From DEPARTMENT OF CLINICAL SCIENCE AND EDUCATION, SÖDERSJUKHUSET
Karolinska Institutet, Stockholm, Sweden

PREHOSPITAL IDENTIFICATION AND PRIORITY OF ACUTE STROKE

Annika Berglund

Stockholm 2015

To be conscious that you are ignorant is a great step to knowledge

Benjamin Disraeli (1804-1881)

Published by Karolinska Institutet.
Printed by AJ E-print AB

ISBN 978-91-7549-917-8

Prehospital identification and priority of acute stroke

THESIS FOR DOCTORAL DEGREE (Ph.D.)

By

Annika Berglund

Principal Supervisor:
Docent Mia von Euler
Karolinska Institutet
Department of Clinical Science and Education, Södersjukhuset
Karolinska Institutet Stroke Research Network at Södersjukhuset

Co-supervisors:
Medicine doctor Katarina Bohm
Karolinska Institutet
Department of Clinical Science and Education, Södersjukhuset

Professor Karin Schenck-Gustafsson
Karolinska Institutet
Department of Medicine Solna
Cardiac Unit

Professor Nils Wahlgren
Karolinska Institutet
Department of Clinical Neuroscience
Division of Neurology

Opponent:
Professor Lars Rosengren
Sahlgrenska Academy at University of Gothenburg
Institute of Neuroscience and Physiology
Department of Clinical Neuroscience and Rehabilitation

Examination Board:
Docent Katarina Jood
Sahlgrenska Academy at University of Gothenburg
Institute of Neuroscience and Physiology
Department of Clinical Neuroscience and rehabilitation

Professor Björn-Ove Suserud
University of Borås
Faculty of Caring Science, Work Life and Social Welfare

Docent Sofia Almerud Österberg
Linnaeus University
Department of Health and Caring Science

To my beloved children, Johanna, Ida and Simon - you are my inspiration and strength,
my dear mother Gullwi and the memory of my dear father Christer and
my partner for life Anders, with the greatest love.

ABSTRACT

Treatment of acute ischemic stroke is time critical and early initiated reperfusion treatment increases the chances of good recovery. However, in 2007, only 3% of ischemic stroke patients were treated with thrombolysis in Sweden. Patients' late arrival to hospital was considered to be one of the reasons for the low treatment rate. The aim of the first study was to evaluate if delay to treatment could be decreased with high priority dispatch of ambulance and thus increase the number of patients eligible for thrombolytic treatment. As high priority of suspected stroke patients is dependent on identification of stroke, the following studies aimed to evaluate identification of stroke.

Study I: Patients (n 942) with suspected stroke within 6 h, aged 18-85 were randomized from EMCC or ambulance to intervention, Priority 1 alarm or control, Priority 2. The intervention group randomized from EMCC arrived to hospital 13 minutes ($p < 0.001$) earlier, and 26 minutes ($p < 0.001$) earlier to stroke unit compared to the control group. Furthermore, twice as many patients in the intervention group (35%, $p < 0.001$) were treated with thrombolysis compared to the patients in the control group (17%). The conclusion of the study was that higher priority, both pre- and in-hospital is favorable for patients with acute stroke.

Study II was a descriptive study of the use of the Face-Arm-Speech-Time test (FAST) in identification of stroke by the EMCC and the ambulance in the patients included in *Study I*. In all, 52% of the patients were correctly identified as stroke/TIA. The EMCC included 71% of the patients with stroke/TIA diagnosis and the ambulance included another 29%. At least one FAST symptom was positive in 64% of the included patients. The positive predictive value, PPV, for FAST was 56% in the EMCC included patients and 74% in the ambulance included patients. The conclusion was that FAST is not enough to support identification of stroke in emergency calls. The study demonstrated that more information of how stroke is expressed in emergency calls concerning stroke is needed to improve identification.

Study III was a descriptive study of symptoms expressed by the caller in emergency calls concerning stroke of the 179 emergency calls included 64% were dispatched as stroke. Speech disturbance (54%), fall or lying position (38%) and altered mental status (27%) were the most common symptoms in calls. FAST symptoms were presented in 64% of the calls and were more commonly presented in calls dispatched as stroke. The FAST symptoms were presented spontaneously by the caller in 90 %. Fall or the patient being in a lying position (66%) was the most dominating problem presented in the stroke calls dispatched as non-stroke. These result show that FAST is rarely asked for and that the calls dispatched as non-stroke often were presented as a fall or the patient being in a lying position. Questions about FAST symptoms in emergency calls with fall/lying position or altered mental status presented may improve identification of stroke.

Study IV was a qualitative study of obstacles and facilitators in communication and interaction of the participants in emergency calls concerning stroke using interpretive phenomenology. Of the 68 emergency calls from *Study III* where fall/lying position were presented, 29 calls were analyzed. The dispatch codes were blinded in the first step of analysis, 13 calls were dispatched as stroke and 16 as non-stroke. The nurses' expertise skills were the identified aspect that could be decisive in identification of stroke. Other important findings were aspects of the first call-taker and nurse that can be influenced to improve identification, such as authority, competence and coaching strategies. The result indicated need of education and training to improve identification of stroke and to support the process of developing expertise skills.

LIST OF SCIENTIFIC PAPERS

I. Berglund A, Svensson L, Sjöstrand C, von Arbin M, von Euler M, Wahlgren N for the HASTA collaborators: Engerström L, Höjeberg B, Käll T-B, Mjörnheim S, Engqvist A.

Higher Prehospital Priority Level of Stroke Improves Thrombolysis Frequency and Time to Stroke Unit: The Hyper Acute STroke Alarm (HASTA) Study

Stroke. 2012;43:2666-2670

II. Berglund A, Svensson L, Wahlgren N, von Euler M for the HASTA collaborators.

Face Arm Speech Time Test Use in the Prehospital Setting, Better in the Ambulance than in the Emergency Medical Communication Center

Cerebrovascular Diseases 2014;37:212–216

III. Berglund A, von Euler M, Schenck-Gustafsson K, Castrén M, Bohm K.

Identification of stroke during the emergency call: a descriptive study of callers' presentation of stroke

BMJ Open. 2015 Apr 28;5(4):e007661

IV. Berglund A, Heikkilä K, Bohm K, Schenck-Gustafsson K, von Euler M

Aspects facilitating or hampering nurses identification of stroke in emergency calls

Submitted to the Journal of Advanced Nursing, JAN 2015

CONTENTS

LIST OF ABBREVIATIONS

ADL	Activity of daily living
ACA	Anterior Cerebral Artery
CBF	Cerebral Blood Flow
CPSS	Cincinnati Prehospital Stroke Scale
CRF	Case Report Form
CT	Computed Tomography
ED	Emergency Department
EMCC	Emergency Medical Communication Center
EMS	Emergency Medical Service
ESO	European Stroke Organization
FAST	Face-Arm-Speech-Time test
HASTA	Hyper Acute STroke Alarm
ICD	International Classification of Diseases
MCA	Middle Cerebral Artery
MRI	Magnetic Resonance Imaging
mRS	Modified Rankin Scale
NIHSS	National Institute of Health Stroke Scale
PCA	Posterior Cerebral Artery
PPV	Positive Predictive Value
SITS	Safe Implementation of Treatments in Stroke
SU	Stroke Unit
r-tPA	Recombinant Tissue-type Plasminogen Activator
TIA	Transient Ischemic Attack

1 PREFACE

Eight years have passed since the project leading up to this thesis started, and I realize that part of the background has a historical perspective. Medical practice has been changed and although I have studied the changes and worked in the new settings I have not quite realized until now how fundamental the changes are.

This thesis focuses on identification and priority of acute stroke which has also been the focus of my clinical work as a stroke nurse when taking care of patients from the emergency department through the in-hospital Stroke-Chain-of-Care. From caring for one patient at a time as a stroke nurse, I became a researcher studying the process of the Acute Stroke-Chain-of-Care with a large number of stroke patients. The studies brought new stimulating challenges to me, especially to my patient oriented work and it have been exiting to get to know stroke and stroke patients from the prehospital perspective. To listen to emergency calls have also given me knowledge and a deeper understanding of the difficulties of assessing and identifying stroke in emergency calls. The studies have resulted in changes in prehospital guidelines and introduction of the identification tool Face-Arm-Speech-Time test, FAST, which is still in use.

It has been a privilege to do research and at the same time use my clinical skills. Now I have the opportunity to link my clinical skills with continued research and to, hopefully, contribute to improvements for stroke patients.

2 INTRODUCTION

This study started with a project aiming to improve the frequencies of thrombolytic treatment in acute ischemic stroke and to reduce time to treatment and time to admission to stroke-units, in Stockholm.

In the year of 2003 thrombolytic treatment was approved in Sweden for treatment of ischemic stroke (1). Intravenous thrombolytic treatment within the first hours of onset can restore the circulation in the brain through recanalization and thus affect the outcome of stroke (2-4). The chances of successful recanalization are strongly time dependent due to the brain tissues sensitivity to oxygen deficiency (5, 6). Until 2003, there was no approved treatment available, in Sweden, to reduce the brain damage of acute stroke. Consequently, stroke was not considered or prioritized as an urgent condition in the prehospital setting and the emergency department. The introduction of thrombolytic treatment was slow and there were great variations in frequencies of thrombolytic treatment as well as in door-to-needle times between the centers. In 2007, five years from approval of thrombolytic treatment, only 3% of all patients with ischemic strokes were treated with intravenous thrombolysis in Sweden and 4% in Stockholm (7). The door-to-needle time was around 60 minutes in Sweden at the time even though thrombolysis was known to be a time-dependent treatment.

Two of the main problems contributing to the low thrombolytic treatment rate were the patients' late arrival to hospital and poor routines to recognize patients eligible for treatment both pre- and in-hospital. In Stockholm the guidelines for priority in dispatching ambulances for acute stroke was Priority 2 of 4 with Priority 1 being the highest priority dispatched.

Treatment and care in stroke units for patients suffering a stroke have been shown to improve the final outcome (8). However, only 59% of the stroke patients in Stockholm were initially treated in a stroke unit and 28% of the stroke patients were never treated in a stroke unit (7). This was the setting for stroke care in 2007 and the reasons for launching the first study in this thesis. The situation of a low rate of thrombolytic treatment and too few patients cared for in a stroke unit called for improvements.

The first study in my thesis aimed to investigate if a higher priority from the Emergency Medical Communication Center (EMCC) would result in an increased number of patients eligible for thrombolytic treatment with decreased delay. The study also aimed to increase the number of patients treated in a stroke unit for improving outcome of stroke.

3 BACKGROUND

3.1 STROKE

Stroke is a vascular disease, caused by disruption of cerebral blood circulation and subsequent cell death. The effects of stroke can be devastating with permanent loss of physical and cognitive functions, or death. Stroke is one of the leading causes of death and neurological disabilities in the world and in Europe stroke is the second most common cause of death, nearly 1.1 million deaths per year (9, 10). In Sweden, approximately 25 000 persons suffers a stroke every year of which 76% have their a first stroke (11). In Sweden the 30-day mortality is 20% (12) and of the surviving patients 80% are living at home after three months, 86% are independent in walking, and 22% are receiving home help services (12).

Stroke is defined by the World Health Organization, WHO, as "A focal (or at times global) neurological impairment of sudden onset, and lasting more than 24 hours (or leading to death), and of presumed vascular origin." (13)

In an adult Caucasian population, stroke is caused by ischemia in 85%, a blockage of a thrombus or an embolus in the cerebral arteries. The brain cells dies due to the oxygen and glucose deficiencies, and the area of dead tissue becomes a cerebral infarction. In 15% of stroke patients, the stroke is caused by a rupture of an artery, leading to an intracranial hemorrhage in 2/3 and a subarachnoid hemorrhage in 1/3 (14, 15).

A transient ischemic attack, TIA, is an ischemic event causing reversible symptoms of a stroke. The WHO definition of TIA is "focal neurological symptoms lasting less than 24 hours" (13). The duration of symptoms is often short, 5-10 minutes or up to one hour (16-18). A TIA is associated with an increased risk of stroke, approximately 10% of patients with a TIA suffer a stroke within the first 90 days after a TIA (19, 20).

The brain is dependent on a constant supply of oxygen and glucose to keep the brain cells, particularly the neurons, active and alive (21). The brain consumes a large amount of oxygen related to the size of the brain, 20% of the total body consumption (22). The normal cerebral blood flow (CBF) is approximately 50-60 ml/100 g tissue/min (17). In CBF below 20 ml/100 g/min the brain tissue is affected and the electrical activity diminished resulting in impaired function of the cells in the affected area (17, 21). Irreversible brain damages occur when the blood flow is decreased below 10 ml/100 g/min and the oxygen and energy supply become insufficient resulting in death of the neurons (17, 21). The reduced blood flow activates a series of neurochemical processes, the injury spreads rapidly and becomes irreversible, an ischemic core. The cells surrounding the ischemic core is called the penumbra, these cells are affected by the limited blood flow and threatened by death but are still within reach for rescuing through reperfusion (21, 23). The penumbra decreases rapidly the first hour after the vessel occlusion and the irreversible damage, the death of the neurons is spread (21). Two million neurons have been estimated to die every minute in the acute phase of stroke, resulting in disruption of 14 billion synapses and 12 km of myelinated fibers (5). Half of the

penumbra have been estimated to be lost after 3 hours and after 6-8 hours most of the neurons are permanently damaged (21). The penumbra means possibilities of reperfusion by therapeutic interventions to restore the blood supply and rescue the threatened cells to recover (15).

3.1.1 Sex and gender

When the studies in this thesis were initiated in 2008, data on sex and gender differences and equalities in stroke were lacking in Stockholm. Given the sex differences in cardiac diseases, and stroke being a closely related disease of vascular etiology it was of interest to explore the relation in stroke (24). The age among men and women are one of the obvious differences, with women being 4-5 years older than men at stroke onset (25-34). In Sweden, the mean age of stroke onset is 76 years but the men are almost 5 years younger, 73 years and the women 78 years (11, 35). Men are dominating in stroke patients younger than 65 years in Sweden, 64% men and 36% women, and also in the age group 65-74 years where there are 62% men and 38% women (11). In contrast, women are dominating among stroke patients ≥85 years, 64% women and 36% men (11). Due to longer life expectancy women are more likely to suffer a stroke, and as risk of stroke increases with older age, women have more stroke events than men overall. The aspect of age complicates comparisons between women and men as age also affects social aspects, comorbidity, treatments and interventions as well as outcome and mortality (35).

It has been shown that women more often live alone prior to stroke (34, 36) which probably is due to higher age. Older age and previous living alone affects the prospects of returning home after stroke, and previous studies show that more women are discharged to nursing homes (25, 31, 35). Regarding differences in severity of stroke between women and men conflicting results are presented in a review of previous studies (26). However, women have greater risk of cardioembolic stroke partly because older age predisposes women for atrial fibrillation resulting in a higher risk of cardioembolic stroke, and cardioembolic stroke is typically more severe (26, 31, 35). Women are reported to have poorer outcome after stroke than men (25, 27, 31), whether the differences remain after adjusting for age and age related component is more difficult to determine. One review suggests that the difference of poorer outcome for women after stroke do remain after adjustments of age and other sex differences in medical history and presentation (25). Nevertheless, mortality in stroke is strongly associated with older age and women with stroke are older (25, 26, 35).

3.1.1.1 The use of Emergency Medical Service, EMS

The EMS includes the emergency call to the EMCC and the ambulance service. Data on EMS use for stroke patients in Stockholm prior to start of *Study I* in 2008 is lacking, but since 2012 arrival of ambulance is registered in the National Stroke Register, Riks-Stroke (7). The data from 2013 shows that 76% of stroke patients in Sweden arrived to hospital with an ambulance of whom 31% were men < 80 year, 20% were women < 80 years, 20% were men ≥ 80 year and 29% women ≥ 80 years (11).

3.1.1.2 Identification, priority and delay

National data of identification rate, priority and delay for stroke patients prior to start of *Study I* in 2008 is lacking.

3.1.1.3 Thrombolytic treatment

Thrombolytic treatment has been shown to be equally beneficial for women and men (37). In the first approval of thrombolytic treatment the age was limited to18-80 years (1) which reduced the eligibility for thrombolytic treatment of female stroke patients. In 2013, no age limit was affecting the decision of thrombolysis. However, less patients with ischemic stroke over 80 years (8%) were treated compared to those under 80 years (13%) in Sweden, equally between the sexes (11). Other studies support the data of no difference in frequencies of men and women and thrombolytic treatment (27, 30, 38). However, women have been reported to be less likely to receive thrombolytic treatment in conflicting study reports (39). The functional outcome after thrombolytic treatment was reported with no significant difference between men and women although men showed higher risk of mortality and symptomatic intracerebral hemorrhage (40-42).

3.1.1.4 Stroke unit care

Data of access to stroke unit care concerning sex were not reported in the National Stroke Register for the years prior to the start of the studies in this thesis, 2007.

3.1.2 Stroke Treatment

The treatment of ischemic stroke aims to restore the blood criculation and reduce the brain damage due to the blockage of blood supply. In Sweden, the first treatments for ischemic stroke become available only in the last decade and before that, stroke was treated as a non-urgent condition. The diagnostic possibilities were improved when computer tomography (CT) scans were introduced in clinical practice in the late 80's and the possibility to differentiate ischemic from hemorrhage stroke opened up for new opportunities of treatment. Previously, treatment had been available for subarachnoid hemorrhage and exceptionally for intracerebral hemorrhage and malignant ischemic stroke where decompressive treatment could be considered to avoid lethal compression of the brain (17). The treatments available in ischemic stroke before approval of thrombolysis was directed to limiting the effects of stroke and avoiding further vascular incidents or complications. Thrombolytic treatment to restore the circulation was approved for acute treatment of stroke in 2003 in Sweden (1). To consider thrombolytic treatment, intracerebral hemorrhage needs to be excluded by a CT scan or Magnetic Resonance Imaging (MRI) (1).

To measure disability and dependency in ADL in stroke the Modified Rankin Scale (mRS) is used, **Fel! Hittar inte referenskälla.**. Clinical trials such as the studies of thrombolytic treatment used the mRS scores to describe outcome in the patients treated compared to the patients not treated. (43, 44)

The Modified Rankin Scale, mRS

Grade	Description
0	No symptoms at all
1	No significant disability despite symptoms: able to carry out all usual duties and activities
2	Slight diisability: unable to carry out all previous activities but able to look after own affairs without assistance
3	Moderate disability: requiring some help, but able to walkwithout assistance
4	Moderately severe disability: unable to walk without assistance, and unable to attendto own bodily needswithout assistance
5	Severe disability: bedridden, incontinent, and requiring constant nursing care and attention

Figure 1 The Modified Rankin Scale is used to measure disability and dependency after stroke

3.1.3 Thrombolysis

To resolve the thrombus or emboli the thrombolytic agent in stroke, recombinant tissue-type plasminogen activator (r-tPA) is given as intravenous infusion during one hour (1, 2).

The thrombolytic treatment have shown a favorable outcome with modified Rankin Scale, mRS, 0-2 i.e. no symptoms at all or slight disability, in 41% of patients treated with thrombolysis within 3 hours compared to 32% of those without treatment (4). When thrombolysis is given between 3-4.5 hours from stroke onset the favorable outcome of mRS 0-2, was 58% in the treated group compared to 56 % in the non-treated group (45). Another study reported favorable outcome of mRS 0-1 for 52% of the patients treated within 3-4.5 hour compared to 45% of those not treated (46). The result of r-tPA treatment is strongly time dependent and the treatment can cause bleeding complications with deterioration or death (3, 47, 48).

Thrombolytic treatment was approved for ischemic stroke within 3 hours of onset in the United States in 1996, after the study results of NINDS (2). In Sweden, thrombolytic treatment for ischemic stroke was approved of in 2003 within the age of 18-80 years (1). Randomized clinical trials were continued to further define the time window and age limitations (45, 46, 49-51). In Europe the approval of thrombolysis in stroke was given on conditions that the safety aspects were monitored and further studies of extended time windows performed. The approval was given with a list of contraindications and criteria. (1)

In the end of 2008, after the inclusion for *Study I* was closed, the time limit for thrombolysis was extended to 4.5 hours in the Swedish clinical recommendations while awaiting approval for extended time limit. Thrombolytic treatment is still more beneficial given within 3 hour from onset than between 3 - 4.5 hours although there are limited positive effect in outcome up to 4.5 hours (3, 48, 52, 53). The new recommendations were based on studies which also challenged the age limits (45, 46, 52).

The narrow time-window excludes patients from r-tPA treatment as most stroke patients arrive too late to the hospital. Early estimations of the target level for thrombolytic treatment in ischemic stroke have been calculated to 15% (54) and later on up to 24% (55). The rate of thrombolytic treatment prior to the start of the studies included in this thesis was 3% in Sweden which indicated room for improvements. Today the thrombolysis rate in Sweden is 11% of the ischemic stroke and equally distributed among the sexes (11).

3.1.4 Endovascular intervention

In the last decades, treatments for acute ischemic stroke have been developed further with endovascular intervention aiming at restoring the cerebral circulation through recanalization (56-67). Endovascular interventions are still developing regarding techniques and devices, and require specialist competence and resources only available at specialized centers. Recanalization by endovascular intervention is still time dependent and requires examinations with angiography and often also perfusion CT or MRI to locate the blockage, to evaluate if the blockage is attainable and if there is a penumbra with tissue still to be saved. Endovascular intervention can be a complement to thrombolytic treatment or an option when thrombolysis is contraindicated due to unknown time of onset, timeframe outside the 4.5 h window, anticoagulant treatment, or recent surgery. (64-67)

3.2 DELAY

In a historical perspective, stroke has not been considered a high priority emergency condition demanding immediate attention even though stroke is a potentially life threatening condition. The prospect of acute treatment and importance of fast assessment is relatively "new" both to the health care organizations and the public, and the progress towards a high-priority emergency concept has been slow. Another obstacle for delay is that stroke symptoms tend to induce passivity and neglect rather than action because the symptoms do not cause pain, anxiety or alert the patient to act. The delay from onset of symptoms to start of treatment needs to be reduced however; the patient's delay cannot be directly influenced by the Chain-of-Care. Hence, in studies and interventions for improvements the delay is often divided in patients delay, prehospital- and in-hospital delay, Figure 2.

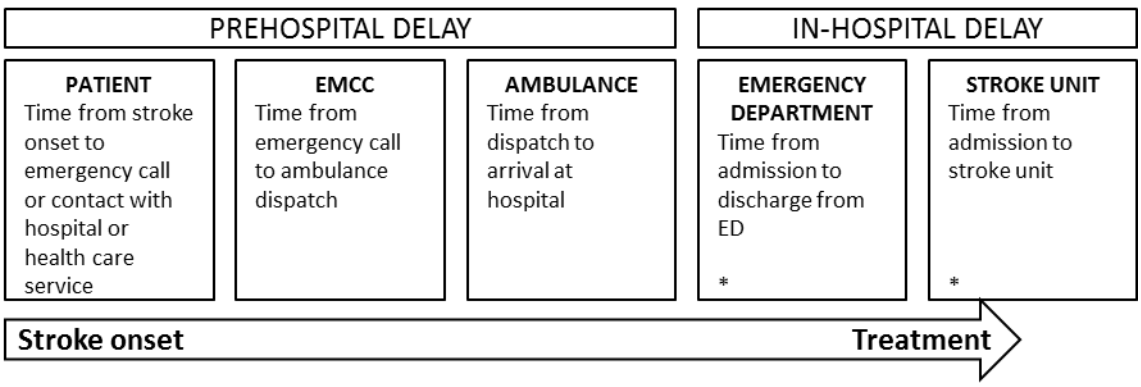

Figure 2 An overview showing the prehospital and in-hospital delay. * CT scan could be performed and thrombolytic treatment started at the emergency department, the stroke unit, or the intensive care unit**.**

3.2.1 Patient delay

Time is critical in treatment of ischemic stroke, every minute counts as early initiated treatment is associated with a more favorable outcome (3, 5, 6). Despite the urgency of treatment many patients arrive late to the hospital, and the patients' delay of seeking help is a major problem in finding the stroke patients eligible for thrombolytic treatment. Reasons for patients' delay have been shown in a previous study to be that stroke and/or the urgency of stroke was not recognized, the patient was living alone, the stroke onset was not witnessed, the patient did not seek medical help, and stroke started at home (68). Unawareness of the urgency of the symptoms was also reported in one third of the stroke patients in another study, while another third waited for the symptoms to vanish (69). Many patients called a relative to consult first and (70-73) some stroke patients were unable to call for help (68, 70).

For many patients arriving to hospital the time of stroke onset is unknown for example when the patient wakes up with stroke symptoms or is unable to tell the time, which excludes thrombolytic treatment. Varying proportions of delay have been reported. One study reported 58% of all patients to have an unknown time of stroke onset and only 18% had an onset within 2 hours when arriving to hospital (74). Another study showed that 35% of the patients arrived to hospital within 6 hours from onset, 39% arrived between 6-24 hour, 18% after 24 hours, and onset was unknown for 9% of the patients (75). In wake up stroke, the time of onset is calculated from the last known time without symptoms which often reach beyond the window of treatment.

To decrease patient delay, public campaigns to recognize symptoms and call for immediate actions have been launched with easy memory-checks such as the Face-Arm-Speech-Time test, and calling the emergency number (76-81). Studies show varied results when investigating the public's knowledge of stroke and furthermore there seems to be a discrepancy between knowledge and action. Recognizing symptoms of stroke is not synonymous to recognizing the emergency of the condition. (72, 82-85)

3.2.2 Prehospital delay

Calling the emergency number concerning stroke is strongly associated with shorter delay (69, 86-98) and is an independent factor in enabling arrival within 2 h of onset (74, 75, 86, 99-103). The EMCC is often the first link in the Acute Stroke-Chain-of-Care which increases the possibilities to reduce delay and improve the care. Activating the EMS enables the first actions of identification and care to be started. The EMS is a prolonged arm of the hospital where the care and treatment starts at scene. Delay can be increased not only by a fast transportation but by early evaluation enabling contact and prenotification to the hospital. The prehospital delay is difficult to compare between different countries as organization, guidelines and distances within the area differs. In the Stockholm catchment area, patients with suspected stroke will be transported to the nearest hospital while in other places the ambulance might by-pass smaller hospitals to get to specialized stroke centers.

3.2.3 In-hospital delay

Prenotification to the receiving hospital by ambulance decreases the in-hospital delay through early activation of the in-hospital Stroke-Chain-of-Care (104-108).

3.2.3.1 Door-to-Needle-Time

The door-to-needle-time (DNT) is defined as the time from the patients' arrival to the hospital to start of treatment. In Stockholm, the door-to-needle time was approximately 60 minutes in 2007 prior to start of *Study I*, according to our local Safe Implementation of Treatments in Stroke, SITS, register. The door-to-needle time in Helsinki was 67 minutes in 2003 but after reorganization the DNT was reduced to 34 minutes in 2005 (86) but many countries reported DNT to be over 60 minutes in 2007 (109, 110).

3.3 IDENTIFICATION OF STROKE

It has been reported that 25-56% of stroke patients recognized their symptoms as stroke (100). Data of dispatchers'- and ambulance nurses' identification in Stockholm, prior to the study in 2008 is lacking. International data of dispatchers' stroke identification varies between 31-57% (111-119). Ambulance personnel have the advantage of being able to evaluate patients face-to-face, and usually have higher numbers of identified stroke (114). Previous studies indicate identification by ambulance personnel between 45-78% (113, 120).

3.3.1 Symptoms of stroke

The area of the brain affected by the impaired arterial blood supply determines the symptoms of a stroke. Depending on size of occlusion or bleeding, location, and collateral blood flow the symptoms can vary from mild to devastating. The large arteries in the brain are divided in the middle cerebral artery (MCA), anterior cerebral artery (ACA), and posterior cerebral artery (PCA). The MCA supplies large parts of the two hemispheres and is the area most frequently affected by a stroke. The ACA supplies the inner part of the hemispheres and the frontal lobe and is a more unusual location of a stroke. The PCA supplies the posterior part of the hemispheres, the occipital lobe, the cerebellum, and the brainstem. (121)

- **Symptoms from MCA** are contralateral hemiparesis, ipsilateral conjugated eye and head deviation, and drowsiness. The cognitive symptoms depend on which hemisphere is affected; aphasia and apraxia is in general caused by left sided injury, while injury in the right hemisphere generally causes hemineglect, agnosia, and confusion.
- **Symptoms from ACA** are weakness in the distal lower limb and lesser in the upper limb, motor hemineglect, transcortical motor aphasia and behavioral disturbance.
- **Symptoms from PCA** are ipsilateral headache, diplopia, rotary or linear vertigo, unsteady gait, hiccup, bilateral or crossed motor or sensory symptoms, disconjugated gaze, decreased level of consciousness, and amnesia. (121)

The symptoms of stroke described above is described from a medical professional perspective which often differs from the laymen's due both in how the symptoms are expressed and which symptoms are observed. The patient may not even be aware of the symptoms and hence not express them.

WHO described symptoms of stroke for laymen by sudden onset of:

- unilateral weakness in face, arm or leg
- unilateral numbness of the face, arm, or leg
- confusion, difficulty speaking or understanding speech
- difficulty seeing with one or both eyes
- difficulty walking, dizziness, loss of balance or coordination
- severe headache with no known cause
- fainting or unconsciousness

(122)

In the professional version, WHO describes symptoms of stroke divided in "General major symptoms" and "Other symptoms", cited in Table 1 (13).

"General major symptoms"	**"Other symptoms"**
Symptoms should be of a presumed vascular origin and should include one or more of the following definite focal or global disturbances of the cerebral function: • Unilateral or bilateral motor impairment (including lack of coordination) • Unilateral or bilateral sensory impairment • Aphasia/dysphasia (non-fluent speech) • Hemianopia (half-sided impairment of visual fields) • Forced gaze (conjugate deviation) • Apraxia of acute onset • Ataxia of acute onset • Perception deficit of acute onset.	• Dizziness, vertigo • Localized headache • Blurred vision of both eyes • Diplopia • Dysarthria (slurred speech) • Impaired cognitive function (including confusion) • Impaired consciousness • Seizures • Dysphagia.

Table 1 WHOs' description of stroke symptoms, cited (13).

3.3.2 Mimics and chameleons

Identification of stroke and TIA can be difficult even in hospital. A previous study reports 69% of the clinical diagnosis of stroke to be correct in hospital (123) supported by a review reporting 10-30% of the stroke patients to be incorrectly diagnosed (91, 124). Symptoms of stroke and TIA can also be found in a numerous other conditions and diagnosis, so called stroke mimics. Differential diagnosis to stroke can be tumors, migraine, epileptic seizures, intoxication, hyper-/hypoglycemia, demyelinating disease, and severe infection. (123-130)

Chameleons of stroke is the opposite of mimics where the stroke is incorrectly identified as other conditions than stroke (131, 132) which may result in delay and inadequate treatment.

A previous study showed stroke specific symptoms like weakness, facial drop, and speech disturbance as well as loss of consciousness to be associated with shorter delay to CT-scan, while difficulties walking and imbalance were associated with longer delay to CT-scan (133).

3.3.3 Face-Arm-Speech-Time test

Figure 3 The Face-Arm-Speech Time test is used to identify stroke by facial weakness, arm weakness and speech disturbances.

To support and increase prehospital identification of stroke different kind of scales and protocols has been used (113, 120, 130, 134-140). In this thesis, the Face-Arm-Speech-Time test, FAST, was introduced in the prehospital setting in Stockholm, both in the EMCC and in the ambulance to support identification in *Study I* and *II*. Most previous studies reported FAST used by ambulance personnel but not by dispatchers. The FAST test was developed from the Cincinnati Prehospital Stroke Scale (CPSS) test that was derived from the National Institute of Health Stroke Scale, NIHSS, in purpose to create a tool for prehospital identification of stroke. FAST and CPSS are similar and test for facial weakness, arm weakness and speech disturbances, Figure 3. (139, 141, 142) The tests are simple and reported to provide good recognition of stroke (138, 143).

In Sweden, a national stroke campaign started in 2011 equivalent with the FAST test but translated to the Swedish "AKUT" with A for Face drop, K for arm/leg weakness, U for speech disturbances and T for time to call the emergency number 112 (76). Similar actions to improve knowledge of stroke among the public have been undertaken internationally (144-149).

3.4 ACUTE STROKE-CHAIN-OF-CARE

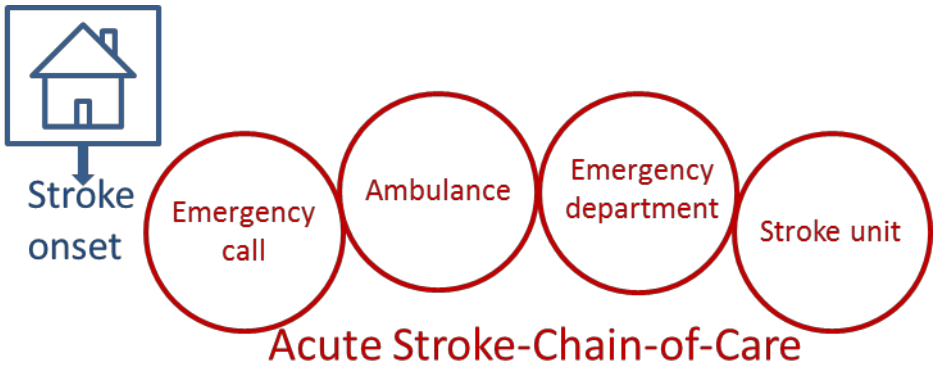

Figure 4 The Acute Stroke-Chain-of-Care.

The acute stroke chain of care starts from the first contact with health care. The most effective start is calling the emergency number, in Sweden number 112, Figure 4. Every part of the chain is important for the best result and treatment for the patient.

3.4.1 Prehospital Stroke-Chain-of-Care

3.4.1.1 Emergency Medical Communication Center

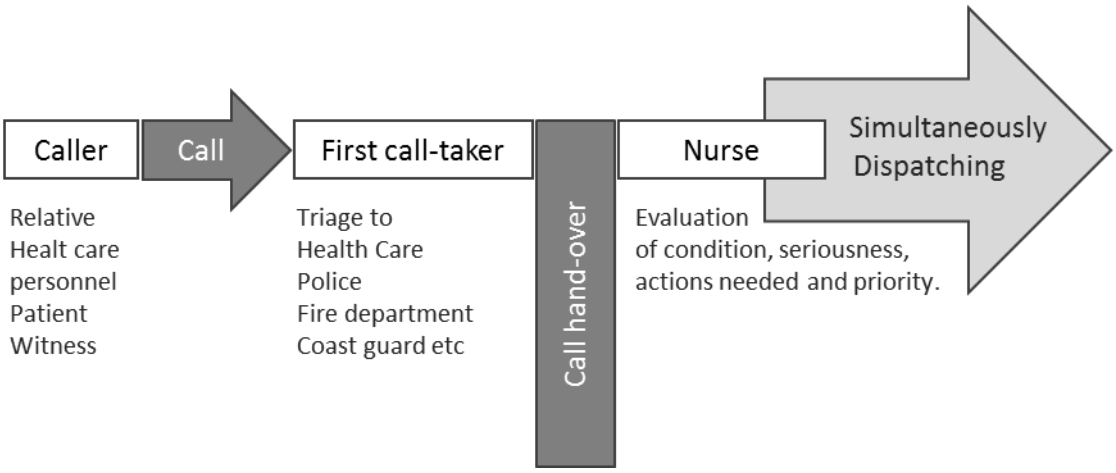

Figure 5 A flow-chart showing the process of the emergency call. Adapted from the manuscript for Study IV, submitted to Journal of Advanced Nursing, JAN, with permission.

The EMCC is often the first link to the health care system and treatment at hospital for stroke patients, Figure 5. The EMCC in Sweden assesses the calls to the national emergency number 112, from 14 centers spread over the country (150). The competence of the call-takers in EMCC was increased in Stockholm 2008, and all emergency calls concerning medical needs were connected to a registered nurse. A 112-call is answered by the first call-taker for triage between police, fire department, medical situations etc. The first call-taker controls the level of consciousness, breathing and general condition before collecting data of address, and connecting the call to a nurse. The nurse evaluates the condition, the urgency and need of action. The condition is given a summed up dispatch code with a priority attached. The ambulance can be dispatched simultaneously during the call or after ended call. For medical support the nurse uses a criterion based index, the Medical index of 30 chapters.

The Medical index is based on symptoms but with some exceptions e.g. stroke is found under the heading "Stroke", and there is no chapter of unilateral weakness, speech disturbances or fall. Thus, to get guidance for identification of stroke the nurse needs to first suspect stroke.

Dispatch Priority

The dispatch codes are predefined and attached with a relating priority according to the guidelines in the Medical index.

The priority levels used are:
Priority 1 - life threatening emergency medical conditions
Priority 2 - urgent but not life threatening medical conditions
Priority 3 - neither life threatening nor urgent medical conditions
Priority 4 - a non-urgent transport to health care services, for example, for a planned diagnostic procedure.

A Priority 1 Alarm calls for immediately response with use of lights and sirens and for a Priority 2 call the goal is to reach the patient within 30 minutes. A Priority 2 call can be interrupted if another Priority 1 alarm is received, while a second ambulance are sent to the original Priority 2 alarm causing an increased delay.

Suspected stroke within the 3-hour-time-window of thrombolytic treatment was a Priority 2 before start of *Study I* in 2008 according to the guidelines for EMCC in Stockholm. The guidelines of priority differed within the country.

Calling 112

Prior to the start of *Study I*, little was known about the number of stroke patients transported with ambulance, or delay in different parts of the Acute Stroke-Chain-of-Care in Sweden. The ambulance use varied in different reports; The European Stroke Organization (ESO) reported an EMS use of about 50% while studies from the US reported 48% (74), 60% in Italy (151) and 70-74% in France (116, 152).

The caller is normally a third person in emergency calls concerning stroke (73, 111, 119, 153-155) which complicates the identification since symptoms are presented from the caller's perspective (156, 157).

Photo: Annika Berglund

3.4.1.2 Ambulance

The ambulance provides advanced medical resources and high medical competence out of hospital which enables evaluation of the condition and first medical treatment at scene. In Stockholm, all ambulance units are manned by a registered nurse, often with a specialist competence for prehospital care. At scene, the ambulance personnel register consciousness, vital signs, and observations relevant for the condition e.g. glucose in stroke. The ambulance guidelines recommend a general approach of A-B-C-D-E control and for stroke the directed evaluation of stroke symptoms e.g. FAST, onset, and history of cardio-vascular diseases, diabetes and medication relevant for stroke (158). The FAST test was introduced in the EMCC, and the ambulance in Stockholm 2008 due to the start of *Study I*.

The ambulance units are dispatched from the EMCC with a priority code indicating the urgency. The dispatch priority is reevaluated when the ambulance personnel arrives at scene.

Prenotification

Prenotification to the receiving hospital by the ambulance is included in all Priority 1 alarms in Sweden. The prenotification alerts the personnel in the hospital and activates the in-hospital Stroke-Chain-of-Care.

3.4.2 In-hospital Stroke-Chain-of-Care

There are seven emergency hospitals in the Stockholm area, serving a population of approximately 2 million inhabitants (159). In Stockholm, no action to reduce door-to-needle time was adapted prior to *Study I* in this thesis, even though Helsinki already in 2000 had started actions for improvement (160). When *Study I* was initiated in 2008, all patients with stroke alarms (Priority 1) arrived to the emergency room for evaluation before CT scan. Thrombolytic treatment was started after arrival to stroke unit or intensive care unit, and there were no procedure for by-passing the emergency department or starting treatment directly after CT-scan at the time.

3.4.2.1 Emergency department

Photo: Fotogruppen at Södersjuhuset

In standard procedure the ambulance priority is re-evaluated when arriving to hospital. Patients with less urgent ambulance priority are re-evaluated and triaged in the emergency department while Priority 1 patients are brought to the emergency room for prompt evaluation and re-priority. In the emergency department the priority relates to the speed of action concerning e.g. CT-scan, monitoring vital functions, symptoms and need of treatment. The priority can be changed during the stay in the emergency department and is not valid during the rest of the in-hospital Stroke-Chain-of-Care in standard procedures.

3.4.2.2 Stroke unit

A stroke unit is an organized in-hospital care with a multidisciplinary team including stroke specialists, nurses and professionals within rehabilitation. The stroke team consists of personnel with interest of stroke, educated and trained in stroke care and working according to stroke guidelines. The patients and their relatives are involved in rehabilitation and information (8, 161). Stroke unit care has a positive effects of the outcome of stroke and is an important part of stroke treatment and care (8). In-hospital stroke unit-care is associated with better outcome, lower mortality, higher rate of independence and more patients living at home one year after stroke (8, 162). The benefits of stroke unit care have been reported to be persistent up to five or ten years after discharge regardless of age, sex or stroke severity and can be accessed by all stroke patients in contrast to thrombolysis which is available for only a few (8).

Prior to start of *Study I*, stroke units were available in all acute hospitals in Stockholm although not all stroke patients were treated in a stroke unit; many stroke patients were initially treated elsewhere in 2007. Of the stroke patients in Stockholm, 72% were cared for in a stroke unit sometimes during the hospital stay, and 41% of the stroke patients were initially treated in a non-stroke ward. (7)

3.5 RATIONALES FOR THE THESIS

In 2007, prior to the start of *Study I*, only 3% of the patients with ischemic stroke were treated with thrombolysis in Sweden, although thrombolytic treatment had been approved since 2003. The time was critical, time window for treatment was 3 hours from onset of stroke, but data of ambulance use, delay and the number of patients eligible for thrombolytic treatment were unknown at the time.

Reducing prehospital and in-hospital delay could result in more patients eligible for thrombolytic treatment as well as a better outcome after treatment. The door-to-needle time was about 60 minutes and could be reduced to increase the effect thrombolysis treatment.

An interventional study of a higher prehospital priority for acute stroke patients gave us an opportunity to study the effect in terms of early arrival to hospital and enabling thrombolytic treatment for stroke patients.

The numbers of patients treated in the stroke unit also showed need of improvements. Forty-one percent of the stroke patients were initially treated in a non-stroke unit and 28% were never treated in a stroke unit. A higher priority given by the EMS system could also affect early arrival and initial care in a stroke unit.

Since dispatch priority is associated with identification of stroke in the EMCC, the identification became an important aspect of the process.

A positive result of the priority intervention would benefit the acute stroke care in Stockholm and improve access to acute treatment with thrombolysis and stroke unit care.

4 AIMS

The overall aim of this thesis was to study identification of stroke by the EMS system and the effects of a higher priority from ambulance dispatch to arrival at stroke unit in acute stroke.

With low rates of thrombolytic treatment in Stockholm and stroke patients arriving late at stroke unit there was a need of improvements. As treatment of acute stroke is time dependent and delay was one of the main obstacles in acute treatment, an increased priority through the Acute Stroke-Chain-of-Care seemed rational, starting from the first link, the EMCC. To increase the priority, stroke needs to be identified already in the emergency call. To facilitate identification of stroke, the Face-Arm-Speech-Time test, FAST, was introduced in the EMCC and the ambulance. This led to the continued studies of identification of stroke, the use of FAST test and other aspects of identification during emergency calls.

4.1 THE SPECIFIC AIMS FOR THE STUDIES IN THIS THESIS

4.1.1 Study I

The aim was to evaluate if a higher priority in acute stroke could:
- increase the number of patients treated with thrombolysis
- increase the number of patients treated in a stroke unit
- reduce time to thrombolytic treatment
- reduce time to arrival at stroke unit
- have serious negative consequences in other high priority medical alarms

4.1.2 Study II

The aim was to evaluate the identification of stroke in the patients included as suspected stroke by the nurse at the EMCC and the ambulance concerning:
- identification of stroke with and without the FAST test compared to stroke diagnosis
- identification of stroke by the EMCC and the ambulance nurses, respectively

4.1.3 Study III

The aim was to explore how stroke was presented by the caller in emergency calls concerning patients with stroke:
- what symptoms are presented during emergency calls concerning patients with stroke
- are there differences of symptoms presented in emergency calls dispatched as stroke compared to the calls dispatched as non-stroke
- are FAST symptoms presented and do they relate to dispatch of stroke

4.1.4 Study IV

The aim was to explore obstacles and facilitators in identification of stroke during emergency calls, with focus on communication and interaction of the caller and the EMCC concerning patients with stroke presented by the caller to have fallen or in a lying position.

5 MATERIALS AND METHODS

Different design and methods have been used in the four studies depending on the aims, Table 2. A randomized clinical trial was performed to study the effect of a higher priority in acute stroke, comparing intervention to control (*Study I*). Identification of stroke in the prehospital setting was evaluated in two descriptive observational studies (*II-III*). In *Study II* correct identification of stroke and the use of FAST by nurses at EMCC and ambulance was evaluated in the patients included with suspected stroke in *Study I*. The identification of stroke was further evaluated in *Study III-IV* from the perspective of the emergency call. In *Study IV* a qualitative method was used to analyze the influence of communication and interaction in identification of stroke in a subgroup of the emergency calls in *Study III*. Table 2

5.1 STUDY DESIGNS

Study	Design	Inclusion criteria	Participants	Setting
Study I	Randomized Clinical Trial Quantitative Prospective	Suspected stroke Onset < 6 hours 18-85 years Previous ADL	942	Emergency call Ambulance Emergency Dep. Stroke unit
Study II	Descriptive Quantitative Prospective	Suspected stroke Onset < 6 hours 18-85 years Previous ADL	900	Emergency call Ambulance
Study III	Descriptive Quantitative Retrospective	Stroke diagnosis ICD I61, I63, I64 A call to 112 Consent	179	Emergency call
Study IV	Qualitative Interpretive Phenomenology Retrospective	Stroke diagnosis ICD I61, I63, I64 A call to 112 Consent	29	Emergency call

Table 2 An overview summarizing the study designs.

The Acute Stroke-Chain-of-Care	Study I	Study II	Study III	Study IV
	Priority	Identification	Identification	Identification
	Suspected stroke		Diagnosed stroke	
EMCC	X	X	X	X
Ambulance	X	X		
Emergency department	X			
Stroke unit	X			

Table 3 An overview of the settings, focus and conditions for the studies.

5.1.1 Study I

Study I, the Hyper Acute STroke Alarm study (HASTA) was a randomized clinical trial where the standard dispatch priority at the time, Priority 2 was compared to an increased priority, Priority 1, in suspected stroke within six hours. Patients randomized to standard priority served as controls and patients randomized to Priority 1 comprised the intervention group. The study start was preceded by education of stroke and the Face-Arm-Speech- Time test for all personnel at the EMCC and the ambulance to facilitate identification of stroke. In hospital, the emergency departments and the stroke units were informed and prepared through meetings and workshops. Stroke and TIA diagnosis were defined from the discharge diagnosis of the International Classification of Diseases codes, ICD, I61 hemorrhagic stroke, I63 ischemic stroke, I64 unspecific stroke and G45 Transient Ischemic Attack. Subarachnoid hemorrhage, ICD I60, was excluded from the study as symptoms and treatments differ from the rest of the stroke diagnoses.

5.1.1.1 Method

Patients with suspected stroke within six hours were identified from the emergency call and randomized by the nurse at the EMCC if the study criteria were fulfilled, Figure 6. The patients were randomized to intervention or control and ambulance was dispatched. If stroke was not identified from EMCC, the ambulance personnel could include the patient at scene. The effect of intervention was then missing from dispatching to arrival at scene as the patients were dispatched as standard; however, they were treated as a stroke alarm at hospital. Criteria for inclusion in the study was suspected stroke within 6 hours, age 18-85 years, and previous independence in activity in daily living (ADL). Patient in need of a Priority 1 of other reasons was excluded.

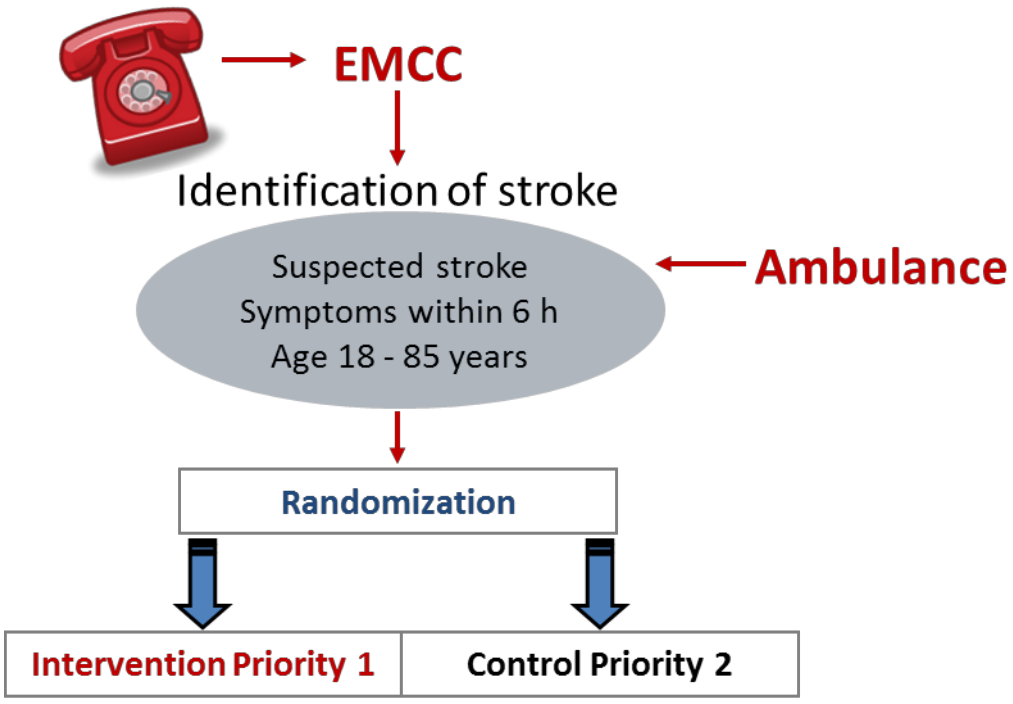

Figure 6 Schematic illustration of randomization procedure in *Study I*.

For the intervention group, the Priority 1 continued all the way to arrival at stroke unit. Priority 1 dispatch comprises immediate dispatch and response with flashing lights. The control group was given Priority 2, the standard priority for suspected stroke in Stockholm before the study. In Priority 2, the ambulance strives to arrive to the patient within 30 minutes from dispatch. However, traffic and long distances affects time consumption, and also a Priority 2 call can be interrupted in favor of another Priority 1 alarm resulting in further increased delay. According to standard procedure, the priority was re-evaluated at scene and if stroke within the 3-hour time limit for thrombolysis was suspected the priority to hospital was increased to Priority 1. This standard procedure with increased priority at scene was maintained in the control group as it was important that the study protocol did not result in any deterioration in medical care for the patients.

5.1.2 Study II

Study II was a quantitative, prospective and descriptive study concerning identification of stroke by the nurses at the EMCC and the ambulance. The importance of identification from EMCC arose in the planning of *Study I* where identification was a prerequisite for the priority intervention. In the study we needed to recognize patients with suspected stroke and onset within 6 hour. To increase and support the prehospital identification of stroke, the Face-Arm-Speech-Time test was introduced in the EMCC and the ambulance for the first time.

5.1.2.1 Method

The patients included in *Study I* were analyzed concerning identification of stroke. The identification of suspected stroke was performed by the nurse at the EMCC or in the ambulance. The use of FAST was optional in the emergency call as a time consuming procedure could be avoided if stroke already was suspected. One or more symptoms of FAST, facial weakness, arm weakness or speech disturbance, was defined as a positive FAST and should be responded to as suspected stroke. Positive FAST was reported in case report forms (CRF). The nurses also had an option to include patients by own suspicion of stroke. The FAST test and the nurses' suspicion of stroke were compared to stroke/TIA diagnosis at hospital discharge. The ambulance personnel completed full FAST for the patients as it was easier to evaluate at scene. In patients with negative FAST test the ambulance personnel could chose the option "own suspicion of stroke".

5.1.2.2 Participants and Setting for Study I-II

The studies were conducted in corporation between the EMCC (SOS Alarm AB), the ambulance companies and the seven emergency hospitals in the area of Stockholm, Sweden, with surroundings. For six month in 2008 from May to November, 942 patients were included through emergency calls to the EMCC or by ambulance personnel at scene.

In *Study II*, 900 of the 942 patients randomized in HASTA were included, Figure 7. In 42 patients the source of inclusion was missing, rendering comparison between EMCC and ambulance included patients impossible.

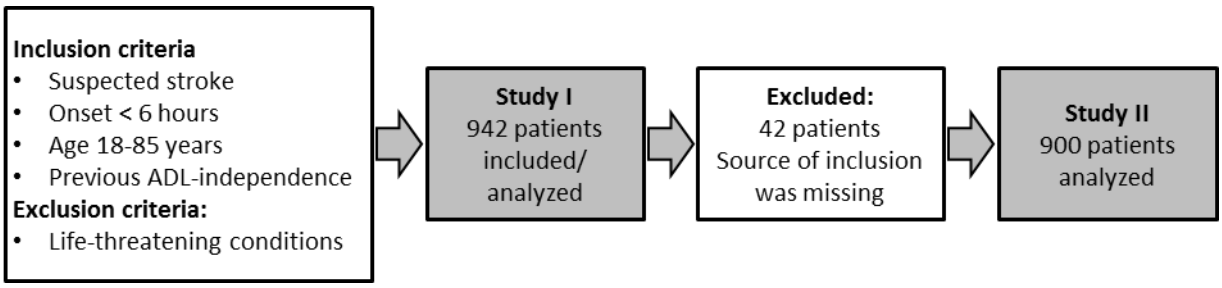

Figure 7 Flowchart of the patients included in *Study I* and *II*.

The data in *Study I* and *II* were analyzed for difference in delay and identification between men and women.

5.1.3 Study III

Study III was a quantitative, retrospective and descriptive study of identification of stroke in emergency calls concerning patients with stroke diagnosis at hospital discharge. The result of *Study II* showed that using FAST for identification of stroke during the emergency call was not enough and thus the problem of identification remained. The intention in *Study III* was to explore how stroke was expressed by the callers in emergency calls, and to learn how to improve stroke identification of emergency calls.

5.1.3.1 Method

Recorded emergency calls concerning patients with stroke were analyzed retrospectively with a data collecting tool for background data of the call and symptoms presented or revealed by questions in the call. The data collecting tool was developed by two researchers after listening to ten emergency calls of stroke, discussing and the finalizing the predefined symptoms when an agreement was reached. The tool included the first mentioned problem, FAST symptoms, and other presented symptoms. Lying position was added to fall in the data collecting tool as lying position may indicate an un-witnessed fall and inability to stand up due to stroke symptoms and therefore relevant. For the same reason problems to walk were added to leg weakness. All calls were analyzed by the same person (AB) and a data collecting tool was filled out for each emergency call.

The listed symptoms were compared between the emergency calls with dispatch code stroke and the emergency calls dispatched as non-stroke by the nurses during the emergency call. Sex difference in the presentation of symptoms were analyzed and presented.

5.1.3.2 Participants and Setting for Study III

Patients discharged with stroke diagnosis from a large teaching hospital in Stockholm (Södersjukhuset), the year 2011 during January-June were listed. Stroke was defined as ICD codes I61 (hemorrhagic stroke), I63 (ischemic stroke), and I64 (unspecific stroke). Of 643 stroke patients identified, 428 arrived to hospital with ambulance and were asked for consent to participate in the study, Figure 8. The consent to retrieve, listen to and transcribe the emergency calls was given by 245 patients or their relatives, orally and/or written.

Calls redirected from the medical guideline and the calls to the ambulance ordering line were excluded as the initial presentation of the problem was lost and/or influenced. After exclusion, 179 patients were included for analysis of the emergency calls. Figure 8

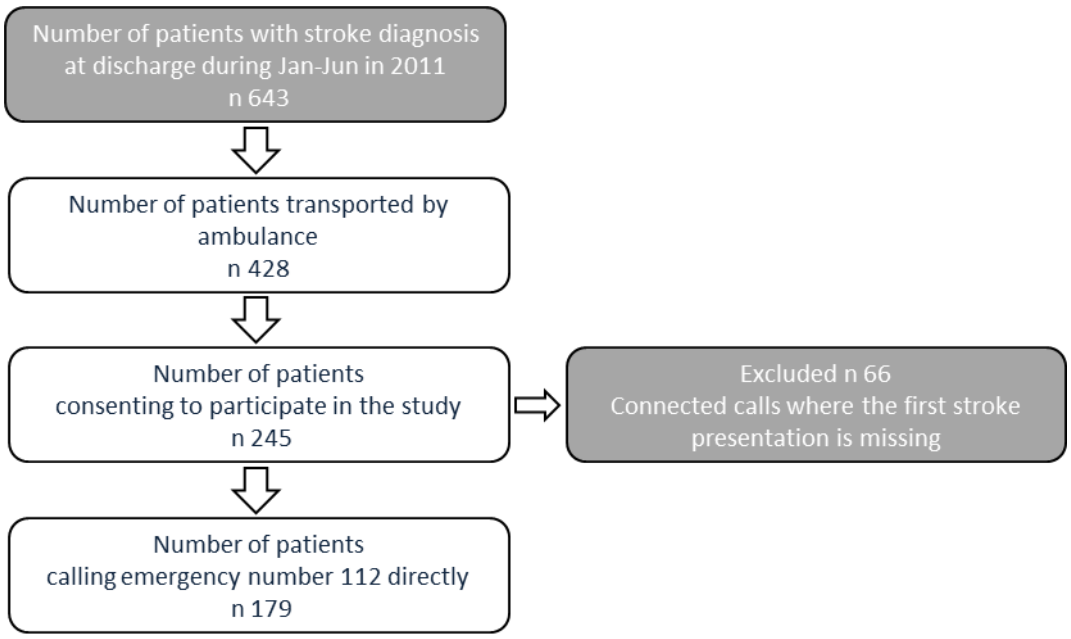

Figure 8 Overview of the inclusion in *Study III*. Adapted from Annika Berglund et al BMJ Open 2015, with permission from BMJ Open.

5.1.4 Study IV

Study IV was a qualitative study of obstacles and facilitators in identification of stroke during emergency calls. In this study, the communication and interaction between the participants related to identification of stroke was in focus. It was obvious when listening to the emergency calls in *Study III*, that there were decisive aspects other than symptoms affecting the identification of stroke. *Study III* showed that fall or being in a lying position was the dominating problem in the emergency calls dispatched as non-stroke; hence these calls were of special interest to investigate further for improving identification of stroke in the future and thus chosen for analysis in S*tudy IV*.

5.1.4.1 Method

Interpretative phenomenology, inspirited by Patricia Benner's approach, was used for the advantage of bringing several perspectives to the analysis (163). The preliminary interpretation of the material showed a complex picture of different factors' influence and the method enables the analysis to go beyond the surface level and to analyze the calls from a holistic perspective. In the analysis, the researchers used their knowledge in the interpretations of the individual's experiences to seek and to reveal deep insight and understanding. There is not one true interpretation but the meaning produced in the findings must be logical, plausible and reflect the reality of the participants. To uncover and explore the phenomena the researcher seeks to get a deeper and extended understanding of the text. To fill the gap of understanding the findings needs to be challenged with engaged reasoning,

extended or turned around in the analysis. The process of analysis proceeds in the writing where new insights were emerging. (163, 164) In addition we also searched for aspects related to gender and possible impacts of power.

5.1.4.2 Participants and Setting for Study IV

In *Study III*, 68 patients were reported to have fallen or being in a lying position and thereby available for inclusion in *Study IV*, Figure 9. First, three paradigm cases were chosen out of the 68 patients presented with fall or lying position. The paradigm cases were calls that drew attention due to different aggravating circumstances. The following patients were included randomly and in all 29 patients were analyzed when saturation was reached.

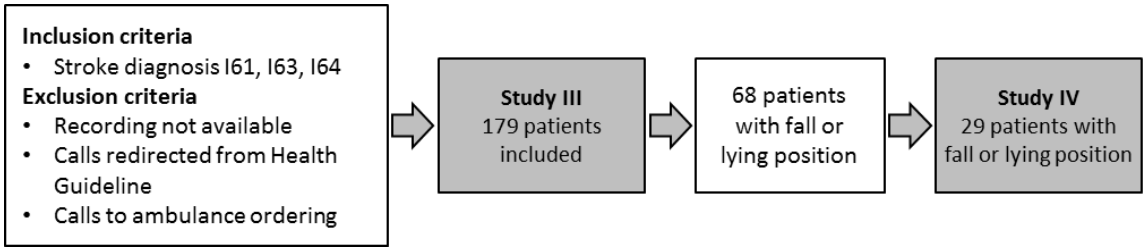

Figure 9 Overview of the patients included in *Study IV*.

5.2 METHODS OF ANALYSIS

5.2.1 Statistics

5.2.1.1 Study I-III

The statistical analysis was performed using SPSS Statistics version 18 in *Study I*, version 20 in *Study II* and version 22 in *Study III* (IBM Corporation, Route 100, Somer, New York 10589 USA).

Descriptive analysis of proportions and positive predictive value (PPV) was performed. The 95% confidence interval (CI) was calculated and when applicable compared to estimate significance (p-value) (165).

- Positive Predictive Value of the FAST test = the number of patients with *positive FAST test* and *stroke/TIA diagnosis*
- Negative Predictive Value of the FAST test = the number of patients with a *negative FAST test* and *no* stroke/TIA diagnosis
- Sensitivity of the FAST test = the number of patients *with* stroke/TIA diagnosis and a *positive FAST test*.
- Specificity of the FAST test = the number of patients *without* stroke/TIA diagnosis and a *negative FAST test*. Figure 10

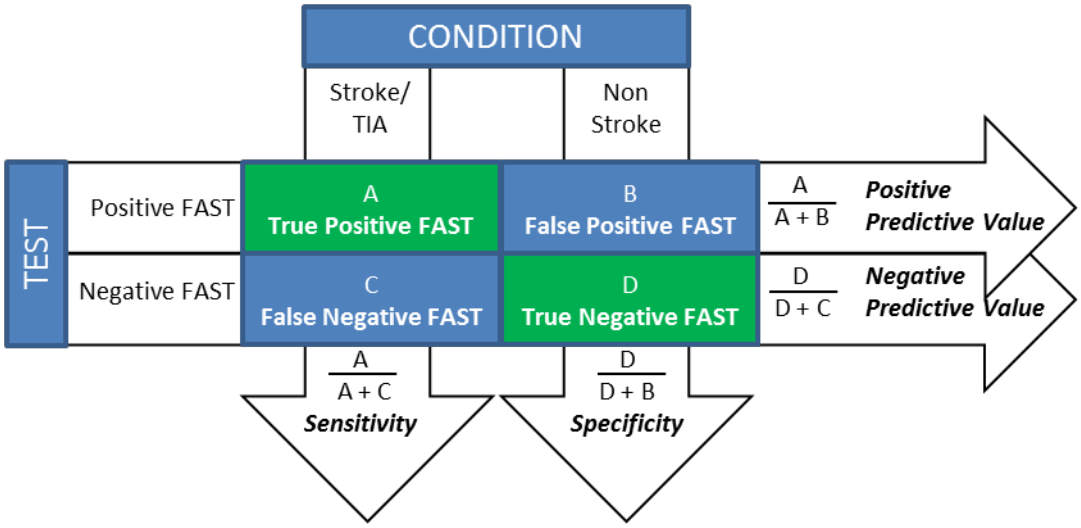

Figure 10 Shows the relation between specificity, sensitivity, PPV and NPV.

To compare groups for statistical significance, Chi 2 and Fischer Exact test were used for categorical data. The continuous data had non normal distribution and was calculated with Mann-Whitney U test for significance. For analysis of interaction concerning sex; logistic regression was used for categorical data, and analysis of variance for continuous data with reservation due to non-normal distribution of the data.

For calculations of delay in *Study I*, the data were separated for patients included from the EMCC and the ambulance units since the priority from dispatch were lost to the patients included at scene. The data of thrombolysis and stroke unit care were analyzed only from the patients relevant for the question, patients treated with thrombolysis and patients with stroke diagnosis.

5.2.2 Qualitative analysis

5.2.2.1 Study IV

Verbatim transcriptions of authentic emergency calls were analyzed. The authors participating in the analysis; Annika Berglund, Mia von Euler and Kristiina Heikkilä have different backgrounds but all have an extensive experience of working with stroke patients. The dispatch code for each patient was blinded in the transcriptions in order for the researchers to be open to the material, without pre-understanding of the nurses' evaluation, as it might have affected the analysis. At first, three emergency calls were chosen as paradigm cases, these calls were notable in the perspective of obstacles in different ways concerning identification of stroke. From the paradigm cases aspects of the situation, person, information and the structure of the call appeared. Details of findings and comments were placed under the aspects to get a better picture. Texts were read and analyzed in an ongoing process, commenting, moving back and forth, from the details to the larger perspectives to answers questions such as "what is this about", and "does this ease identification or hinder it". When we reached saturation and no more new findings appeared in the calls the dispatch codes were uncovered. One of the authors first checked that both identified stroke and non-

identified stroke were analyzed. The findings could now be re-evaluated in relation to identification and the effect of facilitators and obstacles were viewed in a new perspective. Details were abstracted and concluded in themes. Aspects appeared over the process but was also reconsidered and changed along the process, and new aspects emerged in the writing process. The findings were analyzed and processed in dialogue between the three authors, AB, MvE, KH, until all agreed on the interpretation to be the most reasonable.

5.3 ETHICAL CONSIDERATIONS

The Regional Ethical Review Board in Stockholm approved all four studies: *Study I-II* EPN: 2008/383-31/4, *Study III-IV* EPN: 2010/703-31/2 and 13-2010, and additional approval 2012/2055-32. The World Medical Associations' declaration of Helsinki with ethical principles for medical research involving humans (166) has been applied in all studies with the exception of consent in *Study I-II*.

Ethical considerations in the prehospital and acute phase of stroke are dilemmas. To strive for evidence based care and treatments require research and research demands ethics and moral. Not to do research is a poor option, and often the standard procedures lack evidence as well without being evaluated regarding safety, efficacy or quality. Consent from the eligible study participants is one of the foundations in research ethics however in different conditions and situations it is neither possible nor ethical to ask for consent. In acute stroke, the consequences of stroke may affect and hinder the patients' ability to process information and leave consent. The situation in the acute phase pre-hospital and in the emergency department is not an ideal situation to inform and ask for consent to participation in a study. The patient does not have the time to process the information and might experience pressure to consent in order to get cared for.

However, to include the patients able to consent will withdraw many of the stroke patients from research resulting in less knowledge of these patients which in stroke will be patients with severe stroke, aphasia and cognitive impairments as well as the patients who die. The patient groups that are withdrawn from research risk being excluded from implementations of new treatments and care to follow. The study result will be affected as well as the evidence based care and treatments available for those patients.

5.3.1 Study I-II

Study I-II was approved by the Regional Ethics Board without need of consent from the patients or legally authorized representative. To upgrade priority of dispatch in a randomized clinical trial was considered to be a beneficial strategy to find evidence and support for new guidelines prior to implementation. The upgraded priority could have been implemented without evidence of favorable effects or risks for the patient or the health care organisation. Testing and evaluating a higher priority in the controlled setting of a study provides possibility to evaluate both positive and negative effects, prepare the care givers and test the Stroke-Chain-of-Care stepwise.

The study would give an estimation of the volumes to expect in an implementation of Priority 1 for suspected stroke within 6 hours. For the control group, standard procedures were preceded.

The identification of stroke from the EMCC was unknown as well as time of onset at the time. The intervention was not considered to imply a risk for the patients but a possibility to analyze the effect for evidence based care. The study was an opportunity to evaluate any negative effects of other patients with life-threatening conditions, Priority 1 alarms, as resources are limited. Reports of severe incidents were continuously supervised during the study. The fact that the patient did not consent to participate was criticized as well as the randomization between a higher priority and standard procedure. The circumstances of urgency and stress at the emergency call and inclusion did not offer an acceptable situation for consent. To ask for consent in arrears would mean loss of results for a large group of stroke patients which probably would be the patients with most benefits of decreased delay and thrombolytic treatment. In all research the potential benefits must be weighed against the risk and in this particular study, *Study I* and *II*, the benefits were estimated greater than the risks.

The intervention study of higher priority in acute stroke was prematurely terminated due to media attention with consequences among the public, risking the safety for the patients.

5.3.2 Study III-IV

For *Study III* and *IV* consent was given by the patients or relatives for the patients of whom the calls were made. All patients/relatives received written information; most of them by letter but a small group of patients were included during the hospital stay and received oral information as well. The callers have not been able to be asked for consent though as they are not able to identify in the call.

6 RESULTS

6.1 STUDY I-II

In all, 942 patients with suspected stroke were included in the *Study I*, 488 patients in the intervention group and 454 patients in the control group and 53% were discharged with stroke or TIA diagnosis. Most patients were included from the EMCC, 71% and the ambulance personnel included another 25% of the patients at scene not identified by the EMCC. The source of inclusion was missing in 4% of the patients. The median age was 71 years (range, 22-93 years) and 56% of the patients were men.

6.1.1 Sex and gender

There were slightly more men included in *Study I*, 56% and the median age for men was 70 years while the women were 73 years old. The results showed no sex significant differences concerning delay in the Stroke-Chain-of-Care, prehospital or in-hospital, or in thrombolysis treatment.

Concerning identification, speech disturbance was the only significant difference found among women and men. The ambulance personnel reported speech disturbance more frequently in women (56%) with stroke/TIA diagnosis compared to men (42%, $p < 0.001$). There were no other sex differences regarding identification in *Study II*.

6.1.2 Delay

The higher priority showed to be beneficial through the whole Stroke-Chain-of-Care when the patient was identified from the EMCC and the ambulance was dispatched with Priority 1. There was no difference in delay between intervention- or control group of the patients included from the ambulance personnel at scene. The total delay in the Stroke-Chain-of-Care was 26 minutes faster ($p < 0.001$) for the patients in the intervention group compared to the control group, from emergency call to admission at stroke unit, for the patients included from the EMCC. There were no reports of serious adverse events due to competing Priority 1 alarms during the study period.

6.1.2.1 Prehospital

The prehospital delay was 13 minutes shorter ($p < 0.001$) from emergency call to arrival at hospital for the EMCC included patients with higher priority.

The EMCC delay, time from the emergency call to dispatching was three minutes faster for the intervention group ($p < 0.001$) and the ambulance arrived to the patient six minutes faster from dispatch for the intervention group ($p < 0.001$).

Time spent at scene with the patient showed no difference between the intervention- and control group. The ambulance personnel spent 13-14 minutes at scene in the EMCC included patients.

6.1.2.2 In-hospital

In-hospital, the EMCC included intervention group was admitted at stroke unit 20 minutes faster than the control group (p 0.010). The door-to-needle for thrombolytic treatment was 58 and 57 minutes in intervention and control group respectively and showed no significant difference.

6.1.2.3 Thrombolytic treatment and stroke unit care

Most of the patients in the study, 84%, arrived to hospital within the 3-hour time window for thrombolytic treatment with no significant difference between intervention and control groups. Still, twice as many patients with ischemic stroke were treated with thrombolysis in the intervention group, 35% compared to 17% (p <0.001) in the control group.

However there was a significant difference in the patients admitted to stroke unit within the 3-hour time window for thrombolytic treatment. Of the stroke/TIA patients in the intervention group, 61% were admitted to stroke unit within three hours compared to 46% (p 0.008) of the control group. Of the patient with a final stroke/TIA diagnosis, 71% (n 354) was admitted to a stroke unit and about half of them arrived to stroke unit within three hours.

6.1.3 Identification of stroke

The continued analysis of identification in *Study II,* was based on 900 patients as 42 patients were excluded due to unknown source of inclusion. In *Study II,* the identification of stroke was compared between EMCC and ambulance. Of the 900 patients, EMCC included 667 (74%) patients during the emergency call and the ambulance personnel included another 233 (26%) patients at scene, not identified in the EMCC.

Except from stroke/TIA diagnosis (n 472, 52%), 223 (25%) patients had a mix of medical diagnosis at hospital discharge, 166 (18 %) had neurological diagnosis, and 39 (4%) patients were not diagnosed. The patients without diagnosis were patient who were left at home by the ambulance or patients leaving the emergency department before seeing a physician.

6.1.3.1 Emergency Medical Communication Center

Of the 667 patients included through the emergency call, 337 (51%) patients were discharged with stroke/TIA diagnosis.

FAST was reported positive in 494 (74%) of the 667 patients included as suspected stroke from EMCC. The positive predictive value of FAST was 56 %, i.e. of the 494 patients with positive FAST, 279 patients were diagnosed as stroke/TIA. Of the 337 patients with stroke/TIA diagnosis, positive FAST was reported in 279 (83%) patients, and it is remarkable that of the 330 patients with non-stroke diagnosis FAST was positive in 215 (65%) patients. There were also 58 (17%) stroke/TIA patients with no affirmative FAST reported.

The study population was 900 patients included by the EMCC or the ambulance although 233 patients were only evaluated by the ambulance. The stroke /TIA patients missed by EMCC were counted for as not identified in Table 4.

EMCC evaluation	Total n 900	Stroke/TIA n 472	Non stroke n 428	P-value
FAST Positive	494 (55%)	279 (59%)	215 (50%)	<0.001
FAST Non-positive	173 (19%)	58 (12%)	115 (27%)	<0.001
Facial weakness, FAST	131 (14%)	82 (17%)	49 (11%)	0.014
Arm weakness, FAST	205 (23%)	135 (29%)	70 (16%)	<0.001
Speech disturbance, FAST	367 (41%)	208 (44%)	159 (37%)	0.036
Nurse suspicion of stroke	302 (34%)	130 (28%)	172 (40%)	<0.001

Table 4 An overview of FAST noted from EMCC, counted from the total of 900 patients included although the EMCC only evaluated 667 patients as 233 was identified from the ambulance. Adapted from Berglund et al. 2014, with permission from Karger Publishers.

Speech disturbance was the most common symptom in the FAST test even of the non-stroke patients. The nurses alternatively noted own suspicion of stroke, Table 4.

6.1.3.2 The ambulance

The ambulance staff evaluated all 900 patients, Table 5. Of the 233 patients included by the ambulance, 135 (58%) patients were discharged with stroke/TIA diagnosis. The 233 patients included at scene were not identified during the emergency call but stroke was suspected by the ambulance personnel.

FAST was reported positive in 148 (64%) of the 233 patients included as suspected stroke by the ambulance personnel. Of the patients with positive FAST, 108 (73%) patients were diagnosed as stroke/TIA, PPV 73%. Of the patients with stroke/TIA diagnosis (135), positive FAST was reported in 108 (80%) patients and notable is that FAST was positive in 40 (41%) of the 98 patients with non-stroke diagnosis. There were also 27 (20%) of the 135 stroke/TIA patients with no FAST reported.

Ambulance evaluation	Total n 900	Stroke/TIA n 472	Non stroke n 428	P-value
FAST Positive	408 (45%)	301 (64%)	107 (25%)	<0.001
FAST Non-positive	492 (55%)	171 (36%)	321 (75%)	<0.001
Facial weakness, FAST	227 (25%)	180 (38%)	47 (11%)	<0.001
Arm weakness, FAST	244 (27%)	197 (42%)	47 (11%)	<0.001
Speech disturbance, FAST	306 (34%)	225 (48%)	81 (19%)	<0.001
Nurse suspicion of stroke	399 (44%)	269 (57%)	130 (30%)	<0.001

Table 5 The ambulance evaluation of FAST, the ambulance personnel evaluated all 900 patients included. Adapted from Berglund et al. 2014, with permission from Karger Publishers.

Speech disturbance was the most common FAST symptom noted also from the ambulance with arm- and facial weakness close in numbers, Table 5.

6.2 STUDY III-IV

From the results of *Study I*, it was clear that a higher dispatch priority from the EMCC decreased the delay to hospital thus increasing the importance of early identification. However, one third of the stroke/TIA patients were identified first by the ambulance personnel at scene in *Study II,* which affects the delay and the possibility for emergency treatment. To learn more of how to improve early identification of stroke, emergency calls of 179 patients with stroke diagnosis were analyzed in *Study III* concerning symptoms expressed by the caller.

6.2.1 Sex and gender

The median age differed among the calls about women and men, 83 years and 74 years, respectively in the 179 emergency calls analyzed. The symptoms were mostly similarly presented in calls concerning women and men with the exception of altered mental status. Altered mental status was more frequently presented in calls concerning women, 36%, than in men, 18% (p 0.012). For male patients, the caller was more often a relative, 53%, and less often a health care provider, 10 %, compared to female patients where the caller was a relative in 44% and a health care provider in 36%.

6.2.2 Emergency calls of stroke

Of the 179 analyzed emergency calls concerning stroke, 48% of the patients were men. The callers were most often a relative, 49%, a health care provider in 23%, and other persons in 16% of the calls. The patient was the caller in 11% of the calls.

6.2.2.1 Identification of stroke

Sixty-four percent of the emergency calls of stroke were dispatched as stroke while 36% of calls were dispatched with dispatch codes other than stroke. The most common non-stroke dispatch code was “Uncertain data/seriously ill patient” which was about half (n 34, 52%) of the non-stroke dispatches. “Unconsciousness” was the second most common non-stroke dispatch code of which all had Priority 1.

The predefined dispatch codes in the calls were:

- Uncertain data/seriously ill patient (n 34)
- Unconsciousness (n 10)
- Extremity (n 6)
- Seizure (n 3)
- Headache/dizziness (n 3)
- Diabetes (n 2)
- Breathing difficulties/problem (n 2)
- Chest pain/heart disease (n 2)
- Urgent need of care (n 1)
- Suspected suicide/psychiatry (n 1)
- Abdominal/urinary tract (n 1)

6.2.2.2 Dispatch priority

The ambulance was dispatched with Priority 1 in 64% of the calls, Priority 2 in 31% and Priority 3 in 5% of the calls. The emergency calls coded stroke were more often dispatched with Priority 1, 70%, compared to the calls dispatched as non-stroke, 54%.

Onset of symptoms within 6 hours were reported in almost half of the calls (46%) which indicated a Priority 1 dispatch according to the current guideline of stroke. Of the calls with dispatch code Stroke, onset within six hour was presented in 54% compared to 32% of the calls dispatched as non-stroke, Table 6 and Table 7.

Dispatch code Stroke n 114	**Symptom onset < 6 hours** (n)	**Symptom onset > 6 hour** (n)	**Symptom onset unknown** (n)	**Total** (n)
Priority 1	59	9	12	80
Priority 2	1	17	13	31
Priority 3	1	1	1	3
Total	61	27	26	114

Table 6 Time of symptom onset related to dispatch priority for the calls dispatched as stroke. Adapted from Berglund et al. 2015, with permission from BMJ Open.

Dispatch code Non-Stroke n 65	**Symptom onset < 6 hours** (n)	**Symptom onset > 6 hour** (n)	**Symptom onset unknown** (n)	**Total** (n)
Priority 1	14	6	15	35
Priority 2	7	9	8	24
Priority 3	0	5	1	6
Total	21	20	24	65

Table 7 Time of symptom onset related to dispatch priority for the calls dispatched as non-stroke. Adapted from Berglund et al. 2015, with permission from BMJ Open.

Thrombolytic treatment was given to 24% of the patient calls with dispatch code stroke compared to 8% of the patient calls dispatched as a non-stroke.

6.2.2.3 Symptoms presented in emergency calls

Speech disturbance, 54%, fall or lying position, 38%, and altered mental status, 27%, were the most frequently presented symptoms in the 179 emergency calls concerning stroke, Table 8.

In 35 % of the calls, symptoms of FAST, Face-Arm-Speech, were presented in the initial part of the call, and in 64% sometime during the call. FAST was presented spontaneously in 90% and was rarely asked for. Suspicion of stroke was presented by the caller in every other call of which 76% was dispatched as stroke.

The presentation of symptom differed significantly between the calls dispatched as stroke and the calls dispatched as non-stroke. FAST symptoms were presented in 80% of the calls dispatched as stroke with speech disturbance standing out, in 68% of the calls. Facial- and

arm weakness were less presented, in 25 and 21% of the calls respectively. While the calls dispatched as non-stroke showed positive FAST in 35% of the calls, mostly speech disturbance, 31%,and facial- and arm weakness in 2% and 5% respectively. Table 8

Apart from FAST, unilateral symptoms and numbness/sensory loss were significantly more often presented in the calls coded stroke. Altered mental status, a non-traditional stroke symptom, was commonly presented in all stroke calls, 27% with similar distribution in the calls coded stroke and in the calls not coded stroke. Table 8

In the stroke calls not coded stroke, fall or being in a lying position was clearly dominant and presented in 66% of the calls compared to 22% of the calls coded stroke (p <0.001), Table 8. Except from speech disturbances the numbers of stroke specific symptoms were low in the calls dispatched as non-stroke, Table 8. Furthermore, the caller mentioned suspicion of stroke in 32% of the calls dispatched as non-stroke, although more often in the calls dispatched as stroke, 58%.

	Total	**CI (%)**	**Dispatch Code "Stroke"** (n 114)	**CI (%)**	**Other Dispatch Code** (n 65)	**CI (%)**	**Fischer's Exact test P value**
Facial weakness	16% (29)	11-22	25% (28)	17-32	2% (1)	2-4	<0.001
Arm weakness	15% (27)	10-20	21% (24)	14-28	5% (3)	1-10	0.002
Speech disturbance	54% (97)	47-62	68% (77)	59-76	31% (20)	20-42	<0.001
Leg weakness/trouble to walk	20% (35)	14-25	24% (27)	16-32	12% (8)	4-20	ns*
Unilateral symptoms	16% (29)	11-22	23% (26)	15-30	5% (3)	1-10	0.001
Numbness/sensory loss	9% (16)	5-13	13% (15)	7-19	2% (1)	0-4	0.012
Hand weakness	7% (12)	3-10	10% (11)	4-15	2% (1)	0-4	ns*
Impaired vision	3% (5)	0-5	2% (2)	0-4	5% (3)	0-10	ns*
Unsteadiness/poor balance	6% (11)	3-10	8% (9)	3-13	3% (2)	0-7	ns*
Dizziness	8% (14)	4-12	9% (10)	4-14	6% (4)	0-12	ns*
Nausea/vomiting	8% (14)	4-12	8% (9)	3-13	8% (5)	1-14	1.000
Headache	9% (16)	5-13	10% (11)	4-15	8% (5)	1-14	ns*
Altered mental status	27% (49)	21-34	29% (33)	21-37	25% (16)	14-35	ns*
Fall/lying position	38% (68)	31-45	22% (25)	14-30	66% (43)	55-78	<0.001

Table 8 Symptoms presented in 179 emergency calls concerning stroke. Adapted from Berglund A, et al. 2015 with permission from BMJ Open.

* = non significant

As fall or lying position were the most dominating problem in the calls of stroke not recognized by the dispatching nurse, those calls were of particular interest to study more closely.

6.2.3 Factors facilitating and hampering identification

To learn more about how to improve identification of stroke in emergency calls we focused on the calls with fall or lying position presented, the dominating problem presented in the calls not dispatched as stroke.

In the last study, *Study IV*, the emergency calls were analyzed concerning obstacles and facilitators in the identification of stroke in aspects of communication and interaction.

Of the 68 calls presenting fall or lying position, 29 calls were finally analyzed, a mix of calls dispatched as stroke and calls dispatched as non-stroke. The first analysis of the three paradigm cases revealed factors of situation, person and information to influence the identification. An early noticed potential hinder was the call hand-over between the first call-taker and nurse as the communication with the caller was interrupted and the call was restarted. The restart of the call sometimes caused confusion from both caller and nurse and the first presentation of the problem were lost to the nurse.

Six themes emerged during the process of analysis; the patients' ability to express themselves, the callers' knowledge of the patient and stroke, call hand-over, the call-takers' and nurses' authority, nurses' coaching strategy and nurses' skills, Figure 11. When the dispatch codes were un-blinded, the effect of the obstacles and facilitators were matched in the 13 calls identified as stroke and 16 calls dispatched as non-stroke. All themes presented both obstacles and facilitators depending on if the themes were present in a negative or positive form.

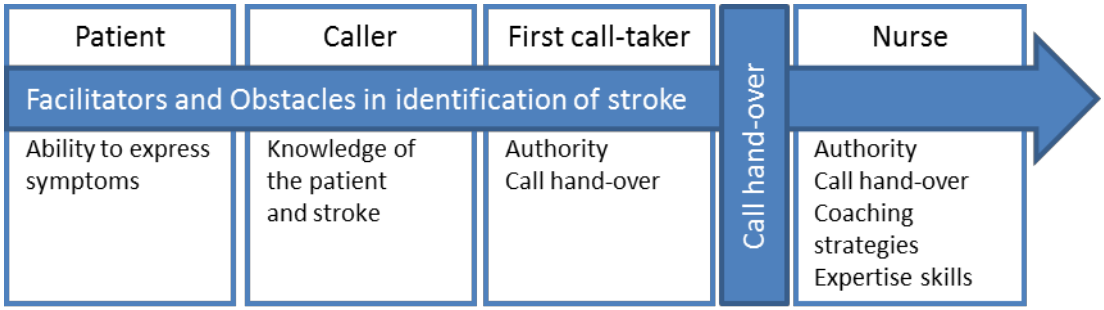

Figure 11 The themes from *Study IV*, found to facilitate or hamper nurses' identification of stroke in the emergency calls.

6.2.3.1 The patients' abilities to express themselves

The information presented in the calls was affected by the patients' ability to express themselves regardless of who made the call. In stroke, the patient's ability to communicate and perceive the symptoms can be affected by speech disturbances or cognitive impairment which affects their contribution of information to the caller. When patients could perceive symptoms of stroke and were able to express them themselves, the symptoms could be specified and the possibilities to identify stroke increased.

6.2.3.2 The callers' knowledge of the patient and stroke

The callers' knowledge was a composition of knowledge of the patient's previous function, symptom onset, and knowledge of stroke. When the caller was familiar with the patient's previous condition, changes in the condition were easier to address to a new event. Presence at stroke onset provided the caller with valuable information for describing development and dysfunction of stroke. When the patient was found, unable to communicate the symptoms, the

caller was left with the obvious findings as a lying position and the presentation in the emergency call risked being unspecific. The caller's knowledge of stroke enabled recognition and presentations of stroke specific symptoms or mentioning of suspicion of stroke which facilitated the identification.

6.2.3.3 The call hand-over

During the call, the first call-taker connects the caller to the nurse which caused negative interruption in the caller's presentation. The initial presentation was often not repeated when the nurse was connected, the call was restarted with both information and time lost.

6.2.3.4 The first call-takers' and nurses' authority

The authority of the first call-takers and the nurses is an indisputable fact which comes with the responsibility of the professions. The medical competence and the role in evaluating and allocating resources give the first call-takers and the nurses an inevitable authority. The authority affected the communication and the interaction between the participants both positively and negatively depending on how the authority was used. Early confirmation of the caller's need of help, support in the call, and good interaction affected the identification positively. In negative use, the authority was found to reduce the callers' contribution of information. Less information was revealed to nurses who did not make an effort to interpret the layman's expressions resulting in.

6.2.3.5 Nurses' coaching strategy

The nurses' coaching strategy was obvious when missing and no new information, valuable for the identification, was revealed. The interaction failed, the nurse was passive and the caller was left without guiding questions. A coaching strategy supported the caller through interaction and answers of question to rule out important issues and steer towards more specific information of the condition. With a coaching strategy, the nurse seemed to have a guide to stepwise lead the caller for relevant information, even when the first problem was vague the nurse seemed to have a strategy forward.

6.2.3.6 Nurses' expertise skills

The only factor found to be decisive in identification of stroke in difficult calls was the nurses' expertise skills. Nurses with expertise skills showed an ability to listen, hear, interpret and analyze the information, situation and the persons important for evaluation. In expertise skills, the nurse's clinical experience was added to the medical knowledge and used for evaluation and identification and also make decisions based on hers/his expertise skills. All calls had a mix of obstacles and facilitators concerning the situation, the persons involved, and the information. However, the nurses' skills were the only factor found to make a difference between identification of stroke or not. There were calls with good prospective that were not identified as stroke and there were calls with poor prospective where stroke were identified.

The dispatch code could not be predicted by the call and there were no clear similarity in the findings of the calls dispatched as stroke or the calls dispatched as non-stroke concerning obstacles and facilitators. Sometimes, the only obvious difference was that in one call the nurse perceived and interpreted the callers' presentation as stroke symptoms while in similar calls, another nurse did not.

7 DISCUSSION

The focus of this thesis is priority and identification of patients with suspected stroke in the Acute Stroke-Chain-of-Care, (Figure 12). Thrombolytic treatment of acute stroke is extremely time dependent and needs to be initiated early after stroke onset to be effective (3, 47, 48). Delay between stroke onset and arrival to hospital is the major reason for low thrombolytic rates, with patients' delay of seeking help presented as the major obstacle of treatment (70, 167). However, the patients' delay is not included in the studies in this thesis, only the delays directly dependent on health care, and the Stroke-Chain-of-Care prehospital and in-hospital, Figure 12.

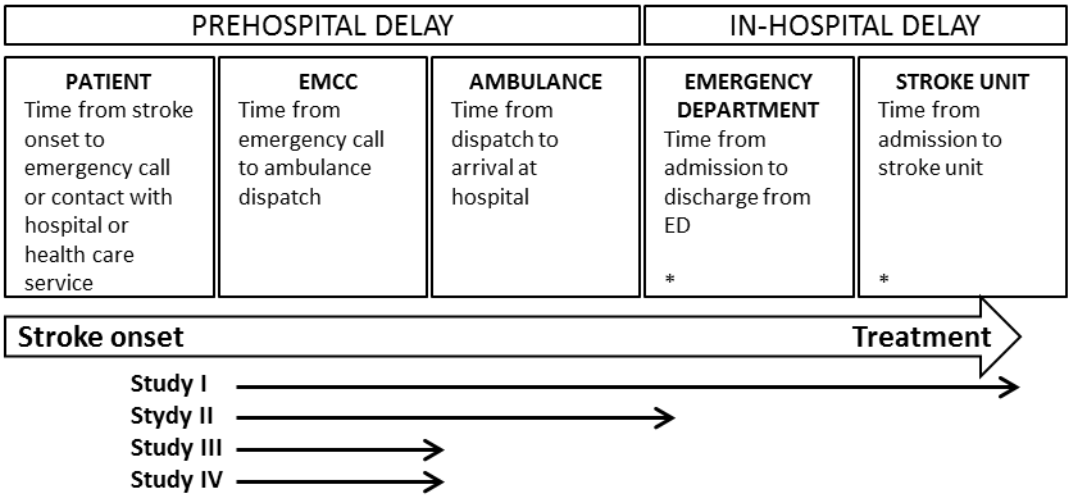

Figure 12 An overview of the prehospital and in-hospital delay in the Acute Stroke-Chain-of-Care and the studies disposition.* CT-scan/MRI and thrombolytic treatment may take place from the ED or the stroke unit.

In *Study I*, the benefits of higher priority was obvious and thus emphasized the importance of early identification of stroke. Prehospital identification of stroke was evaluated in *Study II-IV* with focus on the nurses' identification, symptoms presented, and communication and interactions in emergency calls concerning stroke.

7.1 PREHOSPITAL IDENTIFICATION OF STROKE

Identification of stroke by the dispatchers has previously been shown to shorten the delay to hospital (168). In *Study II*, only 52% of the patients included with suspected stroke were diagnosed as stroke/TIA. The result of using FAST was not optimal, showing a PPV of 56% in the EMCC, and patients with actual stroke/TIA were missed. This raises the question whether FAST is a test with limited usefulness; if FAST misses true stroke while indicating patients with other diagnoses as stroke, if FAST symptoms are not recognized in the patients by those making the emergency calls, or if FAST symptoms are presented to but not recognized at the EMCC. *Study III* revealed 90% of the FAST symptoms to be spontaneously presented in the emergency calls. FAST symptoms were rarely asked for, thus it became obvious that the nurse at the EMCC needs to be prompted to suspect stroke. When symptoms of FAST were lacking or not observed, less stroke patients were dispatched as stroke. By

studying the presented symptoms we found fall/lying position to dominate in the emergency calls dispatched as non-stroke and traditional stroke symptoms were less presented. The results of *Study IV* further demonstrate the difficulties in identifying stroke in emergency calls and prove the importance of the patient's and caller's ability to express symptoms, their knowledge of stroke, and the nurses' skills in identification of stroke.

7.1.1 Identification of stroke by the EMCC dispatchers

Only half of the patients with suspected stroke were correctly identified from the EMCC in *Study II*, which is within the range of previous reported stroke identification by dispatchers between 31 - 63% (111, 114-118, 154, 169, 170) but still in need of improvements.

Stroke patients risk delay of treatment or running out of time for thrombolytic treatment when stroke is not identified from the EMCC. The delay was shown to decrease significantly when dispatchers identify stroke in *Study III* as also in previous studies (117, 154) however, almost a third of the patients with stroke/TIA diagnosis in *Study II* were not recognized by the EMCC but first by the ambulance personnel. Likewise, a previous study found that 20% of the patients with stroke onset within three hour were not identified from the EMCC (116).

Training and protocols have been shown successful in improving the identification rate from the EMCC. Several studies report adjusted routines, implemented stroke protocols and training to successively improve identification and diminish delays (109, 114, 118, 169, 171-178). A study in UK reported an increased identification rate from 63 to 80%, after implementing a training package in identification for the EMCC dispatchers (169).

7.1.1.1 FAST

In Stockholm, the FAST test was used for the first time in a prehospital setting in *Study I* and *II*. *Study II* showed positive FAST in 83% of the patients with stroke/TIA diagnosis included from the EMCC but FAST was also positive in 65% of the patients with suspected stroke but with non-stroke diagnosis. Symptoms of FAST were not always recognized by the EMCC which was obvious from the patients missed by the EMCC and included by the ambulance. In this group, FAST was positive in 80% of the patients with stroke/TIA. Even though FAST symptoms are common in stroke (139, 179), FAST symptoms might not be recognized by the caller and not presented in the emergency call. This is supported by a British study showing that although FAST symptoms was noted in medical records in 27%, FAST was rarely, in less than 5%, mentioned in the first presentation in the emergency call (154).

Speech disturbances were the dominating FAST symptom noted by the EMCC nurses while arm and facial weakness were much less noted which could reflect verbal response to be easier recognized in contact with the patient. In-hospital, FAST showed arm weakness to be the most frequent symptom in patients with stroke/TIA, in a previous study, supporting that speech disturbance might not be the most common symptom but a more notable symptom (179). The function of arm and the face might be less obvious to recognize for a layman especially if the patient have fallen or are in a lying position.

Although the use of FAST or similar tests may not solve the problem of identifying stroke in the emergency call, the use of FAST can improve identification of stroke. Using FAST might serve as a reminder of stroke, and a trigger of stroke suspicion. A large study showed a higher rate of stroke identification, 56%, in centers using CPSS, a test similar to FAST, compared to centers not using CPSS, 34% (118).

7.1.2 Identification of stroke by the ambulance personnel

As expected, the identification rate was higher in the ambulance units compared to the EMCC, reflecting the advantage of face-to-face evaluation. However, there is a great variation in correct identification between 40-79% by ambulance personnel reported in previous studies (113, 120, 130, 138, 180, 181). Identification of stroke by the ambulance personnel is important as it is associated to shorter in-hospital delay in previous studies (68, 120).

7.1.2.1 FAST

In *Study II*, positive FAST was more frequently reported in stroke/TIA-patients evaluated by the ambulance (PPV 73% of patients included by ambulance) compared to FAST reported by the EMCC (PPV 56% of patients included by EMCC). The CPSS (similar to FAST) was previously reported to have a sensitivity of 79% but a low specificity, 23% (113). Similar results were reported in a study of both FAST and CPSS with a sensitivity of 95% and a specificity of 33% (142). In contrast, the dispatchers using a Medical Priority Dispatching protocol one study reported higher sensitivity, 83%, and a PPV of 44% in identification compared to the paramedics using CPSS with sensitivity 44% and a PPV of 40%, in the same study (181). There are also studies reporting high sensitivity, 85% and specificity, 68%, for FAST (143) and sensitivity of 88% and specificity of 79% for CPSS (177).

The inclusion of suspected stroke by the ambulance at scene in *Study I-II* did not show any positive results regarding delay; nevertheless, the inclusion provided information of patients lost for identification during the emergency call. The inclusion by ambulance personnel at scene also confirmed the difficulties in identifying stroke even face-to-face.

In-hospital evaluation of FAST has been presented in stroke/TIA patients in a previous study (179) showing that FAST was present in 76% of the patients which is less than previous presented in studies (81, 141). Even in younger patients, age 18-24, FAST were presented in 69%, FAST was also in presented in 65% of posterior circulation stroke and in patients with TIA 62 %. Arm weakness was the most common FAST symptom 58%, speech disturbance 55% and facial weakness in 38% in-hospital (179).

7.2 DELAY

7.2.1 Prehospital delay

An Australian study reported that high priority ambulance dispatches reduce delay with 13 minutes from call to ambulance arrival at scene, compared to non-urgent ones, confirming

that priority effects delay (120). Their results are comparable to ours where 9 minutes reduced delay from dispatch to ambulance arrival at scene in Priority 1 dispatches where found in *Study I* (120).

In Priority 1 alarm, flashing lights and sirens are used to call for a free path and a faster transport in critical situations and has been reported to save 2.62 minutes to 3.63 minutes in earlier studies compared to no lights and sirens (182, 183). However, lights and sirens are not the only difference between Priority 1 and Priority 2 alarms, in contrast to lower priority, the Priority 1 alarm is immediately sent to the patient and cannot be redirected to another high prioritized alarm. Furthermore all Priority 1 alarm pre-notifies the arrival to the hospital, alerting the stroke team, which has shown to decrease in-hospital delay in stroke patients (104, 107, 120, 184-186).

7.2.2 In-hospital delay

In *Study I* we could show that the in-hospital delay decreased when patients arrived as Priority 1 alarms. A previous study also reported the highest priority and prenotification to reduce in-hospital delay (187). Prenotification has also shown to be associated with increasing number of patients eligible for thrombolytic treatment in several studies (104, 107, 184, 188, 189).

According to the ESO guidelines, the in-hospital delay can account for 16% of the time lost in the acute stroke chain from onset to CT (190). In *Study I*, the in-hospital delay was even more decreased compared to the prehospital for the Priority 1 patients. A previous study supports the result of lower priority in the emergency department to be associated with increased delay (191). In ordinary procedures, the dispatch priority was re-evaluated by the ambulance personnel at scene and by personnel at hospital while in *Study I* the Priority 1 was continued from dispatch to arrival at stroke unit in hospital and thereby the intervention also affected the in-hospital delay. The control group was re-evaluated according to standard procedures. The in-hospital activities are as important as the prehospital to improve door-to-needle time and the thrombolytic treatment rate which is shown in this study as well as other (86, 106, 152, 160, 171, 172, 174, 192-194).

In *Study I*, the intervention reduced prehospital and in-hospital delay, although the door-to-needle time for thrombolysis was not affected by the higher priority. In Sweden the door-to-needle time during 2003-2007 was reported to be 67 minutes and slightly higher than our result of 58 and 57 minutes, and an increased time of 69 minutes for the period 2008-2010 (195). The results from *Study I* also showed shorter door-to-needle times compared to US-data reporting 77 minutes in 2003-2009 and 67 minutes in 2010-2013 (109). Notable is the Helsinki door-to-needle time that was 67 minutes in 2003 but after reorganization already in 2005,was reduced to 34 minutes and 20 minutes in 2011 (86, 105). With different actions and guidelines the door-to-needle time has decreased in many centers and countries worldwide in recent years, for example a study in Austria reported 49 minutes in 2010 and 44 minutes in 2013 (171). In 2013 the median door to needle time was 49 minutes in Stockholm, and 48

minutes in Sweden (11). To effectively lower door-to-needle times in-hospital changes are needed (86, 160, 171, 172, 174, 192, 196).

Of the patients included by the ambulance personnel at scene, no difference in delay was observed which is reasonable concerning the prehospital delay where the effect of higher priority from the EMCC was missing. However, the in-hospital delay did not show any significant difference in delay either which might be explained by the low number of patients in the ambulance included intervention group.

The narrow time-window for acute treatments limits the number of patients eligible, however by decreased delay, prehospital and in-hospital, the number of patients potential for thrombolytic treatment will increase (197).

7.3 THROMBOLYTIC TREATMENT

The thrombolytic treatment rate in *Study I* was 35% and 17% of the ischemic stroke patients in the intervention and control group, respectively. These rates are high partly depending on the target group of patients chosen by the study inclusion criteria, onset within 6 h, age 18-85 years and independence in ADL etc. In comparison, the thrombolysis rate in Stockholm for 2007, was 4% of ischemic stroke patients prior to start of *Study I* (7). Other studies have reported thrombolysis rates of great variation since approval (55, 171, 172, 195, 198-201). The difference in thrombolytic treatment rate between the intervention group (35%) and control group (17%), in *Study I*, was interesting since there was no significant difference in the number of patients arriving to hospital within the 3-hour-time-window for thrombolytic treatment in the two groups. The same number of patients should have been considered for thrombolytic treatment in both groups. However, there was a significant difference in the number of patients arriving to stroke unit within the 3-hour time-window, 61% of patients in the intervention group compared to 46% of the patients in the control group, which might explain the differences. There could be other explanations related to the reception of Priority 1 alarm leading to early evaluation, decision of thrombolytic treatment and early arrival to stroke unit. In some of the participating hospitals stroke competent physicians were placed already in the emergency department while they were placed in the stroke units in other hospitals. Regardless, stroke competent physicians were often called to attend stroke alarms, Priority 1 alarms, in the emergency department which could have affected the difference of thrombolysis between intervention- and control group. A previous study reported patients arriving directly to a stroke center to be more likely to be treated with thrombolysis and also to have a better outcome, supporting the importance of stroke competence (202). Advantages with stroke competence was also supported in a study comparing a neuro emergency department to the main emergency department where decreased delay was reported for the stroke patients treated with thrombolysis in the neurologic emergency department (196).

Improved routines have previously been reported to increase access to thrombolytic treatment (171, 203, 204). An Australian study reports an increase in thrombolytic treatment from 5% to 21%, and reduced delay to treatment when new routines were set up including education,

ambulance protocol, contact between ambulance and neurologist and hospital by-pass (204, 205). A study from Austria showed increased number of stroke patients treated with thrombolysis when extensive changes were made to the routine-care program, from 7% of the ischemic stroke patients treated in 2007 to 17% in 2013 (171). The lesson from these studies is that effectiveness of the Acute Stroke-Chain-of-Care depends on all links of the chain which is confirmed in successful projects of improving routines and guidelines (171, 203-206).

Although the age criteria for thrombolytic treatment was 18-80 years at the time of the study, there were participating centers treating older patients within clinical trials, and therefore the upper age limit was 85 years in *Study I*. Positive results of safety and benefits for thrombolytic treatment in older patients (>80) were reported from other studies after termination of *Study 1* and the higher age limit was successively implemented in clinic (4, 207).

The Hyper Acute STroke Alarm study, HASTA, showed benefits of the highest priority in acute stroke within six hours onset. The planning, preparation, meetings and education for the study were also an effective marketing of acute stroke in the Acute Stroke-Chain-of-Care in Stockholm. Personnel from every part of the links of the Acute Stroke-Chain-of-Care were engaged and cooperated in joined efforts and goals to improve the acute care of stroke.

7.3.1 Stroke unit care

The results of *Study I* showed no increase of stroke patients treated in stroke unit which might had been affected during a longer study period, 72% were treated in stroke unit prior to study start and 71% of the stroke patients in the study. Some of the patients probably arrived earlier as half of the study patients arrived to stroke unit within 3 hours from stroke onset, and there was a significant difference between the Priority 1- and the control group.

7.4 SYMPTOMS PRESENTED IN EMERGENCY CALLS

Study III showed that traditional stroke symptoms were more frequently presented in calls dispatched as stroke compared to calls dispatched as non-stroke.

7.4.1 Traditional stroke symptoms

Traditional stroke symptoms such as speech disturbances, limb weakness, facial weakness, and unilateral symptoms together with callers mentioning suspicion of stroke were more frequently reported in emergency calls dispatched as stroke compared to non-stroke in *Study III* as previously has been described in other studies (114, 116, 155). Identification based on clinical examination also reported traditional stroke symptoms to be strongly associated to diagnostic accuracy of stroke, in a study from an emergency department (208). The result showed that only 4% of the diagnosis were incorrect of the patients presenting traditional symptoms compared to 64% of the patients with non-traditional symptoms, confirming that presentation of traditional stroke symptoms facilitates identification of stroke (208).

Presentations of suspected stroke, facial weakness, weakness/fall, and impaired communication were found to be a predictor for stroke emergency calls concerning stroke according to a previous study (209). At least one of the symptoms was presented in 80% of the stroke calls in the same study (209).

The analysis in *Study III* showed positive FAST to be associated with stroke dispatch, and that calls with dispatch code "Stroke" were given higher priority more often. The calls dispatched as "Stroke" were more often noted with onset within 6 hours however time of onset might not be asked for when stroke is not suspected. Suspicion of stroke is often mentioned by the caller in other studies and in *Study III*, and have been shown to have a strong correlation to stroke diagnosis (73, 111, 114, 155, 210). To be noted, not all of the calls in *Study III* were dispatched as stroke. In non-stroke emergency calls, suspicion of stroke was mentioned by the caller in only 3% compared to 40% in the stroke calls, according to a British study which supports the correlation to correct stroke identification (155).

7.4.2 Non-traditional stroke symptoms

Stroke patients with non-traditional stroke symptoms are at risk to be misdiagnosed according to our and other's studies (115, 116, 131, 208).

Our analysis of emergency calls in *Study III*, showed speech disturbance, fall/lying position and altered mental status to be the most commonly presented symptoms among all stroke calls. Speech disturbances is a traditional stroke symptom while fall/lying position and altered mental status are not. Those symptoms are also presented in other studies of emergency calls, in varied numbers (73, 111, 155, 209). The discrepancy between medically described symptoms of stroke and the callers expression of stroke might be explained by that 1) the caller observe and presents the consequences of stroke symptoms, e.g. fall 2) the caller do not recognize symptoms of stroke 3) the caller uses laymen expressions for symptoms of stroke i.e. the call taker do not recognize the presentation as stroke symptoms 4) stroke symptoms are not present. It seems reasonable to assume that speech disturbances, fall/lying position, altered mental status and trouble walking are the first noticed problems in contact with the patient and therefor presented by the caller in the emergency call. There were no studies found of the consistency between symptoms presented in the emergency calls compared to symptoms presented in ambulance or in-hospital through medical records.

Falls are a common problem among persons aged over 65 years by various causes and constituted 5% of all emergency response according to an Australian study (211), and 8% in a study from UK (212). However, one study showed that fall/collapse was more frequent in emergency calls concerning stroke (38%) compared to emergency calls concerning non-stroke (26%) (155). In contrast, another study reported fall and atypical motor descriptions to be equally frequent in the stroke- and the non-stroke calls (114).

In *Study III*, fall/lying position was significantly more frequent presented (66%) in the calls dispatched as non-stroke, compared to 22% in the calls dispatched as stroke. Several studies have reported fall and collapse to be presented in emergency calls of stroke (115, 116, 119,

154, 155) and one study reported fall in 6% and collapse in 51% of the stroke calls dispatched as non-stroke (115). A large study in UK presented fall or collapse (26%) to be the most common symptoms first mentioned in the emergency call followed by mentioning stroke (25%) (154).

Altered mental status was another non-traditional stroke symptom presented in emergency calls concerning stroke patients (111, 116, 208, 213). In *Study III*, altered mental status was the third most common symptom presented, equally distributed between stroke and non-stroke dispatched calls. In hospital, altered mental status was present in 31% among the stroke not identified as stroke, reported in a previous study (131) although altered mental status is probably termed in other words in medical records. In contrast, confusion and reduced level of consciousness were more frequent in non-stroke patients reported from a study of stroke patients in the emergency department (214).

Non-traditional symptoms of stroke, such as general weakness, altered mental status, altered gait and dizziness resulted in misdiagnosis in 64% of the patients also in the emergency department (208). That result (208) underlines the difficulties in identifying stroke even in the emergency department when the patient is evaluated by medical professional. Another study reports non-traditional stroke symptoms in stroke like general discomfort, chest pain, dyspnea, fall or vertigo to be associated with misdiagnosis (116), although non-traditional symptoms could also origin from stroke mimics.

However, even traditional stroke symptoms like speech disturbances can be difficult to distinguish when expressed in emergency calls. Speech disturbance was the most dominating symptom presented in *Study II* and *III* but also the most common FAST symptom presented in patients with no stroke/TIA diagnosis in *Study II*, in 37% noted by the EMCC and in 19% by the ambulance. Speech disturbances was also presented in 31% of the emergency calls concerning stroke but dispatched as non-stroke in *Study III*. Speech disturbances may relate to a number of different conditions and the expressions of the caller can be important for how speech disturbances is interpret by the nurse.

To have knowledge of stroke symptoms is not the same as recognizing stroke in real life. The different studies concerning knowledge of stroke among the population varies greatly, partly due to methodological issues such as differences in open-ended or closed questions of symptoms (82-85, 100, 144, 190, 215-225). In emergency calls, the layman's presentation of stroke symptoms might be expressed in non-traditional stroke terms or by the consequences of symptoms e.g. leg weakness can result in a fall or a lying position and altered mental status might express speech disturbances, neglect, apraxia or disorientation.

7.5 FACTORS FACILITATING OR HAMPERING NURSES' IDENTIFICATION OF STROKE IN EMERGENCY CALLS

Previous studies in identification of stroke in emergency calls have mostly been focused on symptoms and little is previous presented on how communication and interaction between the participants affects the identification (111, 114, 154, 155, 209).

When listening to the recordings of the emergency calls in *Study III*, it was obvious that not only the symptoms affected the identification of stroke. The communication and interaction of the participants in the call affected the identification of stroke as well and *Study IV* was performed to further explore this. The findings, in S*tudy IV*, were summarized in six themes which presented obstacles and facilitators in identification of stroke in emergency calls concerning stroke with presentation of fall or lying position.

The most important finding in this analysis was the adjustable facilitators and obstacles of the first call-takers' and the nurses' authority, the nurses' coaching strategies, the nurses' expertise skills and the call hand-over that can be improved by the EMCC, Figure 13. Facilitators and obstacles concerning the situation, the patients' ability to express themselves and the callers' knowledge of the patient and stroke was considered to be non-adjustable. Nevertheless, knowledge and awareness of the non-adjustable aspects can be less of a hindrance if the adjustable facilitators are strengthened.

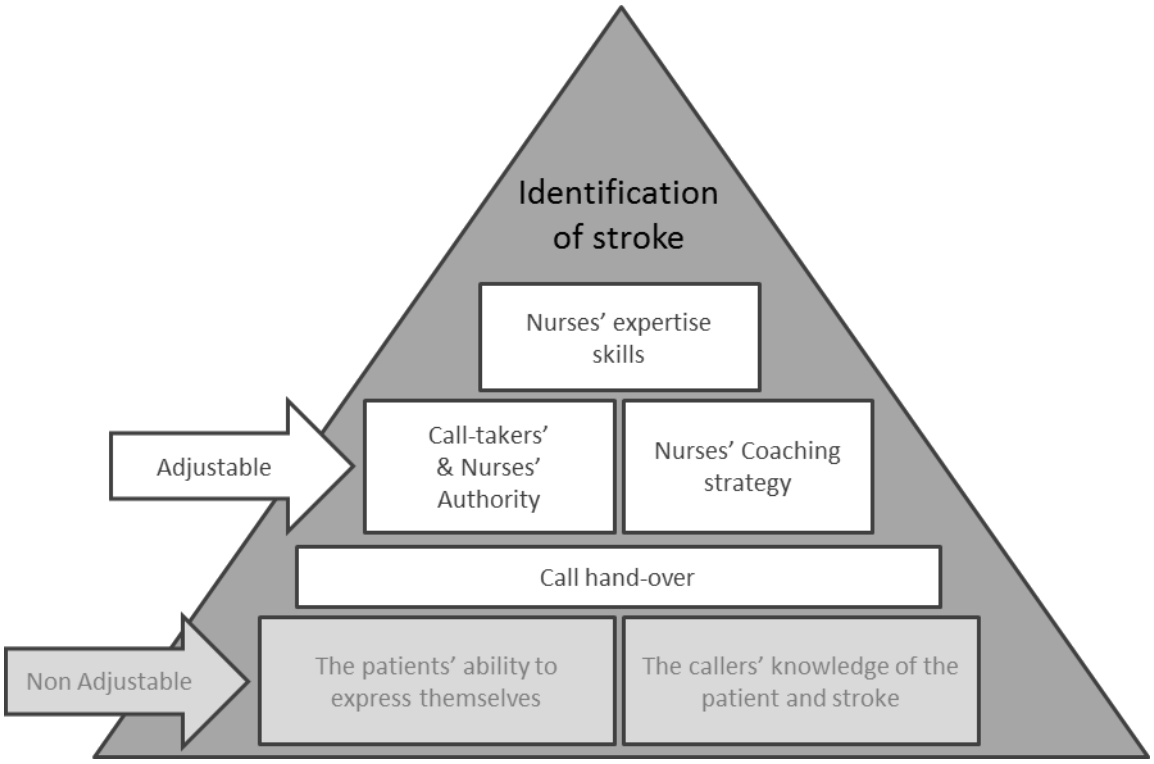

Figure 13 A schematic summary of the findings where the patient and the caller represent the base which cannot be adjusted. The following aspects as the call hand-over, the first call-taker and the nurses' contribution can be adjusted to improve identification. Nurses' expertise skills peak the process of identification as it can become the outmost difference in stroke identification. Adapted from the manuscript for *Study IV* submitted to Journal of Advanced Nursing, JAN, with permission.

The patients' inability to express themselves affects the information given in the emergency call. Furthermore, many stroke patients are unable to communicate their symptoms due to speech disturbances, not perceiving the symptoms of stroke, or not recognizing stroke (73, 93, 226, 227). The fact that the stroke patient rarely is the caller, approximately 2-7% in international studies (73, 111, 119, 155), also affects the information to the EMCC. Fall or the patient being in a lying position might mask symptoms like weakness or unilateral symptoms to the caller if the patient is unable to express the symptoms.

The caller's knowledge of the patient is reflected by presence at stroke onset as well as knowing the patients' previous status for comparison. In *Study IV* we found that a witnessed onset of symptoms provided more detailed information and facilitated identification of stroke. However, in about 20-25% of all stroke events the patient is alone at stroke onset according to previous studies (71-73). The effect of callers' knowledge in identification has been recognized in two other studies (156, 228). Description of symptoms progress, comparison of current status to previous, and presentation of disease specific symptoms was also found to be facilitating factors in assessing emergency calls in one of the previous study (228). While the opposite was reported by another study, lack of information and vague descriptions by the caller hindered the assessment of emergency calls which underlines the role of the caller, and the callers' knowledge of the condition (156). The knowledge of stroke in laymen can be influenced in some extent through public campaigns like in the Swedish Stroke campaign launching the Swedish version of FAST (76).

The authority of the first call-taker s and the nurses was found to affect the identification in our study but have not been verified in other studies. In telephone nursing, power was confirmed in nurses' position and organization, decisions of questions and action, and possession of medical knowledge, while the caller is left with limited choices of seeking help elsewhere (229). For the caller to feel respected, to be confirmed in the need of help and to be taken seriously, a productive authority is central in the first call-takers' and nurses' approach. In interviews of emergency call operators, the operator declared need of respect for the caller, which can be related the aspects of authority in our findings (156). In our analysis in *Study IV*, the authority becomes a part of how medical knowledge was used in communication and interaction, to support and coach the caller, confirming the caller and interacting with respect. Nevertheless, awareness of the authority is important as it might not be obvious but can be a facilitator as well as an obstacle in the identification of stroke in emergency calls.

The nurses' coaching strategies were described in terms of support to the caller, careful and active listening, information, and adequate questioning in other studies (156, 228, 230-232) confirming the findings in *Study IV*. In one of the studies, nurses' coaching strategies were described as an obstacle when reflections of the callers information were lacking, the call was unstructured, questions were not asked or not followed up and the nurse did not lead the call (228). Facilitating aspects of nurses' coaching strategies were found when the nurses asked questions based on given information to make progress in the call (228). Nurses' coaching strategy was also described in adjusted questions, perceptive and improved listening, and developed skills to adjust for lack of visibility of the patient in telephone consultancies (230).

Not being able to see the patient complicates the medical evaluation and decision in telephone consultancy or emergency calls (156, 230, 231). In compensation for the non-visibility the nurses developed skills in communication and interaction for information, advice, comfort and trust according to nurses interviewed before and after working in telephone consultancy (230, 232). The importance of knowledge and developing skills in telephone nursing has been confirmed in several studies. Likewise, the role of active coaching

in communication by accurate questions and strengthening the caller is previously described and matches the finding of nurses coaching strategy. (156, 228-230, 232-234) In our findings in *Study IV*, knowledge, skills and competence were important components for the ability to coach and support the caller in the nurses' coaching strategy.

When competence and skills reach a level of expertise skills the nurse is able to adapt knowledge and skills in interpreting callers' presentation and situation but also to trust the skills for decisions and actions (235). The expert nurse is responsive to the situation and has the skills to pick out the relevant information; a committing approach associated to reaction has developed integrated with "know how" and an ability to grasp the whole (236). In *Study IV*, the final dispatch code could not be predicted by the composition of obstacles, there were calls with seemingly good conditions that were not identified as stroke and calls with seemingly poor conditions that were identified. The nurses' expertise skills were the peak of the obstacles and facilitators found to be decisive in identification of stroke in emergency calls.

To assess emergency calls is a demanding task where incorrect decisions could have critical consequences (156, 231, 232). Identification of stroke in emergency calls is complicated as the differential diagnoses are numerous and the evaluation is performed by phone, often by a third person and a layman. The decisions of dispatch are reported to be challenging, difficult and the nurses feared to make the wrong decisions according to a previous study (231). Another aspect affecting the nurses' assignment described in other studies when interviewing nurses was stress over a heavy workload and potential adverse events, a finding which was missing in our observational analysis (232).

7.6 SEX AND GENDER

The upper age limit of 85 years for inclusion in *Study I-II*, affected the distribution of men and women represented in these studies as mean age for women having a stroke was 78 years compared to 73 years for men in Sweden in 2007 (7). As in many other studies, there were slightly more men (56%) included in S*tudy I-II* (11, 25-34, 36). The age limit affected not only inclusion in *Study I* but even more the rate of thrombolytic treatment, as the upper age limit was 80 years at the time of the study (1). A study estimating the imbalance in accessibility between men and women with an age limits of 80 year showed that 19% of the men and 44% of the women would be excluded (237).

7.6.1 Identification

The results in our studies revealed no significant differences between men and women in identification of stroke. Fewer women (44%) were included in *Study II*, probably due to the upper age limit of 85 years. The distribution of men and women in intervention- and control groups were equal. The proportions of men and women, respectively with a discharge diagnosis of stroke /TIA in S*tudy II* were similar.

The only sex difference found concerning identification of stroke were altered mental status and speech disturbance being more frequently reported in women. Altered mental status was more frequently presented in emergency calls concerning female stroke patients (36%) compared to male patients (18%) in S*tudy III*. Speech disturbances were more frequently noted in women (56%) compered to men (42%) by ambulance personnel in *Study II*. No data of stroke symptoms presented in emergency calls comparing men and women was found in the literature.

One in-hospital study has also reported altered mental status to be significantly more common in women (38). However, in-hospital, altered mental status might be documented as disorientation, confusion or cognitive impairment instead. In emergency calls, altered mental status can describe a variety of problems in a patient who is notably changed in behavior, communication, personality, appearance, or responsiveness. Some of the problems referred to as altered mental status may also be associated with level of consciousness or speech ability.

Previous studies report conflicting results of stroke symptoms found in men and women from in-hospital settings. In some studies women with stroke were reported to have more severe conditions (27, 29, 30, 34, 39) which might be explained by older age and other co-variables related to age. Reduced level of consciousness has also been reported to be more common in women with stroke (31, 34, 238). One study of clinical evaluations reported women to present paralysis and aphasia more frequently (34) while another study by interviews reported women to present less hemiparesis and men to present more imbalance and gait problems (238). Men have also been reported to have gait problem, balance and dizziness more often than women in another study of clinical evaluations (133).

A large study with interviews of stroke patients or their relatives reported non-traditional symptoms such as pain and change in level of consciousness-disorientation to be more frequent in women (238). Another study of patients reported symptoms on questionnaires described weakness being more common in women but no difference in speech disturbance was found (239). Symptoms presented in interviews could be reflecting disparity in perception and verbal presentation of stroke symptoms and not necessary differences in presence of stroke symptoms. It is difficult to compare the results of previous studies as findings depends largely on methods and source of information; medical records, questionnaires, or interviews.

An in-hospital study of FAST symptoms found men to have more presentation of facial weakness (40%, p 0.002) compared to women (36%) but no differences in arm weakness or speech disturbance (179). The same study also reported women to present headache and nausea more often than men (179). Nevertheless, the symptoms evaluated at hospital by professionals might not reflect the symptoms presented by the caller in an emergency call.

Medical records might leave out subjective symptoms or the symptoms experienced by the patient, while interviews focus on the patient's or the relatives' view and questionnaires rely on pre-defined answers. The symptoms from the studies included in this thesis have been

collected from authentic emergency call but cannot be compared to patient's symptoms examined and reported by health care professionals.

Symptoms presented in clinical settings provide very limited information useful in the identification of stroke in the emergency call.

7.6.2 Delay

The use of ambulance is known to be associated with decreased prehospital delay and we did not find any differences between men and women in arrival by ambulance in *Study I*. This is in contrast to other studies where women have been reported to arrive more frequently by ambulance (30). One reason for this discrepancy could be the age limit of 18-85 year in *Study I*, thus excluding a proportion of older women.

In *Study I* we found no significant sex differences in prehospital or in-hospital delay. Previous studies have reported conflicting data concerning delay, most presenting no sex differences in prehospital delay (26, 29) but some reported that women arrived later than men (71, 240, 241). Conflicting data has also been reported in in-hospital delays where some studies found an increased delay for women while other found no difference (26). A recent study from South Korea showed increased delay for women prehospital and in-hospital except for the in-hospital delay for thrombolysis where no significant difference was found (38). Another study presented longer in-hospital delay for women even after adjusted for confounders such as age and presented symptoms (133).

No sex differences have been reported in time to thrombolysis in the previous studies (27, 30, 38). However, several studies have shown women to be less likely to be treated with thrombolysis even after adjustments for age (29, 33, 39, 242, 243). One of the studies reported later arrival to hospital to be the cause of less thrombolytic treatment in women (243), other studies reported no difference in thrombolytic rate between men and women (30, 38, 244). Women are reported to benefit equally or even more from thrombolytic treatment (37, 242).

7.7 TRUSTWORTHINESS

Trustworthiness is described using the concepts of the quantitative and qualitative research. In quantitative studies the concepts of trustworthiness can be presented in validity, reliability and generalizability (245), and in qualitative studies the same can be presented in credibility, dependability, confirmability and transferability (246). For the four studies in this thesis, the descriptions of study designs, participants, settings, methods, analysis and results sets the ground for the trustworthiness. As the result of the qualitative study is not transparent in numbers and measures the trustworthiness for *Study IV* will be further explained.

7.7.1 Study IV

7.7.1.1 Rigor

Interpretive phenomenology is essentially a philosophic theory based on hermeneutics, a method of interpretation and understanding. In *Study IV* interpretive phenomenology according to Patricia Benner was used as a method to analyze data. Traditionally the interpretive phenomenological approach is used through interviews to explore individuals understanding and experience of their lifeworld of the phenomena studied (246). In this study we have analyzed the phenomena of emergency calls concerning stroke without exploring the experience by interviewing the participants but interpreting the transcriptions of authentic emergency calls. The advantage using an interpretive phenomenological approach has been to reach under the surface level and exploring the phenomena from all three participants' perspective (the caller, the first call-taker and the nurse) by constantly asking questions to the material. In the themes we could present a broad perspective including competence, knowledge, authority, and ways of using those aspects positively or negatively. The emergency calls reflect the authentic situation which probably provides other information than the experience of the participants. The disadvantage with not doing interviews has been not to be able to ask questions to the individuals involved of their experience. (247-250)

In the interpretive phenomenological analysis in *Study IV*, we have strived to uncover the meaning of the participants' communication and interaction in the phenomena of the emergency call from the aspect of identification of stroke.

7.7.1.2 Credibility – the confidence in truth of the data

The analysis was based on 68 verbatim transcripts of authentic emergency calls, reflecting a real life situation also the phenomena of interest. There was a mix of emergency calls dispatched as stroke and calls with other dispatch codes, although they all had a stroke diagnosis at hospital discharge. This enabled comparisons between calls "identified" as stroke to the calls "not identified". However, in the first step of analysis the dispatch codes were blinded to allow the researchers to be open to the material and avoid pre-understanding. The calls analyzed were a well-represented mix of the stroke population according to age, sex, stroke severity, symptoms and time from onset. The callers were relatives, patients, health care providers, neighbors and bystanders, and some of the callers were present with the patient, others were not. The first call-takers' and the nurses' responding the calls were equally representing a spread of age, sex, and competence as the EMCC provides a large area, Stockholm and the calls were from all days of the week, 24 h/day.

Three authors with different backgrounds contributed to varied perspectives and understanding, from details to abstractions which decreased the risk of the individual researchers pre-understanding to lead the analysis in the different steps forward. During the process of analysis diverse alternative interpretations were tested to the material through joint discussions to reassure that all aspects were considered for the most relevant interpretation to

appear. In the manuscript, plenty examples are included to allow the reader to follow a concrete occurrence in the emergency calls to the theme, for transparence. (247-250)

7.7.1.3 Dependability – the stability of the data over time

The findings could probably be replicated in a similar setting in Sweden as well as in other countries. However, other countries may have other organizations and routines in accessing emergency calls which would partly affect the findings. The findings are broad and general and will probably be sustainable over time. If a similar analysis had been done 20 years previously, the results might be different as the acute care of stroke has changed dramatically. (247-250)

7.7.1.4 Confirmability – the neutrality of the findings

The findings have been an ongoing process of analysis between the three authors with final agreement to assure the neutrality, and that the findings are interpreted from the participants' contribution and perspective. The findings of the analysis was also reconsidered and re-evaluated after adding the dispatch codes of stroke or non-stroke to the calls. (247-250)

7.7.1.5 Transferability – the generalizability of the data

The EMS system is similar in Sweden which speaks for good transferability. The first sample of 68 calls identified as stroke and not identified chosen for analysis provides for a fair picture of how the emergency calls are performed. The emergency calls of stroke can be assumed to follow the same pattern more or less also elsewhere. The analysis raises similarities, differences and themes in general terms which is likely to be recognized also in other contexts. The results from other studies support ours in *Study IV* indicating that the findings most likely would apply for identification of stroke in emergency calls also in other settings even internationally (156, 228, 230). (247-250)

7.8 LIMITATION

7.8.1 Delay

Due to premature termination, the study cohort in *Study I-II* was smaller than originally planned. This affected the chances of reaching significance in the subgroups. The study was planned and powered for a two years inclusion period but was terminated after six month due to media exposure and criticism of randomized priority and lack of consent from the patients.

A longer study period could have affected identification, delay and thrombolytic treatment by learning of new routines and developing fast-track procedures in *Study I* and *II*. Some stroke centers were unexperienced in thrombolytic treatment and new routines were adapted to increase thrombolytic treatment and fast transfer to stroke unit. The results could have been improved in time particular concerning delay and frequencies of thrombolysis. When the study was terminated the prehospital Priority 1 was implemented in the guidelines for

suspected stroke within six hours. The in-hospital priority and fast-track routines went back to standard.

The door-to-needle time for thrombolytic treatment was not affected by the priority in *Study I* but the numbers treated was small. Some of the participating hospitals, in *Study I*, had little experience of thrombolysis prior to study start, which probably had a detrimental effect on the delay for thrombolysis. The volume of thrombolytic treatments is previously reported to have greater effect in DNT than years of experience (110).

The Priority 1 was not exclusive for the intervention group in *Study I*. This because it was important not to reduce the health care standard for the patients in the control group and thus the control group followed standard guidelines for priority. The patients in the control group could therefore be upgraded to Priority 1 by the ambulance personnel at scene if stroke within 3 hours was suspected. Consequently, the effect of Priority 1 was diminished by a number of Priority 1 also in the control group for the transport from scene to hospital. A limitation of the study is that data of upgraded priority at scene was lacking.

The fast-track and high-priority procedure for stroke patients in *Study I*, was awaited and welcomed by most personnel participating, both prehospital and in-hospital, and to retain the standard care for the patients in the control group was perceived as frustrating. In practice, there were difficulties to switch between fast-track and a slower procedure between the patients. Once some suspected stroke patients were given higher priority, it was perceived as morally and ethically difficult not providing the same care to all patients with suspected stroke. The delay for the control group could have been influenced by the faster procedure for the intervention group as it was difficult to separate the routines and not take advantage of the fast-track.

Except from thrombolytic treatment, effects of early arrival at a stroke unit were not analyzed in our study. An early start of treatment and monitoring in a stroke unit is believed to be an important presumption to reduce the brain damage, consequences of stroke and prevent complications.

7.8.2 Identification

In *Study II*, data is lacking of the patients not identified by the EMCC or the ambulance with stroke/TIA within the criteria during the study period. Information of the stroke/TIA patients missed in inclusion of the study would have provided valuable information of identification. Calculations of sensitivity, specificity and negative predictive value were not possible from the data collected. Data of the patients not identified from the EMCC and ambulance was not collected and the inclusion criteria made it difficult to do retrospectively. To calculate a negative predictive value of FAST, FAST had to be tested in all patients, positively or negatively which was not done by the EMCC. However, the patients included from the ambulance but missed by the EMCC, added some information although the number of patients was small and no significance differences were detected.

It would have been valuable if all FAST items in *Study II* had been tested, positive or negative, in all patients with suspected stroke, however, the FAST test was not mandatory for the nurses at the EMCC. With priority in focus, testing the patients with the FAST during the emergency call via the caller was estimated to be time consuming. Negative FAST symptoms could mean that FAST was just not tested. Thus, sensitivity of the FAST test could not be calculated as the FAST test was optional for the nurse at the EMCC.

The primary focus for inclusion in *Study I* was the priority and the identification was a part of the inclusion criteria which could have affected the result of identification negatively in *Study II*. Criteria of age and time of onset would not have been adequate in a study of the identification. Nevertheless, it was valuable to learn if time of onset was possible to obtain in the emergency calls although there are questions unanswered of how many patients were lacking or excluded due to onset time missing or ≥ 6 hour.

The major limitation in *Study III*, reported symptoms in emergency calls, is the relative low participation rate, 57% of eligible patients/relatives consented to participation. We can only speculate in why patients do not participate but one reason could be inability to read and sign consent. There is a risk that patients with severe stroke, cognitive impairments, aphasia or physical dysfunction could have difficulties in giving consent and might thus be underrepresented in the study. Similarly, patients with limited knowledge of Swedish risk being underrepresented as the information in the informed consent letter was only in Swedish. The low participation rate reflects the problems with consent for persons affected by stroke and the risk of skewed results when a large group of patients are unable to leave consent.

The population in *Study III* was small and from a single center which might limit the generalization, however the aim of the study was to explore and describe what symptoms are presented in emergency calls concerning stroke. The patients participating was representing mild and severe stroke, different ages and the callers were representing a mix of relatives, health care personnel, patients and witnesses.

Different expression of symptoms was clustered in groups representing a symptom in *Study III*. The previous studies have grouped the symptoms differently which complicates comparisons. In *Study III*, lying position was added to fall as a lying position might be an unwitnessed fall, however one could argue that many sick persons calling the emergency number for help are in a lying position. Data of lying position in other emergency calls are unknown, but we found a great difference in lying position presented between the calls dispatched as stroke and those dispatched as non-stroke.

Study III was a follow-up of the FAST test introduced in the EMCC at the start of *Study I* in 2008. To evaluate the use of FAST in identification of stroke in emergency calls turned out to be difficult as FAST is easy to use by memory and is rarely documented. Thus, the symptoms of FAST presented in the emergency call was noted and analyzed.

In *Study IV*, the focus on a specific group of stroke patients presented with fall or lying position might be considered a limitation for the analysis of obstacles and facilitators in identifying stroke. If emergency calls concerning stroke without specific criteria had been selected, other findings might have been revealed. However, patients with fall/lying position were of special interest as we had shown that they were less likely to be dispatched as stroke in *Study III*. Also, this group of patients could be argued to be the most difficult to interpret thus having more possible hindering factors to consider.

7.9 METHODOLIGICAL CONSIDERATIONS

7.9.1 Priority and delay

From a methodological view it would have been preferable if the control group in *Study I* had not been affected by the fast-track in the intervention group. A historical control group could have been one possibility. However, that approach carries other shortcomings, particularly as the concept of stroke as an emergency has changed dramatically over the last decade. Another obstacle with that approach is that twice as many patients would have been eligible for Priority 1 during the study period which could have resulted in difficulties to provide for Priority 1 throughout the Acute Stroke-Chain-of-Care.

7.9.2 Identification

The inclusion criteria for *Study I* limited the group of patients in *Study II*, to patients with suspected stroke within 6 hours, age 18-85 years old and previous ADL independent. For an optimal study design of identification, *Study II* needed other conditions. The focus in the design of the study was the priority. To test all suspected stroke /TIA with a full FAST test would have enabled measures of sensitivity and specificity. Also to test FAST in the emergency department would have enabled further evaluation of the ambulance personnel's FAST testing and the presence of FAST symptoms at hospital. In *Study II*, data from the stroke patients missed by the EMCC and the ambulance personnel are lacking. Information from this group would have added valuable data.

The choice of method for the qualitative analysis of identification was not obvious. Finally, the choice fell on interpretive phenomenology and the process of analysis proceeded well. The data analyzed is also being analyzed with another method, content analysis, with the same purpose and research question to compare the significance of methodological choice. The researchers using content analysis are blinded to the findings in the analysis in interpretive phenomenology, and the results are not finished yet.

8 CONCLUSIONS

The most important intention with the studies in this thesis was to increase the number of stroke patients eligible for thrombolytic treatment and early treatment in a stroke unit with aim to improve the outcome of stroke.

The conclusions of this thesis are:

- Priority 1 alarm from ambulance dispatch to arrival at stroke unit, was shown to reduce prehospital and in-hospital delay and increase the number of patients eligible for thrombolytic treatment. The results clarified the importance of high priority alarm of acute stroke. Furthermore, the importance of identification of stroke in the emergency call was shown.
- Half of the patients with suspected stroke were correctly identified by the EMCC or the ambulance personnel. The EMCC correctly identified 71% of the patients with stroke/TIA but also missed 29%. The identification from the EMCC need to be improved to decrease delay and to find patients eligible for acute treatment of stroke.
- The FAST test was positive in most of the stroke/TIA patients but also in a large number of non-stroke patients in the emergency calls. Even with FAST introduced in the EMCC, many stroke/TIA patients were not recognized in the emergency calls. The ambulance personnel noted positive FAST in 80% of the stroke patients missed by the EMCC indicating that symptoms of FAST might be present but not presented in the emergency calls.
- Almost all positive FAST was spontaneously presented in the emergency calls reflecting that FAST symptoms triggered suspicion of stroke rather than being used to identify stroke. Positive FAST was strongly associated with stroke identification from the EMCC and the ambulance. However, FAST symptoms were not synonymous with stroke dispatch. Although FAST symptoms were presented in the emergency calls concerning stroke patients, one third of the FAST positive stroke calls were dispatched as non-stroke.
- Fall or being in a lying position dominated the symptoms presented in emergency calls dispatched as non-stroke. Fall or lying position might be the obvious problem for the caller and may possibly mask symptoms of stroke. Traditional stroke symptoms were found to be most common in the calls dispatched as stroke and less common in emergency calls dispatched as non-stroke.
- To be able to improve the identification we need to learn more about the emergency calls not identified as stroke. To actively test FAST in calls where fall and lying position is presented might be an effective way of using FAST. This need to be tested and further studies are warranted.
- Nurses' expertise skills were found to be an important and decisive factor the in identification of stroke in emergency calls. The obstacles and facilitators of the first call-taker, the nurse and the structure of the call as were the next important findings as

these can be improved while the aspects of the patient, caller and the situation cannot be changed.

- Differences between men and women were found in the symptoms of stroke. Altered mental status were more often presented in women compared to men in emergency calls of stroke, and speech disturbances were more frequently reported in women by the ambulance personnel. However, there were no significant sex differences found in delay or thrombolytic treatment of stroke.

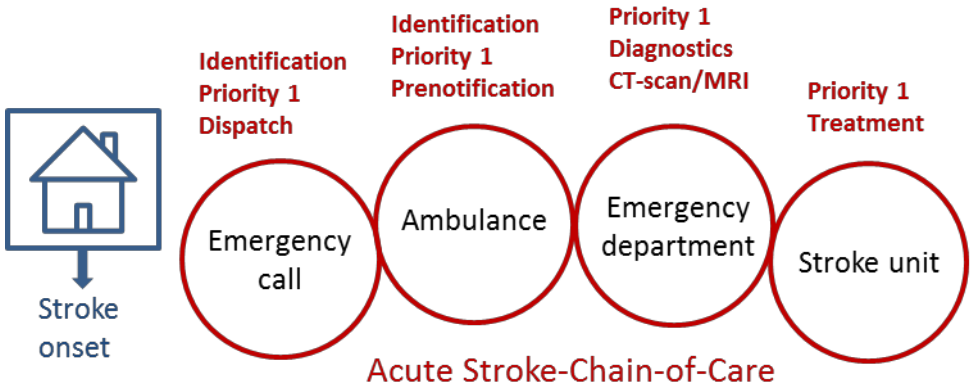

Figure 14 Priority 1 and early identification affects the outcome of stroke through the Acute Stroke-Chain-of-Care.

9 IMPLICATIONS AND FUTURE PERSPECTIVES

The first study in this thesis was started in 2008, since then a lot of activities and initiatives have been implemented to improve delay and increase acute treatment of stroke, including a national campaign for the public about stroke symptoms and acting fast (76).

9.1 DELAY

There is still a need of improvements to decrease delay of stroke patients for thrombolytic- and also endovascular intervention treatments which now are evidence based acute treatment for some patients with ischemic stroke (64, 66, 67, 251-254).

9.1.1 Implementation of Fast-Track

The prehospital Priority 1 was successfully implemented in Stockholm 2008, followed by an increased rate of thrombolytic treatment. The in-hospital Priority 1 was terminated and referred to local routines and procedures of each hospital as the study was terminated. Since *Study I*, many hospitals have implemented local routines with fast-tracks and emergency department by-pass. To reduce delay and improve the acute stroke care Priority 1 should be kept in all parts of the Acute Stroke-Chain-of-Care until the stroke patient is stabilized, monitored, and in care at a stroke unit. To further decrease in-hospital delay, the ambulance units need to establish early contact and communication with stroke physicians at the hospital. To cooperate with the ambulance personnel in identification and triaging also gives feed-back and learning occasions for the ambulance personnel to further develop their skills.

9.1.2 Joined efforts in the Stroke-Chain-of-Care

In a future perspective stroke patients would need to be triaged in the ambulance and steered directly to eligible hospital to further decrease delay of treatment and a more effective use of resources. Patients with wake-up stroke have been recognized in the past years, to sometimes be eligible for endovascular recanalization and studies on thrombolysis in wake up stroke with specified MRI findings are in progress (251-254). The required technique and competence to evaluate eligible patients and perform endovascular recanalization is only available at specialist centers. Steering the patients already from the ambulance would benefit those patients. Today there is a gap between guidelines and priorities of patients with so called wake-up stroke both prehospital and in-hospital in Stockholm. The guidelines for prehospital Priority 1 apply for patients with suspected stroke within six hours and the patients waking up with stroke symptoms might be treated as non-eligible for treatments. Further delay is followed by the conflicting guidelines for ambulance delivering a non-urgent patient for triage in the emergency department as the stroke team is not alerted and the priority follow guidelines of a non-urgent stroke.

The patients' delay is still of interest to improve by continued campaigns to the public and training of recognizing stroke symptoms and to call for action.

9.2 IDENTIFICATION

Further improvements of the prehospital identification are needed to decrease delay and increase patients eligible for treatment in the Acute Stroke-Chain-of-Care.

9.2.1 Support for identification

The use of FAST test could be extended and used to identify stroke in emergency calls not suspected as stroke. To actively ask for FAST symptoms in emergency calls where fall/lying position and/or altered mental status are presented might improve identification of stroke as these problems were common in the emergency calls not identified as stroke. An interventional study with mandatory use of FAST in emergency calls with presentations of fall or lying position could give useful information of how common falls and lying positions are in stroke versus non-stroke emergency calls and whether FAST might be helpful to distinguish stroke symptoms.

Clarifying questions could be developed and tested in order to differentiate stroke symptoms in expressions of non-responsiveness, speech disturbances, altered mental status, fall/lying position and physical function/ability in expressions of the caller.

Further studies could provide more information of differences in emergency calls between stroke, stroke mimics and chameleons. Emergency calls of patients with confirmed stroke could be compared to calls where the nurse suspect stroke in the emergency calls but who are evaluated as non-stroke at hospital.

Interviewing first call-takers and nurses at the EMCC concerning facilitators and obstacles in identification of stroke might bring additional answers and results. It would be interesting to learn what triggers suspicions of stroke in different calls, what may be conflicting information and how identification of stroke could be facilitated and increased.

9.2.2 Training and education

Interventions of education and training of stroke symptoms presentations in emergency calls, communication, and obstacles and facilitators in the emergency calls would be valuable to improve and increase identification. An educational and training intervention for identification of stroke could be developed and tested at the EMCC.

A feed-back intervention to improve learning from own experiences can be used in training for developing skills.

To improve identification at scene and support identification, early contact from the ambulance nurse to the stroke physician at hospital could be evaluated. Using video calls at scene might enable early examination and triage in cooperation with the hospital stroke physician.

10 SAMMANFATTNING

Stroke drabbar ca 25 000 personer i Sverige varje år och är den tredje vanligaste dödsorsaken. Av de som överlever får många kvarstående nedsättningar i funktion och kognition vilket påverkar självständighet såväl som livskvalitet. I 85 % orsakas stroke av en cerebral infarkt, som leder till syre- och näringsbrist i de omkringliggande hjärncellerna, ischemi. Vid ischemisk stroke kan propplösande behandling, trombolys, ges inom de första timmarna i syfte att återställa cirkulationen och minska risken för bestående skador.

Trombolys godkändes för behandling av ischemisk stroke år 2003 i Sverige att ges inom tre timmar från strokedebut för patienter under 80 år. Införandet av trombolysbehandling gick långsamt och år 2007 behandlades endast 3 % av alla patienter med ischemisk stroke med trombolys i Sverige. En av orsakerna anses vara att strokepatienter söker vård sent och att få kommer till sjukhus inom tidsramen för behandlingen. Vård på strokeenhet har också påvisat signifikant förbättrade resultat i daglig funktion och livskvalitet samt minskad dödlighet för strokepatienter. Trots detta vårdades många strokepatienter på andra avdelningar initialt och en del vårdades aldrig på strokeenhet enligt uppgifter för år 2007.

För att förbättra den akuta behandlingen av strokepatienter i Stockholm startades projektet HyperAkut STrokeAlarm, HASTA, år 2008. Syftet var öka antalet patienter som behandlades med trombolys, öka andelen patienter som vårdades på strokeenhet och förkorta tid till behandling och inläggning på strokeenhet.

Studie I, HASTA-studien, syftade till att undersöka om ökad prioritet från SOS Alarm kunde öka andelen strokepatienter som kom till sjukhus i tid för trombolysbehandling, öka andelen patienter som anlände till strokeenhet samt att minska tid mellan strokedebut och trombolysbehandling och vård på strokeenhet. Patienter med misstänkt stroke, debut inom 6 timmar och ålder mellan 18-85 år, randomiserades från SOS Alarm eller ambulansen till ökad prioritet, Prioritet 1, eller kontrollgrupp med Prioritet 2 enligt standard. Under 6 månader inkluderades 942 patienter med misstänkt stroke varav 53 % fick diagnos stroke/TIA vid utskrivning från sjukhuset. Patienterna med Prioritet 1 kom 13 minuter snabbare till sjukhus från larmsamtal, jämfört med patienterna i kontrollgruppen, och 23 minuter snabbare från larmsamtal till ankomst till strokeenhet. Dubbelt så många patienter fick trombolys i Prioritet 1-gruppen jämfört med kontrollgruppen (17 %). För att öka prioriteten hos strokepatienter måste stroke först identifieras varpå de följande studierna kom att inrikta sig på identifiering av stroke i larmsamtal till SOS Alarm.

Studie II syftade till att undersöka identifiering av de patienter som randomiserades för misstänkt stroke i studie I. För att underlätta identifiering av stroke infördes Face-Arm-Speech-Time testet, FAST, (på svenska även benämnt AKUT), på SOS Alarm och i ambulansen i Stockholm. I FAST testas ansiktsförlamning, armsvaghet och talsvårigheter. Användning av FAST var frivilligt för SOS Alarms sjuksköterskor medan ambulanspersonalen skattade alla patienter. I studien analyserades 900 patienter då 42 patienter saknade uppgift om inklusion av SOS Alarm eller ambulans. SOS Alarm

identifierade 71 % av alla stroke/TIA patienter i studien och ambulansen identifierade ytterligare 29 % av patienterna i studien som alltså inte hade identifierats i larmsamtalet. FAST testet visade ett positivt prediktivt värde på 56 % av de SOS Alarm-inkluderade patienterna och 74 % av de ambulansinkluderade patienterna. FAST angavs också positivt i en stor andel patienter som inte fick diagnos stroke/TIA.

Studie III syftade till att undersöka hur stroke presenterades i larmsamtal angående patienter med stroke, vilka symtom som framkom och om FAST symtom presenterades eller efterfrågades. Inspelade autentiska larmsamtal analyserades retrospektivt och av de 179 larmsamtal som analyserades utlarmades 64 % som stroke. Talsvårigheter (54 %), fall eller att patienten befanns liggande (38 %) respektive mental påverkan (27 %) var de vanligast förekommande symtomen. Av de samtal som inte utlarmades som stroke dominerade fall eller att ha hittats i liggande position (66 %). I samtalen som utlarmades som stroke framkom traditionella strokesymtom i högre utsträckning än i de samtal som utlarmades som annat än stroke.

Studie IV syftade till att undersöka hinder och underlättande faktorer för identifiering av stroke i larmsamtal i kommunikation och interaktion. I en tolkande fenomenologisk analys framkom sex olika teman innehållande hinder och möjligheter till identifiering av stroke. De viktigaste fynden var aspekter kring larmoperatörens och sjuksköterskans auktoritet, sjuksköterskans stödjande och vägledande strategier samt sjuksköterskans expertkunskaper vilka alla kan påverkas och förbättras. Faktorer kring patient, inringare och situation kan inte påverkas annat än genom att stärka de påverkbara faktorerna hos larmoperatör och sjuksköterska. Överlämning av larmsamtal från larmoperatör till sjuksköterska var ett potentiellt hinder där information och tid kunde gå förlorat. Sjuksköterskans expertkunskaper var det enda som befanns avgörande för identifiering av stroke i studien.

SLUTSATS

Sammanfattningsvis visar denna avhandling att Prioritet 1 från SOS Alarm förkortar tid för ankomst till strokeenhet och ökar möjlighet till trombolysbehandling för patienter med ischemisk stroke. För korrekt prioritering vid larmsamtal till SOS Alarm behöver tillståndet identifieras som stroke vilket försvåras när strokesymtom inte framkommer. FAST symtom framkommer i 90 % spontant från inringaren och förekommer i högre utsträckning hos patienter som identifierats som stroke av SOS Alarm. Av de strokepatienter som inte identifierades som stroke framkom fall eller att patienten befanns i liggande position som dominerande problem. Därmed skulle FAST test kunna användas aktivt för att öka identifiering av möjlig stroke i larmsamtal där fall/liggande läge presenteras. Andra faktorer som kan stödja och underlätta identifiering av stroke i larmsamtal är auktoritet, stöd och support från larmoperatör och sjuksköterskor samt expert kompetens hos sjuksköterskans på SOS Alarm.

11 ACKNOWLEDGEMENTS

I would like to gratefully thank all of you contributing and making this thesis possible. Numerous persons have inspired, supported, and encouraged me during the process. There have also been lots of persons involved in the studies contributing with commitment and work leading to all this data and results.

In particular I would like to thank all the patients for contribution and bringing new knowledge about stroke.

I wish to express my special thanks to my supervisors:

Mia von Euler, my main supervisor, for your enthusiastic support, your dedication and for always sharing knowledge and ideas. Thank you for having confidence and trust in me.

Katarina Bohm, my supervisor, for support and coaching, for sharing knowledge of the prehospital perspective and letting me join your research group in instructive activities.

Karin Schenck-Gustafsson, my supervisor, for introducing a new interesting perspective of sex and gender in my world, for support and encouragement.

Nils Wahlgren, my supervisor and one of the initiators to the HASTA project, for giving me the opportunity to be a part of the project.

I also would like to thank the following persons who have encouraged me in my work:

Leif Svensson, one of the initiators to the HASTA project, for giving me the opportunity to work in the project, and letting me take part of this exiting journey of learning. Thank you for the challenges, the support and for taking me in to your group of competent co-workers at Stockholms Prehospitala Centrum.

Veronica Vicente, my colleague, for pushing me forward, enthusiastically coaching, explaining and letting me take part of your journey to dissertation. You have really been a source of inspiration.

Tor-Björn Käll for presenting me to opportunities, this time for introducing me to the HASTA project leading to this thesis. For having confidence in me, giving me responsibility and for the cooperation during the years.

Kristiina Heikkilä for guiding me firmly and confidently through the qualitative work, with great skills, patients and adaption to my process of understanding.

Maaret Castrén: for support, ideas and opportunities of studies concerning emergency calls.

Hanna Lachmann and ***Monica Rådestad***, my dear doctoral friends and colleagues, for comfort, encouragement, sharing of knowledge, joy and good food.

Eva Nygren and ***Inger Eriksson***, my friends and colleagues, for support, trust and nice chats on the way.

The Stroke nurses and colleagues at the stroke unit at Södersjukhuset for the contribution in the HASTA project, for support and understanding.

Lina Benson and ***Hans Pettersson*** for help and support with statistical matters.

Anita Hansson-Tyrén for the contribution and great efforts in the HASTA project.

My former colleagues at Stockholms Prehospitala Centrum, SPC, for great inspiration and support.

Nurses and assisting nurses in the ambulance units in Stockholm for your enthusiasm and commitment in the patients, for participating and cooperating in the studies as well as in clinic.

The nurses and call-takers in SOS Alarm AB in Stockholm for your interest and commitment in the studies, for participation, cooperation and teaching me about your challenges and letting me take part of the emergency calls.

The stroke physicians, nurses and assisting nurses in the stroke units , emergency departments and intensive care units involved in the acute stroke care at Danderyds sjukhuset, Karolinska sjukhuset Huddinge and Solna, Capio St Görans sjukhus, Södersjukhuset, Södertälje and Norrtälje sjukhus for contribution and cooperation in the HASTA project.

And finally, all my love to my family that have always been standing behind me, supporting, loving and caring

My dear children Johanna, Ida and ***Simon***
My dear mother Gullwi and her husband ***Mats***
Anders my dear partner in life
You mean everything to me

This thesis was financially supported by Center for Gender Medicine, Kvinnors Hälsa, the Erika Lederhausen Foundation, the Swedish Stroke Association, funding by Karolinska Institutet and from the regional agreement on medical training and clinical research (A.L.F.) between the Stockholm County Council and Karolinska Institutet, the Falck research foundation. This thesis is part of the Fighting Stroke Project (Uppdrag Besegra Stroke) supported by the Swedish Heart and Lung Foundation and Karolinska Institutet; funding from Friends of Karolinska Institutet, USA, and Johanniterorden also support the project.

12 REFERENCES

1. Läkemedelsverket MPA. Läkemedelsverket 2003. 2003;14(1):[Medical Products Agency]. Available from: http://www.lakemedelsverket.se/malgrupp/Halso---sjukvard/Monografier-varderingar/Monografier-Humanlakemedel/Humanlakemedel-Arkiv/Actilyse-alteplas---Ny-indikation/.

2. Tissue plasminogen activator for acute ischemic stroke. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. The New England journal of medicine. 1995;333(24):1581-7.

3. Hacke W, Donnan G, Fieschi C, Kaste M, von Kummer R, Broderick JP, et al. Association of outcome with early stroke treatment: pooled analysis of ATLANTIS, ECASS, and NINDS rt-PA stroke trials. Lancet. 2004;363(9411):768-74.

4. Wardlaw JM, Murray V, Berge E, del Zoppo G, Sandercock P, Lindley RL, et al. Recombinant tissue plasminogen activator for acute ischaemic stroke: an updated systematic review and meta-analysis. Lancet. 2012;379(9834):2364-72.

5. Saver JL. Time is brain--quantified. Stroke. 2006;37(1):263-6.

6. Meretoja A, Keshtkaran M, Saver JL, Tatlisumak T, Parsons MW, Kaste M, et al. Stroke Thrombolysis: Save a Minute, Save a Day. Stroke. 2014.

7. Riks-Stroke. Riks-Stroke The Swedish Stroke register: www.riks-stroke.org; 2007. Årsrapport 2007]. Available from: http://www.riks-stroke.org.

8. Organised inpatient (stroke unit) care for stroke. Cochrane Database Syst Rev. 2013;9:Cd000197.

9. Feigin VL, Forouzanfar MH, Krishnamurthi R, Mensah GA, Connor M, Bennett DA, et al. Global and regional burden of stroke during 1990-2010: findings from the Global Burden of Disease Study 2010. Lancet. 2014;383(9913):245-54.

10. Cardiology ESo. 2012 European Cardiovascular Disease Statistics 2012. 2012 European Cardiovascular Disease Statistics]. Available from: http://www.escardio.org/about/documents/eu-cardiovascular-disease-statistics-2012.pdf.

11. Riks-Stroke. Riks-Stroke The Swedish Stroke register www.riks-stroke.org2013 [cited 2015]. Available from: http://www.riksstroke.org/sve/forskning-statistik-och-verksamhetsutveckling/forskning/arsrapporter/.

12. Appelros P, Jonsson F, Asberg S, Asplund K, Glader EL, Asberg KH, et al. Trends in stroke treatment and outcome between 1995 and 2010: observations from Riks-Stroke, the Swedish stroke register. Cerebrovasc Dis. 2014;37(1):22-9.

13. Organization WH. WHO STEPS Stroke Manual Geneva: World Health Organization; 2006. The WHO STEPwise approach to stroke surveillance]. Available from: http://www.who.int/chp/steps/Manual.pdf.

14. Socialstyrelsen TNBoHaW. Nationella riktlinjer för stroke vård: Socialstyrelsen, The National Board of Health and Welfare; 2009. National guidelines for stroke care 2009]. Available from: http://www.socialstyrelsen.se/Lists/Artikelkatalog/Attachments/17790/2009-11-4.pdf.

15. Donnan GA, Fisher M, Macleod M, Davis SM. Stroke. Lancet. 2008;371(9624):1612-23.

16. Easton JD, Saver JL, Albers GW, Alberts MJ, Chaturvedi S, Feldmann E, et al. Definition and evaluation of transient ischemic attack: a scientific statement for healthcare professionals from the American Heart Association/American Stroke Association Stroke Council; Council on Cardiovascular Surgery and Anesthesia; Council on Cardiovascular Radiology and Intervention; Council on Cardiovascular Nursing; and the Interdisciplinary Council on Peripheral Vascular Disease. The American Academy of Neurology affirms the value of this statement as an educational tool for neurologists. Stroke. 2009;40(6):2276-93.

17. Caplan LR. Caplan's Stroke (Fourth Edition) W.B. Saunders; 2009.

18. Burneo JG, Demaerschalk BM, Jenkins ME. Neurology An Evidence-based Approach. New York, N.Y.: Springer Verlag; 2012.

19. Wu CM, McLaughlin K, Lorenzetti DL, Hill MD, Manns BJ, Ghali WA. Early risk of stroke after transient ischemic attack: a systematic review and meta-analysis. Archives of internal medicine. 2007;167(22):2417-22.

20. Yu AY, Coutts SB. Stroke: Risk assessment to prevent recurrence after mild stroke or TIA. Nature reviews Neurology. 2015;11(3):131-3.

21. Hossmann KA. Pathophysiology and therapy of experimental stroke. Cellular and molecular neurobiology. 2006;26(7-8):1057-83.

22. Doyle KP, Simon RP, Stenzel-Poore MP. Mechanisms of ischemic brain damage. Neuropharmacology. 2008;55(3):310-8.

23. Brouns R, De Deyn PP. The complexity of neurobiological processes in acute ischemic stroke. Clinical neurology and neurosurgery. 2009;111(6):483-95.

24. Stock EO, Redberg R. Cardiovascular disease in women. Current problems in cardiology. 2012;37(11):450-526.

25. Gibson CL. Cerebral ischemic stroke: is gender important? Journal of cerebral blood flow and metabolism : official journal of the International Society of Cerebral Blood Flow and Metabolism. 2013;33(9):1355-61.

26. Reeves MJ, Bushnell CD, Howard G, Gargano JW, Duncan PW, Lynch G, et al. Sex differences in stroke: epidemiology, clinical presentation, medical care, and outcomes. The Lancet Neurology. 2008;7(10):915-26.

27. Santalucia P, Pezzella FR, Sessa M, Monaco S, Torgano G, Anticoli S, et al. Sex differences in clinical presentation, severity and outcome of stroke: results from a hospital-based registry. European journal of internal medicine. 2013;24(2):167-71.

28. Jamieson DG, Skliut M. Gender considerations in stroke management. The neurologist. 2009;15(3):132-41.

29. Reid JM, Dai D, Gubitz GJ, Kapral MK, Christian C, Phillips SJ. Gender differences in stroke examined in a 10-year cohort of patients admitted to a Canadian teaching hospital. Stroke. 2008;39(4):1090-5.

30. Nagaraja N, Bhattacharya P, Mada F, Salowich-Palm L, Hinton S, Millis S, et al. Gender based differences in acute stroke care in Michigan hospitals. Journal of the neurological sciences. 2012;314(1-2):88-91.

31. Niewada M, Kobayashi A, Sandercock PA, Kaminski B, Czlonkowska A. Influence of gender on baseline features and clinical outcomes among 17,370 patients with confirmed ischaemic stroke in the international stroke trial. Neuroepidemiology. 2005;24(3):123-8.

32. Petrea RE, Beiser AS, Seshadri S, Kelly-Hayes M, Kase CS, Wolf PA. Gender differences in stroke incidence and poststroke disability in the Framingham heart study. Stroke. 2009;40(4):1032-7.

33. Gargano JW, Wehner S, Reeves M. Sex differences in acute stroke care in a statewide stroke registry. Stroke. 2008;39(1):24-9.

34. Di Carlo A, Lamassa M, Baldereschi M, Pracucci G, Basile AM, Wolfe CD, et al. Sex differences in the clinical presentation, resource use, and 3-month outcome of acute stroke in Europe: data from a multicenter multinational hospital-based registry. Stroke. 2003;34(5):1114-9.

35. Eriksson M, Glader EL, Norrving B, Terent A, Stegmayr B. Sex differences in stroke care and outcome in the Swedish national quality register for stroke care. Stroke. 2009;40(3):909-14.

36. Glader EL, Stegmayr B, Norrving B, Terent A, Hulter-Asberg K, Wester PO, et al. Sex differences in management and outcome after stroke: a Swedish national perspective. Stroke. 2003;34(8):1970-5.

37. Appelros P, Stegmayr B, Terent A. A review on sex differences in stroke treatment and outcome. Acta neurologica Scandinavica. 2010;121(6):359-69.

38. Park SJ, Shin SD, Ro YS, Song KJ, Oh J. Gender differences in emergency stroke care and hospital outcome in acute ischemic stroke: a multicenter observational study. The American journal of emergency medicine. 2013;31(1):178-84.

39. Reeves M, Bhatt A, Jajou P, Brown M, Lisabeth L. Sex differences in the use of intravenous rt-PA thrombolysis treatment for acute ischemic stroke: a meta-analysis. Stroke. 2009;40(5):1743-9.

40. Lorenzano S, Ahmed N, Falcou A, Mikulik R, Tatlisumak T, Roffe C, et al. Does sex influence the response to intravenous thrombolysis in ischemic stroke?: answers from safe implementation of treatments in Stroke-International Stroke Thrombolysis Register. Stroke. 2013;44(12):3401-6.

41. Meseguer E, Mazighi M, Labreuche J, Arnaiz C, Cabrejo L, Slaoui T, et al. Outcomes of intravenous recombinant tissue plasminogen activator therapy according to gender: a clinical registry study and systematic review. Stroke. 2009;40(6):2104-10.

42. Nathanson D, Patrone C, Nystrom T, von Euler M. Sex, diastolic blood pressure, and outcome after thrombolysis for ischemic stroke. 2014;2014:747458.

43. van Swieten JC, Koudstaal PJ, Visser MC, Schouten HJ, van Gijn J. Interobserver agreement for the assessment of handicap in stroke patients. Stroke. 1988;19(5):604-7.

44. Sulter G, Steen C, De Keyser J. Use of the Barthel index and modified Rankin scale in acute stroke trials. Stroke. 1999;30(8):1538-41.

45. Wahlgren N, Ahmed N, Davalos A, Hacke W, Millan M, Muir K, et al. Thrombolysis with alteplase 3-4.5 h after acute ischaemic stroke (SITS-ISTR): an observational study. Lancet. 2008;372(9646):1303-9.

46. Hacke W, Kaste M, Bluhmki E, Brozman M, Davalos A, Guidetti D, et al. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. The New England journal of medicine. 2008;359(13):1317-29.

47. Wardlaw JM, del Zoppo G, Yamaguchi T. Thrombolysis for acute ischaemic stroke. Cochrane Database Syst Rev. 2000(2):Cd000213.

48. Strbian D, Soinne L, Sairanen T, Happola O, Lindsberg PJ, Tatlisumak T, et al. Ultraearly thrombolysis in acute ischemic stroke is associated with better outcome and lower mortality. Stroke. 2010;41(4):712-6.

49. Ahmed N, Wahlgren N, Grond M, Hennerici M, Lees KR, Mikulik R, et al. Implementation and outcome of thrombolysis with alteplase 3-4.5 h after an acute stroke: an updated analysis from SITS-ISTR. Lancet neurology. 2010;9(9):866-74.

50. Ford GA, Ahmed N, Azevedo E, Grond M, Larrue V, Lindsberg PJ, et al. Intravenous alteplase for stroke in those older than 80 years old. Stroke. 2010;41(11):2568-74.

51. Meretoja A, Putaala J, Tatlisumak T, Atula S, Artto V, Curtze S, et al. Off-label thrombolysis is not associated with poor outcome in patients with stroke. Stroke. 2010;41(7):1450-8.

52. Wardlaw JM, Murray V, Berge E, del Zoppo GJ. Thrombolysis for acute ischaemic stroke. Cochrane Database Syst Rev. 2014;7:Cd000213.

53. Sandercock P, Wardlaw JM, Lindley RI, Dennis M, Cohen G, Murray G, et al. The benefits and harms of intravenous thrombolysis with recombinant tissue plasminogen activator within 6 h of acute ischaemic stroke (the third international stroke trial [IST-3]): a randomised controlled trial. Lancet. 2012;379(9834):2352-63.

54. Grotta JC, Burgin WS, El-Mitwalli A, Long M, Campbell M, Morgenstern LB, et al. Intravenous tissue-type plasminogen activator therapy for ischemic stroke: Houston experience 1996 to 2000. Archives of neurology. 2001;58(12):2009-13.

55. Boode B, Welzen V, Franke C, van Oostenbrugge R. Estimating the number of stroke patients eligible for thrombolytic treatment if delay could be avoided. Cerebrovasc Dis. 2007;23(4):294-8.

56. Berkhemer OA, Fransen PS, Beumer D, van den Berg LA, Lingsma HF, Yoo AJ, et al. A randomized trial of intraarterial treatment for acute ischemic stroke. The New England journal of medicine. 2015;372(1):11-20.

57. Davalos A, Pereira VM, Chapot R, Bonafe A, Andersson T, Gralla J. Retrospective multicenter study of Solitaire FR for revascularization in the treatment of acute ischemic stroke. Stroke. 2012;43(10):2699-705.

58. Andersson T, Kuntze Soderqvist A, Soderman M, Holmin S, Wahlgren N, Kaijser M. Mechanical thrombectomy as the primary treatment for acute basilar artery occlusion: experience from 5 years of practice. Journal of neurointerventional surgery. 2013;5(3):221-5.

59. Sheth SA, Sanossian N, Hao Q, Starkman S, Ali LK, Kim D, et al. Collateral flow as causative of good outcomes in endovascular stroke therapy. Journal of neurointerventional surgery. 2014.

60. Lescher S, Czeppan K, Porto L, Singer OC, Berkefeld J. Acute stroke and obstruction of the extracranial carotid artery combined with intracranial tandem occlusion:

results of interventional revascularization. Cardiovascular and interventional radiology. 2015;38(2):304-13.

61. Deshaies EM, Singla A, Villwock MR, Padalino DJ, Sharma S, Swarnkar A. Early experience with stent retrievers and comparison with previous-generation mechanical thrombectomy devices for acute ischemic stroke. Journal of neurosurgery. 2014;121(1):12-7.

62. Gratz PP, Jung S, Schroth G, Gralla J, Mordasini P, Hsieh K, et al. Outcome of standard and high-risk patients with acute anterior circulation stroke after stent retriever thrombectomy. Stroke. 2014;45(1):152-8.

63. Tomsick TA, Yeatts SD, Liebeskind DS, Carrozzella J, Foster L, Goyal M, et al. Endovascular revascularization results in IMS III: intracranial ICA and M1 occlusions. Journal of neurointerventional surgery. 2014.

64. Goyal M, Demchuk AM, Menon BK, Eesa M, Rempel JL, Thornton J, et al. Randomized assessment of rapid endovascular treatment of ischemic stroke. The New England journal of medicine. 2015;372(11):1019-30.

65. Campbell BC, Mitchell PJ, Kleinig TJ, Dewey HM, Churilov L, Yassi N, et al. Endovascular therapy for ischemic stroke with perfusion-imaging selection. The New England journal of medicine. 2015;372(11):1009-18.

66. Saver JL, Goyal M, Bonafe A, Diener HC, Levy EI, Pereira VM, et al. Stent-Retriever Thrombectomy after Intravenous t-PA vs. t-PA Alone in Stroke. The New England journal of medicine. 2015.

67. Jovin TG, Chamorro A, Cobo E, de Miquel MA, Molina CA, Rovira A, et al. Thrombectomy within 8 Hours after Symptom Onset in Ischemic Stroke. The New England journal of medicine. 2015.

68. Kwan J, Hand P, Sandercock P. A systematic review of barriers to delivery of thrombolysis for acute stroke. Age Ageing. 2004;33(2):116-21.

69. Memis S, Tugrul E, Evci ED, Ergin F. Multiple causes for delay in arrival at hospital in acute stroke patients in Aydin, Turkey. BMC neurology. 2008;8:15.

70. Soomann M, Vibo R, Korv J. Acute stroke: why do some patients arrive in time and others do not? European journal of emergency medicine : official journal of the European Society for Emergency Medicine. 2014.

71. Mandelzweig L, Goldbourt U, Boyko V, Tanne D. Perceptual, social, and behavioral factors associated with delays in seeking medical care in patients with symptoms of acute stroke. Stroke. 2006;37(5):1248-53.

72. Malek AM, Adams RJ, Debenham E, Boan AD, Kazley AS, Hyacinth HI, et al. Patient awareness and perception of stroke symptoms and the use of 911. J Stroke Cerebrovasc Dis. 2014;23(9):2362-71.

73. Mosley I, Nicol M, Donnan G, Patrick I, Dewey H. Stroke symptoms and the decision to call for an ambulance. Stroke. 2007;38(2):361-6.

74. George MG, Tong X, McGruder H, Yoon P, Rosamond W, Winquist A, et al. Paul Coverdell National Acute Stroke Registry Surveillance - four states, 2005-2007. Morbidity and mortality weekly report Surveillance summaries (Washington, DC : 2002). 2009;58(7):1-23.

75. Iosif C, Papathanasiou M, Staboulis E, Gouliamos A. Social factors influencing hospital arrival time in acute ischemic stroke patients. Neuroradiology. 2012;54(4):361-7.

76. Nationella Strokekampanjen www.strokekampanjen.se: The campaign is backed by Sweden's county councils and regions; 2014 [updated 2014-01-22; cited 2014 2014-01-22]. The Swedish National Stroke campaign]. Available from: http://strokekampanjen.se/.

77. Dombrowski SU, Mackintosh JE, Sniehotta FF, Araujo-Soares V, Rodgers H, Thomson RG, et al. The impact of the UK 'Act FAST' stroke awareness campaign: content analysis of patients, witness and primary care clinicians' perceptions. BMC public health. 2013;13(1):915.

78. Dombrowski SU, White M, Mackintosh JE, Gellert P, Araujo-Soares V, Thomson RG, et al. The stroke 'Act FAST' campaign: Remembered but not understood? Int J Stroke. 2014.

79. Miller ET, King KA, Miller R, Kleindorfer D. FAST Stroke Prevention Educational Program for Middle School Students: pilot study results. The Journal of neuroscience nursing : journal of the American Association of Neuroscience Nurses. 2007;39(4):236-42.

80. Bray JE, Mosley I, Bailey M, Barger B, Bladin C. Stroke public awareness campaigns have increased ambulance dispatches for stroke in Melbourne, Australia. Stroke. 2011;42(8):2154-7.

81. Kleindorfer DO, Miller R, Moomaw CJ, Alwell K, Broderick JP, Khoury J, et al. Designing a message for public education regarding stroke: does FAST capture enough stroke? Stroke. 2007;38(10):2864-8.

82. Nordanstig A, Jood K, Rosengren L. Public stroke awareness and intent to call 112 in Sweden. Acta neurologica Scandinavica. 2014;130(6):400-4.

83. Ellis C, Egede LE. Stroke recognition among individuals with stroke risk factors. The American journal of the medical sciences. 2009;337(1):5-10.

84. Milner A, Lewis WJ, Ellis C. Knowledge of stroke risk factors and early warning signs of stroke among students enrolled in allied health programs: a pilot study. Journal of allied health. 2008;37(4):e296-315.

85. Billings-Gagliardi S, Mazor KM. Development and validation of the stroke action test. Stroke. 2005;36(5):1035-9.

86. Puolakka T, Vayrynen T, Happola O, Soinne L, Kuisma M, Lindsberg PJ. Sequential analysis of pretreatment delays in stroke thrombolysis. Academic emergency medicine : official journal of the Society for Academic Emergency Medicine. 2010;17(9):965-9.

87. Nagaraja N, Bhattacharya P, Norris G, Coplin W, Narayanan S, Xavier A, et al. Arrival by ambulance is associated with acute stroke intervention in young adults. Journal of the neurological sciences. 2012;316(1-2):168-9.

88. Sobesky J, Frackowiak M, Zaro Weber O, Hahn M, Moller-Hartmann W, Rudolf J, et al. The Cologne stroke experience: safety and outcome in 450 patients treated with intravenous thrombolysis. Cerebrovasc Dis. 2007;24(1):56-65.

89. Gache K, Couralet M, Nitenberg G, Leleu H, Minvielle E. The role of calling EMS versus using private transportation in improving the management of stroke in France. Prehospital emergency care : official journal of the National Association of EMS Physicians and the National Association of State EMS Directors. 2013;17(2):217-22.

90. Ekundayo OJ, Saver JL, Fonarow GC, Schwamm LH, Xian Y, Zhao X, et al. Patterns of emergency medical services use and its association with timely stroke treatment: findings from get with the guidelines-stroke. Circulation Cardiovascular quality and outcomes. 2013;6(3):262-9.

91. Fassbender K, Balucani C, Walter S, Levine SR, Haass A, Grotta J. Streamlining of prehospital stroke management: the golden hour. Lancet neurology. 2013;12(6):585-96.

92. Schroeder EB, Rosamond WD, Morris DL, Evenson KR, Hinn AR. Determinants of use of emergency medical services in a population with stroke symptoms: the Second Delay in Accessing Stroke Healthcare (DASH II) Study. Stroke. 2000;31(11):2591-6.

93. Derex L, Adeleine P, Nighoghossian N, Honnorat J, Trouillas P. Factors influencing early admission in a French stroke unit. Stroke. 2002;33(1):153-9.

94. Morris DL, Rosamond W, Madden K, Schultz C, Hamilton S. Prehospital and emergency department delays after acute stroke: the Genentech Stroke Presentation Survey. Stroke. 2000;31(11):2585-90.

95. Bohannon RW, Silverman IE, Ahlquist M. Time to emergency department arrival and its determinants in patients with acute ischemic stroke. Connecticut medicine. 2003;67(3):145-8.

96. Sekoranja L, Griesser AC, Wagner G, Njamnshi AK, Temperli P, Herrmann FR, et al. Factors influencing emergency delays in acute stroke management. Swiss medical weekly. 2009;139(27-28):393-9.

97. Rose KM, Rosamond WD, Huston SL, Murphy CV, Tegeler CH. Predictors of time from hospital arrival to initial brain-imaging among suspected stroke patients: the North Carolina Collaborative Stroke Registry. Stroke. 2008;39(12):3262-7.

98. Rosamond WD, Gorton RA, Hinn AR, Hohenhaus SM, Morris DL. Rapid response to stroke symptoms: the Delay in Accessing Stroke Healthcare (DASH) study. Academic emergency medicine : official journal of the Society for Academic Emergency Medicine. 1998;5(1):45-51.

99. Abilleira S, Lucente G, Ribera A, Permanyer-Miralda G, Gallofre M. Patient-related features associated with a delay in seeking care after stroke. European journal of neurology : the official journal of the European Federation of Neurological Societies. 2011;18(6):850-6.

100. Teuschl Y, Brainin M. Stroke education: discrepancies among factors influencing prehospital delay and stroke knowledge. Int J Stroke. 2010;5(3):187-208.

101. Prehospital and hospital delays after stroke onset--United States, 2005-2006. MMWR Morbidity and mortality weekly report. 2007;56(19):474-8.

102. Maestroni A, Mandelli C, Manganaro D, Zecca B, Rossi P, Monzani V, et al. Factors influencing delay in presentation for acute stroke in an emergency department in Milan, Italy. Emergency medicine journal : EMJ. 2008;25(6):340-5.

103. Bae HJ, Kim DH, Yoo NT, Choi JH, Huh JT, Cha JK, et al. Prehospital notification from the emergency medical service reduces the transfer and intra-hospital processing times for acute stroke patients. J Clin Neurol. 2010;6(3):138-42.

104. McKinney JS, Mylavarapu K, Lane J, Roberts V, Ohman-Strickland P, Merlin MA. Hospital prenotification of stroke patients by emergency medical services improves stroke time targets. J Stroke Cerebrovasc Dis. 2013;22(2):113-8.

105. Meretoja A, Strbian D, Mustanoja S, Tatlisumak T, Lindsberg PJ, Kaste M. Reducing in-hospital delay to 20 minutes in stroke thrombolysis. Neurology. 2012;79(4):306-13.

106. Gladstone DJ, Rodan LH, Sahlas DJ, Lee L, Murray BJ, Ween JE, et al. A citywide prehospital protocol increases access to stroke thrombolysis in Toronto. Stroke. 2009;40(12):3841-4.

107. Abdullah AR, Smith EE, Biddinger PD, Kalenderian D, Schwamm LH. Advance hospital notification by EMS in acute stroke is associated with shorter door-to-computed tomography time and increased likelihood of administration of tissue-plasminogen activator. Prehospital emergency care : official journal of the National Association of EMS Physicians and the National Association of State EMS Directors. 2008;12(4):426-31.

108. Kim SK, Lee SY, Bae HJ, Lee YS, Kim SY, Kang MJ, et al. Pre-hospital notification reduced the door-to-needle time for iv t-PA in acute ischaemic stroke. European journal of neurology : the official journal of the European Federation of Neurological Societies. 2009;16(12):1331-5.

109. Fonarow GC, Zhao X, Smith EE, Saver JL, Reeves MJ, Bhatt DL, et al. Door-to-needle times for tissue plasminogen activator administration and clinical outcomes in acute ischemic stroke before and after a quality improvement initiative. JAMA : the journal of the American Medical Association. 2014;311(16):1632-40.

110. Strbian D, Ahmed N, Wahlgren N, Lees KR, Toni D, Roffe C, et al. Trends in Door-to-Thrombolysis Time in the Safe Implementation of Stroke Thrombolysis Registry: Effect of Center Volume and Duration of Registry Membership. Stroke. 2015.

111. Rosamond WD, Evenson KR, Schroeder EB, Morris DL, Johnson AM, Brice JH. Calling emergency medical services for acute stroke: a study of 9-1-1 tapes. Prehospital emergency care : official journal of the National Association of EMS Physicians and the National Association of State EMS Directors. 2005;9(1):19-23.

112. Buck BH, Starkman S, Eckstein M, Kidwell CS, Haines J, Huang R, et al. Dispatcher recognition of stroke using the National Academy Medical Priority Dispatch System. Stroke. 2009;40(6):2027-30.

113. Studnek JR, Asimos A, Dodds J, Swanson D. Assessing the Validity of the Cincinnati Prehospital Stroke Scale and the Medic Prehospital Assessment for Code Stroke in an Urban Emergency Medical Services Agency. Prehospital emergency care : official journal of the National Association of EMS Physicians and the National Association of State EMS Directors. 2013.

114. Krebes S, Ebinger M, Baumann AM, Kellner PA, Rozanski M, Doepp F, et al. Development and validation of a dispatcher identification algorithm for stroke emergencies. Stroke. 2012;43(3):776-81.

115. Deakin CD, Alasaad M, King P, Thompson F. Is ambulance telephone triage using advanced medical priority dispatch protocols able to identify patients with acute stroke correctly? Emergency medicine journal : EMJ. 2009;26(6):442-5.

116. Chenaitia H, Lefevre O, Ho V, Squarcioni C, Pradel V, Fournier M, et al. Emergency medical service in the stroke chain of survival. European journal of emergency

medicine : official journal of the European Society for Emergency Medicine. 2013;20(1):39-44.

117. Caceres JA, Adil MM, Jadhav V, Chaudhry SA, Pawar S, Rodriguez GJ, et al. Diagnosis of Stroke by Emergency Medical Dispatchers and Its Impact on the Prehospital Care of Patients. J Stroke Cerebrovasc Dis. 2013.

118. De Luca A, Giorgi Rossi P, Villa GF. The use of Cincinnati Prehospital Stroke Scale during telephone dispatch interview increases the accuracy in identifying stroke and transient ischemic attack symptoms. BMC health services research. 2013;13:513.

119. Handschu R, Poppe R, Rauss J, Neundorfer B, Erbguth F. Emergency calls in acute stroke. Stroke. 2003;34(4):1005-9.

120. Mosley I, Nicol M, Donnan G, Patrick I, Kerr F, Dewey H. The impact of ambulance practice on acute stroke care. Stroke. 2007;38(10):2765-70.

121. Brainin M, Heiss W-D. Textbook of Stroke Medicine Cambridge: Cambridge University Press; 2009.

122. The World Health Organization W. Facta sheet Cardiovascular diseases 2015. Available from: http://www.who.int/mediacentre/factsheets/fs317/en/.

123. Hand PJ, Kwan J, Lindley RI, Dennis MS, Wardlaw JM. Distinguishing between stroke and mimic at the bedside: the brain attack study. Stroke. 2006;37(3):769-75.

124. Boulter DJ, Schaefer PW. Stroke and stroke mimics: a pattern-based approach. Seminars in roentgenology. 2014;49(1):22-38.

125. Lee W, Frayne J. Transient ischaemic attack clinic: An evaluation of diagnoses and clinical decision making. Journal of clinical neuroscience : official journal of the Neurosurgical Society of Australasia. 2014.

126. Noureddine A, Ghandehari K, Taghi Shakeri M. Differentiation of true transient ischemic attack versus transient ischemic attack mimics. Iranian journal of neurology. 2014;13(3):127-30.

127. Nadarajan V, Perry RJ, Johnson J, Werring DJ. Transient ischaemic attacks: mimics and chameleons. Practical neurology. 2014;14(1):23-31.

128. Jiang HL, Chan CP, Leung YK, Li YM, Graham CA, Rainer TH. Evaluation of the Recognition of Stroke in the Emergency Room (ROSIER) scale in Chinese patients in Hong Kong. PloS one. 2014;9(10):e109762.

129. Kanazawa Y, Morioka T, Arakawa S, Furuta Y, Nakanishi A, Kitazono T. Nonconvulsive Partial Status Epilepticus Mimicking Recurrent Infarction Revealed by Diffusion-weighted and Arterial Spin Labeling Perfusion Magnetic Resonance Images. J Stroke Cerebrovasc Dis. 2015.

130. Harbison J, Hossain O, Jenkinson D, Davis J, Louw SJ, Ford GA. Diagnostic accuracy of stroke referrals from primary care, emergency room physicians, and ambulance staff using the face arm speech test. Stroke. 2003;34(1):71-6.

131. Dupre CM, Libman R, Dupre SI, Katz JM, Rybinnik I, Kwiatkowski T. Stroke chameleons. J Stroke Cerebrovasc Dis. 2014;23(2):374-8.

132. Huff JS. Stroke mimics and chameleons. Emergency medicine clinics of North America. 2002;20(3):583-95.

133. Gargano JW, Wehner S, Reeves MJ. Do presenting symptoms explain sex differences in emergency department delays among patients with acute stroke? Stroke. 2009;40(4):1114-20.

134. Whiteley WN, Wardlaw JM, Dennis MS, Sandercock PA. Clinical scores for the identification of stroke and transient ischaemic attack in the emergency department: a cross-sectional study. Journal of neurology, neurosurgery, and psychiatry. 2011;82(9):1006-10.

135. Kidwell CS, Starkman S, Eckstein M, Weems K, Saver JL. Identifying stroke in the field. Prospective validation of the Los Angeles prehospital stroke screen (LAPSS). Stroke. 2000;31(1):71-6.

136. Frendl DM, Strauss DG, Underhill BK, Goldstein LB. Lack of impact of paramedic training and use of the cincinnati prehospital stroke scale on stroke patient identification and on-scene time. Stroke. 2009;40(3):754-6.

137. Bray JE, Martin J, Cooper G, Barger B, Bernard S, Bladin C. An interventional study to improve paramedic diagnosis of stroke. Prehospital emergency care : official journal of the National Association of EMS Physicians and the National Association of State EMS Directors. 2005;9(3):297-302.

138. Nor AM, McAllister C, Louw SJ, Dyker AG, Davis M, Jenkinson D, et al. Agreement between ambulance paramedic- and physician-recorded neurological signs with Face Arm Speech Test (FAST) in acute stroke patients. Stroke. 2004;35(6):1355-9.

139. Kothari RU, Pancioli A, Liu T, Brott T, Broderick J. Cincinnati Prehospital Stroke Scale: reproducibility and validity. Ann Emerg Med. 1999;33(4):373-8.

140. Brandler ES, Sharma M, Sinert RH, Levine SR. Prehospital stroke scales in urban environments: a systematic review. Neurology. 2014;82(24):2241-9.

141. Kothari R, Hall K, Brott T, Broderick J. Early stroke recognition: developing an out-of-hospital NIH Stroke Scale. Academic emergency medicine : official journal of the Society for Academic Emergency Medicine. 1997;4(10):986-90.

142. Bergs J, Sabbe M, Moons P. Prehospital stroke scales in a Belgian prehospital setting: a pilot study. European journal of emergency medicine : official journal of the European Society for Emergency Medicine. 2010;17(1):2-6.

143. Purrucker JC, Hametner C, Engelbrecht A, Bruckner T, Popp E, Poli S. Comparison of stroke recognition and stroke severity scores for stroke detection in a single cohort. Journal of neurology, neurosurgery, and psychiatry. 2014.

144. Kraywinkel K, Heidrich J, Heuschmann PU, Wagner M, Berger K. Stroke risk perception among participants of a stroke awareness campaign. BMC public health. 2007;7:39.

145. Flynn D, Ford GA, Rodgers H, Price C, Steen N, Thomson RG. A time series evaluation of the FAST National Stroke Awareness Campaign in England. PloS one. 2014;9(8):e104289.

146. Mellon L, Hickey A, Doyle F, Dolan E, Williams D. Can a media campaign change health service use in a population with stroke symptoms? Examination of the first Irish stroke awareness campaign. Emergency medicine journal : EMJ. 2013.

147. Inoue Y, Honda S, Watanabe M, Ando Y. Educational campaigns at point of purchase in rural supermarkets improve stroke knowledge. J Stroke Cerebrovasc Dis. 2015;24(2):480-4.

148. Mikulik R, Goldemund D, Reif M, Brichta J, Neumann J, Jarkovsky J, et al. Calling 911 in response to stroke: no change following a four-year educational campaign. Cerebrovasc Dis. 2011;32(4):342-8.

149. Worthmann H, Schwartz A, Heidenreich F, Sindern E, Lorenz R, Adams HA, et al. Educational campaign on stroke in an urban population in Northern Germany: influence on public stroke awareness and knowledge. Int J Stroke. 2013;8(5):286-92.

150. AB SA. Emergency Medical Communication Center, EMCC, in Sweden: SOS Alarm AB. Emergency Medical Communication Center, EMCC, in Sweden]. Available from: https://www.sosalarm.se/112/.

151. Mazzucco S, Turri G, Mirandola R, Bovi P, Bisoffi G. What is still missing in acute-phase treatment of stroke: a prospective observational study. Neurological sciences : official journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology. 2013;34(4):449-55.

152. Joux J, Olindo S, Girard-Claudon A, Chausson N, Saint-Vil M, Signate A, et al. Prehospital transfer medicalization increases thrombolysis rate in acute ischemic stroke. A French stroke unit experience. Clinical neurology and neurosurgery. 2013;115(9):1583-5.

153. Karlsten R, Elowsson P. Who calls for the ambulance: implications for decision support. A descriptive study from a Swedish dispatch centre. European journal of emergency medicine : official journal of the European Society for Emergency Medicine. 2004;11(3):125-9.

154. Jones SP, Carter B, Ford GA, Gibson JM, Leathley MJ, McAdam JJ, et al. The identification of acute stroke: an analysis of emergency calls. Int J Stroke. 2013;8(6):408-12.

155. Leathley MJ, Jones SP, Gibson JM, Ford GA, McAdam JJ, Quinn T, et al. "Can you send an ambulance please?": a comparison of callers' requests for emergency medical dispatch in non-stroke and stroke calls. Emergency medicine journal : EMJ. 2013.

156. Forslund K, Kihlgren A, Kihlgren M. Operators' experiences of emergency calls. Journal of telemedicine and telecare. 2004;10(5):290-7.

157. Holmström I. Telefonrådgivning inom hälso- och sjukvård. Lund: Studentlitteratur; 2008.

158. Medicinskt ledningsansvariga läkare AISAB F, Samariten. Medicinska Riktlinjer för ambulanssjukvården 2015 [2015-02-01]. Medical guidelines for the ambulance service]. Available from: http://www.vardgivarguiden.se/global/02_patientadministration/patientn%C3%A4ra%20rutiner/ambulanssjukv%C3%A5rd/2015%20medicinska%20behandlingsriktlinjer%20sll.pdf.

159. Sweden SS. SCB Statistics Sweden 2014. Statistics of Sweden. Available from: http://www.scb.se.

160. Lindsberg PJ, Happola O, Kallela M, Valanne L, Kuisma M, Kaste M. Door to thrombolysis: ER reorganization and reduced delays to acute stroke treatment. Neurology. 2006;67(2):334-6.

161. Socialstyrelsen TNBoHaW. Strokesjukvård, Vetenskapligt underlag

för Nationella riktlinjer 2009 Socialstyrelsen; 2009. Available from: http://www.socialstyrelsen.se/SiteCollectionDocuments/nr-stroke-vetenskapligt-underlag-2009-uppdatering.pdf.

162. European Stroke Initiative recommendations for stroke management. European Stroke Council, European Neurological Society and European Federation of Neurological Societies. Cerebrovasc Dis. 2000;10(5):335-51.

163. Benner PE. Interpretive phenomenology : embodiment, caring and ethics in health and illness. London: Sage; 1994.

164. Lopez KA, Willis DG. Descriptive versus interpretive phenomenology: their contributions to nursing knowledge. Qualitative health research. 2004;14(5):726-35.

165. Altman DG. Statistics with confidence : confidence intervals and statistical guidelines. London: BMJ Books; 2000.

166. The World Medical Association W. The World Medical Association Declaration of Helsinki: The World Medical Association 2013 [updated October 2013; cited 2015 January]. Ethical principles for medical research involving human subjects.]. Available from: http://www.wma.net/en/30publications/10policies/b3/index.html.pdf?print-media-type&footer-right=[page]/[toPage].

167. Barber PA, Zhang J, Demchuk AM, Hill MD, Buchan AM. Why are stroke patients excluded from TPA therapy? An analysis of patient eligibility. Neurology. 2001;56(8):1015-20.

168. Caceres JA, Adil MM, Jadhav V, Chaudhry SA, Pawar S, Rodriguez GJ, et al. Diagnosis of stroke by emergency medical dispatchers and its impact on the prehospital care of patients. J Stroke Cerebrovasc Dis. 2013;22(8):e610-4.

169. Watkins CL, Leathley MJ, Jones SP, Ford GA, Quinn T, Sutton CJ. Training emergency services' dispatchers to recognise stroke: an interrupted time-series analysis. BMC health services research. 2013;13:318.

170. Gropen TI, Gokaldas R, Poleshuck R, Spencer J, Janjua N, Szarek M, et al. Factors related to the sensitivity of emergency medical service impression of stroke. Prehospital emergency care : official journal of the National Association of EMS Physicians and the National Association of State EMS Directors. 2014;18(3):387-92.

171. Willeit J, Geley T, Schoch J, Rinner H, Tur A, Kreuzer H, et al. Thrombolysis and clinical outcome in patients with stroke after implementation of the Tyrol Stroke Pathway: a retrospective observational study. Lancet neurology. 2015;14(1):48-56.

172. Sohn SW, Park HS, Cha JK, Nah HW, Kim DH, Kang MJ, et al. A Systemized Stroke Code Significantly Reduced Time Intervals for Using Intravenous Tissue Plasminogen Activator under Magnetic Resonance Imaging Screening. J Stroke Cerebrovasc Dis. 2015;24(2):465-72.

173. Burnett MM, Zimmermann L, Coralic Z, Quon T, Whetstone W, Kim AS. Simple text-messaging intervention is associated with improved door-to-needle times for acute ischemic stroke. Stroke. 2014;45(12):3714-6.

174. Etgen T, Freudenberger T, Schwahn M, Rieder G, Sander D. Multimodal strategy in the successful implementation of a stroke unit in a community hospital. Acta neurologica Scandinavica. 2011;123(6):390-5.

175. De Luca A, Toni D, Lauria L, Sacchetti ML, Giorgi Rossi P, Ferri M, et al. An emergency clinical pathway for stroke patients--results of a cluster randomised trial (isrctn41456865). BMC health services research. 2009;9:14.

176. Hasegawa Y, Sasaki N, Yamada K, Ono H, Kumai J, Tsumura K, et al. Prediction of thrombolytic therapy after stroke-bypass transportation: the Maria Prehospital Stroke Scale score. J Stroke Cerebrovasc Dis. 2013;22(4):514-9.

177. Bray JE, Coughlan K, Barger B, Bladin C. Paramedic diagnosis of stroke: examining long-term use of the Melbourne Ambulance Stroke Screen (MASS) in the field. Stroke. 2010;41(7):1363-6.

178. Chenkin J, Gladstone DJ, Verbeek PR, Lindsay P, Fang J, Black SE, et al. Predictive value of the Ontario prehospital stroke screening tool for the identification of patients with acute stroke. Prehospital emergency care : official journal of the National Association of EMS Physicians and the National Association of State EMS Directors. 2009;13(2):153-9.

179. Kaps M, Grittner U, Jungehulsing G, Tatlisumak T, Kessler C, Schmidt R, et al. Clinical signs in young patients with stroke related to FAST: results of the sifap1 study. BMJ open. 2014;4(11):e005276.

180. Ellison SR, Gratton MC, Schwab RA, Ma OJ. Prehospital dispatch assessment of stroke. Mo Med. 2004;101(1):64-6.

181. Ramanujam P, Guluma KZ, Castillo EM, Chacon M, Jensen MB, Patel E, et al. Accuracy of stroke recognition by emergency medical dispatchers and paramedics--San Diego experience. Prehospital emergency care : official journal of the National Association of EMS Physicians and the National Association of State EMS Directors. 2008;12(3):307-13.

182. Marques-Baptista A, Ohman-Strickland P, Baldino KT, Prasto M, Merlin MA. Utilization of warning lights and siren based on hospital time-critical interventions. Prehospital and disaster medicine. 2010;25(4):335-9.

183. Ho J, Lindquist M. Time saved with the use of emergency warning lights and siren while responding to requests for emergency medical aid in a rural environment. Prehospital emergency care : official journal of the National Association of EMS Physicians and the National Association of State EMS Directors. 2001;5(2):159-62.

184. Lin CB, Peterson ED, Smith EE, Saver JL, Liang L, Xian Y, et al. Emergency medical service hospital prenotification is associated with improved evaluation and treatment of acute ischemic stroke. Circulation Cardiovascular quality and outcomes. 2012;5(4):514-22.

185. Desai JA, Smith EE. Prenotification and other factors involved in rapid tPA administration. Current atherosclerosis reports. 2013;15(7):337.

186. Patel MD, Rose KM, O'Brien EC, Rosamond WD. Prehospital notification by emergency medical services reduces delays in stroke evaluation: findings from the North Carolina stroke care collaborative. Stroke. 2011;42(8):2263-8.

187. Oostema JA, Nasiri M, Chassee T, Reeves MJ. The Quality of Prehospital Ischemic Stroke Care: Compliance with Guidelines and Impact on In-hospital Stroke Response. J Stroke Cerebrovasc Dis. 2014.

188. Prabhakaran S, O'Neill K, Stein-Spencer L, Walter J, Alberts MJ. Prehospital triage to primary stroke centers and rate of stroke thrombolysis. JAMA neurology. 2013;70(9):1126-32.

189. Dalloz MA, Bottin L, Muresan IP, Favrole P, Foulon S, Levy P, et al. Thrombolysis rate and impact of a stroke code: a French hospital experience and a systematic review. Journal of the neurological sciences. 2012;314(1-2):120-5.

190. Executive TESOE, Committee CatEW. European Stroke Organisation, ESO www.eso-stroke.org2008. ESO-Guidelines for Management of Ischaemic Stroke 2008]. Available from: http://www.congrex-switzerland.com/fileadmin/files/2013/eso-stroke/pdf/ESO08_Guidelines_Original_english.pdf.

191. Taylor J, Uchino K, Hussain MS, Carlson JN. Factors associated with delayed evaluation of patients with potential stroke in US EDs. The American journal of emergency medicine. 2014;32(11):1373-7.

192. Mehdiratta M, Woolfenden AR, Chapman KM, Johnston DC, Schulzer M, Beckman J, et al. Reduction in IV t-PA door to needle times using an Acute Stroke Triage Pathway. The Canadian journal of neurological sciences Le journal canadien des sciences neurologiques. 2006;33(2):214-6.

193. Nolte CH, Malzahn U, Kuhnle Y, Ploner CJ, Muller-Nordhorn J, Mockel M. Improvement of door-to-imaging time in acute stroke patients by implementation of an all-points alarm. J Stroke Cerebrovasc Dis. 2013;22(2):149-53.

194. Behrens S, Daffertshofer M, Interthal C, Ellinger K, van Ackern K, Hennerici M. Improvement in stroke quality management by an educational programme. Cerebrovasc Dis. 2002;13(4):262-6.

195. Asplund K, Glader EL, Norrving B, Eriksson M. Effects of extending the time window of thrombolysis to 4.5 hours: observations in the Swedish stroke register (riks-stroke). Stroke. 2011;42(9):2492-7.

196. Greenberg K, Maxwell CR, Moore KD, D'Ambrosio M, Liebman K, Veznedaroglu E, et al. Improved door-to-needle times and neurologic outcomes when intravenous tissue plasminogen activator is administered by emergency physicians with advanced neuroscience training. The American journal of emergency medicine. 2014.

197. Monks T, Pitt M, Stein K, James M. Maximizing the population benefit from thrombolysis in acute ischemic stroke: a modeling study of in-hospital delays. Stroke. 2012;43(10):2706-11.

198. Koennecke HC, Nohr R, Leistner S, Marx P. Intravenous tPA for ischemic stroke team performance over time, safety, and efficacy in a single-center, 2-year experience. Stroke. 2001;32(5):1074-8.

199. Qureshi AI, Kirmani JF, Sayed MA, Safdar A, Ahmed S, Ferguson R, et al. Time to hospital arrival, use of thrombolytics, and in-hospital outcomes in ischemic stroke. Neurology. 2005;64(12):2115-20.

200. Nikkhah K, Avan A, Shoeibi A, Azarpazhooh A, Ghandehari K, Foerch C, et al. Gaps and Hurdles Deter against Following Stroke Guidelines for Thrombolytic Therapy in Iran: Exploring the Problem. J Stroke Cerebrovasc Dis. 2015;24(2):408-15.

201. Minnerup J, Wersching H, Ringelstein EB, Schilling M, Schabitz WR, Wellmann J, et al. Impact of the Extended Thrombolysis Time Window on the Proportion of Recombinant Tissue-Type Plasminogen Activator-Treated Stroke Patients and on Door-to-Needle Time. Stroke. 2011.

202. de la Ossa NP, Sanchez-Ojanguren J, Palomeras E, Millan M, Arenillas JF, Dorado L, et al. Influence of the stroke code activation source on the outcome of acute ischemic stroke patients. Neurology. 2008;70(15):1238-43.

203. Lindsberg PJ, Soinne L, Roine RO, Salonen O, Tatlisumak T, Kallela M, et al. Community-based thrombolytic therapy of acute ischemic stroke in Helsinki. Stroke. 2003;34(6):1443-9.

204. O'Brien W, Crimmins D, Donaldson W, Risti R, Clarke TA, Whyte S, et al. FASTER (Face, Arm, Speech, Time, Emergency Response): experience of Central Coast Stroke Services implementation of a pre-hospital notification system for expedient management of acute stroke. Journal of clinical neuroscience : official journal of the Neurosurgical Society of Australasia. 2012;19(2):241-5.

205. Quain DA, Parsons MW, Loudfoot AR, Spratt NJ, Evans MK, Russell ML, et al. Improving access to acute stroke therapies: a controlled trial of organised pre-hospital and emergency care. The Medical journal of Australia. 2008;189(8):429-33.

206. Binning MJ, Sanfillippo G, Rosen W, D'Ambrosio M, Veznedaroglu E, Liebman K, et al. The Neurological Emergency Room and Pre-hospital Stroke Alert: The Whole is Greater Than the Sum of its Parts. Neurosurgery. 2013.

207. Mishra NK, Ahmed N, Andersen G, Egido JA, Lindsberg PJ, Ringleb PA, et al. Thrombolysis in very elderly people: controlled comparison of SITS International Stroke Thrombolysis Registry and Virtual International Stroke Trials Archive. BMJ (Clinical research ed). 2010;341:c6046.

208. Lever NM, Nystrom KV, Schindler JL, Halliday J, Wira C, 3rd, Funk M. Missed opportunities for recognition of ischemic stroke in the emergency department. Journal of emergency nursing: JEN : official publication of the Emergency Department Nurses Association. 2013;39(5):434-9.

209. Reginella RL, Crocco T, Tadros A, Shackleford A, Davis SM. Predictors of stroke during 9-1-1 calls: opportunities for improving EMS response. Prehospital emergency care : official journal of the National Association of EMS Physicians and the National Association of State EMS Directors. 2006;10(3):369-73.

210. Porteous GH, Corry MD, Smith WS. Emergency medical services dispatcher identification of stroke and transient ischemic attack. Prehospital emergency care : official journal of the National Association of EMS Physicians and the National Association of State EMS Directors. 1999;3(3):211-6.

211. Simpson PM, Bendall JC, Patterson J, Tiedemann A, Middleton PM, Close JC. Epidemiology of ambulance responses to older people who have fallen in New South Wales, Australia. Australasian journal on ageing. 2013;32(3):171-6.

212. Snooks HA, Halter M, Close JC, Cheung WY, Moore F, Roberts SE. Emergency care of older people who fall: a missed opportunity. Quality & safety in health care. 2006;15(6):390-2.

213. Lisabeth LD, Brown DL, Hughes R, Majersik JJ, Morgenstern LB. Acute stroke symptoms: comparing women and men. Stroke. 2009;40(6):2031-6.

214. Nor AM, Davis J, Sen B, Shipsey D, Louw SJ, Dyker AG, et al. The Recognition of Stroke in the Emergency Room (ROSIER) scale: development and validation of a stroke recognition instrument. Lancet neurology. 2005;4(11):727-34.

215. Mosley I, Nicol M, Donnan G, Thrift AG, Dewey HM. What is stroke symptom knowledge? Int J Stroke. 2013.

216. Robinson TG, Reid A, Haunton VJ, Wilson A, Naylor AR. The face arm speech test: does it encourage rapid recognition of important stroke warning symptoms? Emergency medicine journal : EMJ. 2013;30(6):467-71.

217. Blades LL, Oser CS, Dietrich DW, Okon NJ, Rodriguez DV, Burnett AM, et al. Rural community knowledge of stroke warning signs and risk factors. Preventing chronic disease. 2005;2(2):A14.

218. Caruso D, Perez Akly M, Costantini PD, Fridman S, Esnaola MM. Do Elderly Patients Call 911 When Presented with Clinical Scenarios Suggestive of Acute Stroke? A Cross-Sectional Study. Cerebrovasc Dis. 2015;39(2):87-93.

219. Das K, Mondal GP, Dutta AK, Mukherjee B, Mukherjee BB. Awareness of warning symptoms and risk factors of stroke in the general population and in survivors stroke. Journal of clinical neuroscience : official journal of the Neurosurgical Society of Australasia. 2007;14(1):12-6.

220. Greenlund KJ, Neff LJ, Zheng ZJ, Keenan NL, Giles WH, Ayala CA, et al. Low public recognition of major stroke symptoms. American journal of preventive medicine. 2003;25(4):315-9.

221. Marx JJ, Gube C, Faldum A, Kuntze H, Nedelmann M, Haertle B, et al. An educational multimedia campaign improves stroke knowledge and risk perception in different stroke risk groups. European journal of neurology : the official journal of the European Federation of Neurological Societies. 2009;16(5):612-8.

222. Ntaios G, Melikoki V, Perifanos G, Perlepe K, Gioulekas F, Karagiannaki A, et al. Poor Stroke Risk Perception despite Moderate Public Stroke Awareness: Insight from a Cross-sectional National Survey in Greece. J Stroke Cerebrovasc Dis. 2015.

223. Neau JP, Ingrand P, Godeneche G. Awareness within the French population concerning stroke signs, symptoms, and risk factors. Clinical neurology and neurosurgery. 2009;111(8):659-64.

224. Sundseth A, Faiz KW, Ronning OM, Thommessen B. Factors related to knowledge of stroke symptoms and risk factors in a norwegian stroke population. J Stroke Cerebrovasc Dis. 2014;23(7):1849-55.

225. Hux K, Rogers T, Mongar K. Common perceptions about strokes. Journal of community health. 2000;25(1):47-65.

226. Iguchi Y, Wada K, Shibazaki K, Inoue T, Ueno Y, Yamashita S, et al. First impression at stroke onset plays an important role in early hospital arrival. Internal medicine (Tokyo, Japan). 2006;45(7):447-51.

227. Faiz KW, Sundseth A, Thommessen B, Ronning OM. Reasons for low thrombolysis rate in a Norwegian ischemic stroke population. Neurological sciences : official journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology. 2014;35(12):1977-82.

228. Lindstrom V, Heikkila K, Bohm K, Castren M, Falk AC. Barriers and opportunities in assessing calls to emergency medical communication centre - a qualitative study. Scandinavian journal of trauma, resuscitation and emergency medicine. 2014;22(1):61.

229. Leppanen V. Power in telephone-advice nursing. Nursing inquiry. 2010;17(1):15-26.

230. Pettinari CJ, Jessopp L. "Your ears become your eyes": managing the absence of visibility in NHS Direct. Journal of advanced nursing. 2001;36(5):668-75.

231. Ek B, Svedlund M. Registered nurses' experiences of their decision-making at an Emergency Medical Dispatch Centre. Journal of clinical nursing. 2014.

232. Purc-Stephenson RJ, Thrasher C. Nurses' experiences with telephone triage and advice: a meta-ethnography. Journal of advanced nursing. 2010;66(3):482-94.

233. Stacey D, Graham ID, O'Connor AM, Pomey M-P. Barriers and Facilitators Influencing Call Center Nurses' Decision Support for Callers Facing Values-Sensitive Decisions: A Mixed Methods Study. Worldviews on Evidence-Based Nursing. 2005;2(4):184-95.

234. Kaminsky E, Rosenqvist U, Holmstrom I. Telenurses' understanding of work: detective or educator? Journal of advanced nursing. 2009;65(2):382-90.

235. Benner PE. From novice to expert : excellence and power in clinical nursing practice. Upper Saddle River, NJ: Prentice Hall; 2001.

236. Benner PE, Tanner CA, Chesla CA. Expertise in nursing practice : caring, clinical judgment, and ethics. New York, NY: Springer Pub. Co; 1996.

237. Foerch C, Czapowski D, Misselwitz B, Steinmetz H, Neumann-Haefelin T. Gender imbalances induced by age limits in stroke trials. Neuroepidemiology. 2010;35(3):226-30.

238. Labiche LA, Chan W, Saldin KR, Morgenstern LB. Sex and acute stroke presentation. Ann Emerg Med. 2002;40(5):453-60.

239. Barrett KM, Brott TG, Brown RD, Jr., Frankel MR, Worrall BB, Silliman SL, et al. Sex differences in stroke severity, symptoms, and deficits after first-ever ischemic stroke. J Stroke Cerebrovasc Dis. 2007;16(1):34-9.

240. Barr J, McKinley S, O'Brien E, Herkes G. Patient recognition of and response to symptoms of TIA or stroke. Neuroepidemiology. 2006;26(3):168-75.

241. Foerch C, Misselwitz B, Humpich M, Steinmetz H, Neumann-Haefelin T, Sitzer M. Sex disparity in the access of elderly patients to acute stroke care. Stroke. 2007;38(7):2123-6.

242. Sacco S, Cerone D, Carolei A. Gender and stroke: acute phase treatment and prevention. Functional neurology. 2009;24(1):45-52.

243. de Ridder I, Dirks M, Niessen L, Dippel D. Unequal access to treatment with intravenous alteplase for women with acute ischemic stroke. Stroke. 2013;44(9):2610-2.

244. Koton S, Telman G, Kimiagar I, Tanne D. Gender differences in characteristics, management and outcome at discharge and three months after stroke in a national acute stroke registry. International journal of cardiology. 2013;168(4):4081-4.

245. Hulley SB. Designing clinical research. Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins; 2007.

246. Polit DF, Beck CT. Nursing research : generating and assessing evidence for nursing practice. Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins; 2008.

247. Polit DF, Beck CT. Essentials of nursing research : appraising evidence for nursing practice. Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins; 2013.

248. Anfara VA, Brown KM, Mangione TL. Qualitative Analysis on Stage: Making the Research Process More Public. Educational Researcher. 2002;31(7):28-38.

249. Sandelowski M. The problem of rigor in qualitative research. ANS Advances in nursing science. 1986;8(3):27-37.

250. Houghton C, Casey D, Shaw D, Murphy K. Rigour in qualitative case-study research. Nurse researcher. 2013;20(4):12-7.

251. Mokin M, Kan P, Sivakanthan S, Veznedaroglu E, Binning MJ, Liebman KM, et al. Endovascular therapy of wake-up strokes in the modern era of stent retriever thrombectomy. Journal of neurointerventional surgery. 2015.

252. Koga M, Toyoda K, Kimura K, Yamamoto H, Sasaki M, Hamasaki T, et al. THrombolysis for Acute Wake-up and unclear-onset Strokes with alteplase at 0.6 mg/kg (THAWS) Trial. Int J Stroke. 2014;9(8):1117-24.

253. Aghaebrahim A, Leiva-Salinas C, Jadhav AP, Jankowitz B, Zaidi S, Jumaa M, et al. Outcomes after endovascular treatment for anterior circulation stroke presenting as wake-up strokes are not different than those with witnessed onset beyond 8 hours. Journal of neurointerventional surgery. 2014.

254. Thomalla G, Fiebach JB, Ostergaard L, Pedraza S, Thijs V, Nighoghossian N, et al. A multicenter, randomized, double-blind, placebo-controlled trial to test efficacy and safety of magnetic resonance imaging-based thrombolysis in wake-up stroke (WAKE-UP). Int J Stroke. 2014;9(6):829-36.

13 ORIGINAL PAPERS I-IV