The burden of stroke in Sweden

Studies on costs and quality of life based on Riks-Stroke, the Swedish stroke register.

Ola Ghatnekar
# Table of Contents

Table of Contents  
Abstract  
Sammanfattning på svenska  
Abbreviations  
Original papers  
Introduction  
Stroke – risk factors and incidence  
The burden of stroke  
Survival and Quality of Life  
Direct and indirect costs of stroke in Europe and Sweden  
The Riks-Stroke registry  
Management of stroke in Sweden  
Objective  
Methods  
Estimating the burden of disease  
Data sources  
The EuroQol EQ-5D instrument  
Cost calculations (Papers I, II, and IV)  
Statistical methods  
Ethical considerations  
Results  
The societal cost for a first-ever stroke in 1997 (Paper I)  
Inpatient costs for stroke with atrial fibrillation (Paper II)  
Mapping utility weights to patient-reported outcome variables in the RS (Paper III)  
The societal cost for first-ever stroke in 2009 and comparison with 1997 (Paper IV)  
Additional results  
Discussion  
General discussion  
The cost of illness of stroke (Papers I and IV)  
Inpatient costs for stroke with atrial fibrillation (Paper II)  
Mapping utility weights to patient-reported outcome variables in the RS (Paper III)  
Conclusions  
Future developments of Riks-Stroke in health economics  
Acknowledgements  
References  
Appendix (EQ-5D questionnaire)  

i  
ii  
iv  
vi  
vii  
1  
3  
3  
4  
6  
8  
9  
10  
13  
14  
16  
16  
17  
19  
21  
23  
25  
26  
26  
29  
30  
32  
33  
34  
35  
47
Abstract

The costs for managing stroke are not limited to the acute hospital phase but can extend throughout life as mental and physical disabilities are common. These impairments also generate intangible costs in terms of reduced health-related quality of life. The aim of this thesis was to quantify this stroke-related burden with data from Riks-Stroke (RS), the Swedish stroke register.

Resource data and patient characteristics on first-ever stroke patients from RS were complemented with data on additional stroke-related hospitalisations and date of death from the National Board of Health and Welfare. Unit prices for hospital and primary care, secondary drug prevention, home and residential care services, and production losses were taken from official sources. The present value lifetime costs were estimated from the expected survival and discounted by 3%. The EQ-5D quality of life instrument was used on a subset of patients at 3 months after the index event. Standard descriptive and analytic (multivariate regressions) statistical methods were used.

The average lifetime societal present value cost per patient in 2009 (n = 9,064) was approximately €69,000. Of this, home and residential care due to stroke accounted for 59% and indirect costs for productivity losses accounted for 21% (year 2009 prices). Women had higher costs than men in all age groups as they were living alone to a greater extent than men and, therefore, needed more support with activities of daily living (ADL). Patients treated at a stroke unit had a low incremental cost per life-year gained compared to those who were not. The estimated disutility from stroke was greatest for women and the oldest, but the size of the disutility depended on the choice of comparator for the general population. Compared to a cohort from 1997 (n = 4,357), the index hospitalisation costs in 2009 were stable; the cost for recurrent stroke fell; and long-term costs for ADL support increased in part due to a changed age structure. After a revised assumption on the costs for outpatient visits and rehabilitation in 1997, the total cost per patient had increased in 2009.

The effect of atrial fibrillation (AF) on stroke-related inpatient costs was estimated on the basis of 6,611 first-ever stroke patients in 2001. Along with the acute and recurrent hospitalisation, any hospitalisation with stroke as a secondary diagnosis was included. A total of 1,619 patients (24%) had AF, and during the 3-year follow up period their present value inpatient cost was €367 higher than for non-AF stroke patients (€8,914; P<0.01; year 2001 prices). Because the index case fatality was higher among AF patients, the cost difference was higher for patients surviving the first 28 days. A
multivariate regression revealed that AF, diabetes, stroke severity, and death during the 3-year period after the index event were independent cost drivers.

Cross-sectional data sets from 2007 and 2009 were used for mapping patient-reported outcome measures from RS to EQ-5D weights. Three regression techniques (OLS, Tobit, and CLAD) were used on an estimation set (n = 272), and the resulting coefficients were applied to a validation set (n = 272). The mean utility was overestimated with all models and had lower variance than the original data, but could be suitable for group level analyses.

In conclusion, the total societal lifetime direct cost for the approximately 22,000 first-ever stroke patients in Sweden amounted to €1.513 billion, whereof €314 million was due to production losses. As a comparison, the total health care expenditure in Sweden in 2009 was €29.1 billion, although not all home and residential care services were included in this figure. In addition to this burden, about 56,600 quality adjusted life-years were lost due to premature death and disability. As a result of the improved capture of resource data suitable for cost calculations, the RS could be used for cost-effectiveness studies. Including a preference-based quality of life instrument in the RS could allow for cost-utility analyses to be made for comparisons with other conditions. However, it is important to control for patient characteristics in comparator arms in order to avoid bias.


I den första studien som omfattade 4357 personer med insjuknande under 1997, skattades livstidskostnaden per person till €75 635 (2000 års priser). Av detta utgjordes 20 procent av produktionsförluster. Kvinnor hade högre långtidskostnader för omsorgseftersom de i större utsträckning än män var ensamboende. Män hade högre indirekta kostnader p.g.a. för tidig död och reducerad arbetsförmåga eftersom de hade högre löner och var nästan dubbelt så många jämfört med kvinnor i åldersgruppen under 65 år.

Hur förekomsten av riskfaktorn förmaksflimmer (AF) påverkar stroke-relaterade slutenvårdskostnader studerades i en kohort på 6611 personer som nyinsjuknat i stroke 2001. Förutom förstagångs- och ev. återinsjuknande i stroke ingick sjukhusinläggningar med stroke som bidiagnos. Under en 3-års uppföljningstid hade personer med AF (24%) vid indextillfället €367 högre kostnader jämfört med personer utan AF (€8 914; P<0.01; 2001 års priser). Eftersom dödligheten var högre vid AF var skillnaden i kostnader högre för dem som överlevde de första 28 dagarna efter insjuknandet. En statistisk analys visade att diabetes, medvetandegrad vid det akuta omhändertagandet och död inom uppföljningstiden var oberoende kostnadsdrivare.

Tvärsnittsdata, d.v.s. både förstagångs- och återinsjuknade i stroke, under åren 2007 och 2009 användes för att koppla patientrapporterade utfallsmått i RS till EQ-5D-vikter. EQ-5D är ett sjukdomsoberoende frågeformulär för att mäta livskvalitet. Tre regressionsmodeller (OLS, Tobit och CLAD)
användes på en delmängd av observationerna (n=272) för att skatta koefficienterna. Valideringen av modellerna gjordes på en annan delmängd (n=272) som visade att den genomsnittliga EQ-5D-vikten överskattades med samtliga modeller och med lägre varians än originaldatan, men bör kunna användas vid gruppanalyser.

Med en liknande metod som i den första studien skattades livstidskostnaden för 9064 förstagångsinsjuknande under 2009 till €69 000 per patient (2009 års priser). Långtidskostnader för omsorgsbehov utgjorde 59% och indirekta kostnader 21%. Kvinnor hade högre kostnader i alla ålderskategorier p.g.a. högre omsorgsbehov. Patienter som vårdats på stroke-enhet (SU) hade en låg extra kostnad per vunnet levnadsår jämfört med dem som inte fått vård på SU. Den skattade livskvalitetsförlusten p.g.a. stroke var störst för kvinnor och för de äldsta men storleken berodde i stor utsträckning på valet av referenspopulation för den genomsnittliga befolkningen. I förhållande till resultaten i första studien var kostnaderna för slutenvård vid första insjuknandet ungefär desamma men kostnaden för återinsjuknande var lägre. Omsorgskostnaderna ökade framförallt p.g.a. en förändrad åldersstruktur. Ett antagande kring återbesök och rehabilitering visade sig vara kraftigt överskattad i den första studien och reviderades därför för att underlätta jämförelsen.

## Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADL</td>
<td>Activities of Daily Living</td>
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<td>AF</td>
<td>Atrial Fibrillation</td>
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<td>CLAD</td>
<td>Censored Least Absolute Deviation</td>
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<td>CT</td>
<td>Computed Tomography</td>
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<td>DRG</td>
<td>Diagnosis-Related Group</td>
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<td>EQ-5D</td>
<td>EuroQol 5D index</td>
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<td>ICD</td>
<td>International Classification of Diseases</td>
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<td>LOS</td>
<td>Length Of Stay (hospitalisation)</td>
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<td>IPR</td>
<td>Swedish National Inpatient Register</td>
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<td>OLS</td>
<td>Ordinary Least Square</td>
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<td>PROM</td>
<td>Patient Reported Outcome Measure</td>
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<td>QALY</td>
<td>Quality Adjusted Life Years</td>
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<td>QoL</td>
<td>Quality of Life</td>
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<td>RS</td>
<td>The Riks-Stroke registry</td>
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<td>SU</td>
<td>Stroke Unit</td>
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<tr>
<td>TIA</td>
<td>Transient Ischaemic Attack</td>
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<tr>
<td>VAS</td>
<td>Visual Analogue Scale</td>
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Original papers


The original papers will henceforth be referred to with Roman numerals.

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Introduction

Stroke is the second most common cause of death after cardiovascular diseases, and in 2008 it was estimated that 6.1 million persons died worldwide (1.3 million in Europe) due to stroke and other cerebrovascular diseases [1]. Although it has been reported that the age-specific incidence is falling in high-income countries, there is a trend toward increasing incidence in low- and middle-income countries [2, 3]. In Sweden, 30,000 persons have a stroke annually whereof approximately three quarters are first-ever strokes. The number of deaths in Sweden with any stroke diagnosis has fallen steadily since the millennium to around 8,000 in 2011, which means that the number of persons who have experienced a stroke has increased [4].

For those who survive, stroke can have consequences on both physical and mental abilities that require long-term resources for care and nursing. However, the burden of stroke extends beyond the cost for these resources, as increased disability can be seen as an intangible cost in terms of reduced quality of life (QoL). The aim of this thesis was to quantify this burden of stroke based on data from Riks-Stroke, the Swedish stroke register.

Stroke – risk factors and incidence

The brain needs a continuous supply of oxygen and nutrients delivered through the blood, and a disturbance of the blood flow causes immediate damage. The size of the damage depends on the level of flow restriction, the duration of the restriction, and what brain cells are affected. The restriction can be caused by a blockage (ischaemia) or bleeding (haemorrhage) [5]. The vast majority of strokes in Sweden are due to ischaemia (88%) with a thrombotic or an embolic origin [6].

The clinical diagnosis of stroke is defined as a rapid development of clinical signs of mainly focal symptoms of brain function disturbances with an assumed vascular origin that last more than 24 hours or result in death. [5, 7]. A transient ischaemic attack (TIA) has the same definition but it lasts less than 24 hours. Early signs of stroke are sudden face drooping (when part of the face is hanging), arm or leg weakness, or speech difficulty. Often only one side of the body is affected. These three signs can be used for early recognition of stroke or TIA and, together with a quick response, form the acronym FAST (Face, Arm, Speech, and Time) [8]. However, depending on the type and location of the stroke, both the symptoms and the management of stroke differ.

Ischaemic stroke has some risk factors in common with other cardiovascular diseases as their underlying aetiology is atherosclerosis although
there are some evidence for more complexity in stroke [9]. The most common non-modifiable risk factors for suffering a stroke are age, sex and race/ethnicity. Modifiable risk factors include hypertension, atrial fibrillation (AF), diabetes mellitus, dyslipidaemia, physical inactivity, and smoking [10]. Combinations of any of these factors increase the risk for stroke. Although a certain risk factor might have a high risk for stroke, the incidence of stroke might not be very sensitive to this risk factor if it is not prevalent in the general population. Conversely, a prevalent risk with only a moderate relative risk for stroke might have a greater impact on the incidence of stroke [11]. As such, hypertension, AF, smoking, and low physical activity are important risk factors from a population perspective [9].

In most Western countries, the age-standardised stroke incidence has fallen although variations between countries exist [2, 12]. A recent publication has shown that the incidence rate for ischaemic stroke in Sweden has fallen between 1987 and 2010 to such an extent that the number of first-ever strokes has decreased despite an increasingly elderly population [13]. However, the study also indicated that the incidence rate was increasing among those aged 18 to 45 years. The incidence rate increases almost exponentially (by a factor of 2.7) for every 10-year age group starting at age 45 (Figure 1). As such, the incidence rates were 61 per 100,000 person-years for persons aged 45–54 years and 1,278 for persons aged 75–84 years during the period 2005–2010. The incidence of intracerebral haemorrhage (data from 2005–2006) has a less pronounced age relationship [14].

Figure 1. First-ever stroke incidence from 2005 to 2010 by gender

Legend: Isc = ischaemic stroke; IH = intracerebral haemorrhage
Sources: Rosengren et al. [13] and Harmsen et al. [14]
The burden of stroke

Survival and Quality of Life

Each year approximately 30,000 persons suffer a stroke in Sweden, and 25% of these are recurrent strokes occurring within 7 years since the previous stroke (Figure 2). At the same time approximately 8,000 patients die with a stroke diagnosis annually, although survival after stroke is improving. This means that the number of persons who have had a stroke is increasing. In fact, even though age is a strong risk factor and Sweden has an ageing population, the decrease in incidence has led to fewer first-ever strokes in terms of absolute numbers [13]. Favourable trends are also seen in other European countries, but there is a great variability between countries [2, 12, 15].

Figure 2. Development of age-standardised incidence and mortality rate in stroke per 100,000 persons.

Survivors of stroke often suffer from both physical and mental disabilities that reduce their health-related QoL and can be seen as an intangible cost [16, 17]. Although several stroke-specific instruments are available to measure the QoL after stroke, they do not allow for a comparison with other conditions or with the general population [18]. Valuing this intangible cost for reduced QoL in terms of utilities, however, has bearings in economic theory and allows for such comparisons to be made. (See the section Estimating the burden of disease for further details on utilities). Reported
utility values in the literature have been shown to depend on several factors such as age, gender, comorbidities, type and severity of the stroke, etc., and have ranged from 0.00 to 0.70 elicited with the EQ-5D index questionnaire \[16, 19-23\]. Important determinants for reduced utility are depression, activities of daily living (ADL) dependence, and pain. \[20, 24\]. As a comparison, patients with ischaemic heart disease reported a utility in the range of 0.45 to 0.88, patients with heart failure in the range of 0.31 to 0.78, and patients with peripheral vascular disease in the range of 0.33 to 0.78 depending on severity \[25\]. A common limitation with studies measuring utility, however, was the rather small sample sizes.

In Sweden, the utility has been estimated to range between 0.44 and 0.67 in part depending on patient characteristics \[19, 21, 26\]. A similar variation in utility is presented in the section Additional results below based on a formula for translating some of the RS variables into EQ-5D utilities. As a comparison, the utility value for the Swedish general population has been estimated to range from 0.63 to 0.80 depending on gender, age, and study population \[27, 28\]. The reduction in QoL from experiencing a stroke compared to the Swedish population at large would, therefore, constitute the difference in utilities, i.e. the disutility.

The QoL implications are not limited to the person experiencing the stroke but extend also to caregivers \[29-31\]. Rather few studies measuring the disutility for caregivers are available, and those that are have tended to use different methodologies. The disutility has been estimated to range between 0.02 and 0.06 in the UK and Sweden \[32, 33\]. In a study from the Netherlands, a positive effect on QoL was seen among less burdened caregivers (0.08) but a disutility of 0.14 was seen among moderately burdened caregivers compared to the general population. This indicates a non-uniform QoL burden among caregivers \[31, 34\].

### Direct and indirect costs of stroke in Europe and Sweden

The cost of stroke has been estimated in Sweden since the 1980s, but differences in methodology, patient samples, cost perspectives, treatment practices, and organisational changes (e.g. the Ådel reform) limit the value of comparisons \[35-42\]. Comparisons between countries are equally limited due to different treatment practices, health care and nursing structures, and relative prices \[43\]. A common trait, though, is that the acute phase is critical in stroke management and, therefore, consumes a significant amount of resources. Pre-hospital interventions, specialised stroke units (SUs), diagnostic imaging, surgical interventions, and the in-hospital stay all together constitute the major cost item in the first year after stroke \[42, 44\].

A recent study commissioned by the European Brain Council (CDBE2010) estimated the cost for stroke in 30 European countries using a top-down
methodology with costs adjusted for purchasing power parity to better allow for comparisons. The direct cost for incident stroke was estimated to be almost €27 billion during the first year, or €21,000 per patient [45]. A similar result, €20,100 per patient in the first year, was reported in a study analysing first-ever strokes in the Västra Götaland health care region of Sweden (2008 prices) [41].

Due to impairments after the acute phase, resources for rehabilitation, secondary prevention, and ADL support are often required for the rest of the patients’ lives. In many countries, the responsibility for these resources lies with parties other than the formal health care system. In Sweden, such responsibilities fall upon the municipalities which provide a significant portion of the rehabilitation, ADL support at home, and housing for disabled persons. Furthermore, some care is provided by non-compensated caregivers (informal care) and this can be extensive in some countries or settings [46, 47]. These long-term costs for strokes, i.e. those related to a stroke in previous years, were estimated in the CDBE2010 study to be approximately €5,000 per patient per year in Europe [45]. Of this 28% were due to non-medical costs. The corresponding cost per survivor in Paper IV was approximately €6,700 excluding informal care.

Hence, to calculate the total cost for stroke, it is important to consider costs during the remaining years in life regardless of whether a prevalence or incidence approach is taken (see the section Estimating the burden of disease). The CDBE2010 study used a prevalence approach and concluded that the total direct cost for stroke in Europe was €59.1 billion in 2010. The corresponding cost in Sweden was estimated to be €1.2 billion. In addition, €4.9 billion in production losses were due to work absence or early retirement (€0.1 billion in Sweden). In Paper IV, the corresponding lifetime direct costs for Sweden were also estimated to be €1.2 billion, although a discount rate of 3% was applied. For comparison, the direct costs in the CDBE2010 study and Paper IV constituted 4.8% and 4.1% of the total health care expenditures in Europe and Sweden, respectively, although not all home and residential care services were included in these expenditures. The indirect cost was estimated in Paper IV to be €0.3 billion, and this estimate also included production losses due to premature death.

Although the incidence of stroke is falling in many European countries, long-term costs for health care and ADL support will likely continue to increase due to the demographic profile of an ageing population with improved survival. Initiatives for preventive measures and further advances in stroke management are, therefore, important.
The Riks-Stroke registry

The Riks-Stroke registry (RS) is the Swedish national quality registry for acute stroke that was established in 1994 to improve care and to ensure a uniform quality of care across Sweden [48]. The registry includes and analyses stroke defined as “haemorrhagic” (ICD10: I61), “ischaemic” (ICD10: I63) and “stroke not specified as haemorrhagic or ischaemic” (ICD10: I64). Since 1998, the RS covers all hospitals in Sweden that admit acute stroke patients and has currently a coverage of more than 90% of all hospital admissions for first-ever acute stroke [49]. The acute stroke (index) period is defined as the first 28 days after stroke onset and any recurrent strokes within this period are considered part of the index stroke [48].

Data collection in the RS is through case records completed by the hospital staff in the acute phase and by questionnaires administered to surviving patients 3 months after stroke. Since the year 2009, a 12-month follow-up questionnaire has been routinely distributed to survivors [48]. The questionnaires can also be answered by telephone interviews or by a caregiver. The information collected covers patient characteristics and risk factors, health care and process variables, outcome data, and patients’ experiences of the stroke care provided to them. The full case record forms and questionnaires for different years are available in several languages at http://www.riks-stroke.org/.

Riks-Stroke also aims at supporting research in stroke management. To date Riks-Stroke has contributed to several PhD dissertations and insights into the development of baseline stroke patient characteristics [6], improved thrombolysis therapy rates [50-52], increased statin treatment [53], decreasing heparin use [54], the effect of SUs [55], and gender differences in stroke care [56], to mention a few.

Management of stroke in Sweden

In 2000, the National Board of Health and Welfare presented the first national guidelines for prevention, acute management, and rehabilitation of stroke [57]. These were followed by revisions in 2005, 2009, and a minor addition in 2011. The work on a new edition has recently begun. Guidelines for cardiac care were published in 2008, which shared some common preventive measures. These evidence-based recommendations for encouraging preventive practices have contributed to some of the improvements in e.g., patient characteristics at stroke admission and reduced incidence of ischaemic stroke [6, 13, 14].

The development of acute stroke management can be traced in the RS, and the proportion of patients treated at SUs has increased from 60% in
1995 to 89% in 2011. In parallel, the mean number of total hospital bed-days fell from 20 to 15 days in part due to the introduction of early discharge to home for patients with mild or moderate disabilities. Diagnostic imaging (computed tomography) increased from 90% to 98%, and this reduced the diagnosis of undetermined stroke from 9.0% to 1.6% thereby facilitating adequate treatment. The widened time window for thrombolysis therapy, and the introduction of pre-hospital stroke alarm, have had a direct impact on the therapy rates in 2008 and reached 10% in 2011 [58]. Although the coverage in the RS has increased over time, and older data therefore might be underreported, improvements in stroke care and prevention can be seen in Figure 3 as the increase in 28-day survival among first-ever stroke patients and reduction in ADL-dependence at 3 months.

Figure 3. Development of first-ever stroke survival at day 28 and ADL-dependency at month 3 after the index event.

Source: National Board of Health and Welfare, Statistical Database and Riks-Stroke
Objective

The objective of this thesis was to study the burden of stroke in Sweden using data from the RS even though the RS was not originally designed for health economic studies. The studies include analysis of both direct and indirect costs and their decompositions as well as intangible costs in terms of quality of life.

The specific aims of each paper were as follows.

Paper I. To estimate the societal cost for a first-ever stroke in 1997. This cost would represent the value of preventing a stroke event.

Paper II. To analyse the impact of AF and other comorbidities on stroke-related inpatient costs among first-ever stroke patients in Sweden.

Paper III. To develop an algorithm for transferring patient-reported outcome measures in the RS to utility weights to allow for analyses of stroke care developments in terms of QALY gains or losses.

Paper IV. To estimate the societal cost for a first-ever stroke in 2009 and to compare these costs with the estimates from Paper I.
Methods

Estimating the burden of disease

Cost of illness studies, or burden of illness, describe the direct costs (resources consumed as a consequence of the condition), indirect costs (production losses because of morbidity and mortality), and intangible costs (disability or QoL loss). These studies do not compare different interventions, and therefore do not provide guidance on how to allocate scarce health care resources in the “production of health”. Still, they are generally considered part of health economics as they inform decision makers about the scope and size of health problems [17, 59-61]. This information can in turn be used for political prioritising in health care.

An important distinction to make is the epidemiological perspective used, incidence or prevalence, as they can answer different questions. With an incidence approach, costs are estimated for all new cases entering a certain health condition, e.g. the first ever stroke or the first recurrent stroke. In order to account for time preferences, costs occurring in the future are discounted to make them comparable in time (the present value, see below). Such studies provide information on the value of preventive measures and how costs develop with disease progression. Prevalence-based studies describe the cost for all current cases with the condition at a given point in time regardless of when the condition developed. This approach can estimate the total cost, in a certain year, for persons that have ever experienced a stroke. If large enough, prevalence studies can be stratified according to disease progression to describe the development of costs over time. Assuming an epidemiological and an economic steady state, the incidence and prevalence approaches should, in theory, generate the same total cost for the condition at a zero discount rate [62].

The primary goal of burden of illness studies is to capture the costs accrued as a result of the condition studied and not the overall health care consumption or QoL for a person with certain characteristics [59]. Because age is a risk factor for stroke as well as for other conditions, it is important to isolate the resources consumed, or foregone, that are attributable to stroke only, i.e. the excess cost of stroke. This can be done by, for example, estimating total costs for two similar cohorts – one with a condition and one without – and then calculating the difference between the two [59]. It is also possible, as with data from the RS, to control for certain factors that are known to, or expected to, constitute major cost drivers before the onset of the condition, such as the need for home assistance.

Although the intangible costs can be valued in monetary terms by studying the willingness to pay to avoid a condition, they are most often
valued as the loss of health-related QoL. To quantify this loss, instruments that capture the domains in QoL specific to stroke have been developed such as the Stroke Impact Scale and the Stroke-specific Quality of Life Scale [18]. The loss can also be measured as utilities that reveal individuals’ preferences for different health states with different implications on their QoL [17]. The advantages of measuring the burden in terms of utilities instead of life-years or a disease-specific measure is that utilities combine life-years with QoL and they allow comparisons across diseases, i.e. it is a generic measurement. As such, the burden of fatal conditions can be compared with chronic conditions in terms of quality adjusted life-years (QALY). Direct elicitation of utilities can be made by standard gamble (SG; varying probability of death) or time trade-off (TTO; varying time in health states) techniques, but these are complicated and time-consuming tasks. Unlike SG and TTO, rating scales do not include choosing between alternatives and are often considered theoretically inferior [63]. Therefore, easy-to-use questionnaires with multi-attribute health statuses with pre-scored preferences elicited through SG or TTO, so-called tariffs, have been developed to measure utilities indirectly. One such instrument is the EQ-5D that was used in Paper III and is described in the section The EuroQol EQ-5D instrument.

**Data sources**

The cost calculations in this thesis were based on the RS data. The information used covered patient characteristics, health care resources, process variables as well as patient-reported outcome measures. Since the inception of the RS, the acute questionnaire has covered resource variables such as living arrangements and ADL dependency before the stroke, hospital length of stay (LOS), drug treatments at the hospital, post-acute hospitalisations for rehabilitation, and location of discharge (own home, residential home, etc.). In the follow-up questionnaire, living arrangements, ADL dependency, and some patient-reported outcome measures have been surveyed. Over the years more variables have been added and some withdrawn [48]. Table 1 presents an overview of the variables from the RS questionnaires that were used in Papers I, II, III, and IV.

The acute phase questionnaire surveys the patient’s living arrangements and ADL before the stroke. The same questions appear in the follow-up questionnaire, and this allows for estimating the change in ADL and living arrangements due to the stroke. Because stroke mainly affects elderly patients who may suffer from other disabilities, the RS data is well suited for isolating the cost for stroke-related impairments. Furthermore, many of the health care and process variables allow cost calculations in the inpatient
setting and, more recently, also in the outpatient setting, drugs, and production losses.

Because the RS only covered approximately 75% of all stroke patients in 1997, hospital admissions for stroke in Paper I were complemented with data from the National Inpatient Register (IPR) to increase the representativeness of the data [64]. In Paper II, we also included hospitalisations with stroke as secondary diagnosis with data from the IPR. This registry, also known as the Hospital Discharge Register, is held by the Swedish National Board of Health and Welfare and covers more than 99% of all hospital discharges with an 85% to 95% predictive value in diagnosis [65]. In addition, the date of death during the follow-up period in Papers I, II, and IV was taken from the Cause of Death Register that is also held by the Swedish National Board of Health and Welfare. The matching of cases in the RS to the registries at the Swedish National Board of Health and Welfare was performed on the basis of personal identification numbers.
<table>
<thead>
<tr>
<th>Table 1. Riks-Stroke variables used in Papers I to IV</th>
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</thead>
<tbody>
<tr>
<td><strong>Cohort</strong></td>
</tr>
<tr>
<td>Living arrangement</td>
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<tr>
<td>ADL dependency</td>
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<tr>
<td>Secondary drug prevention</td>
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</tr>
<tr>
<td>Out-patient follow-up and dentist visit</td>
</tr>
<tr>
<td>Production losses</td>
</tr>
</tbody>
</table>

Note: LOS = length of stay; adm. = admission; PROM = patient reported outcome measure; w/o = with or without; DRG = diagnosis-related group
The EuroQol EQ-5D instrument

The EQ-5D questionnaire included in Paper III is a generic preference-based instrument for measuring health-related QoL expressed in terms of utility [66]. The term *generic* indicates that it is not a disease-specific instrument that is designed to capture QoL aspects specific to stroke. The advantage is that the same instrument can be used for a variety of conditions to provide a health profile or state, although a disease-specific instrument often is more sensitive to disease-related changes. When these health states are ranked by individuals according to desirability, or *preference* for one health state over another, welfare economics – aiming at maximizing utility – is introduced in the measurement of health [63]. As such, a preference-based instrument is suitable for decisions concerning resource allocation in health care.

The EQ-5D questionnaire covers the following five dimensions of health-related QoL: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression (Appendix). The respondent is asked to report his/her current health as a 1 (no problems), a 2 (some or moderate problems), or a 3 (extreme problems). This allows for 245 unique health states including death and unconsciousness. In order to assign utility weights to these health states, a UK value set, or tariff, is used in lack of a Swedish tariff [67]. These utility weights are, in theory, bounded between 0.0 (death) and 1.0 (full health) where higher values are preferred over lower values, e.g. 0.7 is preferred over 0.4. The UK tariff, however, allows negative values (minimum -0.59), i.e. health states considered worse than dead. The weights can in turn be used to estimate the QALY, i.e. the utility weight times the life years (or survival) in that health state.

In addition, a visual analogue scale (VAS) is included in the EQ-5D questionnaire where the respondent is asked to rate their current health on a “thermometer” ranging from 0 (worst) to 100 (best). While the EQ-5D self-reported classification has shown reasonable psychometric properties in stroke patients, the EQ-5D VAS performed worse [68-70].

Generic preference-based instruments provide a common denominator for assessing health-related QoL. These instruments allow comparisons to be made between diseases or conditions and they are anchored in the valuation of, or preference for, health in the community. Along with disease-specific instruments, the inclusion of generic instruments has, therefore, today become more or less a common standard for outcome evaluations in clinical trials.
Cost calculations (Papers I, II, and IV)

The national stroke DRG weight (DRG code 14; “Specific cerebrovascular disorder, except transient ischaemic attacks”) was used for estimating the cost for acute hospitalisation in Papers I and IV. After the acute phase, patients can be referred to other wards for rehabilitation and costed according to LOS (Paper I) or DRG code 550 (“Rehabilitation of stroke”; Paper IV). Subsequent stroke readmission DRGs during the follow-up were complemented with data from the IPR in Paper I. Patients from the county of Skåne were not included in Paper I (approximately 1,000 observations) because they used a different DRG system.

In Paper II, studying only hospitalisation costs, all LOS with stroke as the primary diagnosis were costed at ward level while admissions due to stroke as a secondary diagnosis were costed by DRG. The rationale for this difference in methods was that DRGs might not be suitable for analysing subgroups [71, 72].

Stroke-related resources for ADL assistance at home were calculated from patient-reported assistance needs with: using the toilet (yes/no); getting dressed (yes/no); and mobility (no assistance needed, assistance outdoors, assistance both indoors and outdoors). Coding the answers as 0 for “no”, 1 for “yes” or “outdoors”, and 2 for “both indoors and outdoors” assistance produced a score ranging from 0 (no assistance needed) to 4 (full assistance needed in all 3 domains). The change in ADL score sums from baseline was estimated at 3- and 12 months (Paper IV) or 24 months (Paper I). The change in score sums (1, 2, 3, or 4) formed the basis for the additional resources needed for home assistance (16, 36, 48, and 76 hours per month, respectively) [73]. Likewise, stroke-related costs were calculated for patients reporting that they had moved to a municipal residential housing facility for elderly and disabled after the stroke.

The RS questions regarding follow-up visits and rehabilitation after hospital discharge have been developed over the years and could, therefore, be used in Paper IV. In Paper I, these costs were based on the control arm of a randomised clinical trial for rehabilitation at home after stroke [74]. This study included the annual number of physician, nurse, and rehabilitation visits among 38 patients undergoing routine rehabilitation.

Since 1998, the quality of information on the prescription of secondary stroke prevention drugs at discharge has increased in the RS questionnaires. However, using drug prescription at discharge as the basis for cost calculations would probably overestimate the true cost due to non-adherence, which might be as low as around 60% after two years [63]. This information was not available for use in Paper I and this is why a national survey on prescription patterns covering approximately 4% of all medical doctors in Sweden was used [75].
Information on labour force participation before and after the stroke as well as vocational rehabilitation was available from the 12-month questionnaire that has been administered since 2009. This information was used for calculating the change in productivity in terms of temporary sick leave, early retirement, part time work, or premature death due to stroke up to the age of 65. In Paper I, production losses for early retirement was based on information from the Swedish National Social Insurance Board. By including these indirect costs, the value of production lost due to the stroke was also considered. Production losses for informal care were not included.

Unit prices for all of the above-mentioned resources were taken from publicly available sources [76-81]. However, health care goods are often non-tradable goods in an imperfect market, and although unit prices in economic theory should represent the opportunity cost, i.e. the value of the benefits for an alternative use of the resource, tariffs and charges are often used [17, 82]. As such, these costs are primarily used for internal invoicing or budgeting purposes and might, therefore, be set to reflect organisational or political decisions. In addition, these unit prices might be based on a patient cohort not representative of the cohort studied thus adding further bias to the analysis. Nevertheless, these unit prices are still used for estimating costs in Swedish health care. Production losses were estimated using the human capital approach – the average gross wage including payroll taxes – to reflect the marginal value of production [17].

To calculate the lifetime costs of stroke, i.e. the costs incurred in year one and onward until death, both costs and effects, when applicable, were discounted by 3%, which was the recommended discount rate in Sweden for health technology assessments [83]. The argument for discounting costs and effects that occur in the future is based on the concept of time preferences – people generally prefer to receive a benefit today and postpone a cost until later rather than the other way around [17]. The formula used to calculate the lifetime present value cost (PVC) to the time of the index stroke was:

\[
PVC = \sum_{n=0}^{W} \left[ \frac{P_{n+1} \times AC_{n+1}}{(1 + r)^n} \right]
\]

where \(P_{n+1}\) is the probability that a person would survive to year \(n+1\) after the first-ever stroke, \(AC_{n+1}\) is the annual cost for a person surviving to age \(n+1\), \(r\) is the discount rate (3%), and \(W\) is the expected lifetime.
Statistical methods

Both descriptive (means and proportions) and analytic (multivariate regression) statistical analyses were performed. The non-parametric Wilcoxon Mann-Whitney U-test was used for analysing costs between patient strata. The Chi-square test was used for categorical variables and the level for significant difference was set to P<0.05.

A multivariate ordinary least square (OLS) regression of logarithmically transformed costs as the dependent variable was performed in Paper II to analyse the impact of certain patient characteristics. A stepwise forward inclusion of explanatory variables was based on Student’s t-test for significance (P<0.05). Re-transformation of the log-OLS model is not suitable for predictive purposes unless the error terms are normally distributed [84, 85].

In Paper III, three different multivariate regression models – OLS, Tobit and censored least absolute deviation (CLAD) – were evaluated to assess their predictive power of EQ-5D weights. Because the EQ-5D space has a ceiling value of 1.0, the two latter models were included as they allow for censored dependent variables. The performance of each model was evaluated based on goodness of fit (R²), mean absolute error, and mean squared error. In accordance with recommendations for mapping processes, plots of observed and predicted EQ-5D scores were also presented [86].

SPSS (IBM SPSS Statistics) versions 11.5.1, 12.02, and 20.0 were used in Papers I, II, and IV, respectively. Stata/IC version 11.2 (Stata Corp) was used in Paper III.

Ethical considerations

All patients included in this thesis were identified through the RS. Participation in the RS is voluntary and patients can deny participation or withdraw consent at any time. The results have been presented in an aggregate form (group level) in order to avoid potential identification of individuals. Data-handling procedures comply with the Swedish Data Inspection Board’s directives and codes of statutes in order to fulfil the Data Protection Act. The Regional Ethical Review Board at Umeå University approved studies on the Riks-Stroke data for Paper I and Paper II (95-168), Paper III (05-075), and Paper IV (2012-403-31M).
Results

The societal cost for a first-ever stroke in 1997 (Paper I)

In total 4,357 patients who had experienced their first-ever stroke during the first 6 months of 1997 were included in Paper I. Women were on average 5 years older (77 years) than men at the time of their first stroke, and the survival rate was higher for women in all age-groups except for the youngest (<65 years; Table 2 in Paper I). However, due to differences in age-group sizes the overall fatality rate was higher for women.

The average expected societal excess lifetime PVC was estimated to €75,590 in year 2000 prices (€1 = SEK8.45) based on extrapolation of the costs in year 4 to the rest of life according to adjusted life tables. Indirect costs for deaths before the age of 65, which was the official retirement age, and early retirement constituted 20% of the PVC.

The index stroke hospital admission was, on average, 22 days and amounted to €8,308 (Figure 4). Apart from the first year, costs for social services in terms of home assistance needs and residential housing due to the stroke constituted the greatest cost item and was, on average, €3,900 per year for surviving patients. Costs for outpatient follow-up visits, stroke rehabilitation, and drugs amounted on average to €2,200 per year per survivor, although these were based on assumptions and, therefore, might be less representative.

Figure 4. Direct annual costs per patient surviving the previous year after first-ever stroke in 1997.
Women lived alone to a greater extent and had higher needs for ADL support than men after the stroke. Hence, they had higher annual costs for social services. In combination with a longer life expectancy, the lifetime direct cost was higher for women in all age groups (Figure 5). The societal PVC was estimated to €76,663 for men and €74,556 for women, whereof indirect costs constituted 25% and 14% for men and women, respectively.

Figure 5. Lifetime direct costs attributable to first-ever stroke in 1997.
Inpatient costs for stroke with atrial fibrillation (Paper II)

Using the same incidence approach as in Paper I, 6,611 patients experiencing their first stroke during the first 6 months of 2001 were included in the analysis. Of these, a total of 1,619 (24%) patients were diagnosed with AF. The AF patients had more risk factors for stroke such as higher age, diabetes, and hypertension as well as greater stroke severity at admission and higher 3-year case fatality.

Inpatient costs for the index stroke, recurrent strokes, and other hospitalisations with a secondary diagnosis of stroke amounted to €9,300 and €8,900 for patients with and without AF, respectively, during the 3-year study period (Table 2). This was a result of 0.6 longer LOS and a higher frequency of recurrent strokes (AF: 15% vs. non-AF: 13%). However, the case fatality among patients with AF was higher than for those without AF during the first 28 days after the index event. For patients surviving this period, and thus exposed to a longer period of possible re-hospitalisations due to stroke, the 3-year cost increased to €10,200 and €9,400 for patients with and without AF, respectively. Furthermore, the presence of AF among patients aged less than 65 increased costs by 46% compared with those without AF.

Table 2. 3-year discounted stroke-related hospitalisation cost by strata, in 2001 Euro

<table>
<thead>
<tr>
<th></th>
<th>All patients</th>
<th>Index event survivors only</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All ages</td>
<td>All ages</td>
</tr>
<tr>
<td><strong>AF</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean cost</td>
<td>9,281</td>
<td>10,192</td>
</tr>
<tr>
<td>n</td>
<td>1,619</td>
<td>1,401</td>
</tr>
<tr>
<td><strong>Non-AF</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean cost</td>
<td>8,914</td>
<td>9,374</td>
</tr>
<tr>
<td>n</td>
<td>4,992</td>
<td>4,633</td>
</tr>
<tr>
<td>Cost difference</td>
<td>367*</td>
<td>818*</td>
</tr>
</tbody>
</table>

Legend: * denotes statistically significant difference (P<0.05)

Note: discount rate = 3%; index event defined as first 28 days after stroke onset; €1 = SEK9.25

In a linear regression with log-transformed 3-year costs, we controlled for the direct cost-driving elements such as exposure time to re-hospitalisations and the number of recurrent strokes during the study period (Table 3). Atrial fibrillation and diabetes increased inpatient costs by 11% and 18%, respectively while younger age-groups were less costly when 18 variables were controlled for.
Table 3. Determinants of 3-year stroke-related inpatient costs (log-transformed).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Exp(β)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Constant</strong></td>
<td>2584.29</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td><strong>Patient characteristics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male gender</td>
<td>0.95</td>
<td>0.02</td>
</tr>
<tr>
<td>Age &lt;65 years</td>
<td>0.90</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Age 65–74 years</td>
<td>0.90</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Institutional living</td>
<td>0.72</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Awake but sluggish on admission to hospital</td>
<td>1.60</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td><strong>Risk factors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation (AF)</td>
<td>1.11</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.18</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Interaction term: AF * Diabetes</td>
<td>0.87</td>
<td>0.03</td>
</tr>
<tr>
<td><strong>Inpatient management at index event</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Computed tomography</td>
<td>1.63</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Stroke unit</td>
<td>1.15</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td><strong>Number of recurrent strokes during the 3-year period</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>2.19</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>2</td>
<td>3.35</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>3 or more</td>
<td>6.95</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td><strong>Exposure time</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death within 3 years</td>
<td>1.32</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Death at index event</td>
<td>0.35</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td><strong>Health care region</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Northern Sweden</td>
<td>1.09</td>
<td>0.04</td>
</tr>
<tr>
<td>Stockholm-Gotland</td>
<td>0.92</td>
<td>0.01</td>
</tr>
<tr>
<td>Västra Götaland</td>
<td>1.15</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td><strong>Adjusted R²</strong></td>
<td></td>
<td>0.21</td>
</tr>
</tbody>
</table>

Legend: Exp(b) = exponentiated regression coefficient
Mapping utility weights to patient-reported outcome variables in the RS (Paper III)

In total, 544 observations with complete patient characteristics and EQ-5D index responses at 3 months after the index event were analysed. Of these, 105 and 439 were collected in 2006 and 2009, respectively, and statistically significant differences between the samples (P<0.05) were found in age, the proportion of patients admitted to an SU, ischaemic strokes (ICD-10: I63), and responses provided by a next of kin or health care professional (Table 1 in Paper III). Apart from admissions to an SU, these differences were considered sample selection biases. Only the frequency of AF differed in the random estimation and validation sets.

All three regression models generated consistent coefficients in terms of sign, although the size of the coefficients varied. The RS variables that had the greatest impact on utility were “Moody always” (compared to “Never or almost never moody”) and “Restricted mobility” (compared to “Full mobility”) (Figure 6). The coefficients could be seen as the impact a certain disability has on the measured utility. Only the coefficients for “Toilet assistance” and “Proxy response” were not statistically significant.

Figure 6. Regression coefficients for selected RS variables with EQ-5D weights as dependent variables.

Note: ns = not statistically significant (P≥0.05); OLS = ordinary least square; CLAD = censored least absolute deviation
Compared to the observed utility (0.60), all models over-estimated the mean and had lower variation. The prediction tests indicated that the OLS model was best suited for group-level prediction (mean utility 0.64) but also had the most compressed variation and did not attain the maximum EQ-5D weight of 1.00 (OLS max=0.90) (Table 3 in Paper 3). Furthermore, all three models were better at predicting utility weights that were greater than or equal to 0.5 than they were at predicting weights less than 0.50 (P<0.01). In other words, the regression models provided more accurate predictions for better health states than for worse health states.
The societal cost for first-ever stroke in 2009 and comparison with 1997 (Paper IV)

In total 9,064 patients who had experienced their first-ever stroke during the first 6 months of 2009 were included in Paper IV. Women were on average 5 years older (77 years) than men and were more frequently living alone with a higher need for home assistance or at residential housing (nursing home, service flat, etc.). Women also had a more severe stroke at admission and were more prone to have an AF and hypertension diagnosis.

The expected societal excess lifetime PVC were €69,685 and €67,846 for women and men, respectively (P=0.03), whereof 14% (women) and 30% (men) were indirect costs. Almost €10,000 was due to stroke hospitalisations in the first year, while costs for recurrent stroke hospitalisations were low (Figure 7). Municipality care, that is, costs for increased need for home assistance to perform ADL and residential housing due to the stroke, constituted a substantial long-term cost, especially for women. Production losses from premature death, temporary sick leave, and reduced productivity for patients aged less than 65 years falls over time as survivors reach the age of 65 years.

Sub-group analyses revealed that lifetime direct costs decreased with age as a result of shorter expected remaining life-years (Table 4, Paper IV). Irrespective of age, lifetime costs for men were lower than for women due to shorter life expectancy and less need for ADL support.

Figure 7. Annual cost per patient after first-ever stroke by cost item

Note: €1 = SEK10.62
The age structure in Paper IV had changed compared with the results in Paper I with higher fractions of patients aged younger than 65 years and older than 84 years (Figure 8). As a consequence, costs for home assistance and production losses increased in 2009 compared to 1997. Although the number of index hospitalisation days were reduced from 22 in 1997 to 17 in 2009, the hospitalisation cost did not change because the cost per day had risen. Costs for rehabilitation, outpatient visits, secondary drugs, and production losses were not directly comparable as these resources were based on assumptions in Paper I due to a lack of RS data. Using the 2009 cohort values (a more comparable assumption) would result in lifetime direct costs of around €51,400 and €43,700 for women and men, respectively (year 2009 prices), representing an increase in the year 2009 direct costs of 16% and 13%, respectively. Including 2 months of temporary sick leave for patients less than 65 years of age increased indirect costs by 8% in the year 1997 cohort.

Stroke unit care was used to exemplify how the RS data can be used for estimating the cost-effectiveness of technologies used in stroke care. Patients first admitted to an SU had lower lifetime costs than those who were transferred to an SU at a later stage of the hospital admission. Compared to patients not treated at an SU at all, costs were higher but with life-year gains that indicated that treatment at an SU could be cost-effective. However, differences in patient characteristics could have biased the results.

Figure 8. Age distributions in Paper 1 and Paper IV, by gender

<table>
<thead>
<tr>
<th>Age group</th>
<th>Female 1997</th>
<th>Female 2009</th>
<th>Male 1997</th>
<th>Male 2009</th>
</tr>
</thead>
<tbody>
<tr>
<td>84&lt;</td>
<td>11%</td>
<td>15%</td>
<td>11%</td>
<td>17%</td>
</tr>
<tr>
<td>75-84</td>
<td>22%</td>
<td>18%</td>
<td>30%</td>
<td>25%</td>
</tr>
<tr>
<td>65-74</td>
<td>43%</td>
<td>33%</td>
<td>37%</td>
<td>32%</td>
</tr>
<tr>
<td>&lt;65</td>
<td>34%</td>
<td>37%</td>
<td>32%</td>
<td>25%</td>
</tr>
</tbody>
</table>

0% 20% 40% 60% 80% 100%
Additional results

In the 3-month follow-up, 5,709 patients in the 2009 cohort answered the 11 variables that were used in the “transfer to utility” regressions in Paper III (response rate 76%). Patient characteristics were comparable with the sample in Paper III. Applying the OLS regression coefficients, the resulting utility at 3 months for first-ever stroke ranged from 0.48 to 0.74 depending on age and gender (Table 4). However, the OLS model slightly overestimated the utility by 6.7% so the true values could be expected to be lower. To estimate the disutility of stroke compared to the Swedish general population, two different studies representing the general population were used as they presented rather different results. The general QoL was lower in the sample covering the whole of Sweden, and the resulting disutilities from stroke were rather small in some age groups. In the county of Stockholm, the reported general population QoL was higher, especially among women, and, therefore, the disutility from stroke was higher. Applying these disutility weights for long-term disability and utility loss due to premature death would mean a total loss of between 1.8 to 3.4 QALYs for women and 2.2 and 2.8 for men depending on the reference (discount rate 3%). This means that the approximately 22,200 persons that suffered from their first stroke in 2009 lost in total about 56,600 QALYs, that is, on average 2.5 life-years in perfect health or 4.0 life-years for a person aged 75 (utility weight 0.63).

Table 4. Estimated utility and disutility among stroke patients at 3 months post-stroke in 2009 compared to the general population in Sweden.

<table>
<thead>
<tr>
<th>Age group (years)</th>
<th>Year 2009 stroke cohort</th>
<th>Disutility relative to:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Response frequency</td>
</tr>
<tr>
<td>Female</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65</td>
<td>476</td>
<td>76%</td>
</tr>
<tr>
<td>65–74</td>
<td>610</td>
<td>81%</td>
</tr>
<tr>
<td>75–84</td>
<td>919</td>
<td>76%</td>
</tr>
<tr>
<td>84&lt;</td>
<td>689</td>
<td>68%</td>
</tr>
<tr>
<td>Male</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65</td>
<td>792</td>
<td>74%</td>
</tr>
<tr>
<td>65–74</td>
<td>879</td>
<td>83%</td>
</tr>
<tr>
<td>75–84</td>
<td>955</td>
<td>78%</td>
</tr>
<tr>
<td>84&lt;</td>
<td>389</td>
<td>73%</td>
</tr>
</tbody>
</table>
Discussion

General discussion

The health economic discipline and its use in health care decision-making have developed quite remarkably since the beginning of the 2000s. An indication of this is a bibliometric study of publications in health economics over the course of four decades and the development of guidelines for good practice in the field (see http://www.ispor.org/workpaper/downloads.html) [87]. This development is also reflected to some extent in the four papers included in this thesis because they include descriptive, analytic, cost of illness, outcome research and, to a limited degree, cost-effectiveness analyses.

Health economic studies are intended for informing decision makers on consequences not only from past (ex post) but also from future (ex ante) investments in health care. As such, the information at hand is not always available from the same source and this is why references to other research as well as relying on assumptions might be necessary [59]. Weinstein and colleagues concluded the following in their guidelines for decision analytic modelling in health care evaluations:

“Models and their results should be represented as aids to decision making, not as statements of scientific fact; therefore, it is inappropriate to demand that models be validated prospectively before use. However, model assumptions regarding causal structure and parameter estimates should be continually assessed against data, and models should be revised accordingly.”


As a means for decision makers to assess the uncertainty in the results, the interest in, and methods for, sensitivity analyses has developed. And as uncertainty occurs both in costs and effects, outcomes research also evolved strongly in the last decade.

The cost of illness of stroke (Papers I and IV)

Although identical methodology in the 1997 and 2009 cohort studies was strived for, improvements in the RS data allowed for fewer assumptions the 2009 cohort study. In deciding between comparability between studies and representativity of today’s stroke management, the latter was chosen. In accordance with this choice, the lifetime societal cost of stroke for a cohort suffering the first stroke in 1997 was revised in Paper IV. At the time of Paper
I, information on outpatient visits, rehabilitation, secondary drugs, and labour force participation were missing and assumptions had to be made based on the literature and official documents. In the work with Paper IV, however, it was concluded that the assumption on outpatient visits and rehabilitation were over-estimated in the year 1997 cohort as these resources were not supposed to have diminished between the study periods.

By applying a similar cost as in the 2009 cohort study, which might still be an overestimation, the revised lifetime direct cost for the 1997 cohort decreased by 28%. In fact, this assumption changed the comparison from indicating reduced costs between the study periods to an indication of increased costs for managing stroke in 2009. Furthermore, drug costs for secondary prophylaxes were probably overestimated in both studies, although they did not constitute a large cost item. It is well established that drug persistence declines with time for different reasons, and applying information based on the RS data would reduce long-term drug costs in Paper IV by 26% (<1% of the total direct costs) [89, 90]. Likewise, the indirect costs increased by 8% if 2 months of temporary sick leave were added in the 1997 cohort. These earlier shortcomings highlight the importance of continuously reviewing previous work as more detailed data and/or treatment practices become available. Thus, the revised 1997 cohort costs amounted to €62,000 per patient in year 2009 prices (24% indirect costs) compared to €69,000 for the 2009 cohort (21% indirect costs).

In 2003 the number of registrations in the RS levelled off at around 25,000 annually with a national coverage of 85% in 2009 compared to 75% in 1997 [6, 48, 64]. The main improvement in RS coverage during the study period from 1997 to 2009 has been made among incident cases, including patients dying very early after arrival to the hospital, which can explain the increased fatality rate during the index period [6, 91]. At the same time, registrations of the youngest (<65 years) and oldest (85+ years) increased, and the age group differences in survival for men compared to women diminished. These confounders could have introduced bias in the comparison between the cohorts. However, hospitalisation data in Paper I was complemented with information from the IPR that together covered 96% of all first-ever strokes [65]. On the other hand, patients in the southern health care region were excluded due to differences in the DRG-system that introduced a selection bias. As a consequence, it is difficult to compare the representativity in the two studies because bias might have been introduced both through differences in geographical treatment and nursing patterns as well as differences in patient characteristics [92].

Regional variability in unit costs and access to appropriate ADL-assistance has not been taken into account in Papers I, II and IV. In fact, the organisation of municipality services for ADL support has shifted from residential housing to home assistance in the 2000s, with an increasing
threshold for receiving support [93]. Furthermore, a constant age-dependent excess mortality compared to the general population was used for extrapolating survival, which might be a strong assumption. And when estimating the long-term costs, no adjustment was made for potential differences in stroke related excess costs when “moving” from one age-group to another. Hence, the main uncertainty in the cost estimations might not lie in the patient selection but in the resource use and cost calculations. It is, therefore, important that assumptions are explicit and transparent in order to facilitate challenging views and revisions of the results.

Another source for uncertainty in the cost calculations is the choice of methodological approach in estimating the indirect cost for premature death and morbidity. In contrast to the human capital approach used in Papers I and IV, which estimates the potential lost production, the friction cost method includes only lost production until the person is assumed to have been replaced by a newly trained and previously unemployed person [94]. In short, the friction method accounts for unemployment whereas the human capital approach assumes a labour market in a steady state. There are currently no studies on indirect costs for stroke comparing the two methodologies, but the friction cost estimates have been shown to be 44% to 99% lower than the corresponding estimates with the human capital approach depending on the condition studied [94-98].

Ideally, cost calculations of a condition should only include those resources that are accountable to the condition studied, i.e. the excess cost in comparison to a counterfactual scenario [59]. Because age is an important risk factor not only for stroke, it is possible that some of the included cost items might have been attributable to, or shared with, other co-morbidities such as cardiovascular diseases and diabetes. On the other hand, costs for hospital admissions with stroke as a secondary diagnosis were not included. According to Paper II, these admissions constituted 16% of all the admissions during a 3-year period with a mean DRG weight of 1.05. Assuming the same fraction of admissions and DRG weight due to stroke as secondary diagnosis in 2009 would increase the hospitalisation cost by €926 per patient over the 3-year study period.

In summary, the causalities for the cost differences between the 1997 and 2009 cohorts are difficult to disentangle because there were many factors involved, including preventive measures, patient characteristics, data coverage, changes in health care processes, organisation of the ADL support, and unit prices.

The estimated cost of stroke in Paper IV was slightly lower compared to a recent cost of illness study in a health care region covering 1.5 million inhabitants (16% of the Swedish population) [41]. That study estimated the average cost among 3,074 incident stroke patients in the first year to be €20,100 and the lifetime cost to be €80,000 (in year 2008 prices). In Paper
IV the corresponding cost per patient in the first year was €15,100 and the lifetime cost was €69,000 excluding informal care. The main differences between the previous study and Paper IV were the inclusion of pre-hospital costs and informal care (€1,300 in the first year) as well as higher municipality costs for ADL assistance. Furthermore, excess hospitalisation costs were calculated differently. In accordance with our results, their results indicated that municipality costs for ADL assistance constituted a major share of the long-term costs. The size of this share of course reflects the organisation of these resources. In the European CDBD2010 study, which included countries with higher tradition of caregiver nursing, the corresponding share for non-medical costs was 28%. Hence, the gains from investments in health care provided by the county councils can occur in other places in society, e.g. the municipalities or the caregivers. It is therefore important for decision makers to consider the downstream budget implications of the provided care, also called a “silo-mentality” [99, 100].

Data capture of the resources suitable for cost calculations in the RS has improved. This opens the way for comparative effectiveness research studies where the effectiveness of medical interventions or processes is assessed in a naturalistic setting and not in protocol-driven trials for measuring the efficacy [101]. A first attempt at using the RS data for a cost-effectiveness analysis of SUs was made in Paper IV, although the effectiveness had been established previously [55]. The analysis indicated that admission to an SU is life-saving at a low incremental cost. However, it was also noticed that patient characteristics differed between those who were treated at an SU and those who were not, but it was beyond the scope of the study to match patients properly.

Inpatient costs for stroke with atrial fibrillation (Paper II)

Using LOS for calculating hospitalisation costs has the advantage over DRG costing (using a flat rate for stroke hospitalisation) in that it is possible to analyse costs for subgroups more adequately. If there are differences between subgroups in LOS and/or health care management such as frequency of diagnostic imaging, surgery, etc., the true cost difference might be biased with a DRG costing [71, 72]. Correct subgroup estimates are important for decision-making and cost effectiveness analyses concerning these subgroups in order to capture the potential needs and gains properly [102]. In recent years, the RS has included more of these resource variables and this allows more sophisticated cost calculations and subgroup analyses.

In spite of the worse prognosis that has been established for patients with AF, no cost-of-treatment studies comparing the difference in costs were available at the time of publication of Paper II [103]. Although there were several studies describing the cost of illness of AF, only a few studies
analysed the incremental cost for stroke hospitalisations with an AF diagnosis [104-106]. However, those studies did confirm that costs for hospitalisation constituted the majority of direct medical costs.

Paper II also revealed that patient characteristics in subgroups might differ and that this has an impact on the differences in costs. Patients with AF were on average 7 years older and had higher index fatality than patients without AF. Hence, the period during which the patients with AF could consume health care resources was shorter and this effectively reduced the cost difference. Therefore, where the purpose of the study is to analyse differences in subgroups, for example in cost-effectiveness analyses, it is important to control for these confounders because they might have an effect on both outcome variables and costs. Although Paper II only studied hospital costs, including a wider costing perspective as in Paper IV, differences in age might also have stronger effect on the cost difference through rehabilitation, outpatient visits, ADL support, and production losses.

Mapping utility weights to patient-reported outcome variables in the RS (Paper III)

Although the precision of the regression models in Paper III compared well with other studies, they slightly overestimated the utility and consequently underestimated the reduction in health-related QoL compared to the general population [107]. Furthermore, the mapped utilities had lower variance and would, therefore, generally be less accepted among health technology assessment agencies for cost-utility studies and subgroup analysis [108-110]. Still, for group-level analyses they could serve as a valuable tool to assess the historical development in stroke management based on data from the RS [111].

Although the EQ-5D has been shown to have acceptable psychometric properties when applied to stroke, it has some limitations. The responsiveness to improved health was weaker for less severe stroke but it captured changes in ADL dimensions better than some other preference-based generic instruments [68, 69]. This could mean that as the stroke severity decreases the potential for identifying improvements with EQ-5D lessens [6]. Accordingly, the algorithm for translating the RS variables to utilities might need to be revised in the future to accommodate changes in patient characteristics [18].

Several studies have shown that improvements from rehabilitation level off at around 12 weeks, although some domains might take longer to reach such a plateau [112-115]. Using the utilities measured at 3 months as an indicator of longer-term QoL could, therefore, slightly overestimate the disutility. Still, based on data from the RS this potential overestimation of the utility was not detectable with the EQ-5D questionnaire [21].
An important aspect for the representativity of the results was the potential selection bias. Compared to responders, non-responders to the RS follow-up questionnaires were more often older females living alone with ADL dependency before the stroke [116]. Hence, the studies were missing relevant information on resources and QoL for those with the greatest needs. In order to reduce this bias, proxy responses to the RS questionnaire were included in Paper III in spite of their higher rating of disability levels [117].
Conclusions

The total societal lifetime direct cost for the approximately 22,000 first-ever stroke patients in Sweden amounted to €1.513 billion, whereof 21% was due to production losses. In addition, about 56,600 quality adjusted life-years were lost due to premature death and disability. Improvements in preventive care and acute stroke management during the 2000s have resulted in improved outcomes but also in increased direct costs. This was a result of several interlaced factors:

- Improved coverage in the RS resulting in inclusion of early deaths and a changed age structure.
- Longer expected lifetime.
- Long-term costs for ADL assistance constituted a large share of the total lifetime cost even though ADL dependence has fallen as unit costs increased.

Although the absolute number of strokes has fallen, the number of persons who have had a stroke is expected to increase as survival from stroke also improves. The potential gains in terms of both costs and quality of life from continuous efforts in preventing stroke and stroke management could be substantial.

The choice of costing methodology is important when analysing subgroups. Patients with AF had longer inpatient hospital stays than patients without this risk factor, and this would not have been captured unless a cost per day method was chosen. Patients with AF also had higher case fatality during the first 28 days, and this meant that the exposure time for further stroke-related hospitalisations was shorter. Thus fatality is important to consider when interpreting the cost implications in certain patient groups.

Preference-based utilities to measure health-related quality of life allows comparisons between diseases – horizontal comparisons. As such they are suitable for health economic assessments to facilitate decision-making in resource allocation. In the lack of surveyed utilities, mapping was shown to be a valuable alternative for determining these utilities, although its use for horizontal comparisons might be limited.
Future developments of Riks-Stroke in health economics

The improvements in the RS data collection have opened up the possibility for more sophisticated economic analyses. These analyses can be used to assist decision makers in the further development of stroke management. In the case of SUs, for example, the introduction of a pay for performance scheme could be feasible whereby the clinic receives a reward for admitting the patient to a stroke unit at the onset of the stroke and not later [118]. These schemes should not be limited to cost-saving interventions if they are desirable to promote for medical and/or political reasons. Other potential interventions surveyed in the RS that could be assessed are early discharge for home rehabilitation, surgical interventions such as thrombectomy, and drug treatments.

An extension of such studies could be to study the cost implications of an intervention in relation to utility gains. If a preference-based generic multi-attribute instrument, such as the EQ-5D, is included regularly in the RS, it would provide a unique opportunity to assess the cost-utility of different interventions in clinical practice. In the lack of historical data, mapping could serve as a second best tool for assessing the development of health related QoL in stroke care. However, methods for matching patient characteristics in comparator arms need to be applied to avoid bias. As RS has a national coverage, this ought to be fairly easy.

Hopefully these future studies will form a broad and solid basis for decision makers to allocate scarce resources so as to continuously improve stroke care in Sweden.
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Appendix (EQ-5D questionnaire)