STROKE THROMBOLYSIS ON EQUAL TERMS?

IMPLEMENTATION AND ADL OUTCOME

Anna Stecksén

Department of Community Medicine and Rehabilitation,
Department of Public Health and Clinical Medicine,
Umeå 2017
# Table of Contents

Abstract .................................................................................................................. 3
Abbreviations ........................................................................................................... 5
Sammanfattning på svenska ................................................................. 6
Introduction ............................................................................................................. 8
  Stroke ..................................................................................................................... 8
    Aetiology ........................................................................................................... 9
    Epidemiology .................................................................................................... 9
    Reperfusion therapy .......................................................................................... 11
  An equitable health care .................................................................................... 13
    National guidelines ......................................................................................... 13
    Implementation of national guidelines ........................................................ 14
  Rationale .............................................................................................................. 15
  Aims of the thesis .............................................................................................. 17

Materials and Methods ...................................................................................... 18
  Data collection from research interviews (Paper I) ........................................... 18
    The interview guide ......................................................................................... 18
    The sampling procedure of hospitals and informants .................................... 19
    The interviews and the informants ................................................................ 20
  Data from nationwide registers (I-IV) .............................................................. 21
    Riksstroke ......................................................................................................... 21
    LISA and the Cause of Death register ............................................................. 21
    Included variables ........................................................................................... 22
    Study participants in Paper II, III and IV ....................................................... 24
  Analysis .............................................................................................................. 26
  Ethics .................................................................................................................. 28

Results .................................................................................................................. 29
  Facilitators and barriers to implementation of stroke thrombolysis .............. 29
  Hospital stroke thrombolysis rates and stroke severity .................................... 32
  Treatment rates in patient educational groups ................................................. 34
  Sex differences in ADL outcome 1 year post-stroke ...................................... 36

Discussion .......................................................................................................... 41
  Key results ......................................................................................................... 41
  Methodological considerations ....................................................................... 41
    Sampling .......................................................................................................... 41
    Analyses .......................................................................................................... 44
  Discussion of findings ....................................................................................... 47
  Ethical considerations ....................................................................................... 54
  Research and Clinical Implications ............................................................... 55
  Conclusions ....................................................................................................... 56

Acknowledgements ............................................................................................ 57

References .......................................................................................................... 59
Abstract

Stroke thrombolysis is a method for restoring cerebral blood flow after ischemic stroke, with high priority in the Swedish national guidelines. It has shown marked differences in implementation of the method between hospitals, regions and patient groups. The general aim of this thesis were to examine the implementation of ischemic stroke thrombolysis in Swedish routine stroke care with an equity perspective; to gain more insight into the factors that influence implementation, how the treatment has reached patient groups, and differences in long-term outcomes between women and men. Analysis of data from research interviews with clinicians working within stroke care displayed that the facilitators of and barriers to the implementation of stroke thrombolysis could broadly be categorized into those related to individuals, to social interactions and context, and to organizational and resource issues. Key facilitating factors expressed in interviews were work pride and motivation, good leadership, involvement of all staff members in the implementation process, and quality assurance. Major barriers concerned lack of competence and experience, outdated attitudes regarding stroke management, counterproductive power structures, lack of continuity, and insufficient human resources. National quality register data displayed that stroke thrombolysis treatment expanded to reach more patients with mild deficits. Groups with higher education were more likely to receive treatment, compared to groups with lower educational level. These education group differences have, however, decreased over time in relative terms, but not in absolute terms. Further, there were considerable between-hospitals differences in treatment rates for patients with milder deficits, associated with hospital’s overall stroke thrombolysis rates. Moreover, larger non-university hospitals displayed treatment rate differences between educational groups that were not attributable to patient characteristics. Among thrombolysis-treated women and men, that was independent in ADL before their stroke and survived the first year post-stroke, women experienced higher probability to be dependent in ADL at both 3 and 12 months post-stroke, compared to men. This difference remained significant despite comprehensive adjustments for individual characteristics, symptom severity, and acute effects from stroke thrombolysis. This thesis displays that clinicians face barriers and facilitators at several levels, suggesting implementation interventions could be targeted towards both the individual-, the social interactions and context-, and also the organisation and available resources level. Assurance of clinicians’ individual competence, peer support, and clinical leadership seem to be important areas to intervene. Stroke thrombolysis rates have expanded over time, and an increase in stroke thrombolysis delivery to patients with mild stroke symptoms has contributed to this increase. However, it seems considerable differences between hospitals inhibit equity of care delivery.
Socioeconomically disadvantaged groups receive less often stroke thrombolysis. Type of hospital seems to play a role, yet the reasons for this difference are not fully understood. This thesis also display that stroke thrombolysis-treated women that survive 1 year after stroke, appears to face higher risk for dependency in ADL, compared to men.
Abbreviations

ADL Activities of Daily Living
CI Confidence Interval
EMEA European Medicines Agency
LISA Longitudinal Integration Database for Health Insurance and Labour Market Studies (longitudinell integrationsdatabas för sjukförsäkrings- och arbetsmarknadsstudier)
NIHSS National Institute of Health Stroke Scale
NINDS National Institute of Neurological Disorders and Stroke
OR Odds Ratio
RS The Swedish National Quality Register for Stroke Care, Riksstroke
SES Socioeconomic Status
SITS-MOST Safe Implementation of Thrombolysis in Stroke Monitoring Study
TIA Transient Ischemic Attack
WHO World Health Organisation
Sammanfattning på svenska


Syftet med den här avhandlingen var att undersöka implementeringen av trombolysbehandling i svensk strokesjukvård med ett jämlighetsperspektiv; att få reda på mer om de faktorer som påverkar implementeringen, hur behandlingen har nått olika patientgrupper och eventuella könsskillnader i självständighet upp till 1 år efter behandling.

Resultaten visar att läkare och sjuksköterskor verksamma inom svensk strokesjukvård möter framgångsfaktorer och barriärer på individ-, social interaktion och kontext-, och organisations och resurs-nivå. Framgångsfaktorer var stolthet för arbetet, motivation, gott ledarskap, involvering av alla medarbetare i implementeringsarbetet, och kvalitetssäkring. Barriärer var brist på kompetens och erfarenhet, föråldrade attityder till strokevård, maktstrukturer, brist på kontinuitet, och otillräcklig bemanning. Registrerdata visade att trombolysbehandling har ökat över tid, och då nått en högre andel patienter med milda symtom. Patientgrupper med högre utbildningsnivå hade större sannolikhet att få stroke trombolys, i jämförelse med grupper med lägre utbildningsnivå. Dessa skillnader har dock minskat över tid, men en skillnad i absoluta termer kvarstår. Det var betydande skillnader mellan sjukhus i andel
patienter behandlade för milda symtom, och det var associerat med sjukhusens generella behandlingsnivå. Större icke-universitetssjukhus hade skillnader i behandlingsnivå mellan utbildningsgrupperna som inte kunde förklaras av skillnader mellan patienter i fråga om ålder, levnadsförhållanden, samsjuklighet eller svårighetsgrad på symtomen.

För trombolysbehandlade patienter som överlevde ett år och svarade på frågor om självständighet ADL, det vill säga dagliga aktiviteter (toalettbesök, på/avklädnings, förflyttningar) hade kvinnor högre sannolikhet att vara beroende av hjälp i dessa aktiviteter både 3 månader och 1 år efter stroke. Dessa skillnader kunde inte förklaras av skillnader i individuella faktorer såsom samsjuklighet, strokeinsjuknandets svårighetsgrad och effekter av trombolysbehandling.
Introduction

Stroke

Stroke is a non-communicable disease that in 2015 became the second largest cause of disability-adjusted life-years lost globally, second to ischemic heart disease (1). Stroke also counts as the second largest cause of death in the world (2). In 2011 the United Nations adopted a declaration of non-communicable diseases, stating stroke and other non-communicable diseases constitutes a major threat to global health and not only is a medical but also a developmental and political issue of global importance (3). Besides the need for primary prevention is the need for ensuring adherence to effective acute care therapies, rehabilitation, and follow-up efforts important measures to substantially reduce the burden of stroke in people who have developed or survived stroke (4). In the Swedish context stroke consists one of the largest threats to public health. Every year 30 000 individuals have a stroke, and the majority is older than 65 years (5).

Stroke is a term that is used for neurological deficit attributed to an acute focal injury of the central nervous system by a vascular cause (6). The World Health Organization has defined stroke since 1970 as “rapidly developing clinical signs of focal (or global) disturbance of cerebral function, lasting more than 24 hours or leading to death, with no apparent cause other than that of vascular origin”(7). The clinical characteristics include a fast onset and neurological symptoms related to a specific cerebral region. As the supply of oxygen and nutrients is hindered due to obstruction of arterial blood flow, adjacent brain tissue is damaged. Symptoms often include a loss of function but other symptoms such as epilepsy also occurs. As the clinical symptoms depend on the localisation and the extent of the injury, they can be more or less apparent, and with large variation between patients. Classical symptoms communicated through stroke campaigns are hemiparesis and speech impairments (8). Other symptoms include impressive aphasia, balance or walking problems, vertigo, loss of sensory function, visual disturbances, or altered consciousness (5, 9). “Silent infarctions”; thus without clinical signs, are relatively common and regarded as a common cause of cognitive decline. The different types of stroke are commonly denoted as cerebral infarction/ischemic stroke (71-85%), intracerebral haemorrhage (10-11%) and subarachnoid haemorrhages (3-5%). In the remaining 6-15%, the type of injury has not been determined (5). In this thesis, ischemic stroke is in focus.
**Aetiology**

Usually, ischemic stroke is caused by occlusion of specific cerebral arteries (5), and the vascular causes are several, common to denote as cardioembolisation, large-vessel disease and small-vessel disease. Other, less common causes include hemodynamic factors, dissection of cerebral arteries, coagulation disorders, migraine-related stroke and female sex hormones. In about 20% of stroke, the cause remains unknown.

Cardioembolisation to the brain is usually caused by different heart diseases or disorders, among them atrial fibrillation and myocardial infarction. About 65-70% of cardiac emboli end up in the cerebral vessels, most often in the territory of the carotid artery (5). The magnitude of cardiac embolization as a cause of stroke increases with age, as atrial fibrillation is more common among older individuals (5). Large-vessel disease is usually labelled disorders such as atherosclerosis in the carotid artery, aorta or larger brain arteries. Clinical manifestations of atherosclerosis is the cause of more than 50% of all deaths in the western world (10). Atherosclerosis is a process that is associated with inflammation; atherosclerotic plaque consists of inflammatory active cells, more or less prone to rupture. Small-vessel disease is an umbrella term for the vascular cause of stroke in small penetrant arteries, arterioles, starting off larger brain arteries, usually without collaterals. An occlusion in such a vessel is called lacunar infarction and the symptoms are usually milder in comparison to symptoms due to large-vessel disease or cardiac embolization. The cause of lacunar infarctions are not fully revealed but atherosclerosis is one possible cause. Occasionally it is the atherosclerosis is in the larger vessel that causes the blockage of the small arterioles. Sometimes a small cardiac embolization is the cause, but it is less common (5).

**Epidemiology**

Worldwide, the overall stroke burden in the society has increased due to a higher proportion surviving their stroke and thus living with disabilities (11). In Sweden, the overall risk of stroke and mortality from stroke has decreased since the mid-1990s, especially among men and in older age groups. Ischemic stroke has, however, increased within younger age groups (12, 13) and the burden of risk factors for stroke follow similar patterns (14). The risk of recurrent stroke has decreased from 1998 to 2010, and is associated with secondary preventive treatment (15).

At time of their first stroke, women are older (12), and it is more common that they have reduced independency in ADL, a higher comorbidity, and are more likely to be living alone compared to men (9). Further, it has been shown that women have more severe stroke on arrival to hospital, and also higher
frequency of lowered consciousness compared to men (9). In addition, women more often have cardioembolic stroke, which in general is associated with poorer outcome (9). Partly due to their older age, higher stroke severity and comorbidities, women also suffer higher levels of disability and mortality after stroke, compared to men (16, 17).

The burden of risk factors for ischemic stroke and burden of the disease is distributed along a social gradient in Sweden, despite universal health care and an extended social welfare system. Many other health determinants and non-communicable diseases follow similar patterns (12). The risk of ischemic stroke is multifactorial, and manageable life style risk factors include smoking, unhealthy diet, obesity, physical inactivity and psychosocial factors. Medical risk factors include hypertension, diabetes, hyperlipidemia, and previous or current cardiovascular disease, such as atrial fibrillation. Non-manageable risk factors are high age, male sex and some genetic factors (5, 18). Risk factors for stroke are more prevalent in groups with lower educational level (19), and these differences are more pronounced within younger age groups (12). Some risk factors, such as smoking, obesity, alcohol consumption and diabetes also seem to act stronger in groups with lower socioeconomic position (20) and with low self-perceived health (21). Many of these lifestyle-related factors are present already in late adolescence (22). The risk of ischemic stroke is similarly higher among those with lower socioeconomic position, described in Swedish contexts (12, 22, 23) and elsewhere (20, 24). Atrial fibrillation prevalence is lower for women than for men across all age groups (25). Nevertheless, if atrial fibrillation is present, women and particularly older women have an increased risk of stroke, compared to men, a systematic review state (26). The distribution of stroke subtypes varies some between the sexes; women consist the major parts of patients among those with subarachnoid haemorrhage, and men are the majority among patients with cerebral infarction (5).

The initial severity of stroke symptoms is one of the strongest predictors of eventual stroke outcome (5). Notably, it has been shown that increasing community poverty significantly associated with worse stroke severity at presentation, independent of other known factors associated with stroke outcomes (27). Kerr displayed in 2011 that patients in Scotland with stroke with a low socioeconomic status were younger and had a more severe deficit on presentation, and smoking a likely contributor to this (28, 29). However, classic risk factor could not explain the whole excess risk for individuals within low-SES groups (29).

Similarly to the burden of risk factors for acute stroke, does also sub-acute or long-term consequences of stroke follow a similar social gradient; such as stroke recurrence and stroke case fatality in terms of individual (30-32) and
neighbourhood socioeconomy (33) in Sweden, functional outcome at 3 months post-stroke in Berlin (34) and the USA (35), both acute- and post-acute mortality in Italy (36). Neighbourhood educational level was associated with mortality risk from stroke in the USA (37).

**Reperfusion therapy**

**Thrombolytic therapy**

Stroke thrombolysis, sometimes named thrombolytic therapy, for restoring cerebral blood flow for patients with acute ischemic stroke is, to date, considered a standard treatment and has a high priority in international and national guidelines (38, 39). Thrombolytic therapy has been tested with several agents, all acting by converting plasminogen to plasmin. The product label for Swedish routine clinical care is Actilyse®, approved by the Medical authorities in 2002. The active substance in Actilyse® is alteplase, a recombinant tissue plasminogen activator (rt-PA), which is genetically a copy of the naturally occurring substance within the human haemostatic system (40).

The time delay to stroke thrombolysis is critical, given the probability to save the penumbra, the tissue adjacent to the primary injury. At the time of the European approval, 3 hours from first symptom was the upper time limit for treatment. The Swedish Medical Products Agency stated in 2003, similarly to the European approval, that as the risk for intracranial haemorrhage was substantial, treatment could only be given to a lesser proportion carefully selected patients, and only at hospitals with access to required competence (41).

Stroke thrombolysis has since the approval been disseminated throughout all Swedish hospitals admitting acute stroke patients, but treatment rates have been considered unequal between regions, hospital types and patient groups (42). In 2008, overall treatment rates for patients 18-80 years and ischemic stroke reached 8.8%, and university hospitals had the highest treatment rates after adjustments for differences in patient characteristics. Many of those hospitals were also participating in clinical trials for treatment before the approval in 2003. The most rapid increase of treatment rates was in large non-university hospitals. Community hospitals had a 2-3 year delay in implementation, compared to university hospitals. The ECASS III findings of beneficial effect of treatment in the time window 3-4.5 h after stroke onset, published 2008, increased treatment rates in that time window (43). Also, a meta-analysis from 2014 of individual patient data from several randomized trials concluded that despite early increases in fatal intracranial haemorrhage, alteplase significantly improved the overall likelihood of a good stroke outcome at 3-6 months. The proportional benefit increased with early treatment and
remained statistically significant up to at least 4.5 hours after initial stroke symptoms, irrespective of age or stroke severity (44).

Indications and contraindications for treatment have mostly been based on the inclusion criteria for randomised controlled trials for thrombolysis (45), and the benefit of certain inclusion criteria have been discussed (45). Also, despite national and international authorities’ approval of the evidence base for treatment, the overall safety and effect of stroke thrombolysis are and have been under vigorous debate in some clusters internationally. One of the early controversies were related to denial of access of the original data for the NINDS study (46), which laid the base for the approval. Further reassurance of safety and effects from treatment was needed and since the treatment was seen as relatively beneficial for patients, it was reasoned that inclusion of patients to another randomised trial would be unethical. However, eventually an independent committee gained access and published a reanalysis of the NINDS data, supporting the use of thrombolysis for ischemic stroke within 3 hours (47). Critical voices have also doubted the interpretation of the statistical analyses within the larger thrombolysis studies (48, 49).

The Swedish strategy to disseminate treatment and increase treatment rates has been to implement thrombolysis in most of the hospitals admitting patients with acute stroke (42). Findings indicate, however, that regional patterns has played an important role in the dissemination (42), and it was a 5-year delay before the last county council reached up to 2 % level, after the European approval in 2003 (42). Despite that the gaps between the counties decreased over time, there was a more than 7-fold gradient in treatment rates between high- and low-frequency counties in 2008 (42). Safety measures such as frequency of symptomatic intracranial haemorrhages or 90-day case fatality, did not differ in major part between hospital types or departments (42). Subgroups that less frequently received stroke thrombolysis were women, older patients, those living alone or in institution, dependent in ADL before the stroke, with a history of a previous stroke, unconscious on admission and those treated with antiplatelet agents. However, patients with atrial fibrillation had higher chance of receiving treatment (42).

**Thrombectomy**

Ischemic stroke with proved occlusion of the anterior larger brain arteries is a life-threatening condition with very high risk for death or disability. Thrombectomy with stent-retriever is a surgical intervention that has gained more evidence the latest years, with or without simultaneous thrombolytic therapy. The intervention implies that a micro-catheter is piped to the occluded vessel through the groin, and taken backwards, a stent is laid bare, supplanting and catching the thrombus (39). During the years covered in this thesis,
thrombectomy has only been given at a few thrombectomy centres in Sweden (50).

**An equitable health care**

Health care equity is supported by the Swedish law; The Swedish Health Care Act 3:1 states;

*The aim of the health care is a good health and a health care on equal terms for the population. The care should be given with respect for all humans’ equal value and for the dignity of the separate individual. Those with the highest need of health care should be given priority (51).*

The National Board of Health and Welfare describe an equitable health care as;

*..all citizens shall have equal opportunities to receive care and [...] all will be equitable treated, despite factors such as age, sex, sexual orientation, disability, residence, education, social position, country of birth or religious affiliation, and that all citizens have equal right to care and treatment (52).*

At the same time, local autonomy is also supported by the Swedish law, and health care is regionally governed and funded by 21 county councils or regions. These two ideals have been described as a balancing act in that how much freedom should the county councils have and to what extent should health care be equal across the nation (53). Delivery and financing of the health care are the responsibility of the county councils, but planning and arranging the setting of the regulatory framework is increasingly taken over by the state (53). The Swedish state has become more active in governing and regulating health care, with an increased accent on national equity or equivalence, which could be interpreted as increased recentralisation of the Health care (53) with reduced scope for local decision-making.

**National guidelines**

National guidelines, published by the Swedish National Board of Health and Welfare (NBHW), are focused on specific diseases and care areas and constitutes instruments for the state to steer local political authorities These guidelines are primarily directed towards decision-makers at all levels within regions and county councils. The purpose is to achieve equitable and cost-effective health care through an increased extent of best available knowledge to achieve the best possible benefit to patients (54). Accordingly, the separate county councils and regions make decisions upon the implementation within the local conditions (55).
The basis of the decision to create national guidelines for a disease or care area is that a large group is affected, it is a resource-demanding health care field, and there is risk for health care to be unequal (55). Within a national guideline, severe conditions, large need, and interventions with high benefit, and low cost per effect are given high priority. Low priority is given to interventions with small benefit in relation to the cost, or limited scientific support and with existing alternative interventions with greater effect or stronger scientific support. Recommendations are made on a group-level, and the end-decision lies with the separate health professional in the separate clinical situation (55). Stroke is a disease that fulfils several of the requirements to create national guidelines.

**Implementation of national guidelines**

The development of clinical guidelines is unlikely to improve practice and benefit patients unless active steps are taken to ensure their appropriate use, and it is important to understand the factors that impede or enable such implementation (56). The *implementation gap* is often used as a term for the well-known difference between research results and practical use. Once a gap has been identified between what should be done in practice (based on current best evidence) and what is being done in practice, the first step towards reducing a gap is to identify the reasons why it exists (56). Previous quantitative research has provided cues to implementation rates within different regions, hospital types, and certain patient groups. But the identification of barriers to implementing evidence-based care depends largely on qualitative methods (56).

Despite that a majority of Scandinavian doctors regard stroke thrombolytic treatment as beneficial, the implementation in clinical practice has been named poor (42, 57). A study including six different population-based stroke register of six European centres pointed out a need for understanding barriers to implementing evidence-based care both across and within nations, particularly where high-level evidence support their implementation. Suggested questions that required further investigation were focused on potential drivers of care variation; local health system policy, guideline implementation, audit and patient expectation (58). It can be assumed that the local stroke care organisation variation is one cause of treatment variations. Other potential causes are local opinions and views upon indications (and contraindications) for treatment, such as upper age limit (changed in national stroke guidelines in 2014), or risk-benefit judgements for patients with several comorbidities or different symptom severity. One study showed that several cultural characteristics of the hospital organisation were related to thrombolysis rate such as "informal and formal feedback", "a learning culture", and "uncompromising, individual clinical leadership" (59). However, the knowledge
in this field is limited. In order to examine whether stroke thrombolysis is given on equal terms, as postulated by the health care act, there is a need for more information on how stroke thrombolysis has reached patient groups. One hypothesis is that high hospital treatment rates are associated with a high proportion of patients with minor symptoms. Temporal changes in treatment delivery can give a picture of the direction of the development within current acute stroke care disparities.

Access to evidence-based methods within stroke care (38) becomes a particularly interesting area given the differences in both risk, symptom severity and outcome between groups in the society, such as socioeconomic, men and women, or others. Parallel to prevalence of risk factors, can seeking and accessing health care be a determinant of health. It could be so that certain groups, due to less stroke knowledge, seek emergency care too late for treatment (60). Socioeconomic status may impact stroke severity via medication compliance, access to care, and cultural factors, or may be a proxy measure for undiagnosed disease states (27). There is a lack of knowledge regarding in what way access to stroke thrombolysis is distributed along the social gradient in Swedish routine stroke care, for example educational level. Previous research has shown some differences in patient characteristics among patients admitted to different hospital types (61), but it is not known if these differences are mirrored in the access to stroke thrombolysis. Especially, it is necessary to examine whether treatment delivery matches care need for different groups. Among non-thrombolysed patients, women experience a poorer functional outcome after a stroke (16). Several short-terms studies have suggested thrombolysis to potentially equalize the expected sex differences in terms of functional outcome (62-64). However, whether this is the case in Swedish routine stroke care, and whether this pattern goes along in long-term follow-ups, has not been investigated.

Rationale

Stroke entails a major threat to public health and is distributed along a social gradient, with higher burden among disadvantaged groups. According to the Swedish health care act 3:1 (51), the aim of the health care is a good health and a health care on equal terms for the population. The care should be given with respect for all humans’ equal value and for the dignity of the separate individual. Those with the highest need of health care should be given priority. Thus, inequities in health should be addressed.

Thrombolytic therapy for ischemic stroke is a relatively new treatment possibility within advanced acute stroke care that correctly administered, to the right patients, has potential to dramatically and positively affects the ischemic
stroke process. Before the advent of thrombolytic therapy for ischemic stroke, no direct acute care treatment to reduce the extent of the neurological injury has been available. Implementation of stroke thrombolysis in Swedish routine stroke care has shown marked differences between demographic groups, hospital types, and regions (42). Given the tangible differences in treatment rates between Swedish regions and hospitals, this thesis aims to examine more on the reasons and characteristics of these differences. Understanding how innovations make their way into health care practise is important in order to make the most of limited resources.

In what way this treatment has reached socioeconomic groups, given the higher burden of disease for disadvantaged groups, and whether hospitals that implements this treatment uses similar indications for treatment, is either not known. Furthermore, as previous research has displayed that thrombolytic therapy may have the potential to equalise expected sex differences post-stroke, long-term outcome functional outcomes in terms of sex differences have not been investigated. Such information could provide implications for the management of rehabilitation of these patient groups.
Aims of the thesis

The general aim of this thesis were to examine the implementation of ischemic stroke thrombolysis in Swedish routine stroke care with an equity perspective; to gain more insight into the factors that influence implementation, how the treatment has reached patient groups, and differences in long-term outcomes between women and men.

The specific aims were to

I. Analyze the facilitators and barriers to implementation of stroke thrombolysis as perceived by stroke care professionals

II. Examine whether an increasing rate of thrombolysis is partly caused by more patients treated with minor stroke symptoms

III. Examine whether education level of patients is associated with thrombolysis and thrombectomy treatment

IV. Examine sex differences in change in ADL function among patients treated with ischemic stroke thrombolysis in routine clinical care from before stroke onset to 12 months post-stroke
Materials and Methods

In this thesis one qualitative and three quantitative papers are included. An overview is presented in Table 1. Paper I is a qualitative explorative study based on semi-structured research interviews with physicians and nurses working in stroke care at selected Swedish hospitals. Papers II-IV are quantitative observational studies primarily based on data from Riksstroke. Paper II analyzes the stroke severity among patients treated with thrombolysis in Swedish hospitals over time. Paper III analyzes the educational level of patients and their treatment rates. Paper IV includes a prospective analysis of a thrombolysis-treated cohort’s 3- and 12 months outcome in terms of ADL status among women and men.

Data collection from research interviews (Paper I)

A qualitative interview study was set up with clinicians as informants, in order to collect qualitative data on individual experiences from implementation of national guidelines in stroke care. It was considered that knowledge based on qualitative research would complement previous research that had quantitatively explored in what way characteristics within the stroke care organization influenced the dissemination of thrombolysis for ischemic stroke (42, 43).

The interview guide

The author group decided that individual face-to-face interviews were the most appropriate considering the potential sensitiveness of issues related to local performance and cooperation. The interview guide was prepared by two researchers and based on relevant literature (65), and the national guidelines for stroke care (38). Test interviews were conducted within the author group in order to check feasibility, and some adjustments of the interview guide were made. The interview guide covered a number of themes; driving forces for implementation, decisions and support for decisions, cooperation within the hospital, dream scenarios for implementation success, hierarchies within and between hospitals, attitudes to implementation and sources of knowledge. Furthermore, the national guideline recommended stroke care interventions were listed as subjects to talk about of which stroke thrombolysis was the most important. The interview questions were "open-ended" and formulated to suit the unique interview. Examples of questions were: what do the stroke care need for a good and effective implementation of the recommended methods? / What characterises the working at emergency rooms and stroke units that makes implementation of recommended working possible and effective? / What do
different professions within stroke care regard as required in order to overcome barriers for implementation of recommended methods?

**Table 1.** Overview of papers included in the thesis.

<table>
<thead>
<tr>
<th>Paper number</th>
<th>Research question</th>
<th>Data material</th>
<th>Inclusion criteria</th>
<th>Number of subjects</th>
<th>Primary analytical method</th>
<th>Primary outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paper I</td>
<td>What barriers and facilitators for implementation of stroke thrombolysis do clinicians experience?</td>
<td>RS* explorative semi-structured interviews</td>
<td>Physician or nurse working in acute stroke care at Swedish hospitals selected based on performance in RS*.</td>
<td>16 informants from 9 different hospitals</td>
<td>Qualitative content analysis, primarily inductive</td>
<td>Facilitators and barriers for implementation of primarily stroke thrombolysis guidelines</td>
</tr>
<tr>
<td>Paper II</td>
<td>Do the proportion patients treated for mild symptoms contribute to overall treatment rates?</td>
<td>RS* Stroke thrombolysis-treated patients 2007-2010 at hospitals with &gt;70% coverage of NIHSS* score data before treatment</td>
<td></td>
<td>1743</td>
<td>Linear regression</td>
<td>Change in proportion treated patients with NIHSS* 0-5</td>
</tr>
<tr>
<td>Paper III</td>
<td>Is reperfusion therapy equally distributed among patient socioeconomic groups?</td>
<td>RS*, LISA% Non-treated and stroke thrombolysis-treated patients 2003-2009</td>
<td></td>
<td>85885</td>
<td>Multivariable logistic regression</td>
<td>Change in treatment rates over time within educational groups</td>
</tr>
<tr>
<td>Paper IV</td>
<td>Do women and men have similar functional status 1 year after stroke thrombolysis?</td>
<td>RS*, Swedish Tax Office Women and men, ADL* independent before stroke, stroke thrombolysis-treated, surviving 12 months and responding to ADL* questions at 3- and 12 months</td>
<td></td>
<td>4936</td>
<td>Multivariable logistic regression</td>
<td>Sex differences in self-reported ADL* status at 3 and 12 months after treatment.</td>
</tr>
</tbody>
</table>

* Riksstroke
* National Institutes of Health Stroke Scale
% Longitudinal Integration Database for Health Insurance and Labour Market Studies
# Activites of Daily Living

**The sampling procedure of hospitals and informants**

For the sampling procedure, the research group took a quantitative approach and assessed the hospital-specific implementation rates of a few stroke care guidelines. Evaluation was performed using the following data from Riksstroke; proportion of patients with ischemic stroke aged ≤80 years receiving thrombolytic therapy, proportion of patients treated in stroke units (among all patients with stroke), and proportion of patients with ischemic stroke receiving heparin for progressive stroke. Hospital care in stroke units has been proven
beneficial for patients with stroke and has a high priority in national stroke care guidelines (38). Swedish stroke care guidelines from 2001 and onwards advise against heparin for progressive ischemic stroke and this once-common treatment has been under discharge in routine care (38, 66). Based on ranking in the evaluation, hospitals were divided into rapid-, intermediate- and “slow” implementing hospitals. Then, striving for maximum variation in geography, hospital type and implementation level, a number of hospitals were selected for invitation to the study.

Riksstroke has assigned contact persons in each participating hospital in Sweden and first, telephone contact was made with those persons in each selected hospital, referring to our mutual contacts at the Riksstroke office. After informing shortly on the aim of the study, we asked for names of professionals that would fit with our desire to meet with one nurse and one physician, experienced within stroke care and with a leading or coordinating role, at each sampled hospital. A letter with a formal invitation was then sent to the recommended professionals. Those were called by telephone two weeks later, and were asked for their interest to participate in an interview. If interested, a time to meet was set at the comfort of the informant.

Reasons for declining participation were sick-leave (a nurse), lack of time (a physician), and no available fixed physician (one hospital). Two interviews with nurses (at two hospitals) were cancelled one the interview day, one on behalf of the interviewer (me) due to a train delay, and one on behalf of an informant, due to an important and acute meeting. Also, an interview visit at one hospital was cancelled on behalf of the research group, due to time constraints.

**The interviews and the informants**

Sixteen face-to face interviews were carried out in a separate facility at, or adjacent to, the informant’s work place. Totally 9 physicians (2 women) and 7 nurses (all women) participated. Two of the informants, a nurse and a physician in the same hospital, expressed that they wanted to participate together in one interview, which was approved. The interview started with a display of gratitude for the informant taking their time for the interview, followed by a short description of what the study aimed for (examine factors that steers introduction of recommended interventions/treatments and discharge of outdated treatments). Also, acknowledging that stroke care seems to be a thrilling care chain with many actors involved, it was emphasized the interviewer would like to get to know more about the informants experiences from working with implementation of national guidelines. In addition, the informant got the oral information on the voluntariness of the participation and confidentiality of the responses repeated. Then the informant was asked to sign
an informed consent. When the interviews were reaching end the interviewer asked what the informants viewed as most important and if there was anything the informant would like to emphasize. The interviews were audio recorded and subsequently transcribed verbatim. Laughter, sights, pauses or ironic expressions were included within the transcripts in order to facilitate the interpretation.

Data from nationwide registers (I-IV)

There exist a vast number of sources for nation-wide health register data in Sweden. A distinction can be made between the national quality registers and the population-based official health registers. National quality registers holds individually-based data on problems, interventions and results from within health care, are quality reviewed and certified by the national steering group for quality registers (67). Fully expanded, national quality registers can follow up all patients in the country in a specific disease or treatment group. It is also possible to follow up in what way separate county councils, hospitals and clinics manage the care. Sweden is in several ways world-leading in the quality and coverage of national quality registers and in 2017, there were 96 national quality registers in operation. The population-based health registers are runned by central authorities, primarily Statistics Sweden and the National Board of Health and Welfare. All register data uses the Swedish personal numbers to link information, and has comprehensive confidentiality.

Riksstroke

The primary source of data for this thesis, especially papers II-IV, was Riksstroke, the Swedish national quality register for stroke care. Riksstroke was started in 1994 and the primary aim is to monitor and support quality improvement in Swedish stroke care. All Swedish hospitals (n=72 in 2013) admitting acute stroke patients participate in the data registration. The register collects data from both hospital records and structured questionnaires at 3 and 12 months post-stroke. The NBHW has given Riksstroke a ranking score of 1, implicating the register is viewed as mature and with certain characteristics. The register is today globally the oldest register for stroke. Given the 6% false-positive diagnosis of acute stroke in Swedish routine administrative registers (68), actual coverage of the register is estimated to be 94% (61).

LISA and the Cause of Death register

Data on education level for Paper III was extracted from LISA, the Longitudinal Integration Database for Health Insurance and Labour Market Studies (69). The database includes all individuals 16 years of age and older that is registered in Sweden as of December 31 each year. It is administrated by Statistics Sweden
and integrates current data from the labour market, educational and social sectors and is updated every year. For the fourth paper, Riksstroke data were linked with dates of death, if available, from the Cause of Death register. This was done by administrators at the Riksstroke office.

**Included variables**

Variables for inclusion criteria, descriptive analysis and outcome are presented in Table 2. Variables mutual for the quantitative papers II-IV were sex, age, year of onset, smoking, hypertension treatment, atrial fibrillation, previous stroke, diabetes, thrombolysis, hypertension treatment and hospital type. In study II, examining association between proportion of patients with minor stroke and hospital treatment rates, the primary outcome measure was thrombolytic therapy, and the target variable was NIHSS score before treatment. Minor stroke was defined as NIHSS score of 0-5 on admission. In the analysis of treatment rates for patients with different education level (study III), thrombolysis and thrombectomy was used as a combined outcome measure (named reperfusion) and the target variable was education level. In the last study where ADL status at 3 and 12 months post-stroke and -treatment was compared between women and men (paper IV), the outcome variable was ADL independency/dependency.

All sociodemographic, pre-stroke health- and acute care variables, except education level and country of birth, were reported by hospital staff into RS through reading of the patient’s hospital record, from the acute- or post-acute care clinical setting. Sociodemographic variables included in this thesis were sex, age, educational level, and solitary living. Patient educational level, originally extracted from LISA, was at data delivery categorized into primary-, secondary-, and university education. Post-gymnasial education was denoted as university education. Pre-stroke health variables in this thesis were dependency in ADL, institutional living, smoking, hypertension treatment, atrial fibrillation, previous stroke, previous TIA and diabetes.
Table 2. Overview of included variables in Papers I-IV. Type of variable and paper number.

<table>
<thead>
<tr>
<th>Frame</th>
<th>Variable</th>
<th>Attribute</th>
<th>Paper number</th>
<th>I</th>
<th>II</th>
<th>III</th>
<th>IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sociodemographic</td>
<td>Female sex</td>
<td>y/n</td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
<td>T</td>
</tr>
<tr>
<td></td>
<td>Age</td>
<td>continuous/categorical</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Patient’s educational level</td>
<td>categorical</td>
<td>T</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Living alone</td>
<td>y/n</td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Pre-stroke health</td>
<td>ADL dependency</td>
<td>y/n</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Institutional living</td>
<td>y/n</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Smoking</td>
<td>y/n</td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hypertension</td>
<td>y/n</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Atrial fibrillation</td>
<td>y/n</td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Previous stroke</td>
<td>y/n</td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Previous TIA</td>
<td>y/n</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Diabetes</td>
<td>y/n</td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Acute care</td>
<td>Year of onset</td>
<td>year</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hospital type</td>
<td>categorical</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Level of consciousness on admission</td>
<td>categorical</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>NIHSS score before treatment</td>
<td>score (0-42)</td>
<td>O</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Delay to treatment</td>
<td>minutes</td>
<td></td>
<td></td>
<td></td>
<td>x</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Thrombolysis</td>
<td>y/n</td>
<td></td>
<td></td>
<td></td>
<td>x</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Thrombectomy</td>
<td>y/n</td>
<td></td>
<td></td>
<td></td>
<td>O</td>
<td>x</td>
</tr>
<tr>
<td></td>
<td>NIHSS score after treatment</td>
<td>score (0-42)</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>NIHSS score change</td>
<td>score</td>
<td></td>
<td></td>
<td></td>
<td>x</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Stroke unit care</td>
<td>y/n</td>
<td></td>
<td></td>
<td></td>
<td>x</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hemorrhagic transformation</td>
<td>y/n</td>
<td></td>
<td></td>
<td></td>
<td>x</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Heparin for progressive stroke</td>
<td>y/n</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Acetylsalicylic acid treatment</td>
<td>y/n</td>
<td></td>
<td></td>
<td></td>
<td>x</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Other antiplatelet treatment</td>
<td>y/n</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Post-treatment</td>
<td>ADL dependency at 3 months</td>
<td>y/n</td>
<td>O</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>ADL dependency at 12 months</td>
<td>y/n</td>
<td>O</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Time to death (if deceased within 12 months)</td>
<td>Days</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

O primary outcome variable  
O secondary outcome variable  
T target variable  
x variable used for descriptive or other analytical measures  

Acute care variables were year of onset, hospital type, level of consciousness on admission, NIHSS on admission, delay to treatment, thrombolysis, thrombectomy, NIHSS score after treatment, stroke unit care, hemorrhagic
transformation, heparin, acetylsalicylic acid treatment and other antiplatelet treatment. The hospital type variable was at data delivery categorized into community-, larger non-university- and university hospitals. Community hospitals have only basic inpatient specialities (internal medicine surgery, anaesthesiology, radiology and a laboratory). Large non-university hospitals have a wider range of specialities and can provide more advanced diagnostic procedures (e.g. magnetic resonance diagnostics) and interventions (carotid surgery)(61). Riksstroke level of consciousness was used as proxy for stroke severity. Alert/awake corresponds to Reaction Level Scale (RLS 85) 1, drowsy RLS 2-3 and unconscious RLS 4-8(61). Admission level of consciousness had 3 categories that were based on the Reaction Level Scale (RLS 85) score. Pre-treatment and post-treatment (after 24 hours) score on the NIHSS ranged from 0-42, higher score indicated more severe symptoms. However, real-life upper limit is lower than 42 (70). NIHSS change indicated the difference between the second and the first score, so that positive score indicated an improvement.

Delay to treatment indicated the time delay from the first stroke symptom, or last moment known to be symptom-free, to thrombolytic therapy start, in minutes. In Paper IV a roof value of 270 minutes (4.5 hours) was set in order to exclude treatment times violating guideline recommendations, miss-conducted registrations or treatment of posterior circulatory stroke treated within a late time window.

Post-treatment variables were ADL at 3 and 12 months, and time to death, if deceased within 12 months. The ADL measures were collected through the RS 3- and 12 months questionnaires, and therefore self-reported (patient-reported outcome measures, PROMs). Responses could either be given by the former acute stroke patient him-/herself or through the aid of residential care staff, or someone intimate. ADL independency was defined as independent in all three activities. ADL dependency was defined as being dependent of help from others in either one or several of the three questions on mobility, toileting or dressing/undressing. Hemorrhagic transformation indicated intracranial bleeding with symptoms within 36 hours post-stroke and -treatment. Time to death was calculated as the difference in days between the stroke onset and, if deceased within 12 months, a death date.

Study participants in Paper II, III and IV
An overview of included patients in Paper II, III and IV, and patients not included due to missing certain data can be viewed in Table 3. Paper II included 1743 patients, Paper III included 83882 patients, and Paper IV included 4936 patients.
Table 3. Overview of included patients in the quantitative papers (II-IV), and patients not included due to missing outcome data (Paper II and IV) or missing primary independent variable (Paper III).

<table>
<thead>
<tr>
<th>Paper number</th>
<th>II</th>
<th>III</th>
<th>IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short study subject</td>
<td>Stroke severity among thrombolysis-treated patients</td>
<td>Treatment rates in patient education groups</td>
<td>Sex differences in ADL 1 year after stroke thrombolysis</td>
</tr>
<tr>
<td>Included</td>
<td>Not included</td>
<td>Difference between groups, p</td>
<td>Included</td>
</tr>
<tr>
<td>Studied years</td>
<td>2007-2010</td>
<td>Age 18-80 years, ischemic stroke, thrombolysis treatment, individual NIHSS data available at hospitals with &gt;70% available NIHSS data each year</td>
<td>2003-2009</td>
</tr>
<tr>
<td>Inclusion criteria</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total N</td>
<td>1743</td>
<td>1689</td>
<td>83882</td>
</tr>
<tr>
<td>Female, sex, n (%)</td>
<td>668 (38.3)</td>
<td>658 (39.0)</td>
<td>83882 (41.5)</td>
</tr>
<tr>
<td>Age, years, mean/median</td>
<td>69</td>
<td>69</td>
<td>34771 (41.5)</td>
</tr>
<tr>
<td>Not awake, n (%)</td>
<td>274 (15.8)</td>
<td>247 (14.8)</td>
<td>9217 (11.1)</td>
</tr>
</tbody>
</table>

Categorical data was tested for association with the Chi-square test. For Paper II and Paper III, median age is displayed. Difference between groups was tested with the Mann-Whitney U test. For Paper IV, mean age is displayed, and difference between groups was tested with t-test. Md=median
In Paper II, examining stroke severity among patients treated with thrombolysis, 2/9 university hospitals, 8/20 large non-university hospitals and 33/47 community hospitals did not fulfil the inclusion criteria of available NIHSS score in >70% of patients with ischemic stroke, in each year 2007-2010. However, neither mean age, sex- nor level of consciousness distribution differed between included patients and those excluded due to missing NIHSS individual data or due to their hospital reporting NIHSS data below 70% every study year.

In the study on educational level and treatment (Paper III), missing data analysis displayed the proportion women was higher among patients that were excluded due to unknown education, compared to included patients (47.3% vs 41%, p<0.001). The age distribution (p=0.187) were not statistically significant different between the groups. A smaller proportion of patients in the unknown education group were awake on arrival compared to patients with known education level (83.6% vs 88.9%, p<0.001). In Paper IV the sex distribution did not differ between non-respondents to the questionnaires at 3 and 12 months and the patients included in the study (p=0.608). The mean age was somewhat lower for the non-respondents (68.2 vs. 70.6 years) and lowered consciousness on arrival was more common among non-respondents (13.2% vs. 9.8%, p<0.001.

### Analysis

#### Table 4. Included qualitative and quantitative methodology.

<table>
<thead>
<tr>
<th>Methodology</th>
<th>Paper number</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>I</td>
</tr>
<tr>
<td>Qualitative Content Analysis</td>
<td>x</td>
</tr>
<tr>
<td>Mann-Whitney U</td>
<td>x</td>
</tr>
<tr>
<td>Student’s t</td>
<td></td>
</tr>
<tr>
<td>Chi-square</td>
<td>x</td>
</tr>
<tr>
<td>Kruskal-Wallis</td>
<td>x</td>
</tr>
<tr>
<td>Linear correlation</td>
<td>x</td>
</tr>
<tr>
<td>Logistic regression</td>
<td>x</td>
</tr>
<tr>
<td>Likelihood ratio</td>
<td></td>
</tr>
</tbody>
</table>

The research- and author group for Paper I (the interview study) consisted of K.A., professor emeritus and physician with experience of leadership at the national level within governmental agencies for health care, Rikssstroke register management, chair in the Rikssstroke steering committee and clinical work within stroke care; M.E., associate professor and statistician with experience from quantitative research of stroke care; E-L.G., PhD and physician with experience from quantitative research- and clinical work within stroke care; B.L., professor emerita and nurse with extensive knowledge within qualitative content analysis, and me, A.S., the author of this thesis, physiotherapist with a
master in public health that included a postgraduate course on qualitative research methodology. At the time of this study, I had somewhat experience from hospital stroke rehabilitation. In summary, the author group represented both an inside- and outside perspective to guideline implementation in acute stroke care. Qualitative content analysis described by Graneheim and Lundman (71), was used to identify barriers and facilitators for implementation of thrombolysis for ischemic stroke, according to national guidelines for stroke care. Content analysis is a method for analyzing communication in a systematic manner and have been used within nursing and education research (71). The interviews were read-through several times in order to get a sense of the content. With the study aim in mind, codes of interesting content were written by hand alongside the interview text in an enlarged side margin, and those were later rewritten into an electronic document. First, I tried to sort the codes within the electronic document, but later turned into a more “hands-on” approach with cut-out paper notes on a large desk, and organised and sorted the codes into content groups. Post-it-notes were used to write down suggestions of subcategory titles. After several discussions of the structure we examined the identified barriers and facilitators in relation to the taxonomy of theories presented by Grol (72) for help to explain the implementation of change in patient care, and realised they had much in common, so it was decided to organize the subcategories according to that structure. The taxonomy was based on a distinction between (1) theories on factors related to individual professionals, (their cognitions, motivations, routines, styles of learning etc.) that influence change in performance; (2) theories on the influence of social context on the change process (social norms and values in the social network, influence of peers, opinion leaders and role models, and interaction within the system); (3) theories of those factors related to the organisational, administrative or economic context (culture within the organisation, resources, systems of reimbursement, organisation of processes, etc.) Example from the coding and abstraction procedure is given below in table 5.

<table>
<thead>
<tr>
<th>Quote</th>
<th>Code</th>
<th>Sub-subcategory</th>
<th>Subcategory</th>
<th>Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>And if you do more and more, then one as a health professional doesn't get as scared for thrombolysis. Of course I would feel the same thing, if I was unsure with something, then you rather refrain if it is in the boundary country, than go for it. It is large risks too you must not forget that.</td>
<td>with experience one increases knowledge and assurance</td>
<td>Importance of experience and knowledge among staff meeting acute stroke patients</td>
<td>Knowledge</td>
<td>Factors related to the individual</td>
</tr>
</tbody>
</table>
All included papers involve some quantitative data analysis but in different volume. The quantitative analysis in paper I was performed for the sampling of high- intermediate and slow implementing hospitals. It involved absolute numbers and proportions for every hospital, displayed for every year for rates of thrombolysis, stroke unit care and use of heparin for progressive stroke.

Descriptive measures and tables were presented in Papers II-IV, with numbers, proportions, 95 % confidence intervals and p-values from Chi-square test and Student’s t-test. The Chi-square test was used for univariable comparisons with categorical data.

The Student’s t-test was used for analysis of parametrically distributed data. For non-parametric data such as the age distribution within groups with and without NIHSS score (Paper II) or education data (Paper III), the Mann-Whitney U test was used. It assesses distribution of a variable between two independent groups, and is not dependent on normal distribution. The Pearson correlation coefficient, $R$, was used in Paper II to present the strength of the association between the two variables “proportion of patients receiving stroke thrombolysis at each hospital”, and “proportion stroke thrombolysis patients treated at each hospital for minor stroke symptoms”. $R$ can take values from -1 to +1, and a positive $R$ value indicates a positive association between the variables. The Kruskal-Wallis test was used in Paper II for testing whether several non-parametric samples (NIHSS score) had similar distribution. Logistic regression analysis was used to analyse the association between one or several variables and a dichotomous outcome variable, such as minor stroke symptoms or not, in Paper II, treatment or no treatment in Paper III, and ADL dependency or independency in Paper IV. Logistic regression results were presented as odds ratios (OR:s), indicating the strength of association. Multivariable models were used within the logistic regression analysis to adjust for several factors, such as patient characteristics. The Likelihood ratio test was used within the logistic regression modelling for Paper IV, to test, and subsequently to compare, the goodness-of-fit of several models with different combinations of potential confounding factors.

**Ethics**

The study performed for Paper I was considered by the Regional Ethical Board to not be encompassed by the Ethical Review Act. The Regional Ethical Board has approved the Riksstroke database (Dnr 95-168), Paper II (Dnr 07-118M, 20090604), Paper III, (Dnr 2012-321-31M), and Paper IV (Dnr 2015-360-31, and 2016-166-32M).
Results

Facilitators and barriers to implementation of stroke thrombolysis

Facilitators and barriers for stroke guideline implementation, with particular focus on thrombolytic therapy use, were presented in paper I. The results were presented in 3 categories, slightly modified from Grol et al(72), that presented this structure as a taxonomy of theories on the implementation of change and relevant factors in the process of change. The three categories are presented below.

(A) Factors relating to individuals; facilitators in this category were knowledge, work pride, and participation. Informants emphasized the individual professional's knowledge of the thrombolysis treatment and the guidelines for it as crucial for implementation. Decision support systems were suggested as aids. The importance of appropriate knowledge on the possibility of acute care treatment was valid at several levels both within acute stroke care such as at the emergency department and the stroke unit, and also at related units such as the radiology department, within primary health care and at the medical information telephone services. The rapid development within stroke care during the recent decades amplified the work pride and accelerated individual’s motivation to implement acute care guidelines. Also, participation in developmental events and gatherings increased motivation, informants stated. Barriers to implementation in this category were lack of recognition, lack of knowledge, lack of experience and stressful working conditions. Lack of knowledge and also acknowledgement among other hospital staff of the potential in acute care treatment in terms of thrombolysis, in the case of that a patient at another ward had acute stroke symptoms, consisted a barrier. An illustrating quote was “some have view a hundred years old. There is ignorance on the disease, old delusions”. Also, it was claimed that health professionals outside stroke care expressed a view of stroke as a “sad” disease that only tired and rundown professionals worked with. Additionally, the need for public education on stroke symptoms and importance of quick help-seeking behaviour were highlighted. Lack of experience of the clinical routines for treatment for the individual doctor in the clinical decision making was mentioned as a barrier. As the emergency department working schedule involved many physicians, it was not probable for every individual to by experience learn about the treatment and the clinical routines. As a result of the perceived unassurance on treatment routines and indications among colleagues in the clinical setting, clinical leaders tried to write local guidelines, with local adaptation to the guidelines. The exclusion criteria for treatment was by some considered too strict and there was
concern in how to keep to the conflicting indications in the guidelines and in the pharmaceutical authority’s statements. Some illustrating quotes were; [physicians] “could dare a bit more”, and “consider differential diagnostics a bit too much”. On the contrary, it was stated that one must be very careful in the decision making. Summarizing, a central challenge was how to keep to the risks associated with treatment, and at the same time see and keep to the potential benefits. Acknowledging the difficulties in interpreting the indications for treatment, perhaps with limited experience, a physician said; “You can always find a reason to refrain from [using] thrombolysis, and you will never be accused [reprimanded] for it”. Furthermore, a stressful and overburdened working situation, illustrated by an informant as frequent reorganizations, was limiting interest in implementation and made it “easy to go back to the way things were before”.

(B) Facilitators in the category of factors relating to social interaction and context were leadership, attitudes, involvement, meetings, and feedback. Although the description of implementation of clinical guidelines as a task for all professional groups, the importance of good leadership were highlighted and it was seen as important that the leader had good understanding of the clinical challenges in order to have credibility when implementing change. Helping the staff to implement guidelines successfully, the leader should be a good role model, be enthusiastic, adhere close to the clinical guidelines him- or herself, provide feedback and support. Furthermore, it was important that the leader encouraged staff to participate in quality improvement efforts. Throughout the interviews there were comparisons with the local performance vs the implementation of thrombolysis in Helsinki, Finland and this was also valid when discussing leadership style: “Here [in Sweden] there is always someone questioning, why should I do this? In the Swedish mentality, everyone should be able to discuss, there should be a consensus for everything. You cannot please everybody all the time. You have to be authoritarian”. Additionally, it was stated the leader should “take command and avoid time-consuming opinion-based debates”. Involvement in educational campaigns to staff throughout the hospital and also collaboration between subspecialties, was reported as very important, and also collaboration and support from stroke-interested colleagues outside the stroke unit, for example in the radiology department.

Barriers in the ‘social interactions and context’ category were power structures and lack of institutional support. Contraproductive power structures were present both at inter- and intraprofessional level. Highlighted here, the informants considered staff at foremost hospitals with higher speciality level and a given regional-leading role (university hospitals) to lack understanding of the differences in local prerequisites for thrombolysis, in terms of resources, in smaller-volume/community hospitals. Similarly, informants also claimed that
prestige acted as a barrier within neighbouring-hospital discussion in terms of local performance; “we try to write common memos, but it is a slow process with prestige involved. They do not have any explanation for performing so few thrombolytic therapies. They say “we act according to [the guidelines]”. But they obviously do not. It was difficult to discuss”. Also, a sensitive issue appeared when members of the stroke team deviated from agreed routines and informants were “getting one’s own preconceptions on other’s competence or attitude verified”. Some stated it was important with a continuous discussion, but that difficulties sometimes emerged and one physician expressed that it was easier if “somebody in their own rank suggested required change”, to avoid conflicts.

(C) The last category consisted of factors that related to organization and resources. Facilitators in this category were quality assurance, routines, and logistics. Central for implementation were continuous and knowledgeable stroke teams that had possibility to work together with a long-term perspective. Routines for continuous feedback on local thrombolysis performance were helping implementation both in terms of incentives and individual motivation for guideline adherence. A systematic approach to implementation work within regular routines at the stroke unit were also facilitating for implementation. In addition were certain technical or logistic routines expressed or suggested as facilitators, such as one nurse constantly assigned for interventions related to thrombolysis, possibilities related to telemedicine and short within-hospital distance to the radiology department (in order to limit time delay to treatment).

Barriers for the category of factors related to the organisation and resources were lack of continuity, inadequate recruitment/staff, lack of professional identity. Lack of continuity was described as frequent reorganisations, changes in leadership, and staff turnover. Time and energy that could have been spent on adherence to guideline work were spent on changes in the organisation; “Reorganisations break well-functioning teams, where you have worked together, assuring competence, been working together on routines. Workmates disappear and routines are easily demolished. Even though you have proper, fixed routines, it can be hard to stick to them”. Additionally, time and human resources dedicated for implementation work were not sufficient, according to informants. A central aspect was that stroke physicians were too few and this caused vulnerability. Many informants reported difficulties in recruiting both knowledgeable physicians and nurses and highlighted a feeling of loneliness in the responsibility of guideline implementation. In order to compensate for the recruitment difficulties, there were short-term employment of physicians from other hospitals, but those did not contribute very much to improvement work. Problems with recruitment were blamed a perceived low status of stroke care and looking back, more of nursing than medicine. Consequently, informants reported a need for a more pronounced professional identity for health
professionals working with stroke care, such as an establishment of a formal medical speciality or subspecialty. There were comparisons with cardiology, a speciality relatively well-provided with human and financial resources and public awareness, but with similar hospital burdens as for stroke care. Acknowledging the similarities with stroke care in developments of treatment options and disease aetiology, cardiology were suggested as a role model for stroke care expressed with a future hope for more resources; “I believe this hospital has many physicians at the cardiology clinic, and me alone working permanently on this. There are as many myocardial infarctions as ischemic strokes here, but the resources are very unequally balanced”.

**Hospital stroke thrombolysis rates and stroke severity**

After all inclusion criteria were fulfilled, paper II involved 1743 patients treated with alteplase for ischemic stroke, whereof 460 (26.4%) had minor stroke. In both univariate comparisons and multivariate logistic regression analysis, treatment for minor stroke was significantly associated with younger age, no hypertension treatment, and a more specialized hospital type (Table 6). Incidence of intracranial haemorrhage was not statistically different in patients treated for minor stroke (4.9%) compared to patients treated with NIHSS 6 or above (6.2%, p=0.104).

Results displayed an increase over the studied years 2007-2010 in the proportion of patients treated with thrombolysis for a minor stroke (Figure 1). At hospital level, the proportions patients treated for a minor stroke varied between 3.2% and 42%. The proportion of patients treated with stroke thrombolysis for minor stroke symptoms was positively associated with hospital stroke thrombolysis overall treatment level (R=0.549, p<0.001).
Table 6. Number of patients treated with stroke thrombolysis, whereof number and proportions with minor stroke. Odds ratios (OR) and 95% confidence intervals (95% CI) for stroke thrombolysis for minor stroke symptoms, from multivariable logistic regression analysis.

<table>
<thead>
<tr>
<th>Factors</th>
<th>Patients treated with stroke thrombolysis</th>
<th>Whereof patients with minor stroke symptoms</th>
<th>Treatment for minor stroke symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18-64</td>
<td>610</td>
<td>191</td>
<td>31.3</td>
</tr>
<tr>
<td>65-74</td>
<td>668</td>
<td>168</td>
<td>25.1</td>
</tr>
<tr>
<td>75-80</td>
<td>465</td>
<td>101</td>
<td>21.7</td>
</tr>
<tr>
<td>Year of onset</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2007</td>
<td>294</td>
<td>65</td>
<td>22.1</td>
</tr>
<tr>
<td>2008</td>
<td>430</td>
<td>98</td>
<td>22.8</td>
</tr>
<tr>
<td>2009</td>
<td>492</td>
<td>146</td>
<td>29.7</td>
</tr>
<tr>
<td>2010</td>
<td>527</td>
<td>151</td>
<td>28.7</td>
</tr>
<tr>
<td>Hypertension medication</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>790</td>
<td>235</td>
<td>29.7</td>
</tr>
<tr>
<td>Yes</td>
<td>942</td>
<td>222</td>
<td>23.6</td>
</tr>
<tr>
<td>Hospital type</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>University</td>
<td>637</td>
<td>176</td>
<td>27.6</td>
</tr>
<tr>
<td>Large non-uni</td>
<td>796</td>
<td>232</td>
<td>29.1</td>
</tr>
<tr>
<td>Community</td>
<td>310</td>
<td>52</td>
<td>16.8</td>
</tr>
</tbody>
</table>

Ref = reference category.
Figure 1. Proportion (%) of patients in each NIHSS score interval among patients receiving stroke thrombolysis. Q indicates quarter of year.

**Treatment rates in patient educational groups**

Paper III involved 85885 patients, both patients that had been treated with reperfusion therapy and patients that had not been treated. Patients with higher education were to a larger extent males, younger, cohabitants, not living in institution, (i.e. at home), independent in ADL, free from hypertension medication, diabetes mellitus, smoking or atrial fibrillation. Higher education was also associated with a higher consciousness on admission. Comparing hospital types, higher specialization level was associated with a higher proportion of university educated patients (p<0.001). Patients with higher education were more likely to receive reperfusion therapy in comparison to patients with lower education (university- 5.5%, secondary- 4.6%, primary level 3.6%, p<0.001, Figure 2). The relative differences in treatment rates between the educational groups decreased over time (p=0.005), but the absolute differences remained (1.3 percentage units in 2003 and 2.5 percentage units in 2009).
In multivariable analysis, age ≥ 57 years, living alone, dependency in ADL before stroke, diabetes mellitus, history of previous stroke and unconsciousness on admission were negatively associated with treatment. Atrial fibrillation and drowsiness on admission were positively associated with treatment. After adjustment for hospital type in the multivariate model, there were no statistically significant differences between education groups. In multivariable stratification for hospital type, there were only statistically significant treatment differences between educational groups within the group of large non-university hospitals (university educated patients OR 1.20 95% CI 1.04-1.40, secondary educated patients OR 1.14 95% CI 1.01-1.29, primary educated were references category).

![Figure 2](image.png)

**Figure 2.** Proportion of patients with ischemic stroke treated with reperfusion therapy over the years 2003-2009, stratified according to education level.
Sex differences in ADL outcome 1 year post-stroke

The study population in Paper IV included 4936 patients whereof 42.5% were women. The patients were independent in ADL before their ischemic stroke, were treated with stroke thrombolysis, survived 12 months after stroke, and provided answers to the Riksstroke ADL questions at both 3 and 12 months. Mean age was 72.1 years for women and 69.5 years for men (p<0.01, Table 7). The proportion living alone was 37.3% among women and 19.5% among men (p<0.01). Women were more common to have lowered consciousness on arrival to hospital (11.3% for women vs. 8.7% for men, p<0.01). Mean NIHSS score on arrival was 9.1 for women and 8.2 for men (p<0.01). Among patients with available pre-treatment and post-treatment NIHSS score, the mean score difference was 4.5 points for women and 4.0 points for men (p<0.01, both scores indicating neurological improvement).

Women's and men's ADL status at 3 and 12 months and changes between the studied time points are displayed Figure 4. Among women, 76.8% remained independent in ADL at all time points and among men this proportion was 81.3%. Three percent of women and 3.1% of men improved from dependency in ADL at 3 months to independency at 12 months while 3.2% of women and 3.6% of men deteriorated from independency at 3 months to dependency at 12 months. Seventeen percent of women and 11.9% of men were dependent in ADL at both 3 and 12 months.
Table 7. Study population, baseline univariate comparisons of men and women.

<table>
<thead>
<tr>
<th>Variable, unit, measure, n</th>
<th>Total n=4936</th>
<th>Men n=2837 (57.5%)</th>
<th>Women n=2099 (42.5%)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years, mean (median), 4936</td>
<td>70.6 (72)</td>
<td>69.5 (71)</td>
<td>72.1 (74)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Not awake on arrival, n (%), 4916</td>
<td>482 (9.8)</td>
<td>245 (8.7)</td>
<td>237 (11.3)</td>
<td>0.002</td>
</tr>
<tr>
<td>NIHSS before treatment, mean (median), 4916</td>
<td>8.5 (7)</td>
<td>8.2 (7)</td>
<td>9.1 (7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Onset to needle time, min, mean (median), 4936</td>
<td>135 (126)</td>
<td>134 (125)</td>
<td>138 (130)</td>
<td>0.008</td>
</tr>
<tr>
<td>Hemorrhagic transformation n (%), 4936</td>
<td>134 (2.8)</td>
<td>82 (2.9)</td>
<td>52 (2.5)</td>
<td>0.356</td>
</tr>
<tr>
<td>Living alone n (%), 4931</td>
<td>1334 (27.1)</td>
<td>552 (19.5)</td>
<td>782 (37.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension n (%), 4927</td>
<td>2759 (56.0)</td>
<td>1545 (54.5)</td>
<td>1214 (58.0)</td>
<td>0.016</td>
</tr>
<tr>
<td>Diabetes n (%), 4933</td>
<td>766 (15.5)</td>
<td>483 (17.0)</td>
<td>283 (13.5)</td>
<td>0.001</td>
</tr>
<tr>
<td>History of previous stroke n (%), 4929</td>
<td>615 (12.5)</td>
<td>381 (13.5)</td>
<td>234 (11.2)</td>
<td>0.016</td>
</tr>
<tr>
<td>Atrial fibrillation n (%), 4936</td>
<td>1261 (25.6)</td>
<td>665 (23.5)</td>
<td>596 (28.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Smoker n (%), 4666</td>
<td>665 (14.3)</td>
<td>388 (14.5)</td>
<td>277 (13.9)</td>
<td>0.609</td>
</tr>
<tr>
<td>Dependency in ADL 3 months n (%), 4936</td>
<td>845 (17.1)</td>
<td>427 (15.1)</td>
<td>418 (19.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Dependency in ADL 12 months n (%), 4936</td>
<td>866 (17.5)</td>
<td>442 (15.6)</td>
<td>424 (20.2)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Continuous variables (age, NIHSS before treatment and onset to needle time) were tested for differences between sexes with respect to those variables with Student’s t-test. All other variables (categorical) were tested for association with sex with chi-square test. Numbers reported after variable units indicate available (non-missing) measurements.
Figure 4. Flow chart of ADL status from before onset to 3 and 12 months post-stroke. Upper row displays numbers and proportions of patients in ADL independency at the included time points. Conversely, lower row displays patients in ADL dependency at the corresponding time points.

Odds ratios of risk of dependency at 3 and 12 months were higher for women than for men (OR 3 months = 1.403; 95% CI 1.210-1.628; OR 12 months = 1.372; 95% CI 1.184-1.589). In multivariate analyses adjusting for sex, age, history of previous stroke, diabetes, hypertension and level of consciousness on arrival women consistently displayed a higher risk for dependency in ADL both at 3 and 12 months (Table 8, model A). When adding adjustment for neurological status change (NIHSS score difference) after stroke thrombolysis, (Table 8, model B), sex differences remained at both at 3 and 12 months.
Table 8. Multivariate logistic regression models of risk for dependency in ADL at 3 and 12 months post-stroke.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Model A* (n=4936)</th>
<th>Model B* (n=3762)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dependency in ADL at</td>
<td>Dependency in ADL at</td>
</tr>
<tr>
<td></td>
<td>3 months</td>
<td>12 months</td>
</tr>
<tr>
<td></td>
<td>OR* (95% CI%)</td>
<td>OR* (95% CI%)</td>
</tr>
<tr>
<td>Sex, female</td>
<td>1.217 (1.041-1.424)</td>
<td>1.184 (1.014-1.384)</td>
</tr>
<tr>
<td>Age</td>
<td>1.049 (1.040-1.058)</td>
<td>1.055 (1.047-1.064)</td>
</tr>
<tr>
<td>Previous stroke</td>
<td>1.120 (0.897-1.397)</td>
<td>1.402 (1.135-1.731)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.257 (1.026-1.540)</td>
<td>1.385 (1.135-1.688)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.301 (1.101-1.537)</td>
<td>1.313 (1.112-1.551)</td>
</tr>
<tr>
<td>Not awake on arrival</td>
<td>3.235 (2.617-4.000)</td>
<td>2.954 (2.382-3.662)</td>
</tr>
<tr>
<td>NIHSS score on arrival</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>NIHSS score change</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Constant</td>
<td>0.004 (0.000)</td>
<td>0.003 (0.000)</td>
</tr>
</tbody>
</table>

* applied on the total study population (n=4936).
¤ applied on the part of the study population with available NIHSS score change after thrombolytic therapy (n=3762). Level of consciousness on admission is replaced by NIHSS score before treatment as measure of symptom severity, and NIHSS score change after treatment (change in neurological status) is added to the model. Higher NIHSS score indicates higher symptom severity. NIHSS score change indicates post-treatment score minus pre-treatment score, thus positive score difference indicates neurological improvement.

* odds ratio
% confidence interval
**Additional analysis**

As an additional analysis case fatality risk within 3 and 12 months post-stroke was analysed in a population with the same inclusion criteria as in the main analysis, and adding patients with missing ADL-data (non-responders) and patients that were deceased within 12 months (total n=8017). Within 3 months 11.2% of the women and 9.5% of the men were deceased and within 12 months 16.1% of the women and 13.7% of the men (p<0.001). Corresponding unadjusted odds ratios for fatality risk for women were 3 months OR=1.205; 95% CI 1.043-1.393 and 12 months OR=1.210; 95% CI 1.069-1.369. After applying the same adjustments as in model A case fatality risk was lower for women than for men within both 3 (OR=0.839; 95% CI 0.714-0.985) and 12 months (OR=0.838; 95% CI 0.728-0.963).
Discussion

Key results

Results from the studies in this thesis display that the facilitators of and barriers to the implementation of stroke thrombolysis could broadly be categorized into those related to individuals, to social interactions and context, and to organizational and resource issues. Key facilitating factors expressed in interviews were work pride and motivation, good leadership, involvement of all staff members in the implementation process, and quality assurance. Major barriers concerned lack of competence and experience, outdated attitudes regarding stroke management, counterproductive power structures, lack of continuity, and insufficient human resources.

National quality register data showed that stroke thrombolysis treatment expanded to reach more patients with mild deficits. Groups with higher education were more likely to receive treatment, compared to groups with lower educational level. These education group differences have, however, decreased over time in relative terms, but not in absolute terms. Further, there were considerable between-hospitals differences in treatment rates for patients with milder deficits, associated with hospital’s overall stroke thrombolysis rates. Moreover, larger non-university hospitals displayed treatment rate differences between educational groups that were not attributable to individual characteristics. Among thrombolysis-treated women and men, that was independent in ADL before their stroke and survived the first year post-stroke, women experienced higher probability to be dependent in ADL at both 3 and 12 months post-stroke, compared to men. This difference remained significant despite comprehensive adjustments for individual characteristics, symptom severity, and acute effects from stroke thrombolysis.

Methodological considerations

Sampling

Qualitative data

In terms of internal validity or credibility, it may be important to find out if our informants in Paper I were representing a variety of experiences, in order to increase the possibility to shed light on the research question from a variety of aspects. The informants for the interview study were chosen to represent
hospitals with a variety of implementation rates. However, within the group of informants there was in fact quite small variation in terms of experience. With only a few exceptions, our informants were having several years or decades of experience within hospital stroke care. Nevertheless, since our aim was to find out which barriers and facilitators influenced implementation of stroke care guidelines, according to staff working within stroke care, long experience may be considered advantageous.

Credibility also deals with selecting the most appropriate method for data collection, and the amount of data. We chose to arrange individual interviews, given the potential sensitive nature of the issue of local implementation efforts and treatment rates. However, two persons at one hospital were interviewed together. As most of the selected hospitals provided two informants (most of the hospitals provided one nurse and one physician), this could have been an alternative for all the interviews. Nevertheless, sensitive matters regarding the interplay between professions may be more easily expressed if there are no representatives from “other” groups present.

Quantitative data
The validity of register-based research is dependent on the quality of the register data, which may vary. Most of the data material used in this thesis was extracted from Riksstroke, the Swedish Stroke Register. Riksstroke provide high-quality data on day-to-day clinical stroke care with a national perspective. The register was started in 1994, and is unique among stroke registers in that patients, quality of care and community support are followed for one year after the stroke (73). It is also one of the largest stroke registers that exists. Since 1998, all hospitals in Sweden admitting acute stroke participate in the register (n=74 in 2014). In recent years, coverage in Riksstroke has been estimated to be over 90 percent, and the false positive stroke diagnoses among patients in Riksstroke has been shown to be 1.4% (74). In comparison, for the National Patient Registry (NPR), the false positive diagnosis of acute stroke is 6% for first-ever stroke events, and 12% or all stroke events (68). The register does not cover cases with high acute case fatality or “silent” infarctions. However, these individuals would not from natural reasons come into consideration for the treatment analyzed in this thesis. Also, the register does not cover acute stroke care outside of hospitals, such as for individuals with multiple chronic diseases and living in residential care homes (75). Despite that, the register seems to meet almost all criteria for an ideal stroke epidemiological study (76).

Outcome variables
In study II and IV, the National Institutes of Health Stroke Scale (NIHSS) was used as a measure of stroke severity. This measure has become the golden standard for measuring neurological change and clinical deficits after stroke.
Stroke severity is a primary driver of outcome after stroke and correlates with discharge disposition and mortality (70). On each item, the rater gives a pre-defined score according to the response of the patient. NIHSS has been found to be internally consistent, have a moderate weighted kappa value of > 0.4 and is reproducible across a several professions: stroke nurses, vascular neurologists and emergency department physicians (70). However, the NIHSS was primarily designed for use within research trials and the design of the scale assumes that the user has participated in extensive training. Use of the NIHSS by causal, non-research users has not been extensively validated, and it have been suggested that the scale should be used with caution outside research trials (70). Whether all raters that report NIHSS score into Riksstroke in Sweden have participated extensively in such training is not known.

The NIHSS could portray a description of the patient equivalent to the descriptors mild, moderate or severe stroke (70), although the scale may not adequately capture all forms of functional change (77). There are no fully established boundaries to define minor stroke from the NIHSS scale. In Paper II, the NIHSS scale was used to capture the proportion of thrombolysed patients with score 0-5, and this was denoted as patients with “minor stroke”. Fischer et al described that the best suited minor stroke definitions may be score 0 or 1 on every baseline NIHSS item together with normal level of consciousness, or NIHSS ≤3, in order for patients to likely be discharged home and to be independent at 3 months post-stroke. However, Fischer et al state a cut point still is arbitrary, as one score point more or less does not provide any impressive difference and recommend the stroke research community to in consensus define a definite cut point (78).

Measuring socioeconomic status (SES) can be done in different ways. SES is a multidimensional concept and commonly any of or a combination of; income or wealth, occupational status, and educational attainment (79). SES measures can be individual or area-based. Area-based measures have the opportunity to illustrate the physical and cultural local environment in which individuals live. In Paper III we used individual educational attainment as proxy for SES.

In Paper IV, independency or dependency in ADL was used to describe functional status post-stroke and -treatment. ADL dependency is for example associated with increased risk of falls (80), fear of falling (81), depression and reduced quality of life (82). We used the three Riksstroke variables toileting, dressing and mobility to define ADL status. These questions has been validated against the Barthel Index with 92% sensitivity and 91% specificity (83), and the modified Rankin Scale with correlation 0.82 and Cohen’s weighted K 0.85 (84) thus showing a relatively good correlation with standardised measuring instruments.
The multitude of patient categories that present with a stroke, together with their access to treatment and outcome measures could have been further illustrated through the use of etiologic subtype data, either through stratification or multivariable modelling. However, we did not have access to such data, but chose to use the presence of atrial fibrillation as proxy for cardiac embolism. Women, and especially elderly women have higher prevalence of atrial fibrillation (5), also displayed in Paper IV. Univariate analysis showed atrial fibrillation to be associated with ADL dependency both at 3 and 12 months. However, together with other potential confounders, atrial fibrillation did not fit into the multivariable modelling in Paper IV. In a study from Finland, patients with small-vessel disease had the best outcome 3 months after thrombolytic therapy, also after adjustments for stroke severity and age (85).

**Analyses**

**The interview study (Paper I)**

The results in Paper I can be viewed as being on a fairly descriptive and manifest level and to a lesser extent on the level of abstraction or interpretation. The analysis is positivistic flavoured. This approach and focus may have been affected by the composition of the research group. The group were gathered several times to discuss the analysis process and to judge whether to agree upon the findings made in the analysis process in majority performed by the first author. The author group consisted of highly skilled stroke care quality researchers. Their deep knowledge of both clinical reality and scientific literature in the subject increased dependability, but at the same time the majority in the group had less experience from qualitative analysis processes, decreasing the same measure. In qualitative methodology, the methodological approach can be inductive, deductive or abductive. In Paper I, the analysis started with an inductive approach, and at a later stage of the analysis, it turned to a deductive approach using a taxonomy from Grol’s structure of theories on implementation of change (72). In Paper I the concept *theme* was used as to describe the content present in the *categories*. Another, maybe more correct, term is *subcategories* since the concept of *theme* has multiple meanings and creating themes is more a way to link the underlying meanings together in categories, according to Graneheim and Lundman (71).

One basic epistemological assumption underlying qualitative content analysis is that reality can be interpreted in various ways and the understanding is dependent on subjective interpretation. Another presumption that often is taken is that a text always involves multiple meanings and there is always some degree of interpretation when approaching a text (71). The results from the qualitative analysis in this thesis can be interpreted against a context of my own
role and experiences from undergraduate training and clinical work as a physiotherapist; adding social and psychological perspectives on humans, such as work-environmental aspects, learning and between-human interactions as factors influencing human performance and well-being. I believe these skills also influenced the interviews and the questions.

An overall strength of Paper I is the actual qualitative methodology; we explored the factors that stroke care clinicians expressed as important, instead of pre-defining factors of potential importance. The nation-wide approach with sampling of fast-, intermediate-, and slow implementing hospitals gave opportunities of a high variability of experiences. Since there were several evidence-based methods covered within the interviews, only a proportion of the available time were adhered to stroke thrombolysis questions, but the interviews started almost exclusively with addressing implementation of stroke thrombolysis. When the interviewer perceived not much more information was to be given within that subject, the interview moved on to other areas of interest in the interview guide. Follow-up questions at the end of the interviews also provided opportunities for the informant to highlight issues of special importance.

Papers II-IV
A major strength in the quantitative analyses is the very large sample, given the benefits of the stroke register, discussed above. Further, the multivariate analyses included comprehensive adjustments of potential confounding factors. This increases the methodological quality of the studies and facilitates interpretation of the results. In all register-based papers, univariate analysis of potential confounders were explored first, in order to get a sense of the material. At a later stage, variables univariately associated with the outcome was combined in several steps in logistic regression multivariable modelling, to further get to know the data material and to explore in what way the variables contributed to the model. In Paper III, the age variable was at a later analysis stage divided into deciles, to avoid any too crude categorization would “hide” any residual age-confounding between education and treatment, given the strong univariate association between age and treatment. One cannot rule out that other variables may hide residual confounding, although, the majority of Riksstroke variables are dichotomized, diagnosis-based, and not possible to chop into smaller strata. Dichotomization of smoking, for example, may hide a large variability of vascular stress. However, large-scale data collection from day-to-day clinical care must be simple enough to not burden the clinicians too much (73).

In Paper II, the author group hypothesised that the different hospitals’ overall treatment rates was dependent on the proportion patients treated for minor
stroke symptoms at the hospitals, respectively. We found the Pearson correlation coefficient to be equal to 0.549, indicating a positive correlation between the variables, which could be considered moderate. However, one must be careful in the interpretation of such analyses, since a measure of correlation does not give any information on causality, only association. Also, analysis including smaller-volume hospitals may be influenced by random variation of patients in those hospitals. This may also be valid for hospitals with relatively low coverage within the register. To overcome this, it is beneficial to combine data from several years, which was done within Paper II.

In Paper IV, theoretical reasoning was the starting point for the decision to test variables within a multivariable setting. As different multivariable models were examined with the Likelihood ratio test several potential, and interesting, confounding factors were abandoned, although univariately associated with sex, or the outcome, but not contributing enough or having the desired distribution within the models. One such variable was the “delay time to treatment”, that was univariately associated with sex, but not ADL status, and did not fit into the multivariable model. Overall, time delay to treatment has been very limited included in this thesis, despite its potential importance.

**Characteristics of stroke thrombolysis as an implementation object**

Judging the transferability of results may be facilitated by information on the characteristics of the studied implementation object, in this case stroke thrombolysis. A framework of determinants of adoption velocity from Rogers can be used to illustrate whether an implementation object is implemented or not (86). Such a framework may be applied to the data material from the research interviews. The determinants contains five innovation attributes that has been shown to explain approximately half of the variance of the adoption of an innovation (86). The innovation attributes can be outlined as:

**Relative advantage:** If the innovation is perceived as more beneficial than other methods it affects the adoption in a positive direction. Informants witnessed that the potential option of stroke thrombolysis, compared to previously, provided a possibility to affect the ischemic process for patients. One informant said: *before, one just went by such a patient.*

** Compatibility:** If the innovation is regarded as compatible with already existing values, previous experiences and the need among future potential users, it affects the adoption in a positive direction. Similarly to the description above there was a large need to affect the situation for the patient, and the thrombolysis constituted such an opportunity. However, informants reported a previously common misunderstanding that stroke care was something sad and that only the tired or worn-out worked with, and that this view still was present in many departments within the health care. An already stressed and over-
burdened working situation affected the staff’s general interest for implementation of guidelines. It was reported that both nurses and physicians in other departments than the stroke unit (but still involved in the care of patients with stroke) often did not acknowledge the importance of an adequate treatment of the patients.

**Complexity:** If the innovation is perceived as relatively difficult to understand and use it affects the adoption in a negative direction. Many informants witnessed about physician’s insecurity or hesitation to thrombolytic therapy and corresponding routines. Some thought the exclusion criteria for thrombolysis were far too strict, causing unnecessary concern. Physicians were afraid to miss a detail that would possibly represent a risk for complications, and on the contrary this was also making up a frustration; *one could dare more, and I believe one considers differential diagnostics too much*, partly aiming to the far higher treatment rates in Helsinki, Finland. Lack of treatment experience in physicians on duty, partly due to the schedule at the hospital, was considered a problem and also difficulties in recruiting stroke physicians.

**Testability:** If the innovation is perceived as possible to use and experiment with on a smaller scale it may affect the adoption in a positive direction. This aspect represented a minor part of the interview material, but the barrier for treatment might be lower regarding the patients with symptoms corresponding fairly well to the treatment indications, compared to patients with more dubious suitability for treatment.

**Observability:** If the effects of the innovation are visible to others it affects the adoption in a positive direction. The results from successful treatment are often obvious, informants stated. Also, systematic feedback from annual reports of Riksstroke with hospital and regional treatment rates provided incentives for further endeavours.

**Discussion of findings**

This thesis provides information on variation within stroke care in different aspects; patients are different, and so are disease processes, care-givers interpret situations differently, and measures also provide variation. Donabedian has provided a model for examination of health care and evaluating quality of health care (87) with the items *structure, process* and *results*. Structure describes the context in which care is delivered, including facilities, staff, financing and equipment. Process denotes the transactions between patients and providers throughout the delivery of health care. Outcomes (or results) refer to the effects of health care on the health status of patients and populations. The Donabedian model is one of the dominant paradigms for assessing the quality of health care (87). In Paper I the variation in the health
care itself is analysed, partly on a structural level, partly on a process level, as perceived by professionals within stroke care. In paper II and III, the variation between patients is taken into account to produce the process measures “symptom severity among patients treated with stroke thrombolysis” and “administration of stroke thrombolysis” for different education groups. Both Paper II and Paper III involve process measures over time, sometimes called diachronic variation. Such measures can give information on if a measured variation is from chance, or if any pattern can distinguish. Sometimes it is possible to tell about future prospects from a diachronic analysis, given that all other measures are relatively constant (88). The variation in process measures may have two origins; first, the variation between patients in terms of symptoms and individual characteristics, and secondly, variation caused by the health care system itself, such as variation in physicians’ knowledge and experience from thrombolysis. Also, the same individuals that perform the activities in the process has got attitudes and norms, being an important part of the structure, or “social system that have a structure” (88). In Paper IV, the outcome measure ADL independency can be viewed as a result measure, such as the outcome of the processes involved in the stroke care for the individual patient, partly derived from the structural conditions, but also as an outcome of individual characteristics. However, part of the variation can be all natural, acknowledging the uniqueness of every patient, but could also depend on inequity in care.

Facilitators and barriers for implementation of stroke thrombolysis

Overarching this thesis, is the national guidelines’ message of high priority of stroke thrombolysis. However, as found in Paper I, stroke care professionals face barriers and facilitators for implementation of stroke thrombolysis at several levels; the individual level, social interaction and context level, and thirdly, at the organisation and resources level. This finding is supported by the statement that single implementation interventions is unlikely to change the desired measure (72). A recent systematic review of 3 qualitative (one of those were Paper I in this thesis) and 7 quantitative studies published between 1990-2016, aimed at examining the overall barriers and enablers, as perceived by health professionals, that affect how evidence-based practise guidelines for acute stroke care are adopted in hospital settings. The evidence-based practise guidelines examined were foremost stroke thrombolysis, or a combination of stroke thrombolysis and other evidence-based acute care therapies (stroke unit care, aspirin usage and decompressive surgery) (89). The findings in Paper I were similar to the other studies within the review, however the domain ”patient factors” was not covered by study I. This is due to that patient factors were not in focus in Paper I. All other domains (guideline factors, individual health professionals, professional interactions, incentives and resources, and capacity for organisational change) found in a majority of thrombolysis studies, agreed
with the findings in study I. The review authors reported a perceived saturation of potential determinants, given the commonality and recurrence of barriers and enablers presented by the different studies. Also, previous reviews (90, 91) supported the findings in this 2017 review, according to the authors (89).

Staff guideline awareness and knowledge, motivation and expectations on outcome from treatment, covered by the Paper I category “individuals”, were supported by the findings within a qualitative focus group and interviews study by Meurer et al performed within the INSTINCT trial (92, 93), aiming to describe barriers to stroke thrombolysis use in acute stroke. This study suggested that increasing physician familiarity with and motivation to follow guidelines could give highest yield in terms of guideline adherence. Similar findings were presented in a review of health systems factors and approaches associated with thrombolysis administration rates in acute stroke care (94), authors suggesting expertise and experience within such settings is key to increased stroke thrombolysis rates. The systematic review also displayed uncertainty of adverse events from treatment and doubt on the evidence base for the treatment recommendation (89).

Barriers and facilitators are often hypothesized to be determinants of behaviour, but the magnitude of their influence are in studies outweighed by other contextual factors (95). The exploration of barriers and facilitators may also implicitly assume a linear relationship between the factors and the outcome, and not acknowledging that individual barriers (and facilitators) may interact, producing a larger obstacle or facilitator than was possible to predict (95). This thesis provide some information on the social context and the relationships when implementing thrombolysis guidelines within stroke care, rather than straight logistical or technical factors. Checkland, et al. state that an organisations’ internal structures and processes are emergent properties of the social interactions that constitute the organisation (96). According to reports and literature based on Riksstroke data, organisation and practise of acute stroke care differs between hospitals (61, 97). Consequently, one can view the findings in Paper I as small jigsaw pieces for the understanding of the implementation of stroke thrombolysis. While detailed mapping can be helpful for descriptive purposes, it can be viewed as a first step rather than an endpoint for exploratory studies of implementation (98). Similarly, may models such as “barriers and facilitators” constrain analysis if used in isolation (98). It may be important to also look beyond narratives provided by clinicians to the more “messy” reality (96). Models are illustrative and abstract and should not bee seen as reflecting the complexities that exists in reality (98).
Hospital stroke thrombolysis rates and stroke severity

As found in Paper II in this thesis, the increase in treatment rates in Sweden over the studied years, contains an increase in the proportion of patients treated for symptoms representing NIHSS $\leq 5$, often denoted as minor stroke symptoms. However, there has been considerable variation between hospitals in the proportion treated patients with minor symptoms, and at hospital level, these proportions have been associated with overall stroke thrombolysis rates, indicating inequity in care delivery.

The recent national guidelines state there is lack of evidence regarding treatment for minor stroke (39), but do not give any absolute threshold of when to withhold treatment. In the global scientific literature, it has been stated that some contraindications have not been systematically studied, and were introduced on the basis of subgroup analyses or expert opinions to maximise the safety of the treatment in the initial phase of clinical implementation (99). One interpretation of the findings is presence of what is known as treatment indication shifts, that has been described as an inevitable effect of treatment trials with strict inclusion criteria (100). Reasons for treatment indication shifts can be that the patient has heard about the treatment and demands it, that the physician is hoping for a good treatment effect and that it is attractive and perhaps cheaper than the alternative option (100). A second interpretation of the findings in study II, regarding the substantial interhospital differences between proportion patients treated for minor stroke symptoms can be that the evidence base for treatment of minor symptoms invite for local translation of the national guidelines. Local translation of national guidelines may be more specific and describe treatment or care more in detail than the national guidelines and put emphasis on the practical feasibility (72). As mentioned by Rogers, local translation can be beneficial for implementation (86). Risks with local translation of national guidelines are that the well-weighted content in the national guidelines are rewritten so that the evidence is reinterpreted. Also, in areas where the evidence is weaker, there is more room for local translation (72).

Specialized stroke centres often apply less restrictive treatment criteria (45, 99), which is confirmative to the findings in this thesis; university- and large non-university hospitals univariately displayed higher proportions patients treated for minor symptoms, compared to community hospitals. Also, previous research has shown more specialised hospitals implemented thrombolysis faster, with a 2-3 year delay between large non-university hospitals and university hospitals, in the Swedish setting (42). Similar findings were displayed in a review; teaching hospitals and hospitals with larger stroke volumes was associated with increased stroke thrombolysis rates (94). Among hospitals with high stroke
thrombolysis rates, it has been described that there is consensus within the group of physicians of a offensive treatment culture with broad interpretation of treatment indications (94). Well-known in the acute stroke care community, and reported by informants within Paper I, is the treatment rates in Helsinki, Finland, that reported high off-label rates of thrombolysis for ischemic stroke (51%), although without poorer clinical outcome nor increased rates of symptomatic intracerebral haemorrhage (45).

**Treatment rates among patient educational groups**

In study III, stroke reperfusion rates were higher among patients with higher education, compared to patients with lower education. However, the relative gap in treatment rates between patient education groups narrowed over time. Other examples of Swedish socioeconomic stroke care or outcome disparities is inequalities in the prescription of oral anticoagulants as preventive treatment after stroke (101), socioeconomic survival inequality increasing over time since the stroke event (30), and a higher risk of stroke recurrence among disadvantaged groups, prevailing over time (32). There has been a prevailing hypothesis, at least in the Swedish stroke register community, that evidence-based care methods in the initial implementation phases give clearer differences in access between population groups, to later be evened out when the method is more established. For example did Glader et al display that socioeconomic inequalities in access to stroke unit care were evident during the early years, but those were reduced as the capacity for stroke unit care increased (102).

Higher education was associated with a higher specialisation level at the admitting hospital, in Paper III, and the reverse, reflecting what can be called a socioeconomic segmentation. Larger cities in the Swedish setting mostly comprise specialised hospitals, and such cities tend to attract individuals with higher education. Patients admitted in university hospitals were on average 2 years younger than patients admitted to other hospitals. A higher proportion patients were also ADL independent before the first stroke, and less had data on hypertension (61). Whether this pattern was true for patients with only ischemic stroke, and the other inclusion criteria for study III, are not known. Multivariable adjustments, however, adjusted for all these factors. The median door-to-needle time was shortest in university hospitals, followed by large non-university hospitals, compared to community hospitals (61). This suggests that hospital types provide or act as proxy to a factor that steers treatment rates, either local performance within hospital types, indicated previously (42, 61), or the socioeconomical level of the population having stroke living nearby the hospital types, or a combination of these factors. One might speculate if education level has influenced delay times to admission to hospital, and thus access to treatment. Time delay to treatment, although of central importance for
treatment access, was unfortunately not included in study III. However, the analysis displayed that low-educated patients were less likely to receive reperfusion therapy even in the university hospitals.

Judging the treatment benefits and -risks for patients with presence of multiple comorbidities and social factors has been shown difficult (103). The higher disease burden among disadvantaged groups may be a factor that has contributed to the lower treatment rates among groups with lower educational level. Additionally, health literacy may be discussed. Patient help-seeking behaviour is a major source of prehospital delay (104) and many factors other than care need contribute to acute help-seeking behaviour for stroke symptoms and other situations (52). Health literacy is a central determinant for health, together with other factors such as income, income distribution, work and social environment (105). Health literacy can be described as ability to grasp, understand, judge and use health-relevant information and as an individual with stroke rarely gets into contact with the emergency medical services him- or herself (106), being alone usually increases the delay time to medical care. Because of this, both the patient’s and potential bystander’s health literacy may be of importance. Low health literacy can obstruct a mutual communication within the care meeting and thereby make the care less available (107). In a Swedish study examining data from a national public health survey, women, individuals born outside Sweden and those with low education were less prone to seek care despite an experienced need. Distrust towards the health care system was reported a key aspect (108). Convincing and repeated research shows morbidity, and implicit care-need, is highest among low-resource groups within the society (12). On the contrary, has stroke severity, rather than actual knowledge been shown to drive health seeking behaviour in an acute stroke situation (109). Patients with more severe stroke were more likely to arrive at hospital within 4 hours in a European population-based register study (58).

**Sex differences in ADL 1 year post-stroke and treatment**

Displayed in Paper IV in this thesis, women were more likely to be dependent in ADL at both 3 and 12 months post-stroke and thrombolysis treatment, compared to men, despite comprehensive adjustments for sociodemographic variables, comorbidities, stroke severity on admission and neurological status 24 h after treatment. To our awareness, the sex-stratified 12 months follow-up time of functional independency through nation-wide observational data, with relatively high coverage, is unique.

Contrary to our findings, was functional recovery among Swedish thrombolysis-treated men and women similar at 3 months post-discharge, suggesting women may have a higher benefit to stroke thrombolysis, compared to men (110). The
results in Paper 4 could indicate sex differences within stroke care, in secondary preventive treatment, or within rehabilitation. Indications of patient-related differences during the acute care period may be that women may have lower chance of than men of being admitted within the first 3 hours of symptoms (111), best explained by the fact that “surviving spouses” are more likely to be women than men, thus more vulnerable in an acute symptom setting. Similarly has women’s symptoms been reported to be more non-traditional than in men, thereby at risk of delayed recognition of stroke, treatment delay, and less effect from treatment (9). However, our data displayed that the mean effect from stroke thrombolysis were 0.5 NIHSS score points higher in women than in men.

Pharmacological secondary preventive treatment, associated with a reduced risk of recurrent stroke (15), was distributed with inequity in terms of age, income, education and country of birth 2009-2012 in Swedish stroke care (101). Sex differences in access to rehabilitation is difficult to catch through Riksstroke data, as Swedish hospital stroke care is differently organised dependent on region or hospital, and sub-acute rehabilitation facilities may be located within the stroke unit or elsewhere, causing differences in discharge routines. This makes such measures unreliable and reduces validity (61).

Another possible mechanism regarding the functional outcome is the response to rehabilitation; men displayed a higher response to rehabilitation among non-thrombolysed patients with first ischemic stroke, in a study from Italy in 2006 (112). Adjusting for covariates such as stroke severity and age, men displayed a 3 times higher chance to have good autonomy in both stair climbing and ADL. Similar findings were presented in studies from USA, at 90 days post-discharge among non-thrombolysed patients (113). This finding suggests response to rehabilitation may act as a factor influencing functional outcome also after stroke thrombolysis. A Swedish study based on Riksstroke data displayed non-thrombolysed women were at higher risk of deterioration in terms of ADL dependency.

An interesting finding is the results indicating that women have a higher unadjusted case fatality risk within 3 and 12 months after stroke and thrombolysis, but men had a higher adjusted risk. Unfortunately, we do not have any data informing us on cause of death for these patients. Other studies are somewhat conflicting in these terms (64). The results are concurrent with a study from the SITS-MOST register, adjusting observational register data with similar baseline variables as in randomised controlled trials (114).

In a report from Australia clinicians displayed that they do not prioritize or provide rehabilitative therapy during the acute stroke unit stay to patients who are anticipated to be discharged to residential care, deciding this within the first
days after the stroke, regardless of functional improvements. Family support and advocacy for rehabilitation influenced the decision, however (115). Swedish national guidelines does not give any prioritization to certain groups, but as female stroke patients often more often are widowed and live alone at the time of their stroke(116), women’s access to supporting relatives may be more limited, compared to their male counterparts. Also, less access to stroke care rehabilitation for individuals living in residential care homes may be a self-enhancing mechanism, however not catched by our data.

**Ethical considerations**

The concept of researcher ethics or internal research ethics, concerns the craft of research and the responsibilities the researcher has towards the society and the research community (117). Many research ethics problems constitute considerations between the demand for protection for the individual and the demand for research itself. The societal benefits versus the individual’s right to personal integrity (118). The studies in this thesis are in majority based on register data. This has special circumstances with regards to the external research ethics. The external research ethics concerns in what way individuals that participate in research as human test subjects or informants can be treated. How to ensure their protection from harm or insult? The Nordic countries has chosen to let the regional ethical committees represent the public and to judge the ethical aspects for every separate study (119).

Risks associated with register-based research are that data used in research are to be exposed, disseminated and get into “wrong hands”. It is central that data are anonymized or unidentified, and that there are strict rules for confidentiality and data protection (117). Within Riksstroke, personal identification variables is removed from the database immediately after linkage to other data sources, to preserve integrity (73). Also, individuals may be hurt if legal documents and rules hinder research in order to protect individuals(117). Participating hospitals have access to statistics and presentations to analyse own data and make comparisons with national data. Annual reports are also available, both at the national level and at hospital-level (73) and the register has contributed to improvement interventions in Swedish stroke care. Further, Riksstroke is run by medical professionals and representatives of major stroke patient organisations, increasing the legitimacy for hospitals and patients to participate. Riksstroke is funded by governmental and health-care providers’ organisations, securing independency from commercial interests (73). However, the register inclusion is based on the so-called opt-out design, in which the patient must signal he or she refrains from inclusion, otherwise being registered. All patients or their close intimates are informed on the register, the aim, their right to refrain from registering their person records. However, one cannot be sure, given the stress
of a sudden onset of disease, that all individuals nor patient’s intimates are in the consciousness or mood of deciding about being registered or not. In the research work for this thesis, all data have been treated as sensitive person records with appropriate storage and handling precautions. All planned handling of register data have passed through the Regional Ethical Board and results have been spread at national and international health care- and research meetings.

**Research and Clinical Implications**

This thesis provides a step closer to understanding inequity in provision of acute care reperfusion treatment for ischemic stroke. Much is still to elucidate and straighten out.

Since the differences in risk of ischemic stroke between educational groups are more pronounced among younger age groups (12), the future health care and acute stroke care will have to even more match these differences both in terms of acute care treatment and also in terms of primary and secondary prevention, including rehabilitation. This will provide a health care “on equal terms”. Future efforts for a more equitable acute stroke care will have to examine the perceptions of health care staff, of the task specified in the legal health care act. To start, this can be done through another interview study, or observational study, examining views and experiences of staff meeting with patients from lower socioeconomic positions in the acute stroke setting, examining their experiences and peer support in the higher burden of stroke risk factors, incidence, and long-term consequences.

As a result of the acknowledgement of differences between treatment documents, a national program committee for stroke care are currently developing a national decision support (120). Such an innovation could be viewed as an implementation object, and could be subjected to future examinations regarding use, barriers and facilitators for its implementation, with both qualitative and quantitative approaches. It is often assumed or suggested that behavioural change in clinical practise will be more likely if implementation strategies are specifically chosen to address the determinants of practise, such as barriers or obstacles (89, 94, 121). According to a Cochrane review aiming to determine effectiveness of tailored interventions for improvement of clinical practise, the effect is variable and tends to be small or moderate. Partly due to small number of available studies, and need of more research, it is not yet clear how best to tailor implementation interventions and therefore not clear what the effect of an optimally tailored intervention would be (121). As a consequence of the findings in Paper IV, future observational register-based studies of women’s and men’s need of-, access to-, dose-, and
response to rehabilitation and secondary prevention after stroke thrombolysis, are needed. As a consequence of the findings in Paper III, future studies of neighbourhood socioeconomic effect on time to treatment, access to stroke thrombolysis and outcome measures, would yield more knowledge on social stratification in access to evidence-based acute stroke care. Further, there is a lack of agreement on definitions of sensimotor recovery and on approaches to measurements of stroke recovery. Development of such standardizations could provide possibility of pooling data across studies and from different institutions. This lack of agreement hinders the research community’s ability to advance understanding of recovery mechanisms (122).

**Conclusions**

This thesis displays that clinicians face barriers and facilitators at several levels, suggesting implementation interventions could be targeted towards both the individual-, the social interactions and context-, and also the organisation and available resources level. Assurance of clinicians’ individual competence, peer support, and clinical leadership seem to be important areas to intervene. Stroke thrombolysis rates have expanded over time, and an increase in stroke thrombolysis delivery to patients with mild stroke symptoms has contributed to this increase. However, it seems considerable differences between hospitals inhibit equity of care delivery. Further, socioeconomically disadvantaged groups receive less often stroke thrombolysis. Type of hospital seems to play a role, yet the reasons for this difference are not fully understood. This thesis also display that stroke thrombolysis-treated women that survive 1 year after stroke, appears to face higher risk for dependency in ADL, compared to men.
Acknowledgements

This thesis was prepared at the Department of Public Health and Clinical Medicine, Medicine, and the Department of Community Medicine and Rehabilitation, Physiotherapy, Umeå University. I would like to express my most sincere gratitude to everyone involved in this work. I particularly wish to thank:

All the patients in Riksstroke, and all the staff at Swedish hospitals working with the registry. Your participation and work is tremendously valuable. The officials at the Riksstroke administrative office, and the register steering group, making this thesis possible. All the informants providing data to Paper I, thank you for your precious time and your answers to my questions, trying to understand implementation of stroke thrombolysis.

Erik Rosendahl, I am full of admire over the way you bring people, myself and others to grow and believe in their capacity and ability. You have given me such a nice encouragement and incredible support. I don’t know how to thank you. I know I chime in with a choir of voices saying you are so wise. Without your support, this thesis would have never become what it is. Lillemor Lundin-Olsson, without your positioning and help to me, I probably wouldn’t had dare to go further along to finish this thesis. I am full of gratitude for this and help with many other things. Per Wester, all the encouragement and support from you, with your vast knowledge and experience from stroke care and guideline development has been very valuable for me. Mattias Hedlund, thank you for all the help and letting me take part of all your knowledge within neurology and research (and help with fussy templates and difficult forms). The man with the brilliant metaphors, and eye for details! Charlotte Häger, thank you for all the encouragement and good advice throughout these times.

Marie Eriksson, thank you for inviting me into the world of research and thank you for all the knowledge and skills on quality registers and statistics you mediated to me. Kjell Asplund, thank you for letting me take part of your perspectives within the stroke- and quality register areas. I have learned a lot from you. Eva-Lotta Glader, thank you for help and wise words. Bo Carlberg, a million thanks for all support, help and encouragement. Lars Weinehall, thank you for the help and good advice. Ann Sörlin, thank you for support and help with many things!

Chatarina Carlén, physiotherapy, for all the help and orderliness! Kerstin Rosenquist, Eva Karlsson and Catrin Johansson, unit of medicine, for valuable help with many questions. Irene Grundberg, for assistance with interview
transcription. The staff at the university’s Medical Library for help when in need. Henrik Holmberg, for good advice and help with statistics. Per Ivarsson, Unit of Medicine/Riksstroke, and Larry Fredriksson, unit of physiotherapy, for all the invaluable help with fussy computer-related questions. Husservice in the Caring Sciences Building, for help and hey’s!

Professor Bo Norrving, Lund. Register-keeper and pillar. Thank you for encouragement and good advice! Fredrik Jonsson, for valuable chats about registers, and life! Gunilla Stenberg, for your warm-hearted support and good advice. Fellow present and former PhD students and friends at the Unit of Physiotherapy and Unit of Occupational Therapy. I have learned so much and had so much fun from being in this unit and within the PhD student group over the last years. You are such nice and wise people! Heidi Nedergård, Sara Lundell, Anna Sondell, Matthias Tegern, and many more; to write your significance would take another page... All the teachers, researchers and other employees at the units. Continue to make it a good place! Fellow present and former PhD students, and colleagues at the Unit of Medicine, for support, laughs, and fun! Caroline Mellberg, Ulf Nilsson, Camilla Sandberg, Lena Nilsson, Frida Bergman, and others.

Jenny Söderlund; train-Jenny, thank you for all the relaxing lunches together. Nelly Romani-Vestman, for good advice and nice times. Linda Sundberg and Maria Lindqvist, role models and lunch dates. Cissi Berglund, for being so cool and such a friend, despite introverted-me! Maribel Garcia, for advice and being there. Ida Tjerngren, for the best advice in dissertation times and for being you! Sara Ehrström for help with language and for being a wonderful friend. Extended family in Skellefteå, thank you for all the support and good times. Mom & Dad, thank you for all the help, support and encouragement! My precious; Ola, Ebba and Oskar, for being you, for adventures, and reminding me on the most important things in life.
References

3. World Health Organization. UN High-level Meeting on NCDs - summary report of the discussions at the round tables. 2011.


55. Socialstyrelsen. På djupet [Internet]; 2017 [cited 170327]. Podcast: 31.08 min


