper II. The level of agreement between the translated scores and the actual mRS scores was similar to the estimated inter-observer agreement achieved using the mRS but not as high as the structured interview mRS.

A limitation with the translation is that it did not separate the mRS grades 0, 1 and 2. The pre-specified translation algorithm was slightly modified after data-extraction and the level of agreement could have been overestimated. However, the adjustment was minor, and its effect on the estimated agreement was small.

Assessing mRS grades using a telephone interview instead of at a clinical evaluation, is suggested to be a reliable method. Possible problems with inter-observer variability were avoided since the same nurse performed all the interviews. Concerns were raised that two interviews regarding functional outcome, close in time, could be confusing for these patients. Hence, the Riks-Stroke and the mRS assessments were assessed during the same interview. This ensured that there was no change between the assessments. The potential bias that it may have introduced should be no more serious than the bias introduced by an investigator’s previous knowledge of the patient.

**Functional outcome predicts long-term survival**

In Paper III, we found that the influence of disability 3 months after stroke on survival up to 3 years after stroke was substantial. This is an important finding since it indicates that any intervention in the acute phase, that may improve functional status 3 months after the stroke, may also have favourable secondary effects on survival in the long term. The prevalence and impact of prognostic determinants other than disability were in accordance with previous studies. The well-known positive effect of stroke unit care on survival did not reach statistical significance in this study, and the effect may have been diluted since patients who died within three months from their stroke were not included in the analysis of survival. The observed impact of disability on survival was stronger than that of diabetes, smoking and AF, which are all well known prognostic factors. Another recent study investigating the impact of functional outcome 6 months after stroke on long-term survival in patients with ischaemic stroke, supports our findings.

Early after stroke, extensive brain lesion, secondary complications and cardiac disease are the major causes of death. Death due to direct effects of the incident stroke occur mainly within the first week for ischaemic strokes. For intracerebral haemorrhage half of all deaths within 30 days occur during the first 3 days. By 3
months the effects of direct brain damage are likely to have passed. The risk of secondary complications peaks during the first few weeks after stroke, but patients are continuously at risk, and an association between post-stroke complications and severe disability has been recognized in a previous study. We had no information on cause of death, i.e. cardiac causes, which with time account for an increasing proportion of deaths after stroke. However, our results were not affected by adjustment for AF. Another possible co-morbidity is cerebral small vessel disease. That causes lacunar infarcts and affects the white matter in the brain which is likely to affect both functioning and survival after stroke. Stroke patients with dementia are known to have worse prognosis. Hence, another possible explanation could be that a major stroke more often results in more severely impaired functional outcome and increases the risk for dementia and thereby increases the mortality rate.

A study from Denmark has shown that patients who were not treated with oral anticoagulants had higher long-term mortality. In Sweden, only a third of all patients with ischaemic stroke and AF are treated with oral anticoagulants, a low proportion as compared with several other countries. There is a possibility that disabled patients may receive less vigorous secondary prevention such as oral anticoagulants for AF.

Another possible reason for the observed association between functional outcome and survival may be that persons who are more dependent in functional ability are at higher risk of complications, e.g., secondary to immobilization. This may well be so, at least for patients who are bedridden. It is also possible that medical complications may be less vigorously treated in severely disabled patients.

Self-reported depression and use of antidepressants

We observed that self-reported depression was common three months after stroke and identified several factors associated with self-reported depression. The observed prevalence of self-reported depression was low as compared to studies, which have used strict diagnostic criteria for depression. A single question to screen for depression in large cohorts has been shown to be quite specific in diverse populations, including stroke patients. However, the low sensitivity to detect depression using Riks-Stroke’s question as compared with the Prime-MD, suggests that the true prevalence of post-stroke depression was underestimated in this study. The high specificity implies that analyses of risk factors associated with post-stroke depression were not confounded by a large proportion of patients without depressive mood.

Antidepressant medication was reported by a quarter of the patients at 3 months after stroke. The accuracy of self-reported antidepressant use has been reported to be good in other settings. In the present cohort of stroke patients of relatively high age (mean 76 years), under reporting rather than over reporting of drug use is likely. Some of the previous studies on a limited number of patients have used strict diagnostic criteria for depression, whereas depression in the present study was self-reported. With the very frequent use of antidepressant medication, it is likely that most of the decisions to prescribe these drugs are based on general clinical impression and what patients report rather than on strict diagnostic criteria.
No information on the type of antidepressant drugs used was recorded in Riks-Stroke. In Sweden, selective serotonin reuptake inhibitors (SSRIs) accounted for 76% and other newer drugs for 18% of the total sales of antidepressant drugs (data from Apoteket AB) during this period. It is reasonable to assume that only a small minority of stroke patients were treated with tricyclic antidepressants considering the adverse reaction profiles of these drugs in elderly people. There are few randomized trials on SSRIs in the treatment of post-stroke depression. They suggest a moderate beneficial effect, but a considerable proportion of patients with post-stroke depression also recovers spontaneously. The two thirds on antidepressant treatment not reporting depressive mood in the present study may be explained by spontaneous recovery, effect of drug treatment or poor ability of the Riks-Stroke question to detect depression.

One third of the patients on antidepressant treatment reported depressive mood, suggesting insufficient response to the treatment. Riks-Stroke does not include information on when antidepressant drug treatment was initiated or doses used in individual patients. It is therefore possible that, in some patients, treatment times were too short or the dosages were too low for the medication to be fully effective. Even in randomized trials, treatment failures are common. Since antidepressants are widely used in elderly people in Sweden, it is also possible that many depressive people with poor response to antidepressants were on drug treatment already before their stroke. Moreover, side effects of antidepressant drugs may have caused poor compliance or early termination of the treatment, an issue that has not been addressed in large clinical trials. The possibility to crosslink Riks-Stroke with a national register listing all prescribed medicines on an individual level was not available in Sweden at the time of this study. This would have strengthened our results and is a possibility for future studies.

The proportion of patients who reported depressive mood and no antidepressant therapy at 3 months after stroke was substantial (8%). Possible reasons may be difficulties to accurately diagnose post-stroke depression, a pending attitude among physicians to avoid antidepressants after stroke, or that stroke patients are not adequately followed-up after discharge from hospital.

**Methodological issues**

A major strength with register-based studies is the large size of the study populations. In order to allow collection of information on extensive numbers of patients, the number of variables assessed is restricted. As a consequence, no detailed information on initial stroke severity or co morbidities was available. For the same reason, several of the outcome measures, including functional outcome and depressive symptoms, were self-reported by the patients rather than assessed clinically. The mRS grades were estimated from self-reported questions, but the translation algorithm had a high precision with 76% accuracy. Self-reported depressive mood has been validated in a separate study. Nevertheless, several details in our findings, causality in particular, need to be further investigated in future studies with different methodologies.
P-values and confidence intervals have been presented without adjustments for multiple testing. This reduced the risk of a type II error (failing to detect a true difference/association), but enhanced the risk of a type I error (spurious significant difference/association). The sample sizes were large and the studies had high power. The main results would still be valid if we had used a significance level of 0.001, which would preserve the risk of an overall type I error at a low level.

The proportions of missing values and patients lost to follow-up were generally low. It is unlikely that they introduced a bias that has affected our results substantially. The Kappa statistic has become a standard measure of agreement between ratings, but it has also been the subject of controversy. Hence, in Paper II, the Kappa statistic was used together with other types of measures describing agreement.
6 Conclusions

Men and women are managed similarly in hospital regarding most aspects. Higher case fatality and ADL dependency rates were observed in women, but the differences could be explained by women’s higher age and lower level of consciousness on admission to hospital. Women were less likely to receive lipid-lowering drugs at discharge from hospital. They were also less satisfied with the hospital care. Studies with more detailed information on stroke severity and co-morbidities are needed to further explore women’s lower level of consciousness at hospital admission and differences in secondary complications.

Patient-reported functional outcome, as reported in a large quality register, can be transformed into mRS-grades with a high precision. The translation can be useful for future comparative purposes in stroke outcome studies.

Impaired functional outcome after stroke is an independent predictor of poor survival. The association between functional outcome three months after stroke and long-term survival is stronger than that of several other well-known prognostic factors including diabetes, smoking and atrial fibrillation. The causal relationship requires further exploration in studies with other designs.

Self-reported depression is common three months after stroke and was associated with female sex, age below 65 years, living alone or in an institution, and being ADL-dependent. Antidepressant therapy at 3 months was liberally used after stroke, but one half of the patients reporting depressive mood did not receive antidepressant therapy at 3 months after stroke. Clinical practices to detect and treat post-stroke depression may be sub-optimal. Studies using more detailed methodology to assess diagnostic criteria for post-stroke depression and effect of treatment in routine clinical practice are warranted.
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