Spasticity after first-ever stroke

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**Abstract**


The prevalence of spasticity after first-ever stroke is approximately 20%, but there are no data on the prevalence of disabling spasticity. The reported prevalence of pain after stroke varies between 19% and 74%, whether pain is associated with spasticity is not known. Until now, there is no health economic analysis of patients with spasticity after stroke.

**Methods:** Two groups of patients were studied.

*Cohort I* was a cross-sectional survey. A representative sample of 140 patients was investigated 1 year after their first-ever stroke. Spasticity was defined as $\geq 1$ score on the modified Ashworth scale, disabling spasticity was defined as spasticity having such an impact that intervention, e.g. intensive physiotherapy, orthoses or pharmacological treatment, should be offered. Pain was assessed with the Visual Analogue Scale. All direct costs during one year were identified and converted into Purchasing Power Parities US dollar (PPS).

*Cohort II* was a prospective cohort study. Forty-nine patients were examined at day 2–10, at one month, and at six months after their first-ever stroke. Assessment and definitions were similar as for cohort I.

**Results:** Spasticity occurs within 1 month and disabling spasticity occur within 6 months.

After one year, the prevalence of spasticity was 17% and that of disabling spasticity 4%. Disabling spasticity was more frequent in the upper extremity. There was an independent effect of severe upper extremity paresis (OR 22, CI 3.9–125) and age below 65 years (OR 9.5, CI 1.5–60).

The prevalence of stroke-related pain was 21% after one year. Stroke-related pain was associated with paresis (OR 3.1, 95% CI 1.2–7.7), sensory disturbance (OR 3.1, 95% CI 1.1–8.9) and depression (OR 4.1, 95% CI 1.4–13), but not with spasticity as an independent variable.

The majority of the direct costs for one year (78%) were associated with hospitalization, whereas 20% was associated with municipality services. Only 1% of all direct costs were related to primary health care and 1% to medication. The mean (median, inter-quartile range) direct cost for stroke patients with spasticity was PPS 84 195 (72 116, 53 707) compared to PPS 21 842 (12 385, 17 484) for stroke patients without spasticity (P < 0.001).

**Keywords:** stroke, spasticity, upper motor neuron syndrome, UMN syndrome, prevalence, incidence, prediction, disabling spasticity

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To Carin
List of papers

This thesis is based on the following papers, which will be referred to in the text by their Roman numerals:

I  **Prevalence of disabling spasticity 1 year after first-ever stroke.**  

II **Risk factors for stroke-related pain one year after first-ever stroke.**  

III **Four-fold increase in direct costs of stroke-survivors with spasticity compared to stroke-survivors without spasticity – the first year after the event.**  
   Erik Lundström, Anja Smits, Jörgen Borg, Andreas Terént. Submitted manus.

IV **On the time course and determinants of spasticity during the first six months after first-ever stroke.**  
   Erik Lundström, Anja Smits, Andreas Terént, Jörgen Borg. Submitted manus.
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<th>Description</th>
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<tbody>
<tr>
<td>ADL</td>
<td>Activities of Daily Living</td>
</tr>
<tr>
<td>BI</td>
<td>Barthel index</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence Interval</td>
</tr>
<tr>
<td>COI</td>
<td>Cost of Illness (study)</td>
</tr>
<tr>
<td>CT</td>
<td>Computed Tomography</td>
</tr>
<tr>
<td>DS</td>
<td>Disabling spasticity</td>
</tr>
<tr>
<td>ICF</td>
<td>International Classification of Functioning, Disability and Health</td>
</tr>
<tr>
<td>IQR</td>
<td>Inter-quartile range</td>
</tr>
<tr>
<td>MADRS</td>
<td>Montgomery-Åsberg Depression Rating Scale</td>
</tr>
<tr>
<td>MAS</td>
<td>Modified Ashworth scale</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic Resonance Imaging</td>
</tr>
<tr>
<td>mRS</td>
<td>Modified Rankin Scale</td>
</tr>
<tr>
<td>NIHSS</td>
<td>National Institutes of Health Stroke Scale</td>
</tr>
<tr>
<td>OR</td>
<td>Odds Ratio</td>
</tr>
<tr>
<td>Riks-stroke</td>
<td>Swedish Stroke Register</td>
</tr>
<tr>
<td>SAH</td>
<td>Subarachnoid Haemorrhage</td>
</tr>
<tr>
<td>UMN</td>
<td>Upper Motor Neuron</td>
</tr>
<tr>
<td>TIA</td>
<td>Transient Ischemic Attack</td>
</tr>
<tr>
<td>VAS</td>
<td>Visual Analogue Scale (of pain)</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
</tr>
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</table>
Definitions

Incidence
Incidence is the number of new cases of a condition, symptom, death, or injury that arise during a specific period of time, such as a year.

Prevalence
Prevalence is the proportion of people in the entire population who are found to be with disease at a certain point in time (sometimes called a “cross section”), without regard to when they first got the disease.

Stroke
The World Health Organization defines stroke in 1980 as “rapidly developing clinical signs of focal (at times global) disturbance of cerebral function, lasting more than 24 hours or leading to death with no apparent cause other than that of vascular origin.”

Spasticity
The most commonly used is probably that of Lance (1980) “… a motor disorder, characterised by a velocity-dependent increase in tonic stretch reflexes (muscle tone) with exaggerated tendon jerks, resulting from hyper-excitability of the stretch reflex as one component of the Upper Motor Neurone (UMN) syndrome.”

Spasticity
In this thesis defined as $\geq 1$ on the modified Ashworth scale.

Disabling spasticity
In this thesis defined as spasticity having such an impact that intervention, e.g. intensive physiotherapy, orthoses or pharmacological treatment, should be offered. Thus, the presence of disabling spasticity with need for intervention was defined in consensus between us and the patient/caregiver.
Introduction

This thesis is about spasticity after first-ever stroke. It consists of studies of two patient cohorts, as reported in four papers, and the related literature. Paper I-III are based on the same cohort, 140 patients investigated one year after first-ever stroke. Paper IV is based on a second cohort, 49 patients with first-ever stroke, investigated three times; acute, after one month and six months respectively. This study investigates predictors of spasticity.

The Background gives a description of stroke classifications and epidemiology, information of the Swedish Stroke Register and a background of the main measurements used. In addition, it includes a background on pain, in relation to stroke.

It is important to recognize that this is a clinical thesis. It will not look into pathophysiological mechanisms behind spasticity, instead it will address questions like: How common is disabling spasticity? Is spasticity correlated with pain?

Last, but not least, why should anyone bother about spasticity after first-ever stroke? First, stroke is a leading cause of death and disability. Stroke represents a major economic challenge to society. Currently, the clinical burden of stroke and transient ischemic attack exceeds that of coronary heart disease. In Sweden, with a population of nine million inhabitants, about 30,000 patients suffer a stroke annually, whereof 20,000 for the first time. In addition, stroke accounts for 10% of the total number of hospital bed-days in Sweden.

Second, spasticity is a well-known complication after stroke. Health professionals think it is very important to measure spasticity and believe it to be common and treatable. However, the prevalence of spasticity after stroke has only been investigated three times, and the proportion of disabling spasticity has never been investigated.

Third, we can treat spasticity, and policies have changed towards increasing use of intramuscular Botulinum toxin. For these obvious reasons, we need to know the magnitude of the problem in terms of suffering and economics. Stroke is common, but how common is disabling spasticity, e.g. spasticity with a specific need for an intervention?

Finally, spasticity is believed to cause pain. But what are the facts? Is spasticity really correlated with pain?
Background

This chapter gives the background to the thesis. It addresses questions like: How do you define and classify stroke? How common is stroke? What is the Swedish Stroke Register? How do you define spasticity? What previous research has been done of the prevalence of spasticity? It also gives a short background to pain, in relation to stroke and spasticity.

Definition and classification of stroke

The World Health Organization definition of stroke

The World Health Organization (WHO) defines stroke as:

Rapidly developing clinical signs of focal (at times global) disturbance of cerebral function, lasting more than 24 hours or leading to death with no apparent cause other than that of vascular origin.

The WHO definition is a clinical definition. It is not dependent on brain imaging. It includes subarachnoid haemorrhage, intracerebral haemorrhage and cerebral infarction. Subdural haematoma and other traumatic bleedings are excluded by this stroke definition. The reason for the exclusion is that extradural haematoma is usually caused by trauma.

The 24-hour criterion was based on the assumption that if the syndrome persisted for 24 hour, or longer, an injury to brain parenchyma should be detectable by microscopy. If the symptoms lasted for longer than 24 hours it was a stroke, and if the symptoms resolved before the 24-hour limit, it was a Transient Ischemic Attack (TIA). Insights gained from Computed Tomography (CT), Magnetic Resonance Imaging (MRI), and other imagining techniques have changed this assumption. Both stroke and TIA are markers of current or impending disability and a risk of death.

In the latest WHO classification of disease, International Classification of Disease (ICD-10) cerebrovascular diseases are classified into I60–I69, see page 52 in the Appendix. The main classifications of stroke are: Subarachnoid haemorrhage, intracerebral haemorrhage and cerebral infarction. Noteworthy, there is no specific ICD-10 number for cerebellar or brainstem infarction, but the rare disease Moya-Moya has an ICD-10 number (I67.5).
Subclassification of stroke

There is still no uniformity of subclassification of stroke. Before CT considerable interest was focused on time-based subclassification; e.g. Reversible Ischemic Neurological Deficit (RIND) defined as patients with stroke symptoms that resolved in less then one week (or three weeks; various definitions for RIND exists). The use of time-based subclassification has many obvious disadvantages: It adds no useful pathophysiological information, such as whether the stroke is an infarction or haemorrhage, or about which arterial vascular territory is involved.

Classification according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) study

Adams et al 13 developed a system for diagnosis of subtype of ischemic stroke for the Trial of Org 10172 in Acute Stroke Treatment (TOAST) study. The TOAST criteria focus on the underlying cause of stroke and classify ischemic stroke in five subtypes, see Table 1 page 15. The system uses rating system and the results of ancillary diagnostic studies. Hence. The TOAST classification notes the presence or absence of risk factors, the onset and course of the stroke, and the nature of the neurological findings In addition, diagnoses are strongly influenced by the results of diagnostic tests. Possible and probable diagnoses can be made based on the physician’s certainty of diagnosis.

Table 1. TOAST Classification of subtypes of acute ischemic stroke 13

<table>
<thead>
<tr>
<th>Subtype</th>
</tr>
</thead>
<tbody>
<tr>
<td>Large-artery atherosclerosis (embolus/thrombosis)</td>
</tr>
<tr>
<td>Cardio embolism (high-risk/medium-risk)</td>
</tr>
<tr>
<td>Small-vessel occlusion (lacunae)</td>
</tr>
<tr>
<td>Stroke of other determined aetiology</td>
</tr>
<tr>
<td>Stroke of undetermined aetiology</td>
</tr>
<tr>
<td>a) Two or more causes identified</td>
</tr>
<tr>
<td>b) Negative evaluation</td>
</tr>
<tr>
<td>c) Incomplete evaluation</td>
</tr>
</tbody>
</table>

The interrater reliability for the TOAST criteria is moderate 14, 15. Large-artery and cardio embolic subtype diagnoses seems to be most reliable 15.

The TOAST classification system is straightforward and follows a logical progression. It is clinically relevant and can supplement other independent assessments such as the severity of neurological deficits.
Oxfordshire Community Stroke Project classification
Yet another way to subclassify of stroke is the Oxfordshire Community Stroke Project (OCSP) classification. The OCSP classification is a clinical scheme for subdividing first-ever acute stroke based on neurological signs and syndromes only. OCSP contains four subtypes of ischemic stroke: lacunar syndrome (LACS), posterior circulation syndrome (POCS), total anterior circulation syndrome (TACS) and partial anterior circulation syndrome (PACS). The classification is considered easy to communicate and has good interobserver reliability, and has value for predicting recovery.

In short, TACS is defined as large anterior circulation infarct with both cortical and subcortical involvement, PACS is more restricted and predominantly cortical infarcts, LACS is infarcts confined to the territory of the deep perforating arteries, and POCS is infarcts clearly associated with the vertebrobasilar arterial territory.

The definition of stroke in this thesis
In this thesis stroke is defined according to the WHO criterion, e.g. both ischaemic and haemorrhagic stroke are included, but SAH and TIA are excluded. The reason for this is that the patients were included from the Swedish Stroke Register (Riks-Stroke) in Sweden, and to be included in the Riks-Stroke, the patient has a stroke according to the WHO criterion.

It was not possible to subclassify the stroke according to the TOAST or the OCSP. Patients in the Riks-Stroke are registered as ischaemic or haemorrhagic, and in Sweden neither TOAST nor OCSP is standard classification. When I scrutinized the medical record for each patient, there was too much uncertainty for a proper OCSP classification in my first cohort (Paper I–III), and for the second cohort the sample was too small (N = 49) to make a further subclassification of ischaemic stroke.

Current guidelines and recommendations for stroke
The knowledge in the stroke field has expanded substantially the last decades, and as a consequence many countries have published guidelines for stroke. Guidelines for the management of stroke were first published in 1994 by the American Heart Association. The following list presents some important guidelines and recommendations from USA, Canada, UK, Japan, Australia, the European stroke organisation (ESO) and Sweden:

- Expansion of the time window for treatment of acute ischemic stroke with intravenous tissue plasminogen activator (USA, 2009)
- Comprehensive overview of nursing and interdisciplinary care of the acute ischemic stroke patient (USA, 2009)
• Percutaneous device closure of patent foramen ovale for secondary stroke prevention (USA, 2009) 22
• Recommendations for the implementation of telemedicine within stroke systems of care (USA, 2009) 23
• Guidelines for the management of aneurysmal subarachnoid hemorrhage (USA, 2009) 24
• Management of stroke in infants and children (USA, 2008) 25
• Update to the AHA/ASA recommendations for the prevention of stroke in patients with stroke and transient ischemic attack (USA, 2008) 26
• Implementation strategies for emergency medical services within stroke systems of care (USA, 2007) 27
• Guidelines for the management of spontaneous intracerebral hemorrhage in adults (USA, 2007) 28
• Guidelines for the early management of adults with ischemic stroke (USA, 2007) 29
• Management of Adult Stroke Rehabilitation Care: a clinical practice guideline (USA, 2005) 30
• A supplement to the Canadian stroke strategy Canadian best practices recommendations for stroke care (Canada, 2008) 31
• Canadian best practice recommendations for stroke care (Canada, 2006) 32
• Stroke. National clinical guideline for diagnosis and initial management of acute stroke and transient ischemic attack (TIA) (UK, 2008) 33
• National clinical guideline for stroke, 3rd edition (UK, 2008) 34
• Japanese guidelines for the management of stroke (in Japanese, 2004) 35. An outline of these guidelines has been published in English 36
• Clinical guidelines for acute stroke management (Australia, 2007) 37
• Clinical guidelines for stroke rehabilitation and recovery (Australia, 2005) 38
• Life after stroke, New Zealand guideline for management of stroke. (New Zealand, 2003) 39
• Guidelines for management of ischemic stroke and transient ischemic attack 2008 (Europe, 2008) 40
• Evidence-based stroke rehabilitation: an expanded guidance document from the European stroke organisation (ESO) guidelines for management of ischemic stroke and transient ischemic attack 2008 (Europe, 2008) 41
• Karolinska stroke update 2008 consensus statement (Europe, 2008) 42
• Strokesjukvård – vetenskapligt underlag 2009 (Preliminär version, in Swedish; Sweden, 2009) 43

Epidemiology of stroke

Stroke is a major cause of mortality. According to WHO, stroke was the second commonest cause of mortality worldwide in 1990 and the third commonest cause of mortality in more developed countries 44; it is estimated
that stroke causes 5.5 million deaths annually \(^45\). Currently, the clinical burden of stroke and TIA exceeds that of coronary heart disease \(^2\).

In Sweden, with a population of nine million inhabitants, about 30 000 patients are hospitalised due to stroke every year, and 20 000 of these suffer a first-ever stroke \(^3\) \(^46\). The number of deaths in Sweden from stroke was 8388 (men 3555, women 4833) in 2005. \(^47\).

Stroke mortality has declined over recent decades, most notably in Japan, North America, and Western Europe including Sweden \(^44\).

A recent systematic review \(^48\) of population-based studies of the incidence and early case fatality of stroke for the last four decades (1970 to 2008) found a 42% decrease in stroke incidence in high-income countries. In addition, the authors found a more than 100% increase in low to middle-income countries. Table 2 presents some of the information from the article by Feigin et al. \(^48\).

Stroke is also a major cause of long-term disability \(^49\) and the most common cause of disability in developed countries \(^50\).

International comparisons of stroke prevalence are difficult due to low incidence of stroke in some countries, wide between-country variations in the population age structure, and methodological differences.

### The Swedish Stroke Register – Riks-stroke

The Swedish Stroke Register (Riks-stroke) is a national quality register for stroke care that was established in 1994, and from 1998 the register has covered all hospitals in Sweden. The aim of Riks-stroke is to monitor the quality of stroke management and to improve stroke care by providing feedback to all hospitals. Sweden is the first country in the world with a monitoring care that has national coverage \(^51\).

The number of registrations has successively increased and now amounts to more than 24 000 a year for estimated coverage of approximately 90%. The database contains more than 247 000 care episodes in 2006 \(^52\). Studies from Örebro in the late 1990s showed a admission rate of 92% \(^53\) for stroke patients. Another study \(^54\), from 2001–2002 from Lund, had an admission rate of 84%. Both these studies indicate a risk for selection bias.

Information regarding living conditions, vascular risk factor and medication before stroke are collected together with information of stroke management during hospital stay. Three months after the stroke, the patient is contacted by telephone or mail and asked to fill in a questionnaire. All the data are computerised in a database and each hospital receives feedback information. The results from every hospital are compared with an average national data and presents in a report every year. For more information, please visit Riks-Stroke’s home page, http/www.riks-stroke.org.
Table 2. Characteristics of population-based studies. Adapted from 48. Stroke incidence per 100 000 person-years

<table>
<thead>
<tr>
<th>City, Country</th>
<th>Study period</th>
<th>Crude incidence of total stroke (95% CI)</th>
<th>Age-adjusted incidence of total strokes (95% CI)</th>
<th>Hospital admission rate</th>
<th>1 month case fatality of total strokes</th>
<th>CT or MR or autopsi rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rochester, MN, USA</td>
<td>1970–74</td>
<td>122 (114–142)</td>
<td>91 (81-102)</td>
<td>NR</td>
<td>15-24%</td>
<td>43%</td>
</tr>
<tr>
<td>Rochester, MN, USA</td>
<td>1985–89</td>
<td>149 (136–162)</td>
<td>102 (92–112)</td>
<td>85%</td>
<td>14-25%</td>
<td>92%</td>
</tr>
<tr>
<td>Ulan Bator, Mongolia</td>
<td>1971–74</td>
<td>50 (46–54)</td>
<td>78 (71–84)</td>
<td>51%</td>
<td>NR a</td>
<td>NR a</td>
</tr>
<tr>
<td>Malmö, Sweden</td>
<td>1989</td>
<td>225 (206–244)</td>
<td>83 (74–91)</td>
<td>95%</td>
<td>15%</td>
<td>51%</td>
</tr>
<tr>
<td>Söderhamn, Sweden</td>
<td>1975–78</td>
<td>290 (256–324)</td>
<td>254 (223–285)</td>
<td>89%</td>
<td>23%</td>
<td>1%</td>
</tr>
<tr>
<td>Söderhamn, Sweden</td>
<td>1983–86</td>
<td>352 (317–390)</td>
<td>312 (278–347)</td>
<td>95%</td>
<td>22%</td>
<td>38%</td>
</tr>
<tr>
<td>Örebro, Sweden</td>
<td>1999–2000</td>
<td>314 (279–349)</td>
<td>126 (111–140)</td>
<td>92%</td>
<td>19%</td>
<td>84%</td>
</tr>
<tr>
<td>East Lancashire, UK</td>
<td>1994–95</td>
<td>158 (146–171)</td>
<td>74 (67–80)</td>
<td>70%</td>
<td>34%</td>
<td>12%</td>
</tr>
<tr>
<td>Oxfordshire, UK</td>
<td>1981–84</td>
<td>165 (150–181)</td>
<td>102 (92–112)</td>
<td>54%</td>
<td>18%</td>
<td>82%</td>
</tr>
<tr>
<td>Oxfordshire, UK</td>
<td>2002–04</td>
<td>145 (127–162)</td>
<td>73 (64–83)</td>
<td>56%</td>
<td>17%</td>
<td>98%</td>
</tr>
</tbody>
</table>

NR Not reported.
Definition of the Upper Motor Neuron syndrome and spasticity

The clinical phenomena observed after lesions of cortical motor areas or the corticofugal, descending tracts are often referred to as the Upper Motor Neuron (UMN) syndrome, and described as positive and negative symptoms and signs. These phenomena are summarized in Table 3. In addition, rheological changes in involved muscles may occur.

Table 3. Clinical features of the Upper Motor Neuron syndrome

<table>
<thead>
<tr>
<th>Positive symptoms</th>
<th>Negative Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased tendon reflexes with radiation</td>
<td>Muscle weakness</td>
</tr>
<tr>
<td>Clonus</td>
<td>Loss of dexterity</td>
</tr>
<tr>
<td>Positive Babinski’s sign</td>
<td>Fatigueability</td>
</tr>
<tr>
<td>Spasticity</td>
<td></td>
</tr>
<tr>
<td>Extensor spasm</td>
<td></td>
</tr>
<tr>
<td>Flexor spasm</td>
<td></td>
</tr>
<tr>
<td>Mass reflexes</td>
<td></td>
</tr>
<tr>
<td>Dyssynergic patterns of co-contraction during movements</td>
<td></td>
</tr>
<tr>
<td>Associated reactions and other dyssynergic</td>
<td></td>
</tr>
<tr>
<td>and steroetypical spastic dystonia</td>
<td></td>
</tr>
</tbody>
</table>

The UMN syndrome is common after stroke as well as in other central nervous system disorders, e.g. cerebral palsy, multiple sclerosis, traumatic brain injury, spinal cord injury, and neurodegenerative diseases.

In stroke patients, lesions that interrupt the descending tracts typically cause weakness of voluntary movements and loss of dexterity (negative signs) as acute manifestations. One or more of the positive signs, e.g. increased muscle tone, may be present in the acute phase or develop in the post acute phase, and then contribute to motor impairment. The clinical significance and management of spasticity, as one positive sign of the UMN syndrome, is far from clear-cut and the definition of spasticity as well as assessment methods are debated.

The most commonly used definition of spasticity is probably that of Lance from 1980:

“... a motor disorder characterised by a velocity-dependent increase in tonic stretch reflexes (muscle tone) with exaggerated tendon jerks, resulting from hyperexcitability of the stretch reflex as one component of the Upper Motor Neurone (UMN) syndrome.”

The definition by Lance points out that spasticity is only one component of the Upper Motor Neuron (UMN) syndrome and also that spasticity is a sign...
at clinical examination that has a diagnostic value with regard to lesion location but not with regard to impact on motor ability or need for treatment.

Others have suggested a broader use of the term spasticity to be better in accordance with clinical practice. For example, Pandyan have proposed the following definition 57:

“... disordered sensori-motor control, resulting from an upper motor neuron lesion presenting as intermittent or sustained involuntary activation of muscles.”

This definition 57 of spasticity incorporates other positive signs of the UMN syndrome such as abnormal activation of muscles during voluntary movements and flexor spasms 57. Spasticity in this broader sense may interfere with motor function and be disabling with regard to motor function, activity performance and social life.

Not all spasticity is harmful for the patient

Spasticity is not always harmful. In fact, some of the patients use their spasticity as a crutch, and reducing spasticity may do the patient a disservice. The fact that spasticity as such is always bad for the patients is recognised in the current recommendation and guidelines for treatment of spasticity 30, 34, 38, 39, 41, 43, 60-62.

Clinical assessment and management of positive signs of the Upper Motor Neuron syndrome in clinical practice.

Spasticity

At bedside, spasticity is characterized by increased resistance so passive movements over a joint with the patient in a resting, most often supine, relaxed position. Typically, resistance increases at higher movement velocities. Thus, spasticity resists muscle stretch and lengthening of the muscle involved. This has two important consequences. First the muscle tends to remain in a shortened position, which probably contributes to dystonic postures, and also leads to soft tissue changes and contractures 63. Second, voluntary movements might be restricted. If, for example, the patient tries to extend the elbow, spasticity of the stretched flexor muscles will hamper the extension.

Since the muscle stretch reflex is influenced by input from many sources, a number of clinical factors such as limb and body position, pain and infections may have an impact. This has important implications for clinical management and requires that triggering factors be controlled before specific treatments are considered.
Other positive signs of the UMS.

In accordance with Lance’s definition, tendon reflexes are often exaggerated in parallel with the increased resistance to passive movements and there might be clonus. Clonus, i.e., involuntary, repetitive extension and flexion movements is most often observed over the ankle. Clonus might be provoked at the examination of the patient at rest or only be present in certain positions, such as sitting, or activities such as walking. Clonus may be troublesome for the patient if triggered during sitting or walking. Co-activation of muscles by definition needs voluntary activation to be identified, and might impair the voluntary movements during, e.g., walking. In addition, there might be abnormal flexor reflexes, most often observed as Babinski’s sign. Muscle spasms might exhibit extensor or flexor patterns, most often involve lower limbs and are more common after spinal cord lesions than after cerebral lesions.

Rheological changes in the spastic muscle

In addition to the positive and negative phenomena in the UMN syndrome, the muscle and surrounding soft tissue, including tendons, ligaments and the joints, can develop changes resulting in decreased compliance. It is possible, but not proven, that maintaining the joints range through a full range of movement may prevent contractures.

Thus, increased resistance to passive movements often has a neural and a biomechanical component and in advanced conditions, probably soft tissue changes contribute most to the disability.

The pathophysiology of spasticity

The pathophysiology of spasticity is complex. Although the exact pathophysiology of spasticity is unclear, it is known that interruption of descending pathways frequently produces spasticity.

For a better understanding of the pathophysiology of spasticity, I will first review the organisation of the motor systems. The review is based mainly on the excellent textbook *Principles of Neural Sciences* edited by Kandel et al. The different areas in the brain are often referred to as Brodmann’s areas. Korbinian Brodmann originally described these areas in the book *Vergleichende Lokalisationslehre der Grosshirnrinde* published in 1906. This book is available in an English translation by Laurence J Garvey.

The motor systems are organized in three levels

The motor systems are organized hierarchically in three levels. The cortex is the highest level. The primary motor cortex and several premotor areas pro-
ject directly to the spinal cord through the lateral and ventral corticospinal tracts. The corticospinal fibres arise from both pre-central (60%) and post-central (40%) areas. Those controlling motor function within the spinal cord arise from the pre-central cortex; the majority from the primary motor cortex (Brodmann’s area 4) and pre-motor cortex (area 6) 69. The premotor areas are important for co-ordinating and planning complex movement. Post-central areas (primary sensory cortex, area 1, 2, 3) and parietal cortex (area 5, 7) are more concerned with modulation sensory function (*Figure 1*).

*Figure 1*. The motor systems have three levels of control: The forebrain, brain stem and the spinal cord. They are organized both in serial and in parallel. The motor areas of the cerebral cortex can influence the spinal cord either directly or through the descending systems in the brain stem. All three levels receive sensory input and are also under the influence of two independent subcortical systems: the basal ganglia and the cerebellum. Figure from Kandel 56, used with courtesy from the publisher.
The second level of the motor hierarchy is the brain stem. In the brain stem there are two systems, the medial and the lateral, which receive input from the cerebral cortex and subcortical nuclei, and project to the spinal cord. The medial descending systems contribute to the posture by integrating visual, vestibular, and somatosensory information. The lateral descending system control more distal limb muscles, and is important for goal-directed movements, especially of the arm and hand.

The third, and lowest level is the spinal cord. It contains neuronal circuits that mediate reflexes and rhythmic automatisms such as locomotion. Inter neurons and motor neurons receive input from axons from higher centres, and these higher centres can facilitate or inhibit inter neurons in the brain stem.

All three levels of motor systems are organized both in serial and in parallel. In addition, all levels are also under the influence of two independent subcortical systems: the basal ganglia and the cerebellum.

Spasticity and its connection to the motor systems

Spasticity and the other symptoms and signs of the UMN syndrome arise from the disruption of certain descending pathways involved in the motor control 69.

Lesions at the cortical level

Isolated lesions of the primary motor cortex uncommonly produce spasticity – both Brodmann’s areas 4 and 6 must be affected to produce spasticity 69. There are non-pyramidal UMN motor fibres, mainly in area 6, which travel near the pyramidal fibres. These fibres must be involved for the production of spasticity. It has been debated whether these pathways should be called extrapyramidal 70 or parapyramidal 71. In this thesis these fibres will be referred to as parapyramidal to avoid confusion with the extrapyramidal fibres from the basal ganglia that produce rigidity.

The close association of pyramidal and parapyramidal fibres continues in the spinal cord where lesions in the pyramidal fibres produce results similar to those of the primary motor cortex without spasticity.

What are the consequences of a pure motor lesion? In humans, mild hand and foot paresis, mild tendon hyperreflexia, normal tone, and a Babinski’s sign 72 are observed. The majority of the UMN syndrome symptoms are not due to interruption of the pyramidal tracts (except for the Babinski’s sign), but of the parapyramidal fibres 71. Cortical lesions producing spasticity must involve both the primary motor and pre-motor cortices. Such lesions affect both pyramidal and parapyramidal fibres, which run in parallel in the corona radiata and internal capsula.
The brainstem and spinal cord level
At the brainstem level there are two different systems that affect spasticity – one inhibitory and one excitatory. Both of these systems balance the spinal reflexes in the brain stem. The inhibitory area in the reticular formation largely suppresses spinal reflexes. The dorsal reticulospinal tract (DRT) is the ascending tract for the inhibitory centre in the brainstem. The DRT runs in the dorsolateral funiculus, adjacent to the pyramidal tract.

There are two excitatory systems that facilitate spinal stretch reflexes and extensor tone. The main one arises diffusely throughout the brainstem and descends as the median reticulospinal tract. The other is the lateral vestibular nucleus, giving rise to the vestibulo tract. Both of these excitatory systems are located in the ventromedial cord, well away from the pyramidal and the inhibitory tract.

Thus, spasticity arises when the parapyramidal fibres of the inhibitory system are interrupted, either above the medulla (cortex, corona radiata, internal capsula) or of the DRT in the spinal cord.

Differences between spasticity from cerebral and spinal origin
The clinical feature of the UMN syndrome seems to depend less upon the aetiology of the lesion and more upon its location in the neuraxis. However, often there are some differences between the UMN syndrome of a cerebral in comparison with a spinal origin. Table 4 describes the main differences.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Cerebral origin</th>
<th>Spinal origin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severity</td>
<td>Less severe</td>
<td>More often severe</td>
</tr>
<tr>
<td>Involving extensors with a posture of lower limb</td>
<td>Common</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Flexor spasm</td>
<td>Uncommon</td>
<td>Common</td>
</tr>
<tr>
<td>Clasp-knife phenomenon</td>
<td>Uncommon</td>
<td>Common</td>
</tr>
<tr>
<td>Clonus</td>
<td>Less severe</td>
<td>Common</td>
</tr>
</tbody>
</table>

The reasons for these differences are not discussed in this thesis, but may be explained on anatomical grounds.

How do you measure spasticity?
Clinical evaluation of spasticity includes assessment of the velocity-dependent increase of resistance to passive movements to capture the key element of spasticity according to the definition by Lance. In the clinical setting, the most well-known spasticity scales are the original and the modified Ashworth scale (MAS) \(^{73, 74}\). The original Ashworth scale was devel-
oped for measuring spasticity in patients with multiple sclerosis (MS) and is hardly used – most studies use the MAS. The MAS is a six-point ordinal scale; it is easy to use and to communicate, and it has some documented reliability. Table 5 shows the definition of the original Ashworth scale and the MAS.

I have used the MAS for measuring spasticity.

Table 5. The original and modified Ashworth scales

<table>
<thead>
<tr>
<th>Score</th>
<th>Original Ashworth scale</th>
<th>Modified Ashworth scale</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No increase in tone</td>
<td>No increase in tone</td>
</tr>
<tr>
<td>1</td>
<td>Slight increase in tone giving a catch when the limb is moved in flexion or extension</td>
<td>Slight increase in muscle tone, manifested by a catch and release or by minimal resistance at the end of the range of motion when the affected part(s) is moved in flexion or extension</td>
</tr>
<tr>
<td>1+</td>
<td>—</td>
<td>Slight increase in muscle tone, manifested by a catch, followed by minimal resistance throughout the remainder (less than half) of the range of motion</td>
</tr>
<tr>
<td>2</td>
<td>More marked increase in tone but limb easily flexed</td>
<td>More marked increase in muscle tone through most of the range of motion but affected part(s) easily moved</td>
</tr>
<tr>
<td>3</td>
<td>Considerable increase in tone, passive movement difficult</td>
<td>Considerable increase in tone, passive movement difficult</td>
</tr>
<tr>
<td>4</td>
<td>Limb rigid in flexion or extension</td>
<td>Affected part(s) rigid in flexion or extension</td>
</tr>
</tbody>
</table>

Problems with the modified Ashworth scale

MAS does not differentiate mechanical and neural components of an increased resistance to passive movements. Another limitation is that performance parameters are not standardized. Thus, neither the position the limb should have nor the speed of the movement is specified. Recently, the reliability of MAS has been demonstrated for certain movements by use of standardized positions and movement velocities according to the resistance to passive movement (REPAS).

Another scale, the Tone Assessment Scale, developed by Gregson et al., has not been extensively used. Neither has the Tardieu scale, which considers the dynamic properties of spasticity. Various neurophysiological methods have been described, but none of them are used in clinical settings and they are scarcely used in research.
What is disability?

What is disability? At first this question might seem easy to answer. However, the concept is complex and the use of the term disability varies. Recently, WHO has proposed a new definition in the International Classification of Functioning, Disability and Health (ICF) \(^81\). The ICF approach to functioning and disability is biopsychosocial and it tries to integrate \textit{medical} and \textit{social} aspects. A purely medical model would see disability as a consequence of a disease or trauma and medical cure as the solution. A purely social model would regard disability as mainly a contextual problem and ask for social solutions. An integrated approach is obviously relevant to medical conditions with ongoing, complex impairments. ICF is considered relevant for clinical settings, health services or surveys at both the individual and population level, and has gained increasing attention not least in rehabilitation medicine and neurorehabilitation.

In ICF, disability is used as an umbrella term for impairment of function, activity limitation or participation restrictions. Thus, ICF complements ICD-10, and is looking beyond mortality and disease. The definitions in ICF contain commonly used anchor points for assessments so that they can be translated into questionnaires. Results from existing assessment instruments can be coded in ICF terms.

An overview of the ICF

The ICF classification has two parts, each with two components:

- **Part 1. Functioning and Disability**
  - a) Body Function and Structure
  - b) Activities and Participation

- **Part 2. Contextual Factors**
  - c) Environmental Factors
  - d) Personal Factors

Each component can be expressed in both positive (functioning) and negative terms (disability). The components are further divided in domains. The domains are the units of classification. Table 6 is an overview of ICF \(^81\).

Definitions of terms in the ICF

The following terminology is used in the ICF \(^82\):

- \textit{Disability} is an umbrella term for impairment, activity limitation and participation restrictions.

- \textit{Body function} is the physiological functions of body system, including psychological functions.

- \textit{Body structure} are the structural or anatomical parts of the body such as organs, limbs and their components classified according to body systems.
Although Body function and Body structure are classified in two different sections, these two classifications are designed for use in parallel.

*Activity* is the execution of a task or action by an individual.

*Participation* is a person’s involvement in a life situation.

*Contextual factors* are the factors that together constitute the complete context of an individual’s life and in particular the background.

*Environmental factors* are all external factors for the individual, including the physical world, other persons, social services, rules and laws.

*Personal factors* are factors that relate to the individual such as age, gender, social status and so on.

<table>
<thead>
<tr>
<th>Table 6. <em>An overview of ICF</em>[^83]</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Part 1: Functioning and disability</strong></td>
</tr>
<tr>
<td>Components</td>
</tr>
<tr>
<td>Domains</td>
</tr>
<tr>
<td>Contracts</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Positive aspects</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Negative aspects</td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

Is spasticity harmful?

Table 7 shows how the Royal Collage of Physicians, UK,[^60] describe the harmful effects of spasticity according to the ICF in their guideline for treatment of spasticity.
<table>
<thead>
<tr>
<th>ICF level</th>
<th>Problem</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Impairment</td>
<td>Muscle spasms</td>
<td>Pain</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Difficulty with seating and posture</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fatigue</td>
</tr>
<tr>
<td></td>
<td>Abnormal trunk and limb posture</td>
<td>Contractures</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pressure sores</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Deformity</td>
</tr>
<tr>
<td></td>
<td>Pain</td>
<td>Distress and low mood</td>
</tr>
<tr>
<td>Activity</td>
<td>Activity function loss</td>
<td>Reduced mobility</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Inability to use limbs in function</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Difficulty with sexual intercourse</td>
</tr>
<tr>
<td></td>
<td>Passive function loss</td>
<td>Difficulty with self-care and hygiene</td>
</tr>
<tr>
<td></td>
<td>Impact of any/all of the above</td>
<td>Poor self-esteem/self-image</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Reduced social interaction</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Impact on family relationships</td>
</tr>
</tbody>
</table>

Activity and participation after stroke

There are two scales that are frequently used for assessment of activity and participation in stroke patients: The modified Rankin scale (mRS) and the Barthel Index (BI). Both mRS and BI are ordinal scales.

The mRS was first published in 1957. In 1988 it was modified to improve its comprehensiveness. The validity and inter-rater reliability is well documented. The current version of the mRS running from 0 (no disability) to 6 (death).

A structured interview can be used to assign patients to the right mRS grade. The interview consists of five sections corresponding to the level of disability on the mRS. The best available information should be used; information can be obtained from the patient, next of kin, or caregiver. The mRS in presented in the Appendix, page 81, with some exemplified questions from the structured interview. Focus on the mRS lies on personal-ADL, e.g. management of self-care (bathing, dressing, transportation), but the mRS 1 could represent an instrumental-ADL. Instrumental-ADL is activities that is not fundamental for an individual, but enables an individual to live independently in the community (e.g. using a phone or managing money).

In many studies the mRS is dichotomized into excellent (0–1 vs. 2–6) or good (0–2 vs. 3–6) outcome. Sometimes shift analysis is used, e.g. comparing the outcome between the treatment and control across the entire ordinal scale. Shift analysis is better than dichotomizing when there is a small benefit across all ranges of stroke severity.
The BI \(^9\) is a scale with documented validity after stroke \(^9\). The BI is focused on personal-ADL (Appendix).

These disability scales yield information about disability related to the activity and participation component according to the ICF. Disabilities captured might reflect the impact of any motor or other neurological impairment after stroke. Thus, the scales do not address the relative impact of specific impairments, or the individual perception of various disabilities.

**Definition of disabling spasticity in this thesis**

In order to compare the results of our studies we used the modified Ashworth scale to capture one of the positive signs of the UMS and an MAS score of 1 or more was referred to as spasticity. However, as discussed above, spasticity in this sense is not a problem per se. In fact, some patients may use their spasticity for mobility, and then treating spasticity might cause problems instead of solving them. On the other hand, spasticity according to the proposed broader definition, may interfere with motor performance as previously discussed.

There is no single assessment instrument that captures all relevant aspects of spasticity according to this broader definition. Neither is there a single measure that addresses spasticity-related disability. Therefore, we used a comprehensive clinical evaluation to achieve a clinically relevant estimate of the prevalence of disabling spasticity after first-ever stroke in addition to conventional measures of disability (the mRS and Barthel Index).

The clinical evaluation comprised a detailed history and clinical examination of motor performance to identify any *intermittent or sustained involuntary activation of muscles* in accordance with the broader definition \(^5\). Further, by use of a semi-structured interview, we tried to evaluate if there was any disabling effect of these phenomena, as based on observation at the examination and the patients’ history. Thus, we tried to disentangle any impact on motor function, limb positioning, mobility or activities of daily living (e.g. personal hygiene, dressing) – or on pain conditions or sleep. Finally, we used clinical judgement to decide, in dialogue with the patient and/or caregiver, whether there was a need for intervention targeted specifically to any of the identified spasticity phenomena, such as intense physiotherapy, orthoses or drug treatment. If so, we used the term *disabling spasticity* for this condition in accordance with how disability is defined by the ICF.

Disabling spasticity was defined, as spasticity having such an impact that intervention, e.g. intensive physiotherapy, orthoses or pharmacological treatment, should be offered. Thus, the presence of disabling spasticity with need for intervention was defined in consensus between us and the patient/caregiver.
Limitations of our definition of disabling spasticity
Clearly our definition of disabling spasticity has certain limitations. Even if all patients exhibited an MAS score $\geq 1$, this finding is open to various interpretations. Further, the clinical evaluation and the final decision on need for treatment are subject to the same weaknesses as all clinical evaluations. However, these were performed in a clinical setting with a considerable experience in the area. In addition, the procedure is in accordance with the current concept that individualised goal setting and attainment might be more sensitive and clinically relevant for interventions and outcome assessment in complex disorders including spasticity after stroke $^{92, 93}$. Finally, conventional disability measures – the mRS and BI – were also used and allowed comparisons on the group level.

Who did the assessments?
I assessed all patients, and all patients exhibiting any signs or symptoms of spasticity were also assessed by my main supervisor (JB), as well as a physiotherapist and/or occupational therapist, who were members of a neurorehabilitation team specialised in motor disorders.

Pharmacological management of spasticity
Assessment of spasticity often requires a multiprofessional team in order to evaluate the troublesome effect of spasticity. It must be recognized that some patients use their increased tone for walking and sometimes the best treatment may be no treatment. In addition, the medication may have side effects with greater impairment than spasticity itself.

Treatment goals must be set for the rehabilitation and discussed with the patient and their care giver $^{94}$. The primary treatment of spasticity is physical. The physical treatment should be continued even if a pharmacological treatment is started $^{94}$. The first step in the management is to assure that noxious and external stimuli are diminished $^{95}$, e.g. pain, incontinence, constipation, infections, and pressure sores. The next step is to assess the indications for pharmacological treatment. Some of the indications are listed in Table 8.
Table 8. *Indications for pharmacological treatment of spasticity* 

<table>
<thead>
<tr>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increasing tone despite physical stretching/casting limbs</td>
</tr>
<tr>
<td>Pain</td>
</tr>
<tr>
<td>Prevention and treatment of contracture formation</td>
</tr>
<tr>
<td>Prevention of deformities</td>
</tr>
<tr>
<td>Prevention and treatment of dysphagia</td>
</tr>
<tr>
<td>Preservation of skin hygiene</td>
</tr>
<tr>
<td>Preservation of sexual functioning</td>
</tr>
<tr>
<td>Decrease carer burden to perform carer tasks</td>
</tr>
<tr>
<td>Cosmetic effect</td>
</tr>
</tbody>
</table>

Oral medications are often associated with side, such as drowsiness, vertigo, ataxia, memory deficit and confusion. In the 1990s botulinum toxin was introduced, and it emerged as treatment of choice for focal spasticity. Neurolysis with phenol might be effective but is associated with side effects such as dysesthesia and oedema. The following section will briefly outline the medical treatment of spasticity. I will not discuss physiotherapy, occupational therapy and surgical treatment.

**Oral anti-spastic medications**

**Baclofen**

Baclofen is the most commonly used medication and it has been used for over 40 years. Multiple sclerosis and spinal cord lesion are the most frequent studied diseases, and baclofen reduces spasticity and spasms for these diseases. The effect on spasticity of cerebral origin seems more limited.

Baclofen is an analogue of gamma-aminobutyric acid (GABA), which is one of the main inhibitory neurotransmitters in the central nervous system. Baclofen binds to a presynaptic GABA$_B$-receptor, calcium influx is inhibited, and the release of excitatory neurotransmitters is suppressed. The plasma half-life is 3.5 hours. Only a small fraction crosses the blood-brain barrier.

**Benzodiazepine**

The effect of benzodiazepines is mediated through GABA$_A$-receptors. Benzodiazepines binds to a specific benzodiazepine site in the post synaptic GABA$_A$-receptors that booster the inhibitory effect. Various subtypes of benzodiazepine receptors have slightly different actions. Alpha 1 is responsible for sedative effects, whereas alpha 2 is responsible for the anti-anxiety effects. The anticonvulsant effects are mediated through alpha 1, alpha 2 and alpha 5. All benzodiazepines on the market combine all these receptor subtypes, and bearing in mind that 40% of the neurons in the brain are GABA-dependent, it is easy to understand why benzodiazepines have side-effects.
**Diazepam**

Diazepam has been used as an anti-spastic drug for over 40 years and its effectiveness has been demonstrated in two double-blind, cross-over trials \(^{100, 101}\). Diazepam is problematic to use in stroke patients because of its sedation side-effect.

**Dantrolene sodium**

Dantrolene sodium acts peripherally on muscle fibres through suppressing the release of calcium ions from the sarcoplasmic reticulum \(^{102}\). Some evidence suggests that dantrolene work better for spasticity after stroke \(^{103, 104}\). Dantrolene has side-effects that limit its use; it might cause transient abnormalities in liver function, as well as fatal hepatitis in 0.2% of the patients. Liver function must be checked regularly.

**Tizanidine**

Tizanidine has been tested in several randomized, double-blinded, placebo-controlled studies for multiple sclerosis and spinal cord injury \(^{105-108}\). The anti-spastic effect is similar to that of baclofen \(^{109-111}\) and diazepam \(^{112}\). In addition, there are some advantages with tizanidine: muscle strength is more preserved and the side-effects are milder compared to both baclofen and diazepam.

Tizanidine is an alfa-adrenergic agonist.

A clinical significant increase in liver enzymes can occur in 5–7% of patients. The liver enzymes normalises after withdrawal of the drug. Serious tizanidine hepatic injury has been reported. Liver function must be checked regularly.

**Clonidine**

There is no double-blind, placebo-controlled study of clonidine. Two trials have found that clonidine reduced spasticity in patients with spinal cord lesions \(^{113, 114}\).

**Intramuscular injection with botulinum toxin**

Botulinum toxin (BTX) is the most potent neurotoxin known. It acts by binding presynaptically on the cholinergic nerve terminals and decreasing the releasing of acetylcholine, causing a neuromuscular block. There are seven different neurotoxins: A, B, C, D, E, F and G. They are antigenically and serologically different but structurally similar. Human botulism is caused by types A, B, E and F. Types C and D cause toxicity only in animals.

Botulinum toxin A (BTX-A) was first used for strabism in the late 1970s \(^{115}\). It is now used for a wide range of diseases including focal dystonia, cervical dystonia, task specific dystonias, and hemifacial spasm. In a consensus
statement from 2009 on the use of BTX-A in adult spasticity, it was concluded that BTX-A is a valuable treatment in the management of spasticity after a stroke. Currently there are two different BTX in the Swedish market: BTX-A and botulinum toxin B (BTX-B). The benefits of BTX are that a specific muscle can be treated, and that there are few side-effects. BTX is considered expensive.

Intrathecal treatment with baclofen

The first description of the use of intrathecal baclofen (ITB) was in a small study of six patients in 1985. In 1996, the U.S. Food and Drug Administration approved the use of ITB therapy for severe spasticity of cerebral origin. However, the evidence basis is still weak.

Previous studies of the prevalence of spasticity after first-ever stroke

There are three prior studies of the frequency of spasticity after stroke and the result of the studies are not consistent. Two follow-up studies of a Swedish cohort, using the MAS, report a spasticity frequency of 19% in patients examined 3 months and 18 months after stroke. One UK study reports a frequency of 39% in patients examined 1-year after stroke. The discrepancy might be related to various study settings and samples. In UK approximately 50–70% of the stroke patients are admitted to hospital in comparison with 95% in Sweden, probably leading to more severe stroke hospitalised in the UK. An overview of the previous studies on spasticity after stroke is presented in Table 9.
<table>
<thead>
<tr>
<th>Study type</th>
<th>Watkins</th>
<th>Sommerfeld</th>
<th>Welmer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inclusion criteria</td>
<td>First-ever and recurrent stroke</td>
<td>First-ever stroke.</td>
<td>Same as Sommerfeld</td>
</tr>
<tr>
<td>Exclusion</td>
<td>TIA and SAH</td>
<td>TIA and cerebellar stroke.</td>
<td>Same as Sommerfeld</td>
</tr>
<tr>
<td>Inclusion period</td>
<td>Jan-Jun 1996</td>
<td>Jun 2001-Mar 2002, consecutively recruited, not weekends and holidays</td>
<td>Same as Sommerfeld</td>
</tr>
<tr>
<td>Recruitment</td>
<td>270 included at stroke onset. 134 (50%) died within 12 months. 106 consented to follow-up.</td>
<td>109 patients included dand in the acute phase. During the follow-up 14 patients was excluded or lost to follow-up at 3 months. (4 had a recurrent stroke, 4 died, 5 claimed to be fully recovered an declined to participate, and 1 could not be located).</td>
<td>They did a follow-up of the Sommerfeld cohort. At 3 months there were 95 patients and 29 patients were excluded or lost to follow-up at 18 months. (9 had a recurrent stroke, 15 died, 4 declined to participate, whereof 1 claimed to be fully recovered, and 1 could not be located).</td>
</tr>
<tr>
<td>Number of patients</td>
<td>59</td>
<td>109 (acute) and 95 (at 3 months).</td>
<td>66</td>
</tr>
<tr>
<td>with first-ever stroke</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>70 a</td>
<td>78</td>
<td>76</td>
</tr>
<tr>
<td>Percent women</td>
<td>NR b</td>
<td>63%</td>
<td>67%</td>
</tr>
<tr>
<td>Haemorrhage stroke</td>
<td>17% c</td>
<td>NR b</td>
<td>14%</td>
</tr>
<tr>
<td>Measurement of spasticity</td>
<td>MAS and Tone Assessment Scale</td>
<td>MAS</td>
<td>MAS</td>
</tr>
<tr>
<td>Hospital, Country</td>
<td>University Hospital Aintree, UK</td>
<td>Danderyd Hospital, Sweden</td>
<td>Danderyd Hospital, Sweden</td>
</tr>
<tr>
<td>Percent spasticity</td>
<td>39% at 12 months</td>
<td>21% in the acute phase and 19% at 3 months</td>
<td>20% at 18 months</td>
</tr>
</tbody>
</table>

* a Mean age for the whole sample, not specified for first-ever stroke.  
  b NR Not reported in the article.  
  c The percentage is based on the 84% who underwent a CT of the brain.

Previous studies 6-8 have reported on some weak or moderate associations between spasticity, activity performance and health-related quality of life. However, data on the prevalence of disabling spasticity (DS) are scarce.

Prevalence of spasticity in other diseases

Spasticity can occur in other diseases than stroke. Spasticity affects between 37–78% of patients with multiple sclerosis 121, 122, 40% of those with spinal
cord injury \textsuperscript{123} and, more than 90\% with cerebral paresis \textsuperscript{124}. Wedekind et al. \textsuperscript{125} investigated the 1-year outcome of 32 survivors with severe traumatic brain injury (TBI). The patients were divided into two groups; those with brain stem injury (mid-brain and pons, \(n = 15\)), and those without brain stem lesions (\(n = 17\)). After 1 year 8/15 (53\%) in the brain stem group, and 3/17 (18\%) had spasticity, respectively. Unfortunately, the authors did not mention how they assessed spasticity. However, it is evident that a brain stem lesion negatively affects spasticity.

**Definition of pain**

The International Association for the Study of Pain (IASP) defines pain as \textsuperscript{126}:

> An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage

The IASP emphasises that inability to communicate verbally does not exclude that a person could experience pain, and that pain is always subjective. Pain is the experience we associate with actual or potential tissue damage.

Further, IASP states that many people report pain in the absence of tissue damage or any likely pathophysiological cause. IASP concludes that there is usually no way to distinguish their experience from pain due to tissue damage. If they regard their experience as pain and if they report it in the same way as pain caused by tissue damage, it should be accepted as pain. The IASP argues that this definition avoids connecting pain to stimulus.

**Pain can be classified as nociceptive or neuropathic**

Pain can be classified as *nociceptive* or *neuropathic* pain.

Typically, nociceptive pain is well localized, constant and often described as aching or throbbing. The pain is mediated via nociceptors. These nociceptors sense and respond to parts of the body, which suffer from damage. Nociceptive pain is usually time limited and responds well to treatment with opioids.

Neuropathic pain is the result of an injury or malfunction in the peripheral or central nervous system. The pain can persist for years beyond the apparent healing of the damaged tissue. The neuropathic pain is often burning, lancinating, or described as an electric shock. In addition, light touch may result in pain. Neuropathic pain tends to respond less well with opioids, but may respond to other drugs such as anti-seizure and tricyclic antidepressant medications.
Measuring pain

Because pain is of subjective nature, it cannot be measured in an objective way. In studies to assess pain the visual analogue scale (VAS) has been used. The VAS typically consists of a 100-mm line without subdivisions or numbers, anchored at either end by an extreme statement as “I have no pain at all” and “My pain is as bad as it could possibly be” 127. The individual is asked to mark on the line their current state between these two extremes, and the position of which is measured in millimetres from the lower end.

Examination of the VAS has suggested that outside the stroke population it is reliable and accurate for pain 128. However, there is debate about the validity of the VAS for older patients 129, and stroke patients are generally older. In addition, stroke patients often suffer from cognitive deficit, hemianopia and inattention, making it even more difficult to use scales. To overcome these problems, vertical and mechanical “slide-rule” versions have been used 130. Subjects with stroke are less likely than an age-matched control group to correctly complete subjective rating scales, including VAS 131, but at the same time VAS was the most sensitive scale examined although it was the scale with the most mistakes.

In spite of its limitation, the VAS is reasonably to use in the stroke population.

Prevalence of pain worldwide

The reported prevalence of pain in the general population varies considerably. A Canadian study 132 estimated that 11% of the general population had persistent pain and had experienced that pain within the preceding 2 weeks. According to a Swedish postal survey 133, including persons aged 18–84, any pain or discomfort, was reported by 66%. Their questionnaire consisted of two pain scales: one for pain intensity and one for how much the pain troubled and affected the individual. Forty percent reported pain, which affected them “to quite a high degree”, or more and was “like being stiff after exercise” or worse, lasting more then 6 months. In a recent survey of chronic pain in Europe 134, screening persons aged ≥ 18 years, 19% of 46,394 respondents had suffered pain for ≥ 6 months, had experienced pain in the last month and several times during the last week. Even if these prevalence rates vary, probably reflecting different definitions of pain, time frame for reported pain, sample characteristics and other factors, it is clear that pain is common in the general population.

In addition, chronic pain occurs often concomitant with depression 135-138. Depression after stroke is very common; in an systematic review of 51 observational studies 139 the pooled estimate for depression after stroke was 33%.
Thus, both pain and depression are common in the population and may coincide in patients with stroke.

Prevalence of pain among stroke patients

The reported prevalence of pain after stroke varies between 19–74% \(^{140-144}\). Most previous studies have focused on specific clinical conditions, e.g. central post-stroke pain \(^{145}\) or shoulder pain \(^{142-144}\). Data on the overall prevalence and characteristics of pain after stroke are scarce. One population-based study of Appelros \(^{146}\) reports the overall prevalence of stroke-related pain at one year after first-ever stroke to be 11%. In another recent study by Jönsson \(^{147}\), 21% of the patients reported moderate to severe pain at 16 months after first-ever stroke, but in this study prior- and post-stroke pain were not differentiated. Both studies indicated an association between pain and sensorimotor impairments according to the NIHSS.

Previous studies of the correlation between spasticity and pain after first-ever stroke

Spasticity is believed to cause pain, but no study has investigated the correlation between spasticity and pain after first-ever stroke.

Cost of illness studies

Stroke represents a major economic challenge to society \(^{1}\). Currently, the clinical burden of stroke and transient ischaemic attack exceeds that of coronary heart disease \(^{2}\). Over the years there has been an increased number of Cost of Illness (COI) studies \(^{1, 4, 148-156}\). Stroke is accountable for 10% of the total number of hospital bed-days in Sweden, and the direct costs of stroke accounts for 76% of the total cost of stroke \(^{4}\).

There are no empirical data on health economics for spasticity after stroke. To date, three top-down studies \(^{157-159}\) have assessed the economic impact of botulinum toxin, and all three studies indicate that treatment with botulinum toxin is cost-effective. However, the studies \(^{157-159}\) use Delphi panel survey \(^{160}\), e.g. based solely on expert opinions and as such subject to bias and inaccuracy. The Delphi model is reliable of evaluating expert opinions in areas where empirical knowledge is not available, but more knowledge is needed to estimate the economic burden for spasticity after stroke. An ongoing phase IV study with botulinum toxin \(^{161}\) is investigating whether patients who have had a stroke and suffer from spasticity might benefit from
being given Botox® in addition to standard care. Patients will be enrolled in this study at about 33 locations in Europe and Canada.

Organisation of the health care system in Sweden

Sweden is divided into 290 municipalities, 18 county councils and 2 regions. There is no hierarchical relation between municipalities, county councils and regions since all have their own self-governing local authorities with responsibility for different activities. The Parliament, Riksdagen is the supreme political decision-making body. Municipalities are responsible for matters relating to the inhabitants of the municipality and their immediate environment. Sweden’s municipalities are responsible for a larger share of public services in comparison with the situation in most other countries. Three-quarters of the activities of the municipalities are directly related to demographic factors and are determined by the number of inhabitants, their age and their state of health. Elderly care and care of the disabled are also important tasks for the municipalities and account for almost 30% of their budgets. Care and assistance is provided in the home and in nursing homes 162.

The main task of the county councils and regions is health care. The health care system is financed via taxes. The county councils and regions are responsible for ensuring that everyone living in Sweden has access to good health care. Health care is largely tax-financed in guarantee that people have access to the same high level of care regardless of where they live. On average, patient fees account for 3% of the overall revenues of county councils and regions 162.

There are over 1,000 local medical centres, doctors’ surgeries and district nursing clinics throughout the country. Together, these form the primary care structure, which is the foundation of the Swedish healthcare system. At local medical centres, patients can be treated for all the health problems that do not require the technical and medical resources of a hospital. In addition, Sweden has more than 70 hospitals at county level and 9 regional/university hospitals. The most advanced technical equipment is only available at these hospitals and highly-specialised care has been concentrated here 162.

Organisation of the health care system in Uppsala county

Uppsala county has two hospitals: Uppsala University Hospital and Enköping Hospital. Uppsala University Hospital is a university hospital but also serves as a local hospital for the inhabitants in the county. In the catchment area for the hospital there are 26 medical centres and 6 private medical centres.
Different methods in cost of illness studies

Comparison of cost of illness (COI) studies is hampered by problems: They have been conducted in various countries at different time spans, using different analytic approaches. In a review article by Evers et al. they developed a check list to enable a systematic comparison between COI studies. Table 10 describes the items in their check list. \(^{148}\)

Table 10. Checklist for Cost of illness studies. Developed by Evers et al. \(^{148}\)

<table>
<thead>
<tr>
<th>Main item</th>
</tr>
</thead>
<tbody>
<tr>
<td>Design part</td>
</tr>
<tr>
<td>Year of publication</td>
</tr>
<tr>
<td>Sponsor</td>
</tr>
<tr>
<td>Country</td>
</tr>
<tr>
<td>Year of COI</td>
</tr>
<tr>
<td>Currency used and price year</td>
</tr>
<tr>
<td>Perspective of analysis</td>
</tr>
<tr>
<td>COI study type (disease specific/general)</td>
</tr>
<tr>
<td>COI study design (incidence/prevalence)</td>
</tr>
<tr>
<td>COI estimation procedure (top-down/bottom-up)</td>
</tr>
<tr>
<td>Unit of measurement (year, 1st year, and lifetime costs)</td>
</tr>
<tr>
<td>Data source population</td>
</tr>
<tr>
<td>Population size</td>
</tr>
<tr>
<td>Inclusion and exclusion criteria</td>
</tr>
<tr>
<td>Patient recruitment (inpatient, outpatient, open population)</td>
</tr>
<tr>
<td>Cost part</td>
</tr>
<tr>
<td>Costs included (direct, indirect, co-morbidity)</td>
</tr>
<tr>
<td>Costs measurement (questionnaire, diary, etc)</td>
</tr>
<tr>
<td>Costs valuation (market prices, tariffs)</td>
</tr>
<tr>
<td>Costs reported (total direct costs, costs per health care sector)</td>
</tr>
</tbody>
</table>
### Outline of the thesis

#### Table 11. Outline of the thesis

<table>
<thead>
<tr>
<th></th>
<th>Cohort I</th>
<th>Cohort II</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study type</strong></td>
<td>Cross-sectional study</td>
<td>Cohort study</td>
</tr>
<tr>
<td><strong>When investigated</strong></td>
<td>1 year post stroke</td>
<td>At three times: Acute (2 to 10 days after stroke), 1 month, and 6 months post stroke</td>
</tr>
<tr>
<td><strong>Eligible</strong></td>
<td>Catchment area for Uppsala University Hospital. Included via Riks-stroke.</td>
<td>Catchment area for Uppsala University Hospital. Consecutively included at the stroke unit.</td>
</tr>
<tr>
<td><strong>Inclusion criteria</strong></td>
<td>(a) Resident in the catchment area, (b) above 18 years, (c) a first-ever stroke (cerebral infarction or intracerebral hemorrhage) and survive 1 year, and (d) ability to give informed consent.</td>
<td>(a) Resident in the catchment area, (b) age between 18–84, (c) a first-ever stroke (cerebral infarction or intracerebral haemorrhage), (d) ability to give informed consent, (e) any paresis in the face, arm, hand or leg, at stroke onset.</td>
</tr>
<tr>
<td><strong>Exclusion criteria</strong></td>
<td>(a) Any other neurological disorder, which might affect muscle tone, (b) TIA, and (c) subarachnoid haemorrhage.</td>
<td>Same as cohort I</td>
</tr>
<tr>
<td><strong>Number of patients</strong></td>
<td>140</td>
<td>49</td>
</tr>
<tr>
<td><strong>Paper(s) based on</strong></td>
<td>Paper I–III</td>
<td>Paper IV</td>
</tr>
</tbody>
</table>
Aims

Paper I
To estimate the prevalence of disabling spasticity 1 year after first-ever stroke.

Paper II
To determine whether spasticity 1 year after first-ever stroke correlates to pain.

Paper III
To estimate the direct costs related to spasticity for patients who had had a first-ever stroke and who had survived for 12 months.

Paper IV
To explore the occurrence of spasticity according to modified Ashworth scale and of disabling spasticity during the first six months after first-ever stroke as well as risk factors for spasticity.
Methods for Paper I–III

This Chapter describes the methods used in Paper I–III. First, the study design and study population followed by case ascertainment. Second, the assessment methods and definitions. Table 13 illustrate the key parameters for the study.

Study design

It is a cross-sectional study carried out 1 year after first-ever stroke. Cross-sectional studies are observational studies suitable for estimating the point prevalence of a condition in the population. As we do not know when the event occurs prior to the study, we can only say that there is an association between the investigated factor and a disease, and not that the factor per se has caused the disease. Further, we cannot estimate the incidence and trends over time.

In addition, Paper III can be described as: a disease-specific, incidence-based, bottom-up, including direct costs.

Study population

At the time of the study period, the area of Uppsala University Hospital health care district consisted of four municipalities (Uppsala, Knivsta, Tierp and Östhammar) with approximately 244 000 inhabitants. In the area there were 26 communities and six privately owned primary health care centres.

Case ascertainment

Patients were recruited from the Riks-stroke. For more information about the Riks-stroke, see page 15. The medical history of the stroke patients was carefully reviewed to exclude prior stroke and any neurological disorder, which might affect muscle tone. No multiple overlapping methods were used.

Eligible for the study were stroke patients hospitalized at Uppsala University Hospital between January 2003 and April 2004.
Inclusion and exclusion criteria

Inclusion criteria were: (a) resident in the catchment area, (b) above 18 years of age, (c) a first-ever stroke (cerebral infarction or intracerebral haemorrhage) and survive 1 year and (d) ability to give informed consent. Exclusion criteria were: (a) any other neurological disorder, which might affect muscle tone, (b) TIA and (c) subarachnoid haemorrhage. All patients had received an acute CT scan examination.

Sampling procedure

Eligible patients were listed by date of birth (year, month, and day; if two patients were born on the same date, they were ordered by name). To create a representative sample of a manageable size, and equally large age groups, a cluster sample was created in the following way; patients were stratified by age in four groups: 18–64, 65–74, 75–84 years, and 85 or more years of age. All patients in the youngest (18–64 years) and oldest (85 years or more) age group were invited to participate. Every second patient aged 65–74 years and every third patient aged 75–84 years were invited to participate. If a patient in the age groups 65–74 and 75–84 years denied participation, the reason for this was noted, and the next patient on the list was invited to participate.

A patient who fell ill on January 2003 was examined in January 2004 ± 1 month. Patients were invited first by a letter, and after a week, a phone call. In total, 163 patients were invited, and 140 patients (86%) of these accepted to participate. In the youngest age group, the main reasons for non-participation were lack of time and no perceived health problems whereas in the oldest age group, the main reason was general fatigue. Due to a relative high loss of non-participations in the youngest and oldest age groups, the inclusion period were extended four months (January–April 2004) for these groups.

If a patient did not manage to visit the hospital, a house call was offered. In total, 30 house calls were made, mainly to elderly patients. Figure 1 describes the number of patients by age group at each step in creation of the study sample.
Figure 2. Number of patients by age groups at each step in creation of the study sample

<table>
<thead>
<tr>
<th>Age Group</th>
<th>18-54 yr</th>
<th>65-74 yr</th>
<th>75-84 yr</th>
<th>85+ yr</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients with first-ever stroke</td>
<td>61</td>
<td>78</td>
<td>196</td>
<td>83</td>
<td>418</td>
</tr>
<tr>
<td>Patients surviving one year</td>
<td>54</td>
<td>71</td>
<td>159</td>
<td>43</td>
<td>327</td>
</tr>
<tr>
<td>Eligible for the study</td>
<td>49</td>
<td>68</td>
<td>146</td>
<td>26</td>
<td>289</td>
</tr>
<tr>
<td>Invited to participate in the study</td>
<td>49</td>
<td>37</td>
<td>45</td>
<td>32</td>
<td>163</td>
</tr>
<tr>
<td>Study sample</td>
<td>43</td>
<td>37</td>
<td>39</td>
<td>21</td>
<td>140</td>
</tr>
</tbody>
</table>

Not eligible, e.g. wrong catchment area, wrong diagnosis other neurological diseases/Parkinson
n = 38

Sample losses

<table>
<thead>
<tr>
<th>Age Group</th>
<th>16-64 yr</th>
<th>65-74 yr</th>
<th>75-84 yr</th>
<th>85+ yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Did not have the strength</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>Did not want to participate</td>
<td>4</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Lost to follow-up</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>3</td>
</tr>
</tbody>
</table>
Comparison between participants and non-participants
Participants and non-participants did not differ with regard to age, gender, stroke type (ischaemic versus haemorrhagic), stroke severity according to the Reaction Level Scale (RLS-85) score, initial motor impairments or length of stay in hospital (Table 12). RLS-85\textsuperscript{163,164} is an ordinal coma scale used to indicate injury severity in Riks-stroke, where the results are stratified in three levels: RLS 1 (alert and oriented), RLS 2–3 (drowsy or confused to very drowsy or confused responding to strong stimuli) and RLS 4–8 (unconscious, only reflex or no response to stimuli). The initial motor impairments were categorized according to maximal severity of paresis observed during the first 7 days after the stroke: no or minor paresis, moderate paresis/walking without assistance or severe paresis/assisted walking or unable to walk.

Table 12. Stroke onset characteristics of participants and non-participants

<table>
<thead>
<tr>
<th></th>
<th>Participants (N = 140)</th>
<th>Non-participants (N = 23)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), years</td>
<td>71 (13)</td>
<td>76 (15)</td>
</tr>
<tr>
<td>Women, n (%)</td>
<td>67 (48)</td>
<td>11 (48)</td>
</tr>
<tr>
<td>Stroke type</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischaemic stroke, n (%)</td>
<td>124 (89)</td>
<td>20 (87)</td>
</tr>
<tr>
<td>Haemorrhagic stroke, n (%)</td>
<td>16 (11)</td>
<td>3 (13)</td>
</tr>
<tr>
<td>Stroke severity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RLS a 1 (alert and oriented, n, %)</td>
<td>127 (91)</td>
<td>21 (91)</td>
</tr>
<tr>
<td>RLS 2-3 (drowsy or confused, n, %)</td>
<td>12 (8.6)</td>
<td>2 (8.7)</td>
</tr>
<tr>
<td>RLS 4-8 (unconscious, %)</td>
<td>1 (0.7)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Motor impairment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No or minor paresis, n (%)</td>
<td>47 (34)</td>
<td>9 (39)</td>
</tr>
<tr>
<td>Moderate paresis/walking without assistance, n (%)</td>
<td>48 (34)</td>
<td>9 (39)</td>
</tr>
<tr>
<td>Severe paresis/assisted walking</td>
<td>45 (32)</td>
<td>5 (22)</td>
</tr>
<tr>
<td>Length of stay in hospital, median (min–max)</td>
<td>8 (1–70)</td>
<td>11 (1–82)</td>
</tr>
</tbody>
</table>

\textsuperscript{a} RLS. Reaction Level Scale. On all items, the difference between participants and non-participants was non-significant.

Methods and definitions

Stroke severity was measured with the NIHSS
Stroke severity was estimated with the National Institutes of Health Stroke Scale (NIHSS). NIHSS is an ordinal scale that assesses level of consciousness, speech, language, cognition, inattention, visual field abnormalities, motor and sensory impairment, and ataxia. Confusingly, there have been different variants of the NIHSS during the years. The original NIHSS had 15 items\textsuperscript{165}, in 2003 a modified NIHSS were presented\textsuperscript{166} with 11 items. At the
time I started the study, a 12-item scale with a maximum of 46 points were used. The 46-point scale included the hand. I have used the 46-point scale.

Currently, the whole of Sweden, and probably the rest of the world use an 11-item NIHSS, with a maximum point of 42 (not including the hand). For an exact description of the 46-point scale (Appendix).

The NIHSS is considered reliable and valid as well as quick and easy to use. Recognized limitations of the NIHSS include overestimation of left hemisphere stroke and underestimation of brainstem and cerebellar stroke.

Spasticity

In spite of its limitation, the modified Ashworth scale (MAS) is established and we used it in our studies to enable comparisons with previous studies in the area. For more detailed description and discussion of the scale, see page 25.

For definition and assessment of disabling spasticity, I refer to page 30.

Study variables for cohort I

Table 13 outlines the study variables for cohort I.

Table 13. The study variables for cohort I (Paper I, II and III)

<table>
<thead>
<tr>
<th>Variable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Review of the inclusion and exclusion criteria</td>
</tr>
<tr>
<td>Review of the past medical history including medication</td>
</tr>
<tr>
<td>Written and oral consent, by patient or next of kin</td>
</tr>
<tr>
<td>Stroke characteristics (ischemic/haemorrhagic, stroke side)</td>
</tr>
<tr>
<td>Information from Riks-stroke (acute and 3-months)</td>
</tr>
<tr>
<td>Basic information on living, social service etc (same questions as in Riks-stroke, 3 months)</td>
</tr>
<tr>
<td>Modified Rankin Scale (mRS)</td>
</tr>
<tr>
<td>Bartel’s Index</td>
</tr>
<tr>
<td>National Institutes of Stroke Scale (NIHSS)</td>
</tr>
<tr>
<td>Reflexes and Babinski’s sign</td>
</tr>
<tr>
<td>Modified Ashworth scale (MAS)</td>
</tr>
<tr>
<td>Pain (VAS); location of pain; stroke-related vs. not stroke-related</td>
</tr>
<tr>
<td>Depression (Montgomery-Åsberg Depression Scale, MADRS)</td>
</tr>
<tr>
<td>Handedness (right, left, ambidexter)</td>
</tr>
</tbody>
</table>
Health economic parameters

For Paper III we have followed a checklist developed by Evers et al. 148, to enable systematic comparison between cost of illness (COI) studies. According to their checklist our study can be described in the following terms:

Perspective of analysis

We had a broad health care sector perspective. We did not intend to estimate the economic costs for the individual.

Study type, design, estimation procedures, cost included, and unit of measurement

The design was disease-specific, incidence-based, bottom-up, including direct costs. In a bottom-up analysis the costs are based on real costs. A group of patients with a specific disease is followed for a time period. Our patients were followed during one year after a first-ever stroke and all direct costs (both stroke and non-stroke related) were included. The Swedish currency (SEK) was converted into Purchasing Power Parities 170 (PPP) at the exchange rate of 9.34 SEK for 1 PPP (2003 value) 171. PPP are exchange rates that measure the purchasing power of different national currencies. It is recommended to convert local currencies into PPP 148 because this eliminates the variation in monetary levels between countries. A PPP equals the purchasing power of $1 in the US.

Included in the estimation of the direct costs

Costs for hospitalization

The patient administrative system at Uppsala University Hospital enabled us to get access to specific costs for each patient related to hospitalization, e.g. costs for medical personnel, diagnostic investigations, medication and laboratory tests at all levels of care – intensive care, intermediate care, stroke unit, medical ward and inpatient rehabilitation. The different costs are shown in Table 3, Paper III. Costs in connection with re-admittances to hospital, occurring during the first year after the event, were also included in the analyses.

Costs after discharge

Primary health care

We scrutinized the medical records of the primary health care (both community and private care) for each patient after discharge from the hospital, and recorded all outpatient visits at general practitioners (GPs), district nurses,
physiotherapists, occupational therapists, dieticians, and speech therapists. The primary health care administration assisted in calculation total costs for each patient, based on the following tariffs: A physician’s consultation equals $164, and the price for other consultations or treatments is $48.

**Medication**

All medications for each patient at one year after stroke were recorded, and costs were calculated assuming that the same medication was used during the whole period of one year. The specific costs for each medication were obtained from the national catalogue of registered medications in Sweden 2003, FASS 2003.

**Municipality**

The economic department of the municipalities, both of the city of Uppsala and of neighbouring townships, assisted in providing the total costs for each patient in our cohort regarding home help service, residential and nursing home, adjustment of housing, transportation, food delivery and home alarm. For costs, see Table 3 in Paper III.

**Statistics**

The text under the heading *Statistics* is based on three books 172-174, and I have chosen not to give the exact reference for every statement. Instead I try to explain why I have used a specific statistical method in my sample. The statistics has been discussed with a statistician before and after the study.

First the different variables were characterized into either: **categorial** (qualitative) or **numerical** (quantitative). The categorial variables were further divided into **nominal** (categories are mutually exclusive and not ordered, e.g. gender), and **ordinal** (categories are mutually exclusive and ordered, e.g. spasticity graded in the modified Ashworth Scale (MAS). Spasticity was dichotomized into spasticity (e.g. MAS ≥ 1 in any of the investigated joints) versus no spasticity (e.g. MAS = 0). In addition, we also dichotomized the sample into disabling spasticity versus no disabling spasticity. Table 14 illustrates some of the variables, their definitions, scale type and statistics used.
Table 14. *Examples of variables, their definitions, scale types and statistics used for cohort I.*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Definition</th>
<th>Scale type</th>
<th>Statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>Male/female</td>
<td>Nominal</td>
<td>Chi-square</td>
</tr>
<tr>
<td>Spasticity</td>
<td>MAS ≥ 1 in any of the joints</td>
<td>Ordinal</td>
<td>Chi-square</td>
</tr>
<tr>
<td>Age group</td>
<td>&lt; 65 y, 65-74 y, 75-84 y, ≥ 85 y</td>
<td>Ordinal</td>
<td>Chi-square</td>
</tr>
<tr>
<td>Age</td>
<td>Age at stroke onset</td>
<td>Numeric</td>
<td>Mann-Whitney U-test</td>
</tr>
<tr>
<td>NIHSS score a</td>
<td>See page 78</td>
<td>Numeric</td>
<td>Mann-Whitney U-test</td>
</tr>
<tr>
<td>Direct costs</td>
<td></td>
<td>Numeric</td>
<td>Mann-Whitney U-test</td>
</tr>
</tbody>
</table>

*Although NIHSS is an ordinal scale, it is treated as a numeric scale in the stroke literature.*

Second, the numerical variables were explored for normal distribution. Age was skewed to the left, NIHSS score and direct costs were skewed to the right; hence we used median as an average measure, and inter-quartile range for spread. Square transformation of age (due to skewing to the left) did not accomplish normal distribution; neither did logarithmic transformation of the NIHSS score. However, logarithmic transformation of the direct cost did accomplish a fairly normal distribution (mean/median = 4.28; skewness = 0.045; kurtosis = -0.156).

Since all numerical variables were non-normally distributed we used non-parametric tests.

Identifying of outliers and extremes were done graphically with SPSS.

The statistics were performed with SPSS version 13 for PC for Paper I, and SPSS version 16 for Macintosh for Paper II–IV.

**Comparing two unrelated groups – univariate analysis**

Third, we wanted to compare patients with and without spasticity; hence the sample was divided into those with spasticity, and those without spasticity. These two groups can be regarded as *unrelated*. The numeric variables were non-normally distributed; hence we used Mann-Whitney *U*-test for univariate analysis. For categorial data we used chi-square, and when expected less than 5, Fisher’s exact test.

Fourth, the sample was divided into those with disabling versus non-disabling spasticity. The same statistics as for spasticity versus no spasticity was used.

**Comparing more than two unrelated groups**

In addition, we compared the direct costs for different patient groups regarding mRS and MAS with the Kruskal-Wallis test in Paper III.

---

1 Sometimes terms like *unpaired* or *independent* are used, but all these terms describe the same thing – two unrelated groups are being compared.
Multiple logistic regression
In Paper I we wanted to explore the influence of variables identified in the univariate analyses for disabling spasticity (DS). We wanted to which explanatory variable that predicted DS. In the model, the following variables were entered as independent variables: age (65 years or less versus > 65 years of age), stroke type (ischemic or haemorrhagic), and severe paresis of the arm (> 2 points on NIHSS item 5). The regression analysis was by use of backward elimination (likelihood ratio) in order to minimize effects of interaction between explanatory variables. Odds ratio was given with 95% confidence interval.

Ethics
Before entering the study, the patients received written and oral information. All participating patients gave informed consent (oral and written). In the case of language difficulties, next of kin gave the informed consent. The study was approved by the regional Human Ethics Committee (Ups. 03–595).
Methods for Paper IV

This Chapter gives some additional information of the methods used in Paper IV. For more detailed information, see Methods in Paper IV. Table 15 illustrates the key parameters for the study.

Study design

Details of the study design and inclusion procedures are presented in *Figure 3*. It a cohort study. The patients were assessed three times: at baseline, at 1 month and at 6 months.

![Consort flow diagram for the patient sample](image)

*Figure 3. Consort flow diagram for the patient sample*

Study population

The study population was the same as for cohort I, see page 43.
Case ascertainment

Patients were consecutively recruited from Uppsala University Hospital between February 2005 and March 2008, with the last follow-up in September 2008. The medical history of the stroke patients was carefully reviewed to exclude prior stroke and any neurological disorder, which might affect muscle tone. No multiple overlapping methods were used.

In total, 50 patients were recruited, but 1 patient was excluded during the course of study because of a revised diagnosis of brain tumour instead of stroke, leaving 49 eligible patients.

All acute assessments and most of the follow-ups were done at the Uppsala University Hospital. In total 144 investigations were performed of which 32 were home-visits. All patients were investigated by me. Patients with any spasticity (measured with the MAS) were also investigated by my supervisor, professor Jörgen Borg.

Inclusion and exclusion criteria

Inclusion criteria were: (a) resident in the catchment area, (b) age between 18-84 years, (c) a first-ever stroke (cerebral infarction or intracerebral haemorrhage), (d) any paresis in the face, arm, hand or leg, at stroke onset, and (e) ability to give informed consent.

Exclusion criteria were: (a) any other neurological disorder, which might affect muscle tone, (b) TIA and (c) subarachnoid haemorrhage.

All had received an acute CT scan examination.

Baseline assessment

The baseline assessment was undertaken between 2 to 10 days after the first-ever stroke. The inclusion and exclusion criteria were reviewed to ensure that the participant was eligible. Participants underwent a clinical assessment and were asked to complete a battery of assessments, see Table 15.

Follow-up at 1 month and 6 months

The patients were follow-up at two visits, at 1 month and at 6 months after the event.
Table 15. Study schedule of cohort II (Paper IV)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline Day 2-10</th>
<th>Visit 2 1 month</th>
<th>Visit 3 6 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Review inclusion/exclusion criteria</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Review of the past medical history</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Written and oral informed consent</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Concomitant medications (inc anti-spasticity treatment)</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Stroke characteristics (ischemic/haemorrhagic, stroke side)</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre stroke function (mRS, depression, pain)</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Modified Rankin Scale (mRS)</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Barthel’s Index</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>National Institutes of Stroke Scale (NIHSS)</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Reflexes and Babinski’s sign</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Modified Ashworth scale (MAS)</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Pain (VAS); location, stroke-related vs not stroke-related</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Depression (Montgomery-Åsberg Depression Scale)</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Handedness (right, left, ambidexter)</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quality of Life question (5-point Lickert scale)</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
</tbody>
</table>

Methods of assessments and definitions

We used the same methods and definition as in cohort I, see page 46 in addition, and we interviewed the patients about their pre stroke function (mRS, depression and pain).

Statistics

Descriptive statistics were used for baseline characteristics and for some of the follow-up data.

Univariate analyses compared the clinical characteristics of patients with no spasticity versus patients with spasticity at one month and at 6 months after stroke. Since the parameters age and NIHSS did not show Gaussian distributions, we used the Mann-Whitney test to compare the two groups. The univariate analysis was performed with chi-square for categorical data. When expected values were less than 5, Fisher’s exact test was used.

A multiple logistic regression analysis was performed to explore the impact of factors that were identified in the univariate analysis to be correlated with spasticity at one month. The time point one month was chosen because we found that spasticity was evident as early as one month after stroke. In the logistic regression model, the following variables were entered as independent variables: age, stroke type (ischaemic or haemorrhagic), severe pa-
resis of the arm and sensory disturbance. The regression analysis was made by use of backward elimination (Likelihood Ratio) to minimise effects of interaction between explanatory variables. Odds ratios are given with 95% confidence intervals.

Cochrane’s Q test was used to analyse whether the frequency of spasticity changed during the study period.

Statistics were performed by use of SPSS version 16.0 for Macintosh.

Ethics

Before entering the study, the patients received written and oral information. All participating patients gave informed consent (oral and written). In the case of language difficulties, next of kin gave the informed consent. The study was approved by the regional Human Ethics Committee (Ups 2004: M–444).
This chapter reports only on the main results for Paper I–III. For more extensive results, I refer to the respective paper.

The results for the whole sample

The mean age for the sample was 71 years. For distribution of the age, see Figure 4.

Figure 4. Age distribution of the sample.

The age distribution was skewed to the left and had a non-normal distribution. Mean age (95% CI) was 71 years (69–73). Median age (inter-quartile range) was 73 year (18). The proportion of women was 48%. Moreover,
87% had had ischaemic strokes. In the acute phase, 91% were alert and oriented, i.e. Reaction of Level Scale 1.

One year post stroke the median National Institute of Stroke Scale (NIHSS) was 3 (range 0–21), see Figure 5.

![Figure 5. NIHSS distribution 1 year after stroke for the whole sample.](image)

**Prevalence of spasticity**

The frequency of spasticity was 18% (25/140 patients) and the frequency of disabling was 6% (8/140 patients). The estimated prevalence of spasticity in the total study population, when the different weights of the age groups were considered, was 17% and the estimated prevalence of disabling spasticity was 4%.

Table 16 illustrate a univariate analysis of spasticity and disabling spasticity. I have compared patients with no spastic versus patients with spasticity, and disabling spasticity, respectively.
Table 16. Comparison between patients with no spasticity versus patients with spasticity and disabling spasticity, respectively

<table>
<thead>
<tr>
<th></th>
<th>No spasticity (n=115)</th>
<th>Spasticity (n=25)</th>
<th>Sign. a</th>
<th>Disabling spasticity (n=8)</th>
<th>Sign. a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD)</td>
<td>71.0 (13.4)</td>
<td>72.4 (12.1)</td>
<td>Ns b</td>
<td>60.7 (11.4)</td>
<td>P = 0.02</td>
</tr>
<tr>
<td>Women (%)</td>
<td>45.2</td>
<td>60.0</td>
<td>Ns b</td>
<td>50</td>
<td>Ns 1</td>
</tr>
<tr>
<td>Stroke type</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic (%)</td>
<td>88.7</td>
<td>88.0</td>
<td>Ns b</td>
<td>62.5</td>
<td>P = 0.048</td>
</tr>
<tr>
<td>Haemorrhagic (%)</td>
<td>11.3</td>
<td>12.0</td>
<td>Ns b</td>
<td>37.5</td>
<td></td>
</tr>
<tr>
<td>Stroke side (lesion side)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td>53.9</td>
<td>60.0</td>
<td>Ns 2</td>
<td>25.0</td>
<td>Ns 2</td>
</tr>
<tr>
<td>Left</td>
<td>41.7</td>
<td>40.0</td>
<td>Ns 2</td>
<td>75.0</td>
<td>Ns 2</td>
</tr>
<tr>
<td>Bilateral</td>
<td>4.3</td>
<td>0</td>
<td>Ns 2</td>
<td>0</td>
<td>Ns 2</td>
</tr>
<tr>
<td>Discharged to home</td>
<td>88.7</td>
<td>36.0</td>
<td>P &lt; 0.001</td>
<td>25.0</td>
<td>P &lt; 0.001</td>
</tr>
<tr>
<td>Stroke severity 1 year post stroke</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NIHSS, mean (SD)</td>
<td>1.1 (1.6)</td>
<td>9.3 (5.5)</td>
<td>P &lt; 0.001</td>
<td>11.6 (4.5)</td>
<td>P &lt; 0.001</td>
</tr>
<tr>
<td>Severe paresis in the arm c %</td>
<td>0</td>
<td>64.0</td>
<td>P &lt; 0.001</td>
<td>62.5</td>
<td>P &lt; 0.001</td>
</tr>
<tr>
<td>Disability 1 year post stroke</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mRS 0-2 (%)</td>
<td>52</td>
<td>8</td>
<td>P &lt; 0.001</td>
<td>0</td>
<td>P &lt; 0.009</td>
</tr>
<tr>
<td>mRS 3-5 (%)</td>
<td>48</td>
<td>92</td>
<td>100</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BI 0-95 points (%)</td>
<td>51</td>
<td>96</td>
<td>P &lt; 0.001</td>
<td>88</td>
<td>P &lt; 0.005</td>
</tr>
</tbody>
</table>

a Sign. significance, b Ns Not statistically significant, P > 0.05. c Severe paresis in the arm, e.g. more than 2 points on item 5 on the NIHSS.

Multiple logistic regression for disabling spasticity

Disabling spasticity (DS) was more common in patients under 65 years, with severe arm paresis and haemorrhagic stroke. Including these explanatory variables in a multiple logistic regression analysis, stroke-type lost its significance. Table 17 shows the multiple regression for DS.

Table 17. Multiple logistic regression. Factors associated with Disabling spasticity. The regression analysis was by use of backward elimination (likelihood ratio).

<table>
<thead>
<tr>
<th>Dependent variable</th>
<th>Independent variable</th>
<th>Odds ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disabling spasticity</td>
<td>Severe arm paresis</td>
<td>22</td>
<td>3.9–125</td>
</tr>
<tr>
<td></td>
<td>Age &lt; 65 years</td>
<td>10</td>
<td>1.5–60</td>
</tr>
</tbody>
</table>

Spasticity in relation to other parameters

Table 18 gives an overview of data on all patients with spasticity. Among the patients with disabling spasticity, 1 patient had only an Ashworth grading of maximum 1+. In addition, 2 patients with the highest MAS, which is
4, were not classified as disabling spasticity. This illustrates that the MAS is not a disability scale. Thus, there were patients with low MAS score, who fulfilled our criteria for disabling spasticity and, vice versa, patients with a high MAS score who did not fulfil these criteria.

Table 18. Severity of spasticity for the whole sample

<table>
<thead>
<tr>
<th>Severity of spasticity</th>
<th>Spasticity (n = 25)</th>
<th>Disabling spasticity (n = 8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAS maximum 1</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>MAS maximum 1+</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>MAS maximum 2</td>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td>MAS maximum 3</td>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td>MAS maximum 4</td>
<td>3</td>
<td>1</td>
</tr>
</tbody>
</table>

Table 21 shows all patients with spasticity (n = 25). The table is sorted in the following order: First all 8 patients with disabling spasticity, and second, the grade of spasticity (maximum score of the MAS).

Distribution of the spasticity

Of the 25 patients with spasticity, 10 patients had spasticity only in the upper extremity, 1 had spasticity only in the lower extremity, and 14 patients had spasticity in both upper and lower extremities. Thus, 24 of 25 exhibited spasticity in the upper extremities.

Amongst the 8 patients with DS, 3 patients had spasticity only in the upper extremities; none had spasticity only in the lower extremities, whilst 5 patients had spasticity in both upper and lower extremities.

Prevalence of pain

The frequency of any pain in the study sample was 49%. The frequency of stroke related pain was 21%, and 28% had pain not related to first-ever stroke.

Pain in relation to demographic data, sensorimotor impairments and depression

Pain was not correlated to age, gender, stroke type or disabling spasticity. In a univariate analysis stroke related pain correlated to more severe stroke (NIHSS > 4), any paresis, sensory disturbance, depression, and spasticity, see Table 19.
Table 19. Comparison between No pain, Pain related to stroke, and Pain not related to stroke

<table>
<thead>
<tr>
<th></th>
<th>No pain (n = 71)</th>
<th>Pain related to stroke (n = 39)</th>
<th>Pain not related to stroke (n = 30)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, year (mean, SD)</td>
<td>70 (14)</td>
<td>70 (14)</td>
<td>74 (10)</td>
<td>P = 0.28</td>
</tr>
<tr>
<td>Women, n (%)</td>
<td>34 (48)</td>
<td>10 (33)</td>
<td>23 (59)</td>
<td>P = 0.11</td>
</tr>
<tr>
<td>Ischaemic stroke a n (%)</td>
<td>61 (86)</td>
<td>29 (97)</td>
<td>34 (87)</td>
<td>P = 0.29</td>
</tr>
<tr>
<td>VAS (mean, 95% CI)</td>
<td>-</td>
<td>42 (32–52)</td>
<td>42 (35–49)</td>
<td>P = 0.97</td>
</tr>
<tr>
<td>Disabling spasticity, n</td>
<td>4</td>
<td>4</td>
<td>0</td>
<td>P = 0.061</td>
</tr>
<tr>
<td>NIHSS b (mean, 95% CI)</td>
<td>2.4 (1.5–3.3)</td>
<td>5.2 (3.1–7.3)</td>
<td>0.9 (0.35–1.5)</td>
<td>P &lt; 0.001</td>
</tr>
<tr>
<td>Any paresis, n (%)</td>
<td>24 (34)</td>
<td>17 (44)</td>
<td>5 (17)</td>
<td>P = 0.001</td>
</tr>
<tr>
<td>Sensory disturbance c n (%)</td>
<td>11 (15)</td>
<td>11 (28)</td>
<td>2 (7)</td>
<td>P = 0.002</td>
</tr>
<tr>
<td>Depression d, n (%)</td>
<td>5 (7)</td>
<td>8 (27)</td>
<td>6 (15)</td>
<td>P = 0.029</td>
</tr>
<tr>
<td>Spasticity e, n (%)</td>
<td>11 (16)</td>
<td>12 (40)</td>
<td>2 (5)</td>
<td>P = 0.001</td>
</tr>
<tr>
<td>Use of painkillers, n (%)</td>
<td>1 (1)</td>
<td>2 (7)</td>
<td>4 (10)</td>
<td>–</td>
</tr>
<tr>
<td>Use of antidepressant, n (%)</td>
<td>4 (3)</td>
<td>6 (4)</td>
<td>2 (1)</td>
<td>–</td>
</tr>
</tbody>
</table>

a Stroke was classified into ischaemic or haemorrhagic, b NIHSS = National Institute of Health Stroke Scale, c Item 8 on the NIHSS, d Depression was assessed with Montgomery-Åsberg Depression Scale, where depression is suspected when > 11 points, e Spasticity was assessed with the Modified Ashworth Scale and a MAS /g149 1 was regarded as spasticity.

Multiple logistic regression for pain

In a multivariate analyses, stroke severity and spasticity lost its significance while any paresis, sensory disturbance and depression remained predictors for pain related to stroke. Table 20 shows the multiple regression for stroke related pain.

Table 20. Multiple logistic regression. Factors associated with stroke-related pain. The regression analysis was by use of backward elimination (likelihood ratio).

<table>
<thead>
<tr>
<th>Dependent variable</th>
<th>Independent variable</th>
<th>Odds ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke related pain</td>
<td>Any paresis</td>
<td>3.1</td>
<td>1.2–7.7</td>
</tr>
<tr>
<td></td>
<td>Sensory disturbance</td>
<td>3.1</td>
<td>1.1–8.9</td>
</tr>
<tr>
<td></td>
<td>Depression</td>
<td>4.1</td>
<td>1.4–13</td>
</tr>
</tbody>
</table>

Distribution and intensity of pain

Among patients with stroke related pain, pain in the lower extremity and shoulder pain were most common. Only 4 patients (3%) had central pain. The mean VAS score for stroke related pain was 42 (95% CI 32–52), almost identical as pain not related to stroke.
Figure 6. Comparison between Pain related to stroke versus Pain not related to stroke.
Table 21. *An overview of study data from cohort I of all patients with spasticity (n=25)*

<table>
<thead>
<tr>
<th>Age (year)</th>
<th>Gender</th>
<th>Stroke type</th>
<th>Disabling spasticity</th>
<th>Max MAS score</th>
<th>NIHSS</th>
<th>mRS</th>
<th>Barthel Index</th>
<th>VAS</th>
<th>Direct costs b</th>
<th>Patient # c</th>
</tr>
</thead>
<tbody>
<tr>
<td>75</td>
<td>F</td>
<td>Ischaemic</td>
<td>Yes</td>
<td>4</td>
<td>14</td>
<td>4</td>
<td>45</td>
<td>0</td>
<td>115 571</td>
<td>54</td>
</tr>
<tr>
<td>59</td>
<td>M</td>
<td>Ischaemic</td>
<td>Yes</td>
<td>3</td>
<td>12</td>
<td>4</td>
<td>80</td>
<td>14</td>
<td>248 542</td>
<td>120</td>
</tr>
<tr>
<td>80</td>
<td>M</td>
<td>Ischaemic</td>
<td>Yes</td>
<td>3</td>
<td>12</td>
<td>4</td>
<td>35</td>
<td>0</td>
<td>101 565</td>
<td>89</td>
</tr>
<tr>
<td>46</td>
<td>F</td>
<td>Ischaemic</td>
<td>Yes</td>
<td>3</td>
<td>7</td>
<td>2</td>
<td>100</td>
<td>23</td>
<td>55 911</td>
<td>138</td>
</tr>
<tr>
<td>62</td>
<td>M</td>
<td>Ischaemic</td>
<td>Yes</td>
<td>2</td>
<td>15</td>
<td>4</td>
<td>80</td>
<td>25</td>
<td>230 030</td>
<td>60</td>
</tr>
<tr>
<td>54</td>
<td>M</td>
<td>Haemorrhagic</td>
<td>Yes</td>
<td>2</td>
<td>3</td>
<td>3</td>
<td>80</td>
<td>45</td>
<td>110 961</td>
<td>125</td>
</tr>
<tr>
<td>56</td>
<td>F</td>
<td>Haemorrhagic</td>
<td>Yes</td>
<td>2</td>
<td>17</td>
<td>3</td>
<td>70</td>
<td>0</td>
<td>45 382</td>
<td>40</td>
</tr>
<tr>
<td>54</td>
<td>F</td>
<td>Haemorrhagic</td>
<td>Yes</td>
<td>1+</td>
<td>13</td>
<td>2</td>
<td>85</td>
<td>0</td>
<td>380 521</td>
<td>73</td>
</tr>
<tr>
<td>64</td>
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<td>Ischaemic</td>
<td>No</td>
<td>4</td>
<td>11</td>
<td>4</td>
<td>50</td>
<td>15</td>
<td>120 529</td>
<td>127</td>
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<tr>
<td>73</td>
<td>M</td>
<td>Ischaemic</td>
<td>No</td>
<td>4</td>
<td>9</td>
<td>3</td>
<td>40</td>
<td>40</td>
<td>87 260</td>
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<tr>
<td>72</td>
<td>M</td>
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<td>No</td>
<td>3</td>
<td>10</td>
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<td>114 443</td>
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<td>5</td>
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<td>4</td>
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<td>83</td>
<td>M</td>
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<td>No</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>85</td>
<td>17</td>
<td>78 515</td>
<td>44</td>
</tr>
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<td>F</td>
<td>Ischaemic</td>
<td>No</td>
<td>2</td>
<td>0</td>
<td>1</td>
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<td>0</td>
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<tr>
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<td>9</td>
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<td>0</td>
<td>40 434</td>
<td>28</td>
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<tr>
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<td>M</td>
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<td>No</td>
<td>1+</td>
<td>11</td>
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<td>70</td>
<td>67781</td>
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<tr>
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<td>No</td>
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<td>5</td>
<td>15</td>
<td>50</td>
<td>32 426</td>
<td>136</td>
</tr>
<tr>
<td>73</td>
<td>F</td>
<td>Ischaemic</td>
<td>No</td>
<td>1</td>
<td>12</td>
<td>3</td>
<td>40</td>
<td>72</td>
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</tr>
<tr>
<td>82</td>
<td>F</td>
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<td>No</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>95</td>
<td>0</td>
<td>104 536</td>
<td>14</td>
</tr>
</tbody>
</table>

*a Gender F = female, M = Man, b Costs in PPP$, c Patient internal number in the cohort.
Conclusions and future research

In this Chapter I will summarize the conclusions of my thesis. I will discuss the strengths and weaknesses of my thesis. Finally, I will outline future research.

Methods for the two cohorts

Cohort I – strengths and weaknesses

The first cohort is a cross-sectional survey. A cross-sectional survey is observational and can be used to estimate point prevalence and to explore associations between variables and an outcome. A cross-sectional study gives a picture of the frequency of a disease at a specific moment. However, importantly, a cross-sectional study does not prove that an investigated variable causes the outcome. The advantages with this type of study, are that it is relatively simple and cheap to perform.

Paper I–III are based on 140 first-ever stroke investigated 1 year after their stroke. The sample was selected from Riks-Stroke. At Uppsala University Hospital we have two dedicated nurses that scrutinize all hospital patients to identify possible stroke. Our own quality work (data not published) has shown a wrong diagnosis in the discharge registry of 10%. When registered in the Riks-Stroke, every stroke diagnosis is scrutinized, and patients with wrong diagnosis are not entered in the Riks-stroke. However, it is a hospital based registry, and we did not use all of the techniques for case ascertainment described by Malmgren et al. and Sudlow et al.

First, the sample was not collected prospectively. It was a cross sectional survey of stroke patients surviving one year. Consequently we have no baseline assessments of spasticity. Moreover, between the first-ever stroke and the follow-up one year later 22% of the patients had died.

Second, we did not use a complete community-based case ascertainment, based on multiple overlapping sources. The reason for not doing a prospective and a complete community-based case ascertainment was lack of resources. I had some valuable help from the stroke co-ordinators and the secretary for the rehabilitation medicine, but most of the work I had to do myself. It is considerable work to organize 140 investigation (cohort I) and
three follow-ups for 49 patients (cohort II). To look for stroke cases outside the hospital was not a realistic option.

Although we did not use all of the techniques described by Malmgren and Sudow, the study used the WHO criteria for stroke; it was first-ever strokes only, it was a fairly large, well-defined, stable and representative population. In addition, stroke was presented as ischaemic or haemorrhagic, and CT of the brain was done on all patients.

Finally, when we did a dropout analysis, there was no significant difference between participants and non-participants.

In short, the sample was representative although it did not fulfil all criteria for a perfect epidemiological study.

Cohort II – strengths and weaknesses

Paper IV is a cohort study. A cohort study is observational; an investigator does nothing to affect the outcome, but simply observes what happens. Cohort studies are useful for prognosis and natural history as well as aetiology. If a cross-sectional study is like a picture, a cohort study is more like a film. Although the most convincing evidence comes from randomized controlled studies, information from observational studies can be used provided that they meet a number of criteria. The most cited criteria for assessing causality were proposed by Hill as early as 1965:

- The cause must precede the effect
- The association should be plausible
- There should be consistent results from a number of studies
- The association between the cause and the effect should be strong
- There should be a dose-response relationship with the effect
- Removing of the factor of interest should reduce the risk of the disease.

Patients in cohort II were recruited consecutively from the stroke unit at Uppsala University Hospital. Two additional inclusion criteria were added; the patient had to have an initial paresis (in the face or arm or leg), and there was an upper age limit (84 years); and as a consequence of that, the incidence figures are not representative for an unselected population. However, the reason for the paresis criterion was that we wanted to have more patients with spasticity in order to test some predictors for spasticity. In addition, when including patients consecutively, there is always a selection bias.

Measuring spasticity with the modified Ashworth scale (MAS) – what is the catch?

The most common scale for measuring spasticity is the modified Ashworth scale (MAS) which is considered reliable. Recognized limi-
tions of the scale include that it captures only one feature of spasticity, i.e. resistance to passive movement, and that it does not differentiate the effects of reflex hyperexcitability from those of biomechanical factors.76,77

Platz et al.78 have suggested a summary rating scale for resistance to passive movement (REPAS): in fact REPAS is a standardized MAS. At the time we started our studies REPAS was not available.

We used the MAS because it is the most widely used scale and to enable comparison with previous studies.

The definition of Disabling spasticity

One may criticize our definition of disabling spasticity (DS) as being vague and arbitrary, but for complex phenomena such as disability there is no single scale that can capture all aspects. Moreover, there is no uniform and valid assessment instrument for activity related manifestations of spasticity such as dystonic posturing, arm flexion or crawling toes during gait.

Spasticity as such, is not altogether a bad thing. Some patients use their spasticity as a crutch, and treating it may be doing someone a disservice. Thus, the analysis must be individualized and consider all aspects of disability, which is common practice in rehabilitation medicine.179

Recently, formalized goal setting and use of goal attainment scaling (GAS) has been introduced in this field.92,180-185

In contrast to Barthel Index (BI) and modified Rankin Scale (mRS), both of which consist of predefined items, GAS identifies individual goals. For example, patients with spasticity after a stroke might want to decrease the spasticity in order to improve mobility or to reduce pain. GAS can be used in clinical practice and create realistic expectations for the patients. The disadvantage with GAS, on the other hand, is that you the goal is measured with “an elastic band”.181 Because of that, many authors suggest that one should use the GAS and standardized methods side by side.

Results

Disabling spasticity

This thesis is the first to report on DS after first-ever stroke. The prevalence of DS is low (4%) but corresponds to a large number of patients because stroke is so common. If 4% of first-ever stroke in Sweden have DS, this means that 800 new patients each year deserve further attention with regard to prevention and treatment. The prevalence of DS is even higher; if a stroke patient is assumed to survives 5 years, it would be 4000 patient patients with DS in Sweden at the moment.
Treatment policies have changed towards increasing use of intramuscular Botulinum toxin\(^9\), which is currently considered as the treatment option for limb spasticity with the strongest evidence basis\(^{186-188}\). However, treatment with Botulinum toxin is expensive, and to estimate the cost for treatment it is important to know the magnitude of the problem.

Severe upper extremity paresis one year after stroke was associated with a 22 times higher risk for DS (OR 22, 95% CI 3.9–125). This finding is pathophysiological reasonable – because voluntary and reflex motor networks are anatomically and functionally related.

Age below 65 years increased the odds for DS with a factor of ten (OR 9.5, 95% CI 1.5–60). Although efforts for reducing non-participation in the older ages, selection bias cannot be ruled out.

The confidence interval for the odds ratio was wide, so the association between DS and severe paresis in the arm and younger age, must be interpreted cautiously. Furthermore, since the survey is cross-sectional we can just claim that the findings are an association. Our studies cannot explain why DS was more common in the younger population.

Pain and spasticity

This thesis is the first to study the association between pain and spasticity and first-ever stroke. Pain is believed to be a common problem after spasticity. Stroke-related pain was significantly higher among patients with spasticity (41%) compared to patients without spasticity (5%), however, when analysing the significant parameters in a multiple logistic regression, spasticity lost its significance. How can we explain the somewhat surprising result? As pointed out in an editorial by Sheean\(^{189}\) the spasticity in our cohort might have been too mild to cause spasticity. Another reason could be that we classified the stroke-related and not stroke-related pain wrong.

Our results indicate that motor and sensory impairment were associated with a 3–4 fold risk for developing stroke related pain. Both sensory, and motor impairment might increase the risk for abnormal musculo-skeletal loading, which might lead to strain injuries and pain.

Spasticity and direct costs

This thesis is the first to report the direct costs related to spasticity after stroke. Direct costs for stroke patients with spasticity are four times higher than the costs for non-spasticity stroke patients. The costs for stroke are huge as is the variation of costs in stroke between and within countries\(^{190}\). Reliable estimates of the costs are crucial for allocation of resources, and it is likely that specific estimations have to be made for different countries and regularly updated. Since the study was done before botulinum toxin was introduced in Sweden for spasticity after stroke (no patient was excluded due
to prior use of botulinum toxin), our estimate can be regarded as a base line for the costs in Sweden around 2004.

The rehabilitation gap in the primary care
This thesis illustrates a rehabilitation gap. After discharge from the hospital care only 4% met a physiotherapist, 2% an occupational therapist, and 1% visit a dietician. In addition, no (0%) visits were made to a speech therapist. These figures are surprisingly low. It must be added, though, that patients had full access to the rehabilitation team during their hospital-based period.

The temporal course of spasticity
This thesis adds some new knowledge about the temporal course of spasticity after first-ever stroke (Table 22). Moreover, some of my data show divergent results in comparison with prior studies.

Table 22. The temporal course of spasticity.

<table>
<thead>
<tr>
<th>Time after stroke</th>
<th>Percent spasticity</th>
<th>Year (published)</th>
<th>Country</th>
<th>First author</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute</td>
<td>21%</td>
<td>2004</td>
<td>Sweden</td>
<td>Sommerfeld 7</td>
</tr>
<tr>
<td>Acute</td>
<td>4%</td>
<td>2009 a</td>
<td>Sweden</td>
<td>Lundström</td>
</tr>
<tr>
<td>1 month</td>
<td>27%</td>
<td>2009 a</td>
<td>Sweden</td>
<td>Lundström</td>
</tr>
<tr>
<td>3 months</td>
<td>19%</td>
<td>2004</td>
<td>Sweden</td>
<td>Sommerfeld 7</td>
</tr>
<tr>
<td>6 months</td>
<td>23%</td>
<td>2009 a</td>
<td>Sweden</td>
<td>Lundström</td>
</tr>
<tr>
<td>12 months</td>
<td>39%</td>
<td>2002</td>
<td>UK</td>
<td>Watkins 6</td>
</tr>
<tr>
<td>12 months</td>
<td>17%</td>
<td>2008</td>
<td>Sweden</td>
<td>Lundström 191</td>
</tr>
<tr>
<td>18 months</td>
<td>20%</td>
<td>2006</td>
<td>Sweden</td>
<td>Welmer 8</td>
</tr>
</tbody>
</table>

*a Data from Paper IV in this thesis.

Differences in the prevalence of spasticity in the acute phase and at 12 months after first-ever stroke
Sommerfeld 7 et al. reported 21% spasticity in the acute phase, more than 5 time higher than in my cohort. The reason for this difference is unclear for me; we used the same definitions for spasticity. The timing of the measurement is almost identical, but also minor differences in this respect might play a role. The clinical settings are slightly different; Sommerfeld recruited their patients from a geriatric ward whereas I recruited from Riks-stroke. However, this small difference can scarcely explain a 5-fold variation in spasticity. In addition, the occurrence of spasticity is around 20% after 3 and 18 months 7,8 in the same cohort from Sommerfeld in line with my findings at 12 months.

Watkins et al. 6 on the other hand has a higher prevalence 12 months post stroke – 39% – compared to our prevalence, 17%. This discrepancy is somewhat easier to explain. Watkins has a high mortality, 50% in one year,
probably reflecting a more severe stroke population. The hospitalization rate is generally lower in UK than in Sweden, see Table 9 page 35, probably leading to a selection bias towards more severe stroke in the UK study.

Future research
Finally, what about the future research in the field of spasticity after first-ever stroke? This last part outlines some questions and areas of interest:

Clinical measurements and pathophysiology
- How can the different components in the UMN syndrome be quantified?
- What is the relation between these components and voluntary motor control?
- Studies of the neurobiological basis of spasticity with modern imaging and neurophysiological methods.

Prevention and treatment
- Can early treatment prevent the development of disabling spasticity?
- Can a combination of intensive physiotherapy and focal, pharmacological treatment reduce spasticity and improve function for patients with severe paresis in the chronic phase.

Subarachnoid haemorrhage and traumatic brain injury
- What is the incidence and prevalence of spasticity after subarachnoidal haemorrhage and traumatic brain injury?
Acknowledgements

John Donne said: No man is an island. I do not know whether Donne wrote a thesis, but his words from the 17th century certainly holds true for me. No PhD-student prospers in isolation. I appreciate all the help I had throughout the years, and acknowledge the following persons:

- Professor Jörgen Borg, my supervisor, for introducing me into the world of rehabilitation medicine, always interesting in discussion of a manuscript.
- Professor Andreas Terént, my co-supervisor, who originally got me into stroke medicine. For encourage me and always available for questions.
- Associate professor Anja Smits, my co-supervisor, for all support and unceasingly improving my manuscripts.
- Professor emeritus Sten-Magnus Aquilonius, who introduced me to neurology and neuroscience, and for helping me in moments of despair.
- All colleagues at the department of neurology and the stroke unit at Uppsala University Hospital.
- Secretary Gun Schönnings, probably one of the kindest persons I have ever met.
- Secretary Lotta Sjölander, for all help and support.
- Lisa Johnsson and Ulla-Britt Söderström, both stroke co-ordinators, providing me essential help for recruiting Riks-stroke patients.
- Harry Smits and Steve Scott-Robson for proofreading of my manuscript.
- All patients in my studies. There will be nothing without you.
- My parents, Ingegerd and Bo, for support throughout my life.
- My wife, Carin, and our children Ludvig, Gustav and Edvard for making my life worthwhile living. Love and respect.
- Finally, I will also acknowledge Uppsala University, Selander’s foundation and Stroke riksförbundet for financial support.

No man is an island, entire of itself...any man's death diminishes me, because I am involved in mankind; and therefore never send to know for whom the bell tolls; it tolls for thee.

---

2 John Donne (1572-1631); Devotions Upon Emergent Occasions and Seuerall Steps in My Sicknes - Meditation XVII, published 1624.


Jag har studerat två grupper av strokepatienter. Den första gruppen bestod av 140 individer som jag undersökt ett år efter deras förstagångsstroke. Den andra gruppen, 49 personer, undersökte jag vid tre tillfällen; akut, efter en månad och efter sex månader.

Här redovisar jag mina fem viktigaste slutsatser och skissar på framtida forskningsfält.

Inom ett år utvecklar en femtedel spasticitet

Min undersökning visade att 17 % av patienterna utvecklar spasticitet inom ett år. Denna siffra överensstämmer med andra undersökningar från Sverige. Sommerfeld och medarbeterare rapporterade 19 % spasticitet efter 3 må-

Table 23. Faktaruta om spasticitet

<table>
<thead>
<tr>
<th>Vad är spasticitet och hur mäter man det?</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Vanliga sjukdomar som leder till spasticitet är: Multipel skleros, traumatisk hjärnskada, traumatisk skada av ryggmärgen, cerebral pares och stroke.</td>
</tr>
<tr>
<td>• Den vanligaste metoden för att mäta spasticitet är den modifierade Ashworthskalan, som förkortas MAS. Med den skalan graderar man motståndet man känner när man böjer och sträcker i leden. MAS = 0 är det normala, MAS = 4 betyder mycket kraftigt motstånd, knappt att man orkar böja i leden.</td>
</tr>
<tr>
<td>• Det finns flera problem med skalan: den är inte standardiserad ( ska patienten undersökas i stående, sittande eller liggande), det finns inga regler för hur snabbt ska man böja och sträcka över leden och man har dessutom inte angivit vilka leder som ska ingå vid undersökningen. Skalan kan heller inte skilja mellan den s.k. neurogena komponenten (den del som beror på nervskada) i spasticiteten och den del som beror på förändringar i muskler och senor.</td>
</tr>
<tr>
<td>• Spasticitet definierade vi som ≥ 1 på MAS. Det innebär en spasticitet som är lika med eller större än då man känner ett litet hugg av rörelsemotstånd.</td>
</tr>
<tr>
<td>• Funktionshindrande spasticitet definierade vi som en spasticitet som påverkade den dagliga aktiviteten så att det krävdes intensiv sjukgymnastisk behandling, ortoser (skener) eller behandling med mediciner, t.ex. botulinumtoxin direkt in i muskeln.</td>
</tr>
</tbody>
</table>

Spasticiteten uppträder inom en månad.
Funktionshindrande spasticitet tar längre tid att utveckla.

En liten del av strokepatienterna utvecklar funktionshindrande spasticitet ett år efter stroke


Alla patienter med spasticitet inte ska behandlas. Vissa patienter använder sig spasticiteten som en krycka, och om man då ger muskelavslappande läkemedel till dem så förlorar de sin förmågan att förflytta sig.

Min avhandling är det första försöket att beskriva den undergrupp av patienter.

Går det att förutsäga vilka som får funktionshindrande spasticitet? Med hjälp av en statistisk metod har jag visat att en uttalad svaghet i armen ökade risken för funktionshindrande spasticitet 22 gånger. Ålder under 65 år ökade risken för funktionshindrande spasticitet cirka 10 gånger.

### Table 24. Faktaruta om stroke

<table>
<thead>
<tr>
<th>Vad är stroke?</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Om symtomen går över inom 24 timmar kallas det transitorisk ischemisk attack (TIA).</td>
</tr>
<tr>
<td>- I WHO:s definition ingår både hjärninfarkt och hjärnblödning. Hjärninfarkt utgör 85 % av fallen och blödningarna resterande 15 %. Blödningarna kan i sin tur delas upp i intracerebrala blödningar (blödningar inne i hjärnan) och subaraknoidala blödningar (vanligen ett sprucket pulsåderbräck).</td>
</tr>
</tbody>
</table>

Patienter med spasticitet har fyra gånger högre kostnader det första året

Jag har gjort den första undersökningen av hur mycket patienter med spasticitet efter stroke kostar. Medelkostnaden för strokepatienter med spasticitet var fyra gånger högre – 84 195 dollar (PPPS³) jämfört med patienter utan spasticitet – 21 842 PPP$. Skillnaden var statistiskt signifikant.

³ För att möjliggöra internationell jämförelse omvandlade jag svenska kronor till så kallad köpraft-index dollar (engelska: Purchasing Power Parities, PPP$).

Om besvären är betydande kan man prova olika läkemedel som gör att musklerna slappnar av. Det finns olika former av läkemedel: tablettar, injektioner i muskeln och i utvalda fall kan man ge medicinen direkt i ryggmärgskanalen. Problemet med tabbékbehandlingen är att den ofta ger biverkningar i form av trötthet och yrsel. Behandlingen med injektioner i muskler eller ryggmärgskanalen är effektiv men dyr. Resultatet av min forskning kan användas som ett utgångsvärde för hälsoekonomiska beräkningar Det har tidigare inte funnits några uppgifter om vad spasticitet kostar. Och även om kostnaden för läkemedel är hög så är det mycket möjligt att även den avancerade behandlingen med sprutor i musklerna och ryggmärgskanalen lönar sig.

Smärta är vanligt efter en stroke men spasticitet ger ingen oberoende riskökning för stroke-relaterad smärta

I litteraturen förekommer det ofta uppgifter om att det är vanligt med smärta och spasticitet. Min avhandling är den första som undersöker sambandet mellan smärta och spasticitet efter förstagångsstroke. Visserligen var stroke-relaterad smärta betydligt vanligare hos patienter med spasticitet (41 %) jämfört med patienter utan spasticitet (4 %), men när jag undersökte sambandet med en statistisk metod så gav spasticitet ingen oberoende riskökning för smärta. Ett skäl kan vara att spasticitet och nedsatt kraft är starkt sammanvända och att nedsatt kraft fick starkare genomslag i analysen. En annan förklaring kan vara att spasticiteten var för lindrig för att orsaka smärta. Ytterligare en möjlighet är att jag har klassificerat stroke-relaterad smärta felaktigt. Meningen med att klassificera smärta som antingen stroke-relaterad eller inte stroke-relaterad var att inte skylja all smärta på en stroke. I de flesta fall var det inte svårt. Patienten sade: ”Ont i ryggen, det har jag alltid haft.” Ibland var det dock svårt att avgöra och i de fall jag var tveksam, så klassificerade jag det som stroke-relaterad. Till sist, förklaringen till smärtan kanske låg i felaktig belastning av kroppen och störd känsel. Min statistiska analys...
visade nämligen att känselnedsättning och nedsatt kraft vardera gav en tre till fyra gånger riskökning för stroke-relaterad smärta.

Förslag på framtida forskning inom fältet.

Hur ser då framtiden ut inom spasticitetsforskningen? Jag avslutar denna populärvetenskapliga sammanfattning med att skissa på några frågor och fält för framtida forskning inom tre huvudområden: Kliniska mätmetoder och sjukdomsutveckling, förebyggande behandling, och andra skadegrupper.

Kliniska mätmetoder

- Hur kan man förbättra kvantifiering av spasticitet och andra reflexstörningar?
- Vilken är relationen mellan dessa och viljemässig kontroll?
- Studier av spasticitetens bakomliggande mekanismer med användning av moderna avbildnings- och neurofysiologiska metoder.

Förebyggande och behandla

- Kan tidig behandling förhindra utveckling av funktionshindrande spasticitet?
- Kan kombinationen av intensiv, målinriktad funktionsträning och lokal, farmakologisk behandling minska spasticitet och förbättra funktion i den kroniska fasen?

Andra skadegrupper

- Hur många utvecklar funktionshindrande spasticitet av patienter med traumatisk hjärnskada respektive subaraknoidala blödningar?
WHO's International Classification of Cerebrovascular Disease

WHO's International Classification of Disease (ICD-10) for cerebrovascular diseases (I60-I69)

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I60</td>
<td><strong>Subarachnoid haemorrhage</strong></td>
</tr>
<tr>
<td></td>
<td>Includes: Ruptured cerebral aneurysm.</td>
</tr>
<tr>
<td></td>
<td>Excluded: sequel of subarachnoid haemorrhage (I69.0)</td>
</tr>
<tr>
<td>I60.0</td>
<td>Subarachnoid haemorrhage from carotid siphon and bifurcation</td>
</tr>
<tr>
<td>I60.1</td>
<td>Subarachnoid haemorrhage from middle cerebral artery</td>
</tr>
<tr>
<td>I60.2</td>
<td>Subarachnoid haemorrhage from anterior cerebral artery</td>
</tr>
<tr>
<td>I60.3</td>
<td>Subarachnoid haemorrhage from posterior cerebral artery</td>
</tr>
<tr>
<td>I60.4</td>
<td>Subarachnoid haemorrhage from basilar artery</td>
</tr>
<tr>
<td>I60.5</td>
<td>Subarachnoid haemorrhage from vertebral artery</td>
</tr>
<tr>
<td>I60.6</td>
<td>Subarachnoid haemorrhage from other intracranial artery</td>
</tr>
<tr>
<td></td>
<td>Multiple involvement of intracranial arteries</td>
</tr>
<tr>
<td>I60.7</td>
<td>Subarachnoid haemorrhage from intracranial artery, unspecified</td>
</tr>
<tr>
<td></td>
<td>Ruptured (congenital) berry aneurysm NOS</td>
</tr>
<tr>
<td>I60.8</td>
<td>Other subarachnoid haemorrhage</td>
</tr>
<tr>
<td></td>
<td>Meningial haemorrhage</td>
</tr>
<tr>
<td></td>
<td>Rupture of cerebral arteriovenous malformation</td>
</tr>
<tr>
<td>I60.9</td>
<td>Subarachnoid haemorrhage, unspecified</td>
</tr>
<tr>
<td>I61</td>
<td><strong>Intracerebral haemorrhage</strong></td>
</tr>
<tr>
<td></td>
<td>Excluded: sequel of intracerebral haemorrhage (I69.1)</td>
</tr>
<tr>
<td>I61.0</td>
<td>Intracerebral haemorrhage in hemisphere, sub cortical</td>
</tr>
<tr>
<td></td>
<td>Deep intracerebral haemorrhage</td>
</tr>
<tr>
<td>I61.1</td>
<td>Intracerebral haemorrhage in hemisphere, cortical</td>
</tr>
<tr>
<td></td>
<td>Cerebral lobe haemorrhage</td>
</tr>
<tr>
<td></td>
<td>Superficial intracerebral haemorrhage</td>
</tr>
<tr>
<td>I61.2</td>
<td>Intracerebral haemorrhage, unspecified</td>
</tr>
<tr>
<td>I61.3</td>
<td>Intracerebral haemorrhage in brain stem</td>
</tr>
<tr>
<td>I61.4</td>
<td>Intracerebral haemorrhage in cerebellum</td>
</tr>
<tr>
<td>I61.5</td>
<td>Intracerebral haemorrhage, Intraventricular</td>
</tr>
<tr>
<td>I61.6</td>
<td>Intracerebral haemorrhage, multiple localized</td>
</tr>
<tr>
<td>I61.8</td>
<td>Other intracerebral haemorrhage</td>
</tr>
<tr>
<td>I61.9</td>
<td>Intracerebral haemorrhage, unspecified</td>
</tr>
</tbody>
</table>
WHO:s International Classification… *Continued*

### I62 Other no traumatic intracranial haemorrhage
- Excluded: sequele of intracranial haemorrhage (I69.2)

#### I62.0 Subdural haemorrhage (acute) (nontraumatic)

#### I62.1 Nontraumatic extradural haemorrhage

#### I62.9 Intracranial haemorrhage (nontraumatic), unspecified

### I63 Cerebral infarction
- Included: occlusion and stenosis of cerebral and precerebral arteries, resulting in cerebral infarction
- Excluded: sequele of cerebral infarction (I69.3)

#### I63.0 Cerebral infarction due to thrombosis of precerebral arteries

#### I63.1 Cerebral infarction due to embolism of precerebral arteries

#### I63.2 Cerebral infarction due to unspecified occlusion or stenosis of precerebral arteries

#### I63.3 Cerebral infarction due to thrombosis of cerebral arteries

#### I63.4 Cerebral infarction due to embolism of cerebral arteries

#### I63.5 Cerebral infarction due to unspecified occlusion or stenosis of cerebral arteries

#### I63.6 Cerebral infarction due to cerebral venous thrombosis, nonpyogenic

#### I63.8 Other cerebral infarction

#### I63.9 Cerebral infarction, unspecified

### I64 Stroke, not specified as haemorrhage or infarction
- Excludes: sequele of stroke (I69.4)

### I65 Occlusion and stenosis of precerebral arteries, not resulting in cerebral infarct
- Includes: embolism, narrowing, obstruction (complete or partial), thrombosis
- Excludes: when causing cerebral infarction (I63.-)

#### I65.0 Occlusion and stenosis of vertebral artery

#### I65.1 Occlusion and stenosis of basilar artery

#### I65.2 Occlusion and stenosis of carotid artery

#### I65.3 Occlusion and stenosis of multiple and bilateral precerebral arteries

#### I65.8 Occlusion and stenosis of other precerebral artery

#### I65.9 Occlusion and stenosis of unspecified precerebral artery

### I66 Occlusion and stenosis of cerebral arteries, not resulting in cerebral infarct
- Includes: embolism, narrowing, obstruction (complete or partial), thrombosis
- Excludes: when causing cerebral infarction (I63.-)

#### I66.0 Occlusion and stenosis of middle cerebral artery

#### I66.1 Occlusion and stenosis of anterior cerebral artery

#### I66.2 Occlusion and stenosis of posterior cerebral artery

#### I66.3 Occlusion and stenosis of cerebellar arteries

#### I66.4 Occlusion and stenosis of multiple and bilateral cerebral arteries

#### I66.8 Occlusion and stenosis of other cerebral artery

#### I66.9 Occlusion and stenosis of unspecified cerebral artery
WHO’s International Classification… Continued

I67  Other cerebrovascular diseases
   Excludes: sequele of the listed conditions (I69.0)
I67.0  Dissection of cerebral arteries, nonruptured
   Excluded: ruptured cerebral arteries (I60.7)
I67.1  Cerebral aneurysm, nonruptured
   Includes: arteriovenous fistula
   Excludes: congenital cerebral aneurysm, nonruptured (Q28.–)
I67.2  Cerebral arteriosclerosis
I67.3  Progressive vascular leukoencephalopathy (Binswanger’s disease)
   Excludes: subcortical vascular dementia (F01.2)
I67.4  Hypertensive encephalopathy
I67.5  Moya-Moya disease
I67.6  Nonpyogenic thrombosis of intracranial venous system
   Excludes: when causing infarction (I63.6)
I67.7  Cerebral arthritis, not elsewhere classified
I67.8  Other specified cerebrovascular disease
   Acute cerebrovascular insufficiency NOS
   Cerebral ischemia (chronic)
I67.9  Cerebrovascular disease, unspecified
I68  Cerebrovascular disorder in disease classified elsewhere
I68.0*  Cerebral amyloid angiopathy (E85.-+)
I68.1*  Cerebral arteritis in infectious and parasitic disease classified elsewhere
   - listerial (A32.8+)
   - syphilitic (A52.0+)
   - tuberculosis (A18.8+)
I68.2*  Cerebral arteritis in other diseases classified elsewhere
   Cerebral arteritis in systemic lupus erythematosus (M32.1+)
I68.8  Other cerebrovascular disorders in diseases classified elsewhere

I69  Sequele of cerebrovascular disease
   Note: This category is to be used to indicate conditions in I60 – I67 as the cause
   of sequele, themselves classified elsewhere. The “sequele” include conditions
   specified as such or as late effect, or those present one year or more after onset of
   the causal condition.
I69.0  Sequele of subarachnoidal haemorrhage
I69.1  Sequele of intracerebral haemorrhage
I69.2  Sequele of other nontraumatic intracranial haemorrhage
I69.3  Sequele of cerebral infarction
I69.4  Sequele of stroke, not specified as haemorrhage or infarction
I69.8  Sequele of other and unspecified cerebrovascular diseases
The original and the modified Ashworth scale

Table 25. *The original and the modified Ashworth scale*

<table>
<thead>
<tr>
<th>Score</th>
<th>Original Ashworth scale</th>
<th>Modified Ashworth scale</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No increase in tone</td>
<td>No increase in tone</td>
</tr>
<tr>
<td>1</td>
<td>Slight increase in tone giving a catch when the limb is moved in flexion or extension</td>
<td>Slight increase in muscle tone, manifested by a catch and release or by minimal resistance at the end of the range of motion when the affected part(s) is moved in flexion or extension</td>
</tr>
<tr>
<td>1+</td>
<td>–</td>
<td>Slight increase in muscle tone, manifested by a catch, followed by minimal resistance throughout the remainder (less than half) of the range of motion</td>
</tr>
<tr>
<td>2</td>
<td>More marked increase in tone but limb easily flexed</td>
<td>More marked increase in muscle tone through most of the range of motion but affected part(s) easily moved</td>
</tr>
<tr>
<td>3</td>
<td>Considerable increase in tone, passive movement difficult</td>
<td>Considerable increase in tone, passive movement difficult.</td>
</tr>
<tr>
<td>4</td>
<td>Limb rigid in flexion or extension</td>
<td>Affected part(s) rigid in flexion or extension</td>
</tr>
</tbody>
</table>
### National Institutes of Health Stroke Scale (NIHSS)

Table 26. *The NIHSS (12 item, maximum 46 points, short version). Adapted from* [192].

<table>
<thead>
<tr>
<th>Item</th>
<th>Description</th>
<th>Max. point</th>
</tr>
</thead>
</table>
| 1a. Level of Consciousness (LOC) | 0 = Alert  
1 = Arousable by minor stimulation  
2 = Requires repeated stimulation  
3 = Coma | 3 |
| 1b. LOC Questions | 0 = Answers both correctly.  
1 = Answers one correctly.  
2 = Answers neither correctly | 2 |
| 1c. LOC Commands | 0 = Obeys boths correctly.  
1 = Obeys one correctly.  
2 = Both incorrectly. | 2 |
| 2. Best Gaze: | 0 = Normal.  
1 = Partial gaze palsy.  
2 = Forced gaze palzy. | 2 |
| 3. Visual fields | 0 = No visual loss.  
1 = Partial hemianopia.  
2 = Complete hemianopia.  
3 = Bilateral hemianopia (blind including cortical blindness). | 3 |
| 4. Facial Palsy | 0 = Normal symmetrical movements.  
1 = Minor paralysis (flattened nasolabial fold, asymmetry on smiling).  
2 = Partial paralysis (total or near-total paralysis of lower face).  
3 = Complete paralysis of one or both sides (absence of facial movement in the upper and lower face). | 3 |
<table>
<thead>
<tr>
<th></th>
<th>Description</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td><strong>Motor function, arm</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0 = Normal</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>1 = Drift</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2 = Some effort against gravity</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3 = No effort against gravity; limb falls.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4 = No movement.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5a. Left Arm</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5b. Right Arm</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td><strong>Motor function, leg</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0 = Normal</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>1 = Drift</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2 = Some effort against gravity</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3 = No effort against gravity</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4 = No movement.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>6a. Left Leg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>6b. Right Leg</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td><strong>Limb Ataxia</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0 = Absent</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>1 = Present in one limb</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2 = Present in two limbs</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td><strong>Sensory</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Use pinprick to test arms, legs, trunk and face, compare side to side</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0 = Normal; no sensory loss</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>1 = Mild-to-moderate sensory loss</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2 = Severe to total sensory loss</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td><strong>Best Language</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0 = No aphasia; normal</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>1 = Mild-to-moderate aphasia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2 = Severe aphasia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3 = Mute, global aphasia</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td><strong>Dysarthria</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ask patient to read several words</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>0 = Normal</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1 = Mild-to-moderate dysarthria</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2 = Severe dysarthria</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td><strong>Extinction and Inattention</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Use visual double stimulation or sensory double stimulation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0 = Normal</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>1 = Inattention or extinction to bilateral simultaneous stimulation in one of the sensory modalities</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2 = Severe hemi-inattention or hemi-inattention to more than one modality</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td><strong>Hand function</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0 = Normal</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>1 = Flexion within 5 seconds</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2 = No voluntary extension of the hand.</td>
<td></td>
</tr>
</tbody>
</table>

**TOTAL SCORE** 46
Modified Rankin Scale (mRS)

Table 27. Modified Rankin Scale

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
<th>Exemplified questions from structured interview</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No symptoms at all</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>No significant disability despite symptoms; able to carry out all usual duties and activities.</td>
<td>Symptoms as a result of the stroke. Can be any symptoms or problems reported by the patients or found in neurological examination; difficulty reading or writing, speaking or finding the right word, weakness in extremity; however the patient is able to carry out all usual duties and activities.</td>
</tr>
<tr>
<td>2</td>
<td>Slight disability; unable to carry out all previous activities but able to look after own affairs without assistance.</td>
<td>Concentration on change. Change should come from impairment. Possible improvement in the future is no relevant. Questions like: &quot;Since stroke has there been a change in your ability to work?&quot;, &quot;Since stroke has there been changes in your ability to look after your family at home?&quot;</td>
</tr>
<tr>
<td>3</td>
<td>Moderate disability; requiring some help, but able to walk without assistance.</td>
<td>Assistance is the key word to separate mRS 3 and mRS 4. Questions like: &quot;Is assistance essential for eating; using the toilet; routine daily hygiene; walking; preparing a simple meal; basic household expenses; local travel?&quot;</td>
</tr>
<tr>
<td>4</td>
<td>Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance.</td>
<td>In mRS 4, the patient require assistance, see above.</td>
</tr>
<tr>
<td>5</td>
<td>Severe disability; bedridden, incontinent and requiring constant nursing care and attention.</td>
<td>Constant care means that someone need to be available at all times.</td>
</tr>
<tr>
<td>6</td>
<td>Dead.</td>
<td></td>
</tr>
</tbody>
</table>
## Barthel Index (BI)

**Table 28. The Barthel Index (BI)**

<table>
<thead>
<tr>
<th>Activity</th>
<th>0 = unable</th>
<th>5 = needs help cutting, spreading butter, etc., or requires modified diet</th>
<th>10 = independent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feeding</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bathing</td>
<td>0 = dependent</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grooming</td>
<td>0 = needs to help with personal care</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dressing</td>
<td>0 = dependent</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bowels</td>
<td>0 = incontinent (or needs to be given enemas)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bladder</td>
<td>0 = incontinent, or catheterized and unable to</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>manage alone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Toilet use</td>
<td>0 = dependent</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transfer (bed to chair</td>
<td>0 = unable, no sitting balance</td>
<td></td>
<td></td>
</tr>
<tr>
<td>and back)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mobility (on level surfaces)</td>
<td>0 = immobile or &lt; 50 yards</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stairs</td>
<td>0 = unable</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Purchasing Power Parities

Table 29. What are Purchasing Power Parities?

<table>
<thead>
<tr>
<th>What are Purchasing Power Parities (PPP)?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Purchasing Power Parities (PPP) are currency rates that equalise the purchasing power of different currencies by eliminating the differences in price levels between countries. The model with PPP were developed by the Swedish professor of economics at Stockholm University, Gustav Cassel, in 1918 (^{193}). PPP are exchange rates for a given basket of goods and services. It is important to note that PPP are not a currency, it is a current rate that tries to equalise the purchasing power of different currencies. The PPP often presents as PPP US dollar (PPPS), where a PPP$ equals the purchasing power of $1 in the US. We have used the PPP exchange rated given by the Organisation for Economic Co-operation and Development (OECD). The OECD presents PPP as PPP$ (<a href="http://www.oecd.org/dataoecd/59/10/37984252.pdf">http://www.oecd.org/dataoecd/59/10/37984252.pdf</a>).</td>
</tr>
</tbody>
</table>

If you buy goods for 1000 Swedish Krona (SEK) in Sweden you get goods for 1069 in the US, 1452 in Greece, and 965 in Irland, respectively.

The advantage with PPP are that it tries to compensate not only for different exchange rates between countries, but it also includes different costs between countries \(^{194}\). For example, the Chinese Yuan are kept low by the Chinese government through a constant invest of the trade surplus in foreign currencies, especially of the US governmental securities, e.g. *lending money* to the US enabling them to buy cheaper Chinese products \(^{195}\) \(^{196}\). In 2003 the average exchange rate was $1 = 8.3 Yuan \(^{197}\). The World Bank estimate of PPP, however, was 1PPPS = 1.8 Yuan \(^{198}\).

The uses of PPP have been criticized. The statistical basket of goods varies between countries. For example, Japanese people do not eat yoghurt in the same amount as Europeans. In addition, some goods may be considered differently, and be differently priced due to market availability between countries. For example, a Big Mac in the US is a cheap product for the low end segment of the market, but in India, a Big Mac is highly priced due to the rarity of the product – the Big Mac is therefore a product of the more wealthy parts of the population of India.
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18. Mead GE, Lewis SC, Wardlaw JM, Dennis MS, Warlow CP. How well does the oxfordshire community stroke project classification predict the site and size of the infarct on brain imaging? Journal of neurology, neurosurgery, and psychiatry. 2000;68:558-562


58. Malhotra S, Pandyan AD, Day CR, Jones PW, Hermens H. Spasticity, an impairment that is poorly defined and poorly measured. Clinical rehabilitation. 2009


64. Knutsson E, Richards C. Different types of disturbed motor control in gait of hemiparetic patients. *Brain*. 1979;102:405-430


84. Rankin J. Cerebral vascular accidents in patients over the age of 60. II. Prognosis. *Scottish medical journal*. 1957;2:200-215


89. Saver JL, Gornbein J. Treatment effects for which shift or binary analyses are advantageous in acute stroke trials. *Neurology*. 2009;72:1310-1315


142. McLean DE. Medical complications experienced by a cohort of stroke survivors during inpatient, tertiary-level stroke rehabilitation. *Archives of physical medicine and rehabilitation*. 2004;85:466-469


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