

Anaesthesiology and Intensive Care Medicine  
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# **STROKE AND THE EMERGENCY MEDICAL SERVICES**

## **ENHANCING PERFORMANCE WITHIN THE CHAIN OF SURVIVAL**

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ACADEMIC DISSERTATION

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*History is made at night.*

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## ABSTRACT

Stroke is an important cause of death and disability in working age population. Eight out of 10 strokes are ischaemic and caused by the occlusion of a cerebral artery. The occluded vessel can be opened using intravenous thrombolytic treatment (IVT) or endovascular thrombectomy (EVT) within the first few hours after symptom onset. However, only a small proportion of all stroke patients have been able to receive this treatment mostly due to late hospital admission. Although the in-hospital pretreatment delay has been dramatically decreased by streamlining the operational efficiency of emergency departments, prehospital stroke care has received little attention.

The aim of the research done for this thesis was to describe the current performance of the Finnish emergency medical service (EMS) system in prehospital stroke care and explore new innovations to improve it. The study consisted of one retrospective and three prospective studies based on a combination of prehospital and in-hospital data.

The prehospital time intervals were analysed sequentially by studying a sample of 335 consecutive stroke patients who received IVT at Helsinki University Hospital (HUH) from 2003 to 2005. The consistent annual decrease in mean onset-to-treatment time (OTT) was reciprocated by the increasing number of treated patients. Both the OTT and the door-to-treatment time (DTT) were significantly reduced, whereas none of the prehospital time intervals (onset-to-door time, symptom-to-dispatch time, transportation time) changed appreciably. Alarm delay was shortened in proportion to stroke severity. The percentage of functionally independent patients in each group was expectedly strongly influenced by initial symptom severity, and the patients with more severe strokes tended to be older. The patients' median and IQR at baseline National Institutes of Health Stroke Scale (NIHSS) score was 10 points (IQR 7–16 points) and median modified Rankin Scale (mRS) score at 3 months was 2 (IQR 1–4). A total of 148 patients (55%) had a favourable outcome (mRS  $\leq 2$ ). Along with the expected predictors, age [OR 0.57 (95% CI, 0.42–0.77)] and stroke severity [OR 0.83 (95% CI, 0.78–0.88)], DTT [OR 0.47 (95% CI, 0.22–0.97)] remained as a predictor of a good outcome in the following regression analysis.

Enhancing the EMS performance by increasing the number of personnel on the scene was studied in the city of Tampere from 2010 to 2011. During the study period the ambulance personnel filled a case report form of 77 suspected acute stroke patients. The patients were divided into groups based on the use of a supportive fire engine unit on the scene and on-scene time (OST) duration. Despite that the fire engine support more than doubled the number of EMS personnel on the scene, no

change in OST or other prehospital time intervals was observed. Regression analysis showed that only the use of stroke code in ambulance dispatch was associated independently with a short OST (<22 minutes) [OR 3.95 (95% CI, 1.28–12.21)].

The significance of emergency phone call processing and prehospital symptom recognition and patient management in early hospital arrival and treatment was studied using a consecutive cohort of 308 patients who received recanalization therapy at HUH between 2010 and 2011. The emergency medical dispatchers (EMDs) used the stroke code in over two thirds of the calls and dispatched over 80% of the ambulances with high priority. The paramedics suspected over 90% of the patients were having a stroke and transported the patients using the high priority designation at nearly the same frequency. Bivariate analysis revealed the most predominant predictors of early hospital arrival (<90 minutes) and treatment (<2 hours) were transport using the stroke code ( $p < 0.01$ ), transport using the high priority designation ( $p < 0.001$ ), and short onset-to-call time (OCT) ( $p < 0.001$ ) and OST ( $p < 0.05$ ). Regarding the Face Arm Speech Time -algorithm, observing arm weakness in the paramedic examination clearly expedited the early treatment ( $p < 0.001$ ). The call-to-dispatch and ambulance response times were significantly shorter for early arrivals but the time differences were rather small (<1 minute). Although the most significant additional delay for late arriving patients (OTT > 2h) was the OCT (41 minutes), the single most dominant operational variable in the mean additional delays was OST, with >2 minutes of added delay. A binary logistic regression analysis revealed that the influences of ambulance transport using high priority and OCT prevailed as significant in both dichotomies of ODT <90 and OTT <120 minutes.

In 2015, a 45-minute training session and interactive follow-up group discussion was given to all ambulance crews operating in the HUH area. The aim of the training package was to ensure that ambulance transport of a “stroke thrombolysis candidate” would begin within the target interval of 20 minutes after arriving beside the patient. The EMS performance was measured four months before and after the training package was implemented. During the study period, the EMS transported 289 patients who were identified as potential thrombolysis candidates by EMDs and managed accordingly by the ambulance crews using the stroke code with high priority and a prenotification to the ED. 141 patients were registered before and 148 after the implementation of the training package. The groups did not differ in terms of patient age, sex, frequency of physician’s telephone consultations, or number of advanced life support–trained crews ( $p > 0.1$ ), but the training programme was found to decrease the OST from 25 to 22.5 minutes. However, this did not translate into net savings in the overall dispatch-to-hospital time, which remained at 45 minutes. ( $p > 0.1$ ) Consultation with a physician via telephone was associated with a longer OST in the univariate comparisons and multivariable regression model [OR 0.546 (95% CI, 0.333-0.893)], whereas ALS training of the EMS personnel promoted a

shorter OST [OR 1.760 (95% CI, 1.070-2.895)] when compared to basic life support-trained crews. Participation in the training programme showed a strong trend toward shorter OST durations ( $p > 0.05$ ).

As a conclusion, the most significant delays of the prehospital phase were seen in the decision to call the emergency phone number and OST. The EMDs successfully identified over two thirds and the ambulance crews >90% of acute stroke patients. Early emergency call, more severe symptoms and high priority ambulance transport were the most important determinants of early hospital arrival and treatment. Dispatching fire engine crews to support ambulances on the scene was not associated with decreased OST. However, implementing a systematic training package for EMS staff successfully decreased the OST by 10% and decreased the need to consult a physician.



## LIST OF PUBLICATIONS

- I. Puolakka T, Väyrynen T, Häppölä O, Soinne L, Kuisma M, Lindsberg PJ. Sequential analysis of pretreatment delays in stroke thrombolysis. *Acad Emerg Med* 2010;9:965–9.
- II. Puolakka T, Väyrynen T, Erkkilä E-P, Kuisma M. Fire engine support and on-scene time in prehospital stroke care – A prospective observational study. *Prehosp Disaster Med* 2016;3:278–81.
- III. Puolakka T, Strbian D, Harve H, Kuisma M, Lindsberg PJ. Prehospital phase of the stroke chain of survival: a prospective observational study. *J Am Heart Assoc* 2016;5:e002808.
- IV. Puolakka T, Kuisma M, Länkimäki S, Puolakka J, Hallikainen J, Rantanen K, Lindsberg PJ. Cutting the prehospital on-scene time of stroke thrombolysis in Helsinki: A prospective interventional study. *Stroke* 2016;47:3038–40.

## ABBREVIATIONS

ABCDE	Airway, breathing, circulation, disability, exposure
ALS	Advanced Life Support
BLS	Basic Life Support
CPSS	Cincinnati Prehospital Stroke Scale
CTA	Computer tomography angiography
DTT	Door-to-treatment time
ED	Emergency department
EMCC	Emergency medical communication centre
EMD	Emergency medical dispatcher
EMS	Emergency medical services
EMT	Emergency medical technician
EVT	Endovascular thrombectomy
FAST	Face Arm Speech (Time) -test
GBD	Global Burden of Disease
GCS	Glasgow Coma Score
HEMS	Helicopter emergency medical services
HUH	Helsinki University Hospital
ICH	Intracerebral haematoma
IQR	Interquartile range
IVT	Intravenous thrombolysis
LVO	Large-vessel occlusion
MICU	Mobile intensive care unit
MRI	Magnetic resonance imaging
mRS	modified Rankin Scale
MSU	Mobile Stroke Unit
NCCT	Non-contrast computer tomography
NIHSS	National Institutes of Health Stroke Scale
OCT	Onset-to-call time
ODT	Onset-to-door time
OST	On-scene time
OTT	Onset-to-treatment time
PCT	Perfusion computer tomography
RACE	Rapid Arterial Occlusion Evaluation -scale
rtPA	recombinant tissue Plasminogen Activator
SD	Standard deviation

SITS-MOST	Safe Implementation of Thrombolysis for Stroke – Monitoring Study
STEMO	Stroke Emergency Mobile
TIA	Transient ischaemic attack
TOAST	Trial of Org 10172 in Acute Stroke Treatment –scale

# 1 INTRODUCTION

Stroke is the second most common cause of death in the world and the most important cause of physical disability in working age populations. (Centers for Disease Control and Prevention 2009) It leads to a loss of quality-adjusted life expectancy that has been compared to a head injury sustained by a non-helmeted motorcyclist [Global Burden of Disease (GBD) Mortality and Causes of Death Collaborators 2016, Lee et al. 2010]. The consequential financial costs to society and health care systems worldwide are substantial (Meretoja et al. 2011a, Agency for Healthcare Research and Quality 2016). For the patients and their relatives stroke is an insidious emergency. Instead of clear warning signs it causes an uncommon bodily sensation – a sudden loss of function. The patient may be unable to seek medical care due to her/his sudden impairment or totally unaware of becoming acutely ill. Instead of a natural sense of urgency, stroke frequently causes confusion in the patients, their relatives and bystanders, further delaying hospital arrival (Alberts et al. 1990).

Although the possibilities to prevent the direct neuronal damage caused by intracerebral haemorrhage using early surgical techniques (Mendelow et al. 2005, Mendelow et al. 2013) or medical management (Mayer et al. 2008, Qureshi et al. 2016) are still few, the occluded cerebral artery in ischaemic stroke has become a prominent target for recanalization therapies. Since the mid-1990's, the development of intravenous thrombolysis (IVT) and endovascular thrombectomy (EVT) have dramatically increased the patients' odds for a good outcome by preventing loss of life, reducing disability and restoring neurological function. (del Zoppo et al. 1998, Wahlgren et al. 2007, Berkhemer et al. 2015) The development of acute stroke therapies has also led to a tremendous change in the prehospital care of acute neurological patients. In the early 1990's, suspected strokes were still frequently designated as 'non-urgent' by the emergency medical dispatchers (EMDs) and ambulances transported the patients without the need for lights and sirens. No one was in a hurry since specific treatment was not available. In 2017, ischaemic stroke is no longer a 'dead loss' but a neurological emergency where 'saving a minute can save the patient a whole day' (Gomez 1993, Camarata et al. 1994, Meretoja et al. 2014).

Unfortunately, recovery through recanalisation is not only a time-dependent but also a time-limited process where the results are better when the treatment is given earlier (Wahlgren et al. 2007, Hacke et al. 2008, Strbian et al 2013, Berkhemer et al. 2015). Since the patient's hospital arrival is often delayed, only few a percent of all stroke patients have been eligible to receive recanalization treatment (Barber et al. 2001, Wahlgren et al. 2007, Tong et al. 2012). Helsinki University Hospital (HUH)

has been actively involved from the beginning in the development of acute stroke treatment strategies. (Lindsberg et al. 2003, Lindsberg et al. 2006) By improving the in-hospital performance and developing a closer co-operation with the emergency medical service (EMS) system, the pretreatment delay has dramatically decreased and more patients have been able to receive acute stroke therapies. As a result of long-standing quality-assurance effort that was implemented to streamline the emergency department (ED) process, the door-to-treatment time (DTT) in Helsinki is among the fastest in the world. (Meretoja et al. 2012)

Currently, the EMS system has a critical position in the 'stroke chain of survival'. It is responsible of the rapid identification of acute stroke symptoms, stabilization of vital life functions, transportation of the patient to the appropriate hospital and alerting the stroke team (Jauch et al. 2010, Jauch et al. 2013). Arriving at the hospital via ambulance has been associated with shorter onset-to-treatment time (OTT) and increased likelihood of receiving IVT (Morris et al. 2000, Wojner et al. 2003, Turan et al. 2005). Nevertheless, only a fraction of all stroke patients can be currently treated within the 'golden hour'. (Fassbender et al. 2013) After the ED performance has reached a practical minimum delay, the relative proportion of prehospital delay has increased and thus the focus for shortening the onset to treatment delay is now on the prehospital environment (Meretoja et al. 2012).

The aim of this study was to describe the current performance of the EMS system in prehospital stroke care and explore new innovations to improve it.

## 2 REVIEW OF LITERATURE

### 2.1 ACUTE ISCHAEMIC STROKE

The human brain is the most complex structure known in the universe and one of the most densely perfused organs in the human body. It is not only the centre of the whole nervous system but also regulates other vital organs controlling many functions essential to human life. In an acute stroke, a sudden disruption in the brain circulation leads to the loss of cerebral function in the affected region. Approximately four out of five strokes are found to be ischaemic whereas the other one out of five are caused by intracranial haemorrhage (Thrift et al. 2001, Feigin et al. 2003). However, some variations to this exist in published reports due to ethnic dissimilarities and also methodological study differences. According to the American Heart Association, ischaemic stroke currently accounts for 87%, intracerebral haemorrhage (ICH) 10% and subarachnoid haemorrhage 3% of all stroke patients in the United States. (Mozaffarian et al. 2015) A study based on Finnish registry data found that the cause of the first-ever stroke suffered by the patients was ischaemic in 79%, ICH in 14% and subarachnoid haemorrhage in 7% of the cases (Meretoja et al. 2011b). The difference may be partially explained by the high incidence of intracranial aneurysms in the Finnish population (de Rooij et al. 2007).

#### 2.1.1 AETIOLOGY

An analysis of German and Finnish registries using the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification revealed that approximately 26% of strokes were caused by cardiac embolization, 20% by large vessel atherosclerosis, 20% by intracranial small vessel atherosclerosis, 7% by several simultaneous ethiological factors, 4% by other determined ethiological factors and 23% by unknown or cryptogenic causes (Grau et al. 2001, Putaala et al. 2009). The atypical causes for ischaemic stroke, including carotid and vertebral artery dissection and venous sinus thrombosis, are more prevalent in the young (<50 years old) (Grau et al. 2001, Stam 2005, Debette & Leys 2009, Putaala et al. 2009). Stroke in the young is also more often the result of a complex combination of underlying pathology such as genetic conditions such as blood vessel wall weakness, structural abnormalities such as patent foramen ovale and artero-venous malformation or acquired prothrombotic

states such as acute infection and pregnancy (Larrue et al. 2011). In fact, over 200 potential causes for ischaemic stroke have been described (Saver & Tamburi 1999, Bogousslavsky & Caplan 2008). Cryptogenic stroke has been estimated to account for as much as 10 to 40% of all ischaemic stroke cases in different registries (Saver 2016). Cerebral arteriopathy has been the most common cause of ischaemic stroke in children accounting for more than 50% of the cases (Ganesan et al. 2003, Mackay et al. 2011). Nearly half of paediatric strokes are haemorrhagic (Broderick et al. 1993, Kleindorfer et al. 2006, Agrawal et al. 2009).

In a transient ischaemic attack (TIA) the aetiology is similar to that of an ischaemic stroke. However, the cause of the ischaemia remains transient and the period of ischaemia is also correspondingly short. A typical TIA usually lasts only 2–15 minutes and, by definition, no permanent tissue damage can be seen in the following imaging studies (Easton et al. 2009). Transient symptoms also make the diagnosis heavily dependent on patient history and interview, which makes the diagnosis challenging and often uncertain. On the other hand, ischaemic lesions can be detected by magnetic resonance imaging (MRI) despite the patient meeting the criteria for TIA. In addition, silent strokes, which are imaging positive infarctions without apparent corresponding neurological deficits, are frequently seen as incidental findings. (Kidwell et al. 1999, Vermeer et al. 2003, Saini et al. 2015) Therefore, TIA is frequently excluded from stroke registries (Johnston 2002). This is problematic since patients with TIA are at significant risk of having a stroke. It is estimated that 12 to 30 percent of patients report a history of TIA before their stroke and approximately one in four of them occur within hours before the stroke (Hankey et al. 1995, Rothwell et al. 2005, Hackam et al. 2009). Moreover, 10 to 20 percent of patients having their first-ever TIA will have a stroke within the next 90 days and 50 percent of these cases occur within 48 hours after the TIA (Johnston et al. 2000). In general, the patient's risk of having a stroke within 24 hours after a TIA is 5% (Johnston et al. 2000, Lovett et al. 2003).

## 2.1.2 RISK FACTORS

Cerebral ischaemia is most frequently the result of atherosclerosis or cardioemboli. Many of the general risk factors for stroke are similar to other cardiovascular diseases. Some of these cannot be affected by medical intervention (Table 1). However, over 90% of all stroke cases in each major region of the world, among all ethnic groups, in men and women and in all ages could be prevented by taking into account the 10 most important potentially modifiable risk factors: previous history of hypertension or blood pressure 140/90 mmHg or higher, apolipoprotein (Apo)A/ApoB ratio, regular physical activity, diet, waist-to-hip ratio, psychosocial factors, current smoking, cardiac causes, alcohol consumption and diabetes mellitus. Hypertension

is the most important medically modifiable risk factor, and is more associated with ICH, whereas current smoking, diabetes, apolipoproteins and cardiac causes are associated with ischaemic stroke (O'Donnel et al. 2016).

**Table 1.** Risk factors of cerebrovascular diseases.

<b>Non-modifiable factors</b>	<b>Modifiable in daily living</b>	<b>Modifiable through medical management</b>
Age (Seshadri & Wolf 2007)	Decreased dietary vitamin D intake (Brøndum-Jacobsen et al. 2013)	Cardiovascular diseases (Ferro 2003, O'Donnel et al. 2010)
Ethnic background (Howard et al. 2016)	Diet (O'Donnel et al. 2010)	Cervical artery stenosis (Autret et al. 1987)
Gender (Wolf et al. 1992, Traylor et al. 2012)	Excessive alcohol consumption (O'Donnel et al. 2010, Sundell et al. 2008)	Diabetes (O'Donnel et al. 2010)
Genetics (Traylor et al. 2012)	Illicit drug use (Fonseca & Ferro 2013)	Dyslipidemia (O'Donnel et al. 2010)
	Inadequate physical activity (Hu et al. 2005, O'Donnel et al. 2010)	Hormonal treatment (Farquhar et al. 2009)
	Increased salt intake (Strazzullo et al. 2009)	Hypertension (Kannel et al. 1970)
	Low level of training and low socioeconomic position (Cesaroni et al. 2009)	Migrane (Spector et al. 2010)
	Obesity (Strazzullo et al. 2010)	Periodontal disease (Lafon et al. 2014)
	Psychological stress (Huang et al. 2015)	Prothrombotic state (Ferro et al. 2010)
	Smoking (Shinton & Beevers 1989)	Snoring and sleep apnea (Dyken & Im 2009)

### 2.1.3 EPIDEMIOLOGY AND SIGNIFICANCE

According to a systematic review that combined the results of 15 epidemiological studies, the worldwide prevalence of stroke in people aged over 65 years has varied between 59–93 per 1000 in men and 32–62 per 1000 in women in different countries (Feigin et al. 2003). The same dataset shows that the incidence of ischaemic stroke for people aged 55 years or more ranged from 3.4–5.2 per 1000 person-years. The median age at onset was 60.8 years for men and 74.8 years for women. Age is the most important risk factor of stroke. Of the approximately 16.9 million people who have a first-ever stroke globally each year, one third is younger than 65 years of age (Feigin et al. 2014). Patients aged over 85 years old make up almost 20% whereas patients aged between 20–34 years represented less than 0.5% (Russo et al. 2011, Singhal et al. 2013). Correspondingly, stroke among children is very uncommon.



In the United States the estimated annual incidence is 4.6 per 100 000 children aged 0-19 years. (Agrawal et al. 2009)

The self-reported, physician-diagnosed prevalence of TIA was 2.3% or roughly 5 million people in the United States according to a nation-wide survey. The incidence of TIA has varied from 0.52 to 0.83 per 1000 person years in different reports. (Brown et al. 1998, Kleindorfer et al. 2005, Cancelli et al. 2011) However, the true number of TIA patients is probably higher since many patients that experience transient neurological symptoms fail to report them to their healthcare providers (Johnston et al. 2003).

Stroke is the second most important cause of death in the world and the fourth in the developed countries. (Feigin et al. 2003, GBD Mortality and Cause of Death Collaborators 2016) It is responsible of approximately 10-12% of the overall mortality worldwide; – half of which is the result of ischaemic stroke. In the developed countries the mortality to stroke was reported to be 60.54 per 100 000 in the year 2010 (Feigin et al. 2014). For example in the United States, over 795 000 people suffer a stroke and nearly 130 000 die as a result of it every year. Although the numbers may seem high, the majority of global burden of stroke is still seen in low- and middle-income countries. (Krishnamurthi et al. 2013)

Stroke is a leading cause of serious long-term physical disability. (Centers for Disease Control and Prevention 2009) In the United States, fewer than half of all discharged stroke patients can return directly to their homes, one third are discharged to nursing homes and one fourth to rehabilitation services (Buntin et al. 2010). The resulting costs to society are substantial. In the United States alone, the combined direct and indirect costs of stroke are estimated to be \$33.6 billion of which \$17.5 billion are direct medical costs including hospital stays, ED visits, prescribed medications and home health care provision (Agency for Healthcare Research and Quality 2016). It is forecast that the medical stroke-related costs are going to nearly triple during the next two decades with the majority of costs arising from patients 65 to 79 years of age (Ovbiagele et al. 2013).

Although the age-adjusted mortality rate for ischaemic stroke has decreased significantly during the past two decades, the absolute number of people who suffer a stroke each year in addition to stroke-related deaths have increased (Feigin et al. 2014). The quality of stroke treatment has improved, but the population in the developed countries is rapidly aging and cardiovascular risk factors such as obesity and glucose tolerance can even affect younger cohorts. Although the proportion of stroke patients younger than 50 years old has increased both in Europe and the United States, the mean age of patients having a stroke has increased (Béjot et al. 2014, Kissela et al. 2012). More elderly patients are also at higher risk of death, have higher disability, have longer hospital periods and are less likely to be discharged to their own homes. (Saposnik et al. 2009, Forti et al. 2013)

Finland has a population of 5.49 million (in 2015), and roughly 15 000 people in the country suffer an ischaemic stroke each year (National Institute for Health and Welfare 2016). The median age of patients suffering a first-ever stroke in Finland was 72.7 years in 2010, 51% of the patients were men and 11% of the patients had a recurring incident within one year (Meretoja et al. 2010). The calculated case-fatality rate for first-ever stroke using Finnish registry-based data was 8.6% at 28 days and for one-year mortality 19%. At one year after stroke, 10% of the patients had died in the sequelae of stroke, 5% due to a recurring stroke and 40% due to other cardiovascular disease (Meretoja et al. 2011b). The mean stroke patient life-time-costs based on life expectancy and a 5-year follow-up was estimated for 2003 to be 86 000 euros of which two thirds are directly caused by stroke (Meretoja 2012).

#### 2.1.4 PATHOPHYSIOLOGY

Although the human brain is only 2% of total body weight, it receives 15% of the total cardiac output and is responsible of 20% of total oxygen consumption and 25% of total body glucose utilization in a resting man (Clark & Sokoloff 1999). The high-energy demand and high metabolic activity of the brain require a complex regulation of blood flow. Despite any changes in systemic blood pressure the cerebral blood flow must be constant and a balance between less and more heavily used areas of the brain must be maintained. This 'functional hyperemia' is achieved by controlling both neuronal activity and vascular resistance in both intra- and extracranial arteries and parenchymal arterioles (Faraci & Heistad 1990, Ballabh et al. 2004). In addition to the systemic blood pressure, the blood gas levels of oxygen ( $pO_2$ ) and especially carbon dioxide ( $pCO_2$ ) act as important regulators of vascular tone that locally governs vasodilatation and vasoconstriction. (Ballabh et al. 2004, Kulik et al. 2008)

As the result of its intrinsic high energy demand and complex fine-tuned regulation of blood flow, the brain tissue is inherently very sensitive to abrupt ischaemia. Neurons can suffer permanent damage within only a few minutes' from the onset of the absence of blood flow such as in the global ischaemia caused by a cardiac arrest. The occlusion of a single cerebral artery in acute ischaemic stroke rarely leads to total cessation of blood flow locally in the affected region. Although a very small core of the ischaemic area is often lost immediately, the large surrounding penumbra still receives a reduced blood flow. Despite having lost its normal function, the penumbra can still be rescued from permanent damage, if the circulation can be returned in time.

If the ischaemia continues, the penumbra and core will eventually become fused into a confluent infarction. In the course of a typical ischaemic stroke it has been estimated that 1.9 million neurons, 14 billion synapses and 12 kilometers of

myelinated fibers are destroyed during each minute (Saver 2006). Moreover, if recanalization and thus reperfusion are achieved, then the affected parenchymal region is susceptible to ischaemia-reperfusion injury. A similar phenomenon has been seen in many organs and it is thought to be mediated by the immunological system. (Elztschig & Eckle 2011) If recanalization is not achieved and thus permits the sizable infarction to progress, then the surrounding parenchyma is eventually damaged as a result of increasing oedema and cytotoxic substances released from the dying neurons. (Simard et al. 2007)

Ultimately, the total extent of the infarction is the sum of several pathophysiological events. It will also depend on largely unmodifiable incidental factors, which are the size and location of the occluded vessel, the extent of the blood flow reduction, the existing collateral circulation, the duration of ischaemia before reperfusion occurs and the adequacy of the reperfusion (Saver 2006). In addition, several modifiable variables, such as blood pressure, body temperature and blood glucose level have an impact in the infarct process, each of which give means to influence the outcome. These modifiable variables can thus be utilized clinically in patient management during the emergency medical procedures and stroke unit care. (Reith et al. 1996, Lindsberg & Roine 2004, Qureshi 2008)

## **2.1.5 CLINICAL PRESENTATION AND DIFFERENTIAL DIAGNOSIS**

Ischaemic stroke is characterised by the sudden onset of focal neurological symptoms which also distinguishes it from many other neurological diseases where the symptoms may be similar but develop within days, weeks or even months. Typically, the symptoms reach their peak within minutes and their nature depends fundamentally according to which part and region of the central nervous system is affected. Although several archetypal clinical stroke syndromes have been described, the symptoms of a single patient are highly dependent of the individual vasculature and the presence of collateral circulation. (Odier & Michel 2010) In clinical practice, it is most important to distinguish anterior and posterior circulation stroke and to identify distinct lacunar strokes, basilar thrombosis and cerebellar and pontine strokes all of which have their specific considerations with regard to acute management (Table 2). Eight out of ten ischaemic strokes can be located in the anterior circulation (Bamford et al. 1991). In hemispheric lesions, the neurological symptoms such as hemiparesis and loss of the visual field are typically contralateral to the side of the cerebral ischaemia (Odier & Michel 2010). The middle cerebral artery and its branches are most commonly affected. Facial droop, speech disturbance and unilateral hemiparesis is also the combination of symptoms most people recognize as 'stroke'. A proximal occlusion of this artery can lead to a malignant stroke syndrome characterized by severe hemispheric symptoms, cerebral

oedema, decreased level of consciousness. These strokes cause high mortality and survivors suffer from significant disability. (Huttner & Schwab 2009)

A posterior circulation stroke often leads to nonspecific symptoms such as vertigo, nausea and gait disorders (Savitz et al. 2007). The patients may complain of ipsilateral migraine-like headache, which is generally atypical for stroke. However, an ipsilateral hemiparesis is possible (Brandt et al. 2000). The basilar artery elongates lengthwise on the ventral pontine surface of the brain stem, where numerous cranial nerve nuclei and the pyramidal tracts are situated close to each other, thus the occlusion of the basilar artery can lead to a varying degree of stroke severity and symptoms. (Odier & Michel 2010, Savitz & Caplan 2005) Dysconjugate gaze and gaze paresis in addition to bulbar symptoms are often present in brain stem lesions. Posterior circulation stroke is often preceded by a TIA hours, days or even several weeks before (Odier & Michel 2010).

**Table 2.** Common clinical stroke syndromes (Odier & Michel 2010).

<b>Anterior circulation</b>	
MCA	Hemiparesis, hemianopsia, ipsilateral conjugated head and eye deviation, aphasia, neglect.
ACA	Predominant lower limb weakness, motor hemineglect, transcortical motor aphasia.
AChA	Pure motor or sensory-motor contralesional hemiparesis.
ICA	Severe stroke, often deteriorated consciousness, concomitant signs of all anterior circulation arteries.
<b>Posterior circulation</b>	
VA, PICA	Ipsilateral V, IX, X, XI cranial nerve palsy, Horner's syndrome, cerebellar ataxia, contralateral pain and temperature deficit.
AICA	Vertigo, vomiting, nystagmus, deafness, tinnitus, peripheral facial palsy, Horner's syndrome, ataxia, dysarthria.
SCA	Ipsilateral limb and gait ataxia, dysarthria, nystagmus, Horner's syndrome.
BA	Highly variable; paresthesias, dysarthria, hemiparesis, dizziness, pathological laughter, pseudoseizures, decreased level of consciousness, quadriplegia, "locked-in" syndrome.
PCA	Predominantly sensory symptoms; visual loss, hemianopsia, spatial disorientation, headache.
<b>Lacunar</b>	
	Limited motor or sensory-motor symptoms, dysarthria-clumsy hand syndrome, ataxic hemiparesis.
<b>Thalamic</b>	
	Mimics cortical stroke symptoms from anterior and posterior circulation; amnesia, cognitive impairment, personality changes, hemiataxia, pain.

ACA= anterior cerebral artery, AChA= anterior chorioidal artery, AICA= anterior inferior cerebellar artery, BA= basilar artery, ICA= internal carotid artery, MCA= middle cerebral artery, PCA= posterior cerebellar artery.

A severe stroke can depress consciousness, affect the patient’s ability to swallow and compromise the ability to keep the airways open and the patient can be in danger of aspirating gastric contents (Homer et al. 1988). However, the majority of stroke patients are conscious and endotracheal intubation is rarely required as a procedure before imaging (Petchy et al. 2014). The onset of a cardioembolic stroke can be dramatic and may include seizures. Moreover, a fall at symptom onset may lead to additional trauma and lying on the floor for an extended time period can cause dehydration further exacerbating the situation. (Bhalla et al. 2000, Jauch et al. 2013)

**Table 3.** Potential “stroke mimics” and differential diagnoses of acute ischaemic stroke (Artto et al. 2012, Mehta et al. 2014).

Conversion disorder	Intracranial haemorrhage
Electrolyte disturbances	Intracranial tumours
Encephalitis	Migrane
Epilepsy	Multiple sclerosis
Functional disorders	Substance abuse
Hypoglycemia	Vestibulocochlear diseases

In patients with moderate or severe anterior circulation stroke symptoms the diagnosis is often straight-forward. However, there are several caveats to stroke diagnostics. Mild, transient or fluctuating symptoms are more challenging to distinguish from mimicking conditions (Table 3). Rarely these ‘stroke-mimics’ have even been subjected to thrombolytic therapy even in a comprehensive stroke centre. (Artto et al. 2012) Patients with right-hemisphere stroke often develop hemispatial neglect, a syndrome where the patient literally neglects one side of the body and the corresponding visual field. Since these patients often do not suffer from aphasia, their symptoms can also be more easily misinterpreted. A Canadian study found that patients with right-hemisphere stroke were almost 50% less likely to receive IVT than patients with left-hemisphere strokes. (Di Legge et al. 2005) Moreover, posterior circulation stroke is much more difficult to identify than anterior circulation stroke. Typical posterior circulation symptoms also occur far less often than expected. (Savitz et al. 2007, Tao et al. 2012)

## 2.1.6 DIAGNOSTIC WORK-UP

The aim of the diagnostic work-up is to distinguish ischaemic stroke from an intracranial haemorrhage and exclude the possibility of mimicking conditions in addition to detecting the presence of contraindications to recanalization therapies.

Suspected acute stroke patients have shown to be a heterogenous group even in well-established, long-standing prehospital stroke services. A Finnish single-centre study that involved prehospital blood sampling and study recruiting of consecutive ‘thrombolysis candidates’, reported that 50% of the patients eventually had ischaemic stroke, 14.4% TIA, 13.5% haemorrhagic stroke and 22.1% a mimicking condition (Mattila et al. 2016).

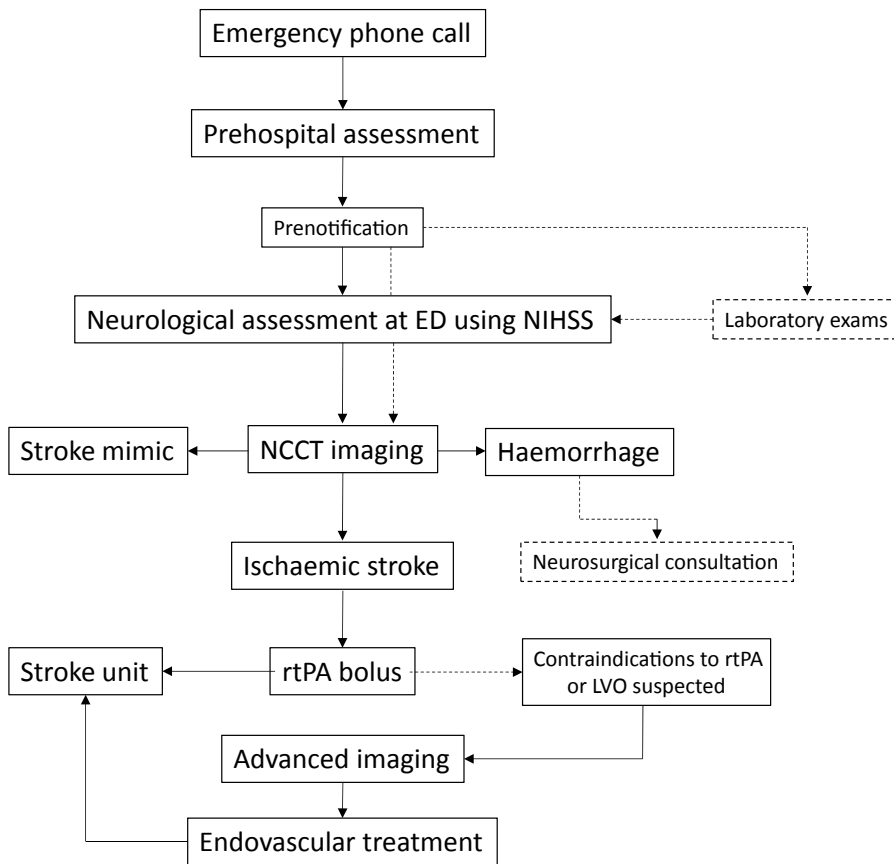
The initial phase of the diagnostic process is completed in less than a half an hour in a well-organized stroke centre. Clinical neurological examination forms the basis for the diagnosis of acute stroke. However, a thorough examination does not only take time but also does not allow the direct comparison of the patient’s symptom severity or preceding functional capacity. This has led to the development of several standardized stroke scales to aid both initial assessment and patient follow-up (Mathew et al. 1972, Orgogozo et al. 1983, Scandinavian Stroke Study Group 1985, Côté et al. 1986, Adams et al. 1987, Bamford et al. 1991, Hantson et al. 1994). Typically, these scales have consisted of items that evaluate the patient’s level of consciousness, sensory functioning and cognitive, motor, and speech responses. At present, the most widely adopted scale in the evaluation of stroke symptom severity is the National Institutes of Health Stroke Scale (NIHSS), which was originally designed as a standardized and reproducible assessment tool for acute stroke in large multi-centre clinical trials (Brott et al. 1989). It has later been widely accepted due to its consistency which has been demonstrated in both inter-examiner and test-retest scenarios. (Goldstein et al. 1989) The NIHSS was further popularized by the early stroke thrombolysis trials and has become a standard instrument when considering any of recanalization therapy alternatives. (del Zoppo et al. 1998, Clark et al. 1999) A baseline NIHSS score in clinical practice is often obtained at presentation. The evaluation is repeated at regular intervals to monitor the patient’s symptom development. The scale has a maximum of 42 points but since this distribution is non-linear, it is frequently categorized to describe the clinical severity of stroke more accurately. A common categorization divides the scale in three categories where 7 points or less is regarded as mild, 7 to 14 points moderate and 15 points or more a severe stroke (Adams et al. 1999, DeGraba et al. 1999). The median NIHSS scores in IVT have varied between 7 to 12 points with a tendency to decrease as the system gains more experience in the evaluation and treatment of acute stroke (Hacke et al. 2008, Meretoja et al. 2012).

**Table 4.** The modified Rankin Scale (mRS) according to Rankin (1957) and Bonita & Beaglehole (1988).

Score	Description
0	No symptoms at all.
1	No significant disability despite symptoms; able to carry out all usual duties and activities.
2	Slight disability; 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 walk without assistance.
4	Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance.
5	Severe disability; bedridden, incontinent and requiring constant nursing care and attention.
6	Dead.

The patient's functional capacity can also be assessed by using a quantified scale similar to symptom severity. In the setting of acute stroke, this assessment is typically made using the modified Rankin Scale (mRS), which is based on interview and review of the patient's earlier medical history (Rankin 1957, Bonita & Beaglehole 1988). The scale is divided into seven categories of which the categories from 0 to 2 indicate independent functional capacity or good outcome and categories 3 to 5 indicate that the patient is dependent on outside help (Table 4). Although more detailed scales of functional disability such as the Barthel Index and Lawton Instrumental Activities of Daily Living Scale exist, these are more commonly used at hospital discharge and during rehabilitation (Mahoney & Barthel 1965, Lawton & Brody 1969).

An ischaemic and haemorrhagic stroke cannot be reliably distinguished based on physical examination alone, thus modern stroke diagnostics are dependent of rapid imaging studies. A non-contrast computer tomography (NCCT) is the most prevalent acute cerebral imaging modality worldwide. It is highly sensitive in detecting intracranial haemorrhage (von Kummer et al. 2001, DeLaPaz et al. 2011), readily available at most hospitals and it takes less than 60 seconds to complete. The decision to use IVT or EVT can be based on the NCCT and clinical assessment alone. (Wintermark et al. 2013) However, NCCT has been reported to have a poor sensitivity (39%) in showing the early signs of acute ischaemia, especially in the posterior fossa. (von Kummer et al. 1994) The detection also varies among experienced observers, depending on the CT window and level settings, symptom-to-imaging time and the size of infarction (Schriger et al. 1998, Grotta et al. 1999, Kalafut et al. 2000). It can be complemented, however, with an iodised contrast medium to enable the use of CT angiography (CTA) and perfusion CT (PCT).



**Figure 1.** The diagnostic work-up process in acute ischaemic stroke currently in practice in Helsinki University Hospital (HUU Department of Neurology 2016). ED= emergency department, LVO= large vessel occlusion, NCCT= non-contrast computer tomography, NIHSS= National institutes of health stroke scale, rtPA= recombinant tissue Plasminogen Activator

The CTA is highly sensitive (97-100%) and specific (98-100%) in detecting intracranial occlusions and stenosis (Knauth et al. 1997, Shrier et al. 1997, Wildermuth et al. 1998, Graf et al. 2000, Verro et al. 2002, Hirai et al. 2002). It can also be used to identify the exact location of an intracranial bleeding. (Demchuk et al. 2012, Brouwers et al. 2012) The routine use of CTA will increase upon the increasing adoption and use of mechanical endovascular thrombectomy treatment in large vessel occlusions (LVOs) (Goyal et al. 2016, Saver et al. 2016 II).

The PCT is used to estimate the size of the infarct core and the penumbra i.e. the tissue area amenable to recovery by prompt recanalization therapies. (Wintermark et al. 2006, Mayer et al. 2000, Bivard et al. 2011, Bivard et al. 2013) The two important parameters used in PCT imaging are cerebral blood volume and cerebral blood flow. However, the PCT is susceptible to various sources of error and its interpretation requires expertise.



MRI has a better resolution than CT and is better suitable for children and adolescents and during pregnancy since it does not involve ionising radiation. However, the poor availability in the emergency care setting, vulnerability to motion artifacts, high operating costs and inherent time delays have prevented it from becoming the designated imaging modality for the acute phase. According to a joint statement by the American Society of Neuroradiology, the American College of Radiology, and the Society of Neurointerventional Surgery does not nominate a preferred imaging modality and either MRI with diffusion weight imaging and angiography or NCCT + CTA ± PCT maybe used as equivalent options. (Wintermark et al. 2013) However, MRI remains important in the diagnostics of TIA, posterior fossa lesions, cryptogenic stroke and has special indications where specific MR sequences have an important diagnostic role (Kidwell et al. 1999). For example, diffusion weight imaging is very sensitive at showing the smallest acute ischaemic lesions, whereas a magnetic resonance angiography is the preferred choice for imaging when thrombosis of the venous sinuses is suspected (Lafitte et al. 1997). MRI is often performed as a complement to the follow-up imaging during the hospital stay after the initial CT imaging has defined the working diagnosis.

Several blood biomarkers and biomarker panels have been studied to improve the diagnostics of acute ischaemic stroke. However, the sensitivity and specificity of these studies has not surpassed clinical judgement nor circumvented the need for imaging in the diagnosis procedure. (Whiteley et al. 2008 & 2011, Jickling & Sharp 2015) Currently, the laboratory exams taken in the ED mainly serve the exclusion criteria for recanalization therapies. However, the subject is intensely studied and several hundreds of potential biomarkers are currently being tested (Mattila et al. 2016).

## **2.1.7 EVOLUTION OF RECANALIZATION TREATMENT**

Recanalization therapy forms the second tier of stroke treatment between the primary prevention of risk factors and secondary prevention of recurring stroke or TIA. IVT and EVT both aim to open the occluded vessel in the acute phase to return the cerebral perfusion and limit the size of the impending infarction. Both treatment regimes are highly time-dependent and their use is time-limited (Emberson et al. 2014, Saver et al. 2016 II).

IVT is based on the administration of drugs that act as catalysts in the transformation of human tissue plasminogen into plasmin which further dissolves coagulated blood by initiating the degradation of the fibrin matrix. The first drug used was streptokinase, a streptococci-based enzyme, which was first utilized in the treatment of ST-elevation myocardial infarction. (Fletcher et al. 1958) First clinical studies involving streptokinase in the treatment of cerebral ischaemia were published

in the late 1980's. (Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico 1986, Califf et al. 1988) However, the first randomized controlled trials on the use of IVT in acute cerebral ischaemia weren't published until a decade later. Streptokinase was soon replaced by urokinase and eventually by the more modern recombinant tissue plasminogen activator (rtPA) alteplase. Although the patient selection criteria and rtPA dose somewhat differed from current standards, IVT was found to increase the odds for a good outcome after stroke when compared to placebo. (Hacke et al. 1995, Furlan et al. 1999, del Zoppo et al. 1998, Clark et al. 1999) The results were later confirmed in further trials and IVT quickly became a quality standard for acute stroke management [Wahlgren et al. 2007, the Third International Stroke Trial (IST-3) Collaborative Group 2012, Wardlaw et al. 2012].

At first, IVT use had an accepted time window of 3 hours after symptom onset, but after successful follow-up trials, the time limit was extended. The most recent guidelines by the American Heart Association and the American Stroke Association state: *'patients who meet national and international eligibility guidelines, IVT improves functional outcomes at 3 to 6 months when given within 4.5 hours of ischemic stroke and should be administered.'* Further extension of the time window has been discussed and is currently being studied particularly in the setting of wake-up stroke. (IST-3 Collaborative Group 2012, Ahmed et al. 2013, Barreto et al. 2016) Although the benefits of IVT have been widely accepted among neurologists worldwide, the treatment has been viewed as controversial by members of the emergency medicine community particularly in the United States and Australia. Emergency physicians have criticized early IVT trials for having methodological flaws and the rate of intracranial haemorrhage has been considered to be high (Brown et al. 2013, Ellison 2013, Alper et al. 2015, Miller et al. 2015).

In Finland, IVT is considered indicated when the patient has clinical symptoms of ischaemic stroke and the symptom OTT is more than 30 minutes but less than 4.5 hours. The symptoms must also be distinguishable from mimicking conditions and the patient must be able to recover to live a meaningful life. Elderly patients dependent of outside help, terminally ill and patients with recent major surgery (< 10 days) are excluded as are patients with mild symptoms (NIHSS 0-2), evidence of significant anticoagulative medication, risk of haemorrhage and recent ischaemic stroke (<1-3 months). Alteplase (Actilyse®, Boehringer Ingelheim GmbH, Ingelheim, Germany) is administered intravenously according to the patient's body weight (0.9 mg/kg, max. 90 mg). The treatment is initiated by giving 10% of the dose as an intravenous bolus and the rest is given as a 1-hour infusion (HUH Department of Neurology 2016). After the bolus dose is given, the radiological diagnostics may continue with more advanced and time-consuming techniques without delaying the treatment.

The most feared complication of IVT is intracranial bleeding which has occurred at a rate of 5-7% of all treated patients in controlled trials (Hacke et al. 2004, IST-3

Collaborative Group 2012). The incidence of ICH has been less than 1% in control groups receiving placebo. However, when IVT is administered following the ‘Safe Implementation of the Treatment in Acute Stroke – Monitoring Study of Safety (SITS-MOST)’ –criteria the incidence of intracranial bleeding has remained at a little over 2% even when rtPA is used during the last 90 minutes of the current time window.

The efficacy of IVT is strongly time-dependent and its efficacy during the first trimester of the time window is nearly 3-fold better than that of the third trimester (Lees et al. 2010, Emberson et al. 2014). Similar results have been reported in the ‘hyper-acute phase’ as well. (Strbian et al. 2013) A study ‘forecasting’ the effect of speed in stroke thrombolysis in terms of the patient’s lifetime concluded that each minute saved in the treatment process granted the patient on average 1.8 days of healthy life. A benefit was observed regardless of whether the stroke was mild or severe or the patient was young or old. Each 15-minute decrease in treatment delay provided one month of additional disability-free life for the whole study cohort (Meretoja et al. 2014). The international SITS-registry indicate that 55% of thrombolysed stroke patients remain independent in their daily life activities (mRS 0-2) at 3 months after the insult (SITS Collaboration Investigators 2016). The best results have been achieved in patients whose stroke aetiology was small vessel disease (Mustanoja et al. 2011). Transcranial Doppler ultrasound and microbubbles have been used in some centers to amplify the thrombolytic effect (sonothrombolysis) (Karnik et al. 1992, Eggers et al. 2005, Hölscher et al. 2009). However, this has not become common practice and no advantage in producing improved outcomes has been reported in major multicentre trials of sonography-assisted IVT.

**Table 5.** The main results of randomized controlled trials that studied the use of IVT and EVT in acute ischaemic stroke.

Year	Authors	Trial name	Time window	mRS ≤ 2 IVT	mRS ≤ 2 EVT
2013	Broderick et al.	IMS III	3 h	39 %	41 %
2015	Berkhermer et al.	MRCLEAN	6 h	19 %	33 %
2015	Goyal et al.	ESCAPE	12 h	29 %	53 %
2015	Campbell et al.	EXTEND-IA	4.5 h	40 %	71 %
2015	Jovin et al.	REVASCAT	8 h	28 %	44 %
2015	Saver et al.	SWIFT-PRIME	6 h	35 %	60 %
2016	Bracard et al.	THRACE	5 h	42 %	53 %

The modified Rankin Scale (mRS) was evaluated at 90 days after treatment. EVT= endovascular thrombectomy, IVT= intravenous thrombolysis.

The intracranial vasculature is accessed in EVT by intra-arterial catheters via radial or femoral arteries similar to a percutaneous coronary intervention (Rentrop & Blake 1982). However, the EVT in acute stroke has aimed at blood clot removal

rather than balloon dilatation and stents which can still be used in selected cases. In the beginning, only intra-arterial administration of rtPA directly proximal to the clot was used. (Hacke et al. 1988, Casto et al. 1992) However, mechanical clot removal techniques were later developed. In the Mechanical Embolectomy Removal in Cerebral Ischemia (MERCi) trial, the investigators reached a vessel recanalization rate of 48% in an 8-hour time window. The recanalization was also associated with a favourable outcome (Smith et al. 2005). However, in the first multi-center trial on EVT which included both intra-arterial thrombolysis and mechanical thrombectomy using various revascularization devices found no significant benefit compared to IVT alone (Broderick et al. 2013). Although IVT is effective *per se*, its efficacy is poor when the blood clot is located in an LVO. At the other end of the scale, smaller vessels are more difficult to access using EVT and the procedure becomes more prone to complications. Therefore, the patient selection for these treatment alternatives must be accurate and specific. Refocusing the EVT patient selection to this group and the development of new stent-retriever catheters led to several successful studies in 2015-2016, where a 'rescue EVT' after an unsuccessful or contraindicated IVT increased the odds for a good outcome when compared to rtPA alone (Table 5). An EVT probably does not lead to benefit if the radiologically determined infarct core has volume > 100 ml or there is no penumbra left to be saved. Currently, the use of EVT is limited to comprehensive stroke centers due to the complex diagnostic work-up and experience in interventional neuroradiology.

## 2.2 THE PREHOSPITAL CHAIN OF CARE

The purpose of the EMS system is to provide an acute medical assessment and care outside the hospital environment and, if necessary, the transportation of the patient to specialized care facilities in the cases of illness or injury that prevent the patient from seeking medical care by themselves (Langhelle et al. 2004, Pozner et al. 2004). The role of the EMS in acute stroke is vital since imaging studies and treatment have not been commonly available outside the hospital setting. The patients who are still within the time window for recanalization therapies must be rapidly identified and transported to a hospital that provides the necessary diagnostic and treatment capability. However, this requires that all the links in the chain, from the initial symptom recognition and the emergency telephone call onwards, must all work seamlessly as required. (Meretoja & Kaste 2012) After two decades of IVT, delayed hospital admission still remains the most important cause for non-eligibility in recanalization therapies (Tong et al. 2012). The prehospital chain of care has been aptly dubbed as the 'prehospital chain of survival' and stroke management has been compared with severe trauma where the most significant outcome effect is achieved within the golden hour (Saver et al. 2010, Fassbender et al. 2013).

## 2.2.1 CONFIGURATION OF EMS SYSTEMS

The EMS system is activated by calling the emergency telephone number. (Pozner et al. 2004) )Before the introduction of emergency phone numbers, the public had to call directly to the fire or police department, or hospital switchboard to get urgent help. Later, the handling of emergency telephone calls was centralized to emergency medical communication centres (EMCCs). A general emergency number is in use in Europe ('112') and the United States ('911'). (Langhelle et al. 2004, Pozner et al. 2004) The modern dispatcher handling the call not only identifies the type of emergency in question but is also capable of dispatching several different authorities to the scene when necessary. The EMDs working with or within the EMS system may be complemented by firemen, paramedics, physicians and members of law enforcement depending of the country in question (Langhelle et al. 2004, Roessler & Zuzan 2006). The calls are typically designated with specific symptom codes which describe the nature and urgency of the medical problem. Usually the selected code also designate which type of EMS, fire department or law enforcement units are dispatched to the scene.

The EMS systems in different countries have configured to paramedic-based ('Anglo-American') (Pozner et al. 2004, Symons & Schuster 2004, Black & Davies 2005, MacFarlane et al. 2005, Graham et al. 2009) and physician-based ('Franco-German') models (Adnet & Lapostolle 2004, Gomes et al. 2004, Langhelle et al. 2004, Papaspyrou et al. 2004, Roessler & Zuzan 2006). However, national and regional variation does occur and many EMS systems utilize elements from both models. In the paramedic model, the ambulance units are manned by 2 to 3 person crews consisting of emergency medical technicians (EMTs) and paramedics who are responsible of giving prehospital care. However, the patient still has to be transported to the hospital ED for physician's assessment. In the physician-based model, EMT and paramedic units are complemented by physician-manned mobile intensive care units (MICUs) which in response to a 'high risk call' assist the ambulance crews in treating patients that often require advanced life support (ALS) procedures such as endotracheal intubation. MICUs are also capable of advanced diagnostic procedures such as ultrasound. Prehospital emergency physicians also provide telephone consultation to ambulance units in the field and act as EMS medical directors. In many countries, helicopter emergency medical services (HEMS) provide advanced prehospital care and transfer services especially in mountain regions with difficult road access (Pozner et al. 2004, Black & Davies 2005). It is still common that physicians work as part of regular ambulance personnel particularly in Eastern Europe and China (Vaitkaitis et al. 2008, Hung et al. 2009, Taylor et al. 2010). In some countries, the EMS also include rapid response teams that are directly deployed from hospitals. (Spiteri 2008)

## 2.2.2 KNOWLEDGE OF STROKE AMONG THE PUBLIC

Generally more than half of the population in the Western countries have been able to identify brain as the affected organ in acute stroke and name a risk factor and a warning symptom (Reeves et al. 2002, Moreira et al. 2011). However, less than one third of the general public can come up with more than two symptoms or risk factors and even fewer are considered to have an adequate knowledge of stroke or TIA. Similar results have been reported throughout the United States and across Europe and Asia (Kothari et al. 1997, Pancioli et al. 1998, Yoon et al. 2001, Reeves et al. 2002, Greenlund et al. 2003, Parahoo et al. 2003, Centers for Disease Control and Prevention 2004, Ferris et al. 2005, Müller-Nordhorn et al. 2006, Nedeltchev et al. 2007, Evci et al. 2007, Mikulík et al. 2008). Women have been found to have a better overall symptom awareness and knowledge of risk factors than men (Ferris et al. 2005). Racial and ethnic minorities have both an increased risk of having a stroke and a worse overall awareness when compared to the rest of the population (Fussman et al. 2009). Similar associations have been reported with a low socioeconomic status, a lower level of education, an elderly population and also other selected age groups depending on the setting, smoking and hypertension. (Kothari et al. 1997, Reeves et al. 2002, Greenlund et al. 2003) Alarming, the knowledge of risk factors and symptoms appears to be the poorest in those patient groups who are at the greatest risk of having a stroke. Respondents with self-reported risk factors such as hypertension, diabetes and smoking are also largely unaware of their increased risk status. (Pancioli et al. 1998, Reeves et al. 2002) The most common ways of getting information on stroke were television and mass media, and the respondents friends and relatives. General practitioners and other licensed health care workers were named by only 8-22% of the respondents. (Pancioli et al. 1998, Parahoo et al. 2003, Evci et al. 2007) The sources of information have also varied considerably between different age groups and study settings. (Müller-Nordhorn et al. 2006)

The most commonly mentioned warning symptoms in these surveys have been unilateral numbness or weakness and difficulty in speech and understanding. Frequently responses have also included less typical symptoms such as disorientation, dizziness, headache, vision problems in addition to problems of gait and difficulty in walking. However, in Australia blurred vision, double vision or loss of vision from one eye was the most commonly mentioned stroke warning sign. Typical incorrect responses have included shortness of breath and chest pain (Pancioli et al. 1998, Reeves et al. 2002, Schneider et al. 2003). In one study the investigators found that the participants had difficulties in distinguishing a stroke from a 'heart attack' (Reeves et al. 2002). In direct comparison, knowledge of acute myocardial infarction and its symptoms are currently superior to that of acute stroke. Although the overall knowledge of risk factors was estimated to be poor or moderate at best, many

respondents have expressed interest in receiving more information about the condition (Ramsden et al. 1994).

Several studies conducted in different countries have evaluated the efficacy of educational campaigns on stroke knowledge (Silver et al. 2003, Reeves et al. 2008, Kleindorfer et al. 2008, Miyamatsu et al. 2012). Despite the success of many of the campaigns in increasing stroke awareness, they have had little effect on the actual behaviour at the onset of acute stroke symptoms. Moreover, these studies had mainly assessed the change in the participants' intention to act in a hypothetical situation and not in a true medical emergency (Reeves et al. 2008, Fassbender et al. 2013). Another problem with public education campaigns has been their transient effect on the general stroke knowledge. Continuous television advertising has been recommended as the solution, but this is limited by its costs. (Hodgson et al. 2007).

The use of IVT in ischaemic stroke has become more common, thus the public knowledge of stroke has also gradually improved. As early as in 2003, over 80% of women answering an American survey knew that in acute stroke the blood clot can be disintegrated with treatment (Ferris et al. 2005). In a telephone survey conducted in 1995 and 2000, the proportion of respondents who were able to spontaneously name a stroke warning sign increased from 57 to 70% but the ability to spontaneously name a risk factor saw only a minor increase from 68 to 72% (Schneider et al. 2003). Dedicated projects have been launched to teach stroke awareness to school children with successful preliminary results (Williams & Noble 2008, Conley et al. 2010).

Meanwhile, the situation in the developing countries remains difficult. In India, with nearly 20% of the whole world's population, more than half of the respondents were not able to identify any risk factors nor were they aware that stroke is a preventable or a life-threatening disease as late as 2012. (Menon et al. 2014) Nearly 10% of the respondents still believed that oil massage could improve stroke patients or they relied on witchcraft or faith healing instead (Pandian et al. 2005, Menon et al. 2014).

### **2.2.3 THE EMERGENCY TELEPHONE CALL AND EMS SYSTEM ACTIVATION**

Calling the emergency telephone number activates the EMS system. It is the first step in a successful prehospital chain of care. However, it has been estimated that only 38 to 65% of all stroke patients arrive to the hospital via the EMS system (Wein et al. 2000, Lacy et al. 2001, Adeoye et al. 2009). Many who do so have first waited for the symptoms to go away or contacted friends, relatives, local general practitioner or hospital staff for advice (Wester et al. 1999, Mackintosh et al. 2012). As many as 24% to 54% of the patients do not seek help within one hour after symptom onset and many fail to seek help at all (Rosamond et al. 1998, Wester et

al. 1999, Mosley et al. 2007). Others choose to go directly to the hospital using a cab or other methods of private transportation. The help-seeking patterns of different individuals have been shown to be complex. Interview- and population-based studies report that the decision to seek help was affected by symptom severity, living alone, knowledge of stroke, fear of the consequences of stroke, previous negative experience on hospitals, perceptions of the remit of medical services, belonging to an ethnic minority, presence of bystanders and involving a friend or relative in the decision of contacting medical services (Moloczij et al. 2008, Mackintosh et al. 2012). Better stroke knowledge has not been necessarily associated with correct stroke response behaviour or the decision to call the emergency telephone number (Schroeder et al. 2000) but a heightened sense of urgency to seek medical care and the first impression of the symptoms have been suggested to play an important role in the help-seeking process (Rosamond et al. 1998, Schroeder et al. 2000, Iguchi et al. 2006).

Patients with severe symptoms or intracranial haemorrhage are more likely to become unable to call for help by themselves, yet paradoxically the number of these patients have been disproportionately high amongst those who arrive in hospital via EMS transport (Barsan et al. 1993, Williams et al. 1997). According to analyses based on emergency telephone calls, the majority of calls are made by the patient's female family members, mainly wives and daughters. Other common caller groups have been friends, co-workers, bystanders, health care officials and other authorities. It is noteworthy, that the patients themselves make the call in only a few percent of all the cases (Handschu et al. 2003, Jones et al. 2012). The most commonly reported symptoms in the calls have been speech problems, motor disturbances and impaired consciousness whereas less frequently mentioned symptoms and signs have included sensory deficits, vision problems, vertigo and headache. Motor deficits are often described as a loss of function such as the inability to stand up or walk. The presence of aphasia is often described as sudden 'confusion' or a 'change in the patient's state of mind' (Handschu et al. 2003, Chang et al. 2004). A fall has been presented as the first reported problem in as much as every fourth call. Approximately 20-50% of the callers have themselves suspected that the patient was having a stroke. (Handschu et al. 2003, Krebes et al. 2012, Jones et al. 2013)

#### 2.2.4 PREHOSPITAL RECOGNITION OF ACUTE STROKE

In many EMS systems, the dispatch centers process emergency phone calls that also involve fire and rescue and law enforcement. In Finland, the proportion of medical emergencies is a little less than 50% of all emergency calls. (Jarmo Laukkanen, Emergency Response Centre Administration) Detecting acute stroke symptoms based on a telephone call is a challenge itself which is often complicated by the stress and anxiety experienced by the caller on the scene. Despite this, the EMDs have been



reported to correctly identify 30 to 83% of stroke cases (Kothari et al. 1995, Buck et al. 2009, Jones et al. 2013). The organization and methods of stroke identification used by the EMCCs vary between different countries. In the Anglophone countries, the computer-based Medical Priority Dispatch System has been a commonly used tool to classify emergency calls and conduct structured interviews with the caller. However, its performance has been poor when compared to the utilization of prehospital stroke scales in emergency calls. (Krebes et al. 2012, Fassbender et al. 2013). The Cincinnati Prehospital Stroke Scale (CPSS) and Face Arm Speech Test (FAST) are two similar three-item tools that can be easily implemented to call interviews (Krebes et al. 2012, Dami et al. 2015). The directed use of CPSS by laypersons has been shown to be successful in the identification of stroke symptoms. However, the limitation of these studies is that they have been conducted in stress-free environments. (Liferidge et al. 2004, Hurwitz et al. 2005)

The ambulance crews are frequently the first professionals to meet an acute stroke patient. Both patient observation and physical examination give plenty of additional information when compared to the information given in the emergency phone call. Consequentially, EMTs and paramedics have been able to perform better in stroke recognition than the EMD (up to 90% of cases) but the results have varied widely depending on the EMS system in question. After the development of dedicated prehospital stroke scales such as the CPSS (Kothari et al. 1999), FAST (Harbison et al. 2003) and the Los Angeles Prehospital Stroke Screen (LAPSS) (Kidwell et al. 2000), these numbers have significantly improved. In general, FAST and CPSS have been reported to have higher sensitivity than LAPSS while LAPSS has been found to be more specific for stroke. FAST and CPSS consist of only three clinical items whereas the LAPSS is longer and consists of an interview and clinical section. However, the overall performance of the three major stroke scales has been similar in comparative studies (Tables 6 & 7). Improved results have been sought by recombining existing scale elements to ‘tuned-up’ stroke scales (Bray et al. 2005, Bray et al. 2010, Studnek et al. 2013). In addition, several new scale designs have been developed with promising results but they have not seen wider use (Kimura et al. 2008, Hasegawa et al. 2013, Dalvandi et al. 2014, Mao et al. 2016). Systematic reviews have not been able to identify a superior stroke recognition tool. However, many of the original studies have received criticism for having methodological flaws, small sample size and differences in sample stroke incidence, prevalence and prehospital practice (Brandler et al. 2014, Rudd et al. 2015).

**Table 6.** The features of most commonly used prehospital stroke scales.

Stroke Scale item	CPSS (Kothari et al. 1999)	FAST (Harbison et al. 2003)	LAPSS (Kidwell et al. 2000)	MASS (Bray et al. 2005)	Med PACS (Studnek et al. 2013)	OPSS (Chenkin et al. 2009)	ROSIER (Nor et al. 2005)
Age > 45 years	+	-	+	+	-	-	-
No history of seizures	-	-	+	+	+	+	+
Patient not wheelchair-bound or bedridden	-	-	+	+	-	-	-
Blood glucose (mmol/l)	-	-	2.8-22.2	2.8-22.2	2.8-22.2	>4.0	>3.5
Time since symptom onset (hours)	-	-	≤25	-	≤25	<2	-
GCS >10	-	-	-	-	-	+	-
Symptoms not resolved prior to EMS arrival	-	-	-	-	-	+	-
CTAS ≥ 2	-	-	-	-	-	+	-
Patient not terminally ill	-	-	-	-	-	+	-
Syncope ruled out	-	-	-	-	-	-	+
Facial droop	+	+	+	+	+	+	+
Arm drift	+	+	+	+	+	+	+
Leg drift	-	-	-	-	+	+	+
Handgrip	-	-	+	+	-	-	-
Speech difficulty	+	+	-	+	+	+	+
Gaze preference	-	-	-	-	+	-	-
Visual fields	-	-	-	-	-	-	+

CTAS= Canadian Triage and Acuity Scale, CPSS= Cincinnati Prehospital Stroke Scale, FAST= Face Arm Speech Test, GCS= Glasgow Coma Scale, LAPSS= Los Angeles Prehospital Stroke Screen, MASS= Melbourne Ambulance Stroke Screen, Med PACS= Medic Prehospital Assessment for Code Stroke, OPSS= Ontario Prehospital Stroke Screen, ROSIER= Recognition of Stroke in the Emergency Room.

**Table 7.** The performance of most commonly used prehospital stroke scales.

Year	Authors	Sample size	Stroke scale	Sensitivity	Specificity
2000	Kidwell et al.	206	LAPSS	91%	97%
2005	Wojner-Alexandrow et al.	11296	LAPSS	86-95%	98-99%
2005	Bray et al.	100	CPSS	95%	56%
		100	LAPSS	78%	85%
		100	MASS	90%	74%
2009	Chenkin et al.	554	OPSS	92%	86%
2010	Bray et al.	850	CPSS	88%	79%
		850	MASS	83%	85%
2013	Studnek et al.	416	CPSS	79%	24%
		416	Med PACS	74%	33%
2013	Chen et al.	1130	LAPSS	78%	90%
2013	Fothergill et al.	295	FAST	97%	13%
		295	ROSIER	97%	18%
2014	Asimos et al.	1217	CPSS	80%	48%
		1225	LAPSS	74%	48%

CPSS= Cincinnati Prehospital Stroke Scale, FAST= Face Arm Speech Test, LAPSS= Los Angeles Prehospital Stroke Screen, MASS= Melbourne Ambulance Stroke Screen, Med PACS= Medic Prehospital Assessment for Code Stroke, OPSS= Ontario Prehospital Stroke Screening Tool, ROSIER= Recognition of Stroke in the Emergency Room.

The introduction of new stent-retriever thrombectomy techniques has encouraged several study groups to develop a simple stroke scale design to detect LVOs to reroute this patient group directly to comprehensive stroke centers that have neuroradiological intervention capability. These scales have included NIHSS (Brott et al. 1989), shortened NIHSS (Tirschwell et al. 2002), the Los Angeles Motor Scale (Llanes et al. 2004), the 3-Item Stroke Scale (Singer et al. 2005), Cincinnati Prehospital Stroke Severity Scale (Katz et al. 2015), Recognition of Stroke in the Emergency Room (Nor et al. 2005), Rapid Arterial Occlusion Evaluation Scale (RACE) (de la Ossa et al. 2013), Field Assessment Stroke Triage for Emergency Destination (Lima et al. 2016) and the Prehospital Acute Stroke Severity Scale (Hastrup et al. 2016). The highest accuracy has been reached with NIHSS and RACE, but the suggested cut-off values would still result in a loss of opportunity for over 20% of patients. (Turc et al. 2016) Although HEMS paramedics have been able to conduct the NIHSS in the prehospital setting with a moderate to good agreement with stroke team physicians (Kesinger et al. 2015), using this scale requires considerable training and skill.

Currently, the use of prehospital stroke recognition tools is recommended by both the National Academy of Emergency Medical Service Physicians and the American Stroke Association. (Crocco et al. 2007, Acker et al. 2007) However, it has been

estimated that more than 30% of all stroke cases are still missed by prehospital stroke scales and as much as 50% or more of cases designated as suspected stroke have been false positives (Asimos et al. 2014, Brandler et al. 2014, Oostema et al. 2015). This burdens in-hospital stroke teams who at times have to struggle with multiple suspected stroke patients simultaneously. The majority of the prehospital stroke scales have been specifically designed to identify anterior circulation stroke symptoms in adults. The performance of FAST has been found to be inferior in identifying vertebrobasilar symptoms to anterior circulation stroke (Gulli & Markus 2012). Detailed interviews both during the emergency phone calls and on the scene should be focused on atypical stroke symptoms such as sudden nausea, vomiting and vision disturbance, in addition to risk symptoms such as a fall and the symptom onset time. If the word “stroke” is brought up spontaneously, the assumption is often correct. The major caveat with the recognition of LVO is that the existence of collateral circulation can affect significantly on the severity of symptoms measured with any clinical instrument and the definitive information must be acquired using CTA imaging (Turc et al. 2016).

Neuron-specific biomarkers have long been proposed as a solution to diagnostic problems. Although the use of biomarker panels has proven to be feasible even in a prehospital setting, their sensitivity and specificity has not been superior to clinical stroke scales (Vanni et al. 2011, Jickling et al. 2015).

## 2.2.5 PREHOSPITAL PATIENT MANAGEMENT

Which EMS system model performs best in acute stroke care remains unclear and is subject to debate (Dick 2003). A physician-based EMS system does not necessarily mean that MICUs are dispatched to all suspected stroke calls. It has been shown that the majority of all stroke patients can be identified and adequately managed by a two-person basic life support (BLS) ambulance crew and the involvement of an MICU does not necessarily improve the results (Fischer et al. 2008). The prehospital care for acute stroke focuses on the assessment and support of vital life functions according to the universally adapted ABCDE-principles (airway, breathing, circulation, disability, exposure). After arriving at the scene the ambulance crew conducts a concise interview and neurological examination using standardized prehospital stroke screening tool. The most common atypical stroke symptoms and the most common stroke mimics such as epileptic seizures and hypoglycaemia should be kept in mind. The patient is then put on cardiac monitoring and the non-invasive blood pressure and blood oxygen saturation (pulseoximetry) are measured. An intravenous cannula is placed into the forearm and the situation is reported in the prehospital patient report. Any changes in the patient’s condition must be reported since a deterioration or even an improvement in the patient’s condition may alter the physician’s assessment.

Patients with deteriorated consciousness [Glasgow Coma Score (GCS) < 9 points] or brain stem dysfunction are especially at increased risk of airway obstruction due to impaired oropharyngeal mobility and the loss of protective reflexes (Aviv et al. 1996, Milhaud et al. 2004). Although endotracheal intubation is rarely required (Petchy et al. 2014), over 50% of hemiparetic patients have eventually been shown to develop hypoxemia (Sulter et al. 2000). Cheyne-Stokes respiration is a frequent complication of acute stroke and it is associated with decreases in oxygen saturation. Other frequent causes include pneumonia and atelectasis which commonly do not develop until later in the hospital phase. The benefit of routine administration of supplemental oxygen has not been proven, but it is recommended to maintain an oxygen saturation >94%. Excessive oxygen therapy should be avoided as it has been suggested to be harmful at least in cardiac ischaemia (Khoshnood et al. 2015). Data from several studies indicates that patient positioning can influence oxygen saturation, intracranial pressure and cerebral perfusion pressure (Rowat et al. 2001, Schwarz et al. 2002). Limited data suggest that stroke patients with significant pulmonary comorbidities have lower oxygen saturation in the supine position than in more upright positions (Rowat et al. 2001). Lifting the head of the patient's stretcher up by 15-30° may help with oxygenation and to prevent aspiration of the gastric contents. It also improves venous return from the brain via gravity, which may be beneficial in case of elevated intracranial pressure (Rangel-Castillo et al. 2008).

Hypovolemia is common in acute stroke and may predispose to decreased cerebral perfusion further exacerbating the ischaemic brain injury, cause renal impairment, increase stress on the myocardium and potentiate thrombosis. (Jauch et al. 2013) Intravenous fluid therapy is therefore initiated in the prehospital phase with the aim to maintain euolemia. (Bhalla et al. 2000) Stroke patients are frequently hypertensive, which is a sign that can also be used as a clinical clue to distinguish acute stroke from stroke mimics (Gioia et al. 2016). Hypertension is thought to be a protective reaction of the human body to secure adequate cerebral perfusion (Qureshi et al. 2008). Therefore the blood pressure of the patient is usually not decreased actively unless the values are extreme (> 220 mmHg). A 12-lead electrocardiogram is not required unless simultaneous cardiac symptoms are suspected.

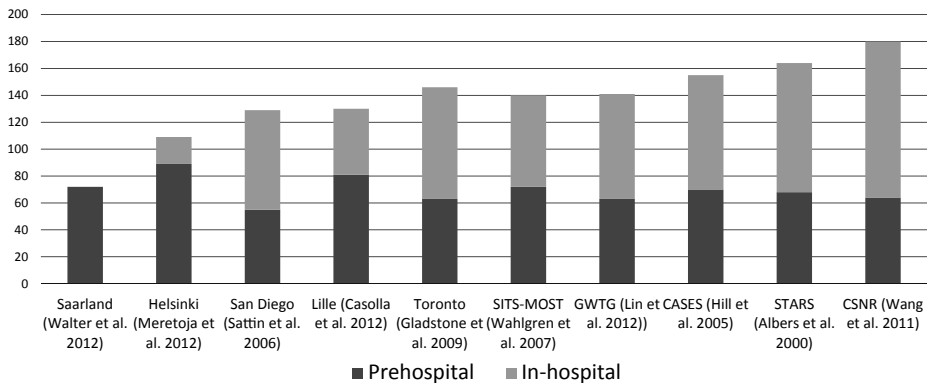
Neuroprotection has been one of the most intriguing fields of medical research in the 21<sup>st</sup> century. Being able to 'buy more time' for the prehospital chain of care and recanalization treatment would immediately benefit thousands of patients worldwide. Although the prehospital administration of potentially neuroprotective drugs has been shown to be feasible, the study drugs have failed to produce significant clinical benefit (Crocco et al. 2003, Saver et al. 2015). Hypothermia has found to be neuroprotective in experimental focal hypoxic brain injury models. (Kuboyama et al. 1993) Many patients undergoing major operative procedures receive therapeutic hypothermia to protect the brain. Mild to moderate hypothermia (33-36°) has been associated with improved neurological outcomes in out-of-hospital cardiac arrest

and it has been successfully implemented even in the prehospital setting (Virkkunen et al. 2004, Kim et al. 2007). However, the treatment is currently the subject of an on-going debate due to the negative results in later trials (Kim et al. 2014). It has been suggested that the treatment effect is actually achieved by preventing hyperthermia instead (Kjaergaard et al. 2015). Moreover, an early multi-center trial found that mild hypothermia did not improve the outcome of patients undergoing surgery for ruptured intracranial aneurysm (Todd et al. 2005). The results have also been mixed for patients with malignant cerebral infarction and ischaemic stroke in general (Georgiadis et al. 2002, Milhaud et al. 2005, den Hertog et al. 2009).

## 2.2.6 DEVELOPMENT OF PREHOSPITAL STROKE PROTOCOLS

Calling the emergency telephone number and arriving at the hospital by ambulance has been associated with not only shorter prehospital delay but also with decreased in-hospital delay and an increased likelihood of IVT (Barer et al 1992, Barsan et al. 1993, Ferro et al. 1994, Fogelholm et al 1996, Salisbury et al. 1998, Morris et al. 1999). On the other hand, even a successful chain of stroke care consists of several steps which make it susceptible to unwanted delay. One of the most prominent obstacles in acute stroke care has been the hesitance of the general public to activate the EMS system by calling the emergency phone number immediately after symptom onset (Kwan et al. 2004 II). Early studies showed that the onset-to-call time (OCT) alone has been responsible for between 27 to 53% of the onset-to-door time (ODT). Significant delays are also caused by misinterpreting stroke symptoms in the emergency call or on the scene. Failure to identify acute stroke may lead to low priority ambulance dispatch or transport and route the patient to a hospital without the necessary neurological services provision. (Chang et al. 2004) The intersection of prehospital and in-hospital care is a critical step. The patient is susceptible to triage and registration delays, ED crowding in addition to delayed physician's assessment and access to imaging. Similar problems are faced when the patient chooses to go directly to the ED without calling the emergency number. For the EMS the solution to this problem has been the same as for all the severely ill patient groups –a prehospital prenotification of a stroke patient en-route. Using a prenotification telephone call has been shown to decrease the in-hospital delay and increase the likelihood of IVT. Patient transport to the hospital ED is usually fast in a metropolitan setting. However, difficult traffic conditions can lead to occasional unexpected delays which are basically impossible to prevent. However, the use of controlled high priority transport crewed by trained EMS personnel may produce a considerable time benefit. HEMS transport especially in mountainous areas has been a fast and reliable way to minimize patient transportation time and increase the likelihood of recanalization treatment (Hutton et al. 2015).

Many EMS systems have been encouraged by early reports to develop systematical stroke protocols and started to measure their system performance (Lindsberg et al. 2006, Sattin et al. 2006, Gladstone et al. 2009, Casolla et al. 2012). Despite some local and regional differences, these protocols share several common features that include the use of a designated stroke code and high priority ('flashing lights and sirens') in the ambulance dispatch and transport and the use of a prehospital stroke



**Figure 2.** The onset-to-treatment time (minutes) distribution to prehospital and in-hospital phases in different city settings and multicentre trials. CASES= Canadian Alteplase for Stroke Effectiveness Study, CSNR= Chinese National Stroke Registry, GWTG= Get With the Guidelines, SITS-MOST= Safe Implementation of Thrombolysis in Stroke - Monitoring Study, STARS= Standard Treatment with Alteplase to Reverse Stroke.

screening tool during the emergency phone call and in the prehospital assessment, a prenotification to the hospital ED and direct transport to a stroke centre thus by-passing nearest hospitals when necessary. In these health care systems, the median OTT has varied between 72-180 minutes in treated patient populations. As a comparison in India, with approximately one fifth of the world's population, the median time to reach the hospital by ambulance in acute stroke was 10 hours (Menon et al. 2014).

The proportion of prehospital and in-hospital segments of total OTT also varies in the Western countries (Figure 2). The most effective concept has been the simultaneous involvement of the prehospital and in-hospital staff to prevent the formation of bottle necks. HUH has been one of the international pioneers of this approach and achieved excellent results. The DTT has been pushed from over 90 minutes to less than 20 minutes and the number of treated patients has increased from fewer than 25 to over 270 a year (Lindsberg et al. 2003, Meretoja et al. 2012). In selected reports up to 14-41% of stroke patients have been reported to receive IVT (Belvis et al. 2005, Abdullah et al. 2008, Quain et al. 2008, Gladstone et al. 2009, Kim et al. 2011, O'Brien et al. 2012, Meretoja et al. 2012, Meretoja & Kaste 2012, Casolla et al. 2013).

However, despite these advances the ODT has still remained at more than one hour in length and seen little change in the era of IVT in acute stroke. There remains considerable potential to improve further the EMS operation. According to a policy statement and early management guidelines issued by the American Stroke Association, EMS systems can measure their performance by using several specific parameters (Table 8). This kind of data is also becoming more readily available through the implementation of electronic prehospital patient reporting and EMS data capturing systems. (Acker et al. 2007, Jauch et al. 2013)

A novel approach to a prehospital stroke protocol and to minimizing the pretreatment delay has been the introduction of mobile stroke unit concept (Fassbender et al. 2013). The Mobile Stroke Unit (MSU) and Stroke Emergency Mobile (STEMO) are specially-designed emergency vehicles that include a NCCT apparatus with telemedical connectivity to the neuroradiologist at local university hospital, a point-of-care laboratory kit and the necessary equipment for IVT administration. The unit is manned by a specially trained ambulance crew, which includes a stroke neurologist capable of performing NIHSS in the field.

**Table 8.** Examples of specific parameters measuring the performance of EMS systems in acute stroke according to a policy statement by the American Stroke Association (Acker et al. 2007).

Parameter to be measured (%)
1. Dispatch using the stroke code.
2. Dispatch using the highest available care available in the shortest amount of time.
3. The time between the receipt of the call and the dispatch of the response team is <90 seconds.
4. EMS system response time is <8 minutes (time elapsed from the receipt of the call by the dispatch entity to the arrival on the scene of a properly equipped and staffed ambulance).
5. Dispatch time <1 minute.
6. Turnout time (the time from a call is received to the unit being enroute) is <1 minute.
7. The on-scene time is <15 minutes (barring extenuating circumstances such as extrication difficulties)
8. Travel time is equivalent to those of trauma or acute myocardial infarction calls.

The concept enables the crew to assess an acute stroke patient, exclude possible contraindications to IVT and begin the treatment before the patient is transported to hospital ED by the unit or another ambulance. (Walter et al. 2010, Ebinger et al. 2013) The concept has proven to be successful in randomized controlled trials (Walter et al. 2012, Ebinger et al. 2014) and it has deemed as highly cost-effective solution in a large metropolitan setting. However, the concept requires a large and dense population to be justified and both its establishment and operation involves high costs (Gyrd-Hansen et al. 2015).



### 3 STUDY QUESTIONS

- What is the temporal composition of the prehospital phase of the stroke chain of survival in the HUH area?
- How do the EMDs and paramedics perform at identifying the “thrombolysis candidates” in the HUH area?
- Is successful stroke recognition during the emergency phone call and prehospital assessment associated with early hospital arrival and treatment?
- Can fire engine crews be utilized to prevent delays in prehospital stroke management?
- Can the OST be decreased by systematical training of EMS staff?

## 4 METHODS

### 4.1 STUDY DESIGN

The study consisted of one retrospective (I) and three prospective cohort studies (II-IV). All the studies were register-based and utilized EMS' operational information, prehospital patient reports and hospital records for HUH and Tampere administration areas. The study plans were approved by the Department of Surgery for I and III, the Department of Emergency Medicine for IV and the department of Neurology for I, III and IV at HUH, Tampere Department of Social Services and Health Care (II), Tampere Area Rescue Department (II) and the Emergency Response Centre Administration (III) –all in Finland. No informed patient consent or ethics review board approval was required according to the Finnish legislation due to the register-based nature of the studies. Personal identifying information was omitted from the study registry before the statistical analysis phase. All the studies were conducted in accordance with the principles of the Declaration of Helsinki and laws governing research conducted in Finland.

### 4.2 STUDY SETTING

The studies were conducted in the HUH area covering the Helsinki metropolitan region, which included the surrounding municipalities of Espoo, Kauniainen, Kerava, Kirkkonummi and Vantaa (I, III, IV), and the Tampere city region (II). HUH provides tertiary care for a population of 1.6 million inhabitants and the 65-bed ED is responsible for all neurological emergencies in its area and the surrounding Uusimaa region 24 hours a day. Paediatric patients are treated separately in the HUH Hospital for Children and Adolescents. Since the start of the routine use of stroke thrombolysis in 1995, HUH has the only comprehensive stroke centre in the region and the largest in Finland. The HUH ED has approximately 30 000 visits a year, of which approximately 1 100 are due to stroke. The EMS in the HUH area is provided by three city-based fire departments that use common stroke care guidelines. Key quality metrics such as stroke severity, selected time intervals (ODT, DTT, OTT) and outcome (mRS) of all patients receiving IVT (and later also EVT) have been systematically registered since the beginning. However, patients that have not receive recanalization therapy are not entered into any registry.

Tampere is the third largest city in Finland after Helsinki and Espoo with 220 000 inhabitants. The EMS are provided by the Tampere Area Rescue Department according to the local stroke protocol with the Tampere University Hospital.

### **4.3 EMERGENCY PHONE CALL PROCESSING**

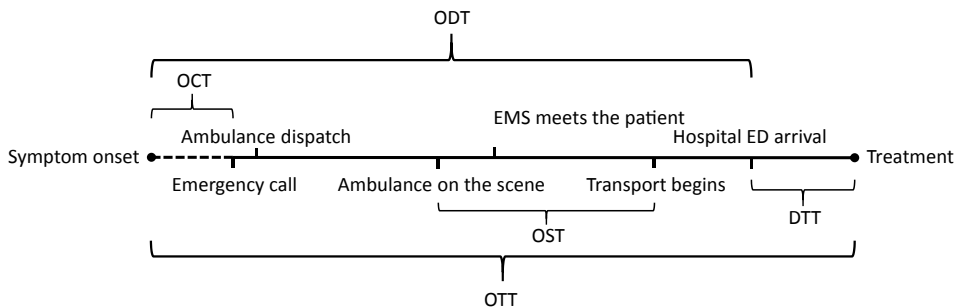
Finland has a general emergency number, 112, and all emergency phone calls are processed in one of the six regional emergency medical communication centers. When responding to a 112 call, the dispatcher verifies the site address and the nature of the emergency. Telephone-based GPS-tracking may be used if necessary. Caller interviews are guided according to symptom-based algorithms. In suspected acute stroke, the dispatcher screens for symptoms according to the FAST algorithm and common stroke-associated complaints such as vertigo, vision problems, nausea and vomiting before making the dispatch decision. The dispatch should be made within 90 seconds after the beginning of the call to be in compliance with the dispatch guidelines. A single positive FAST criterion suffices for dispatch using the symptom code for stroke and acute onset of <5 hours previously to dispatch using high priority (i.e. flashing lights and sirens). If the symptoms remain FAST-negative but suspicion of stroke is high the EMD can still make the dispatch as 'stroke'. Callers are urged to redial 112, especially if the nearest ambulance is far away or the symptoms deteriorate or vanish to update the dispatch code or priority when necessary.

### **4.4 PREHOSPITAL ASSESSMENT**

The ambulance crew interviews the patient and bystanders on the scene in cases of suspected stroke and conducts a quick neurological examination using the FAST algorithm. Blood pressure, heart rate, oxygen saturation, GCS, tympanic temperature, and blood glucose are measured. A breathalyzer may be used to test the presence of alcohol when necessary. An intravenous line is inserted for the initiation of fluid therapy and also to enable later contrast medium administration. If the patient's symptoms and signs clearly fit those of acute stroke and had manifested <5 hours earlier, a prenotification phone call is placed to the ED staff for prompt high-priority transport. The prenotification is made according to a common scheme and includes patient identification data, significant previous illnesses and medication, current symptoms, estimated symptom onset time and estimated time of arrival. Patients with suspected stroke without an identified onset time, apparent TIA or undetermined neurological symptoms are transported using normal priority. In the Helsinki EMS system, atypical symptoms can be discussed on the telephone with

an EMS physician or directly with hospital stroke neurologist and the ambulance crews use an electronic patient reporting system that stores all prehospital patient reports in a common database (Merlot Medi, CGI Group Inc, Canada).

The regional dispatch center responsible for Tampere area uses the same dispatch guidelines as in the rest of the country. The ambulance paramedics are responsible for the prehospital care of the patient and use FAST as tool to screen for stroke symptoms similar to HUH. However, since 2004 the ambulances in Tampere have been supported by a fire engine crew that is dispatched simultaneously with the ambulance in selected high-risk calls such as acute stroke. The fire engine crew assists the ambulance crew in patient examination, interview, reporting, and carrying the patient as well as loading the patient into the ambulance. This has been estimated to be especially beneficial when carrying heavy-weight patients in tall apartment buildings. If the patient's stroke symptoms are not initially identified by the dispatcher, the ambulance may not be accompanied by a fire engine and the ambulance crew will manage the situation independently. The hospital neurologist in Tampere is consulted via telephone by the ambulance crews in all suspected stroke cases within the 4.5-hour treatment window of intravenous thrombolysis which is also part of the hospital prenotification procedure.



**Figure 3.** The most important time stamps and time intervals (brackets) registered in the chain of care from symptom onset to recanalization treatment. DTT= doort-to-treatment time, ED= emergency department, EMS= emergency medical services, OCT= onset-to-call time, ODT= onset-to-door time, OST= on-scene time, OTT= onset-to-treatment time.

## 4.5 PATIENT COHORTS

### 4.5.1 SEQUENTIAL ANALYSIS OF PREHOSPITAL DELAYS IN ACUTE STROKE (I)

Study I involved data collection that covered a 3-year period from 1<sup>st</sup> of January 2003 to 31<sup>st</sup> of December 2005. Specific time intervals relevant to the overall time to treatment with thrombolysis were identified in both the prehospital and hospital

phases. All >16 years old stroke patients who received rtPA at HUH during the study period were included. A trained study nurse and the author extracted the data from the registry. No changes were made in the referral of acute stroke patients during this period, and their annual volume remained constant. Missing time stamped data were retrieved from the EMS dispatch database of the emergency response centre, which registered all incoming emergency calls and related time stamps (Figure 3). The time stamps were based on real-time, computer-guided clocks of the dispatch system and ambulance computers. The emergency call and ambulance dispatch-related time stamps were registered automatically whereas the on-scene arrival, transport, and hospital arrival related time stamps were registered manually by the EMS by tapping the mobile electronic patient reporting computer and by the hospital stroke neurologist administering the rtPA. The registered prehospital variables were onset-to-dispatch time, ambulance response time, OST, transport time, on-scene-to-door time and ODT. Total treatment delay (OTT) was determined using hospital patient registry data on in-hospital delay (DTT). Diastolic and systolic blood pressure, patient age, and sex were also collected. An on-call stroke physician certified to use the NIHSS score assessed stroke severity at hospital arrival and at 7 days post-stroke. A stroke neurologist certified to conduct the mRS assessed the functional outcome at 3 months after rtPA administration. Scores of 0–2 were considered a good outcome.

#### **4.5.2 THE SUPPORTIVE USE OF FIRE ENGINE CREWS IN PREHOSPITAL STROKE CARE (II)**

The study period in study II was one year from 1<sup>st</sup> October 2010 through 30<sup>th</sup> September 2011, during which the ambulance personnel completed a case report form for each >16 years old thrombolysis candidate that had been transported by the EMS. The patients' age, sex, body weight, GCS, symptom onset time, floor number of the building, operational EMS information including dispatch and transport codes, time-stamps, and the total number of personnel on the scene were registered. The patient's body weight was estimated when not available during patient interview. The OST and other prehospital time intervals were calculated based on the acquired time stamps. When data were missing or incomplete the EMS patient report was reconstructed by a study nurse who contacted and interviewed the ambulance crew to complete the patient's report with the missing information, whenever possible. Calls related to the hospital transfers were excluded from the study since they differed significantly from the EMS protocol.

#### **4.5.3 EMERGENCY PHONE CALLS IN ACUTE STROKE (III)**

Study III investigated emergency phone calls for a prospective, consecutive, population-based, observational cohort that consisted of patients who received recanalization therapy between 1<sup>st</sup> January 2010, and 31<sup>st</sup> December 2011. The patients' medical records at HUH were combined with prehospital patient records that had been retrieved from the electronic patient reporting database and with the emergency call discussions from the national Emergency Response Center administration database. All authentic discussions were audited two times by the author and evaluated in terms of the current dispatch guidelines. The resulting information was cross-checked with the prehospital patient reports and hospital records. Electronic time stamps were registered for the beginning and end of the emergency call, EMS operation and IVT administration. Operative time delays were calculated using the time stamps acquired. If several emergency phone calls were made for the same case, the OCT was based on the beginning of the first call. All non-EMS admissions such as taxi transportation, walk-ins and those transported to HUH from other health care institutions were excluded in addition to those with no available electronic patient reporting data and missing or incomplete emergency call discussions.

#### **4.5.4 TRAINING PROGRAMME TO DECREASE THE OST IN PREHOSPITAL STROKE CARE (IV)**

In study IV, a 45-minute training session and an interactive follow-up group session were arranged for all ambulance crews (both advanced and BLS certified) in the HUH area. The aim of the training package was to facilitate that ambulance transport of a 'stroke thrombolysis candidate' would begin within the target interval of 20 minutes after arriving beside the patient. The training was arranged as a part of the routine EMS training, which cover all essential medical themes in a rotating manner. Eventually, it was estimated that roughly 85% of the personnel had participated in the training during a three-month period that strated on 1<sup>st</sup> June 2015 to 31<sup>st</sup> of August 2015. Absence from the training session was mainly due to the summer holiday season.

**Table 9.** Aims and goals of the training package for emergency medical services staff in Helsinki University Hospital (HUH) area. ECG= electrocardiogram, ED= emergency department.

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**Training package goals**

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1. After the patient has been identified as a candidate for intravenous thrombolysis, prehospital operation should be prompt and concise.
  2. Communication is crucial. If anyone thinks the patient might have a stroke, the word 'stroke' should be said aloud.
  3. Emergency medical technicians and paramedics in training should not be allowed to examine the patient or practise procedures if the patient meets the criteria for a thrombolysis candidate.
  4. Instead of a stretcher, a carrying-chair can be used to effectively move the patient to the ambulance. The chair should be taken from the ambulance as soon as the ambulance crew arrives on the scene and beside the patient for the first time.
  5. Intravenous cannulation is attempted three times at most on the scene. Unsuccessful cannulation should be mentioned in the hospital prenotification.
  6. A 12-lead ECG should not be taken without obvious cardiac symptoms – heart rhythm monitoring is enough in most cases.
  7. Make sure that the phone number of the patient's relatives or bystanders is written on the prehospital patient report. The neurologist may need this to acquire additional information or to discuss treatment decisions.
  8. Time should not be used on the scene to gather the patient's clothes or other personal items. The patient's family members can later bring all the necessary items to the hospital.
  9. A prenotification to HUH emergency department should be given immediately after ambulance transport has begun.
  10. If the transport time is estimated to be very short (<10 minutes), consider giving the prenotification on the scene before transport in order to enable necessary preparations in the ED.
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The training package was designed as a joint project by the medical directors for EMS in the HUH area and the senior paramedics and EMTs and EMT-trained firemen at the Helsinki City Rescue Department. The medical directors and the HUH's ED neurologists set the goals for the training content and materials. The EMS staff at the Helsinki City Rescue Department were asked to provide their opinions and practical suggestions on how these goals would be best achieved. The structural design process involved 12 separate 20-minute brainstorming sessions where a total of 149 EMT-firemen provided their development ideas from the grass-root level of prehospital practice. The results were assimilated into a lecture-based training package. Further ideas from the EMS staff were welcomed throughout the project. Cases with very long on-scene times were reviewed by the EMS directors and feedback was given to the staff. Additionally, an on-screen timer that showed the time spent on the scene was added to the electronic patient-reporting system (Merlot Medi, CGI Inc. Canada) used by the EMS to improve time awareness on the scene.

The key practice points targeted by the training programme were to (1) increase general time awareness of the EMS staff (i.e. adding an OST timer function to the paramedics' laptop computers), (2) limit the overall number of emergency on-scene procedures (ie,  $\leq 3$  allowed attempts at intravenous cannulation), (3) transport the patient to the ambulance using a carrying chair instead of a cumbersome stretcher, and (4) transform the general management workflow into a typical load and go setup to automate fast assessment and immediate transport (Table 9).

All >16 years old patients transported by ambulances to the ED of HUH using the stroke code 4 months prior to and after the training period were registered, and their prehospital electronic patient reports were retrieved from the Merlot Medi database. All transportations from other healthcare institutions were excluded. Key operational variables that described EMS performance were compared before (1<sup>st</sup> February to the 31<sup>st</sup> May 2015) and after (1<sup>st</sup> September to 31<sup>st</sup> December 2015) the training period.

## 4.6 DATA ANALYSES

Statistical analyses were performed using versions 16.0 to 21.0 of SPSS statistical package (IBM Corporation; Armonk, New York USA) whichever was the latest available version at the time. Means and standard deviations (SDs) or medians and interquartile ranges (IQRs) were used in the presentation of all continuous variables. Non-parametric and parametric statistical comparison of groups and their distributions were made using Mann-Whitney-U, Pearson's chi-squared test, Fisher's exact test, analysis of variance, and Kruskal-Wallis tests, where appropriate. The p-values less than 0.05 were considered to be significant.

In study I, time interval changes were measured from year to year and their association with the patient's functional outcome (mRS) was assessed. To define the effect of prehospital delays on stroke severity, the patients were divided into three groups according to the patient's first measured NIHSS score: mild (<7), moderate (7–15), and severe (>15) stroke, as described previously. (Adams et al. 1999, DeGraba et al. 1999) Binary logistic regression was used to determine the association between selected variables and functional outcome by applying a backward stepwise approach (likelihood ratio). The selection of model variables was based on clinical judgment of the independent factors that might be associated with the patient outcome. Goodness of fit of the regression model was assessed with the Hosmer-Lemeshow test.

In study II, the patients were divided into groups for univariate analysis based on the use of fire engine support and (short versus long) OST duration. The median OST in the dataset was used as a cut-off value. A binary, backwards logistic, regression



analysis was then conducted with selected variables ( $P < 0.3$ ) to identify the factors independently associated with a short OST.

In study III, the patients were categorized based on early or late hospital arrival and treatment. An ODT of  $\leq 90$  minutes was considered an early hospital arrival, and an OTT of  $\leq 120$  minutes was considered early treatment. The cutoff values selected were based on the earlier reported pretreatment time intervals from the study setting (Lindsberg et al. 2006, Meretoja et al. 2012), those indicated by the available literature (Lees et al. 2010, Fassbender et al. 2013), and the distribution of the obtained data (median values). Variables connected to EMS system operation with  $>90\%$  available data and a univariate  $P < 0.2$  were selected for binary logistic regression analyses to identify factors associated with early hospital arrival and treatment.

In study IV, a dichotomized analysis was made to compare short and long OST duration groups using the sample median as the cut-off point. Variables with  $>90\%$  complete data sets and p-values below 0.2 were selected for regression analysis to determine associations with a short OST.

## 5 RESULTS

### 5.1 GENERAL

In study I, the sample consisted of 335 consecutive stroke patients who received IVT at HUH. Forty-six patients were excluded because they were not brought to the hospital by the EMS or they had a basilar artery occlusion. A total of 289 patients were eligible for the study. In study II, the EMS in Tampere identified 79 thrombolysis candidates. Two patients whom had been transferred from other health care institutions and were excluded from the study. In study III, 623 recanalized patients were identified. Three-hundred-and-thirty-six of these patients arrived at the hospital by ambulance. Sixteen patients were transported to HUH from other health care institutions and 12 cases had missing or partial emergency phone call discussion recordings. A total of 308 patients were included in the study. In study IV, the EMS transported a total of 879 suspected stroke patients to HUH during the 8-month study period. Twenty cases were regarded as interfacility transports. Of the remaining 859 patients, 289 were identified as potential thrombolysis candidates by the emergency medical dispatchers and managed accordingly by the EMS using high priority ambulance transport, the stroke code, and a prenotification to the ED.

### 5.2 THE PREHOSPITAL TIME INTERVALS AND PATIENT OUTCOME (I)

During the study, the median (IQR) onset-to-dispatch time was 13 minutes (5–32 minutes), ODT 71 minutes (55–94 minutes), and OTT 125 minutes (95–153 minutes). The consistent annual decrease in mean OTT was reciprocated by the increase in the number of treated patients from 2003 to 2005 (Table 10). Both the OTT and the DTT were significantly reduced, whereas none of the prehospital time intervals (ODT, onset-to-dispatch time, transportation time) changed appreciably. Onset-to-dispatch times were shortened in proportion to stroke severity (Table 11). Consequently, the group with severe stroke had shorter ODT and OTT than the group with mild symptoms. However, OST tended to increase along with stroke severity, but it did not considerably prolong ODT, and the transportation times were similar in all groups (Tables 10 & 11). The percentage of functionally independent patients

in each group was expectedly strongly influenced by initial symptom severity, and the patients with more severe strokes tended to be older.

**Table 10.** Characteristics and prehospital time intervals of stroke patients receiving IVT at HUH in 2003–2005.

<b>Variable</b>	<b>2003 (n= 58)</b>	<b>2004 (n=82)</b>	<b>2005 (n=149)</b>	<b>p-value</b>
Male, n (%)	33 (56.9)	31 (37.8)	78 (52.3)	0.044
Onset-to-dispatch time, min	11 (5–30)	13 (6–29)	13 (5–40)	0.737
Ambulance response time, min	8 (5–12)	7 (5–10)	8 (5–10)	0.694
On-scene time, min	22 (14–27)	20 (15–27)	21 (15–26)	0.908
Transport time, min	18 (11–22)	23 (15–34)	19 (14–30)	0.019
Onset-to-door time, min	62 (50–100)	74 (57–91)	72 (55–94)	0.441
Door-to-treatment time, min	67 (49–90)	53 (37–67)	34 (22–47)	< 0.001
Onset-to-treatment time, min	149 (117–165)	128 (99–149)	112 (87–148)	< 0.001
NIHSS at ED arrival, points	11 (7–16)	10 (7–18)	9 (6–16)	0.061
mRS ≤ 2 after 3 months, n (%)	26 (44.8)	40 (48.8)	82 (55)	0.220

All time intervals and National Institutes of Health Stroke Scale (NIHSS) presented using median values (interquartile range). ED= emergency department, mRS = modified Rankin Scale.

The patients' median (IQR) baseline NIHSS score was 10 points (7–16 points) and a total of 148 patients (55%) had a favourable treatment outcome (mRS≤2). Selected independent variables entered in dichotomic analysis with a univariate comparison by binary outcome and a backwards logistic regression model (a good outcome as the dependent variable) are shown in Tables 12–13. Together with the expected predictors age and stroke severity, DTT remained in the model as a predictor. In addition, each year was entered in the model as a categorical variable to control secular trends over the years of the study, but this did not appear as a predictor or alter the remaining variables or their significance in any way.

**Table 11.** The patients' prehospital time intervals and outcome according to stroke severity measured using the National Institutes of Health Stroke Scale.

Variable	Mild (<7)	Moderate (7-15)	Severe (>15)	p-value
Patients, n	69	136	84	n/a
Age, years	67 (58-76)	72 (62-78)	74 (65-82)	0.005
Male, n (%)	38 (55.1)	66 (48.5)	38 (45.2)	0.472
Systolic blood pressure, mmHg	165 ± 32	157 ± 33	152 ± 27	0.053
Onset-to-dispatch time, min	25 (12-47)	12 (6-30)	8 (4-24)	< 0.001
Ambulance response time, min	8 (6-10)	8 (5-11)	7 (5-10)	0.154
On-scene time, min	18 (13-26)	21 (15-25)	23 (17-29)	0.005
Transport time, min	19 (15-30)	20 (14-29)	20 (12-30)	0.892
Onset-to-door time, min	82 (62-107)	70 (55-93)	65 (51-90)	0.006
Door-to-treatment time, min	46 (25-67)	43 (29-65)	41 (26-61)	0.972
Onset-to-treatment time, min	136 (110-168)	121 (95-150)	118 (90-148)	0.022
mRS <sub>≤2</sub> after 3 months, n (%)	53 (76.8)	76 (55.9)	19 (22.6)	< 0.001

All time intervals and patients' age in years presented using median (interquartile range). Systolic blood pressure in millimetres of mercury (mmHg) using mean ± standard deviation. mRS= modified Rankin Scale.

**Table 12.** Selected variables according to good versus unfavourable functional treatment outcome at three months after IVT.

Variable	mRS <sub>≤2</sub> (n= 148)	mRS <sub>&gt;2</sub> (n=141)	p-value
Male, n (%)	79 (53.4)	57 (42.5)	0.07
Age, years	67 (58-76)	75 (66-81)	<0.001
Systolic blood pressure, mmHg	159 ± 32	156 ± 32	0.42
NIHSS at ED arrival, points	8 (5-11)	15 (9-18)	<0.001
Onset-to-dispatch time, min	13 (5-36)	11 (5-30)	0.36
Ambulance response time, min	7 (5-10)	7 (5-11)	0.69
On-scene-to-door time, min	41 (33-50)	44 (34-58)	0.75
Door-to-treatment time, min	43 (27-65)	44 (31-66)	0.43

All time intervals and patients' age in years presented using median (interquartile range). Systolic blood pressure in millimetres of mercury (mmHg) using mean ± standard deviation. ED= emergency department, mRS= modified Rankin Scale, NIHSS= National Institutes of Health Stroke Scale.

**Table 13.** Backward logistic regression analysis on favourable functional outcome (mRS  $\leq$ 2) at three months after IVT.

<b>Variable</b>	<b>p-value</b>	<b>Odds ratio (95% confidence interval)</b>
Age (decades)	< 0.001	0.57 (0.42-0.77)
Door-to-treatment time (hours)	0.04	0.47 (0.22-0.97)
NIHSS at ED arrival (points)	< 0.001	0.83 (0.78-0.88)

In the Hosmer-Lemeshow test,  $p=0.62$ . ED= emergency department, NIHSS= National Institutes of Health Stroke Scale.

### 5.3 PERFORMANCE OF FAST IN PREHOSPITAL STROKE RECOGNITION (III)

The EMDs dispatched the ambulance using the stroke code in over 60% of the cases. High priority was used even more often, over 80% of the time. The ambulance crews identified and transported > 90% of the patients using the stroke code, but the rate of high priority transport remained below 90%. There were some differences with the reported FAST-algorithm items and the rates of positive items were lower for the emergency phone call discussions than prehospital examination (Tables 14 & 15). Especially the identification of facial droop and arm weakness appeared to be more difficult during the emergency call than on the scene. There were also significant differences between the call discussions and FAST-items were commonly left undiscussed if a positive item was reported early in the call.

### 5.4 EARLY HOSPITAL ARRIVAL AND TREATMENT (III)

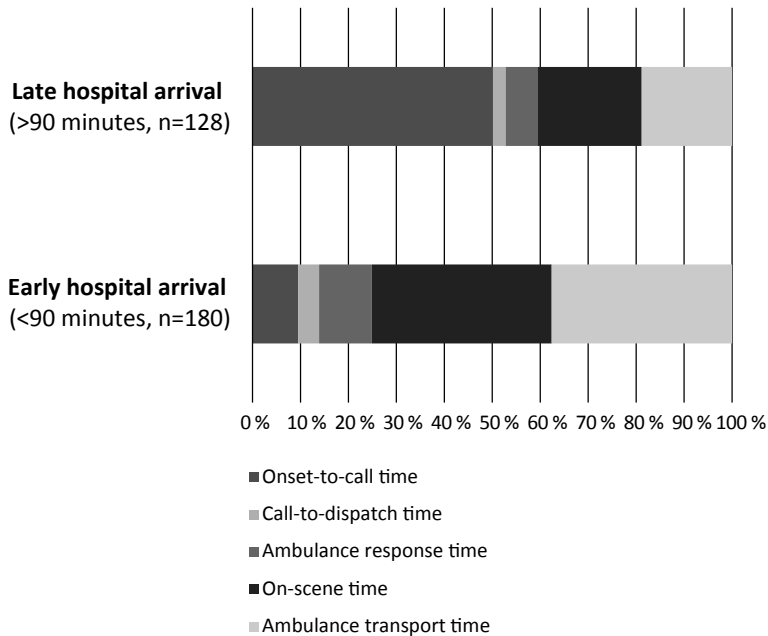
In the bivariate analysis, the most dominant predictors of early hospital arrival and treatment were transport with stroke code, transport using high priority, and short OCT and OST (Table 15). The positive arm weakness symptom in the FAST algorithm in the emergency call and paramedic examination clearly expedited the treatment (Table 14). In the prehospital time intervals analysis, the most significant difference was seen in the OCT duration which took over 50% of the ODT in the late-arriving group. (Table 15, Figure 4) Moreover, the call-to-dispatch and ambulance response times were significantly shorter for early arrivals but the time differences were rather insignificant (<1 minute).

**Table 14.** Dichotomic analysis of patient's symptoms during emergency call processing and paramedic examination in terms of early and late hospital arrival.

Variable	ODT < 90 min (n=180)	ODT > 90 min (n=128)	p-value	OTT < 2h (n=163)	OTT > 2h (n=143)	p-value
<b>Based on the emergency phone call, %</b>						
Facial droop mentioned	57.1	51.0	0.576	58.7	50.0	0.362
Arm weakness mentioned	80.2	64.8	0.033	82.6	61.6	0.004
Speech disturbance mentioned	92.3	91.8	1.000	91.5	92.7	0.813
"Stroke" mentioned	26.7	25.0	0.793	25.8	25.9	1.000
"Fall" mentioned	27.8	27.3	1.000	28.2	26.6	0.798
Patient on the phone	21.7	28.1	0.379	23.3	25.9	0.705
New call suggested by the dispatcher	49.2	42.2	0.247	51.9	39.9	0.039
<b>Based on paramedic examination, %</b>						
Facial droop present	67.9	59.6	0.183	69.9	69.9	0.049
Arm weakness present	77.3	69.6	0.167	83.3	62.9	<0.001
Speech disturbance present	83.2	82.5	0.874	84.2	81.1	0.530
Previous stroke mentioned	11.1	9.4	0.707	12.3	8.4	0.350

ODT= onset-to-door time, OTT= onset-to-treatment time.

In contrast, OST was long (>23.5 minutes) for both early and late-arriving patient groups. In the early-arriving group, it took nearly 40% of the ODT. This analysis revealed that the OST was the the single most dominant operational variable in the mean additional delays, with over two minutes of added delay (Figure 4, Table 15).



**Figure 4.** Sequential presentation of prehospital time intervals according to percentual proportions of total onset-to-door time.

**Table 15.** Dichotomic analysis of patient's symptoms during emergency call processing and paramedic examination in terms of early and late hospital arrival.

Variable	ODT < 90 min (n=180)	ODT > 90 min (n=128)	p-value	OTT < 2h (n=163)	OTT > 2h (n=143)	p-value
Age, years	68 ± 13	67 ± 13	0.414	69 ± 13	67 ± 13	0.102
Men, %	53.9	57.0	0.642	52.1	58.7	0.252
NIHSS at ED arrival, points	8 (5-14)	7 (4-13)	0.116	8 (5-14)	6 (3-13)	0.020
Vertebrobasilar stroke, %	6.1	12.5	0.08	3.7	14.7	0.003
Ambulance dispatch using code stroke, %	68.3	64.8	0.541	70.6	62.9	0.181
Ambulance dispatch using high priority, %	89.4	75.8	0.002	90.2	76.2	0.001
Ambulance transport using stroke code, %	97.8	87.3	0.001	98.8	87.2	<0.001
Ambulance transport using high priority, %	95.5	77.8	<0.001	97.5	77.3	<0.001
Prenotification given to emergency department, %	66.1	60.2	0.247	65.0	62.9	0.057
Onset-to-call time, min	6 (0-16)	60 (18-104)	<0.001	6 (0-16)	47 (9-100)	<0.001
Call duration, min	3 (2-4)	3 (2-4)	0.063	3 (2-4)	3 (2-4)	0.115
Call-to-dispatch time, min	3 (2-4)	3 (2-5)	0.001	3 (2-3)	3 (2-5)	<0.001
Ambulance response time, min	7 (5-9)	8 (6-11)	0.004	7 (5-9)	8 (6-10)	0.035
On-scene time, min	24 (18-31)	26 (20-32)	0.052	24 (17-30)	26 (20-32)	0.010
Transport time, min	24 (14-30)	23 (18-31)	0.531	21 (14-30)	24 (19-32)	0.094

Patients' age presented using mean ± standard deviation. All time intervals and National Institutes of Health Stroke Scale (NIHSS) presented using median (interquartile range). ED= emergency department, ODT= onset-to-door time, OTT= onset-to-treatment time.



**Table 16.** Backwards logistic regression analyses for selected variables associated with early hospital arrival and treatment.

<b>OTT &lt; 2 hours</b>	<b>p-value</b>	<b>Odds ratio (95% confidence interval)</b>
Age	0.083	1.027 (0.996–1.059)
Onset-to-call time	<0.001	0.999 (0.999–0.999)
New call suggested by the dispatcher	0.037	2.235 (1.050–4.760)
Call-to-dispatch time	0.133	0.998 (0.995–1.001)
Dispatch-to-scene time	0.080	0.999 (0.998–1.000)
On-scene time	0.090	0.999 (0.998–1.000)
Arm weakness	0.079	2.114 (0.918–4.869)
Transport using high priority	0.020	0.114 (0.028–0.462)
<b>ODT &lt; 90 minutes</b>		
Onset-to-call time	<0.001	0.999 (0.998–0.999)
Call duration	0.090	0.991 (0.996–1.001)
Call-to-dispatch time	0.139	0.997 (0.992–1.001)
Dispatch-to-scene time	0.001	0.997 (0.996–0.999)
On-scene time	0.001	0.999 (0.998–0.999)
Dispatch using high priority	0.048	5.259 (1.017–27.195)
Transport using high priority	<0.001	0.084 (0.023–0.310)

All odds ratios for time intervals are based on change per minute. ODT= onset-to-door time, OTT= onset-to-treatment time.

The influences of transport using high priority and OCT remained as significant predictors of both early hospital arrival and treatment when subjected to binary logistic regression analysis (Table 16). A possible confounding effect between dispatcher- and EMS-related variables was corrected by rerunning both binary logistic models by removing either dispatcher or EMS variables, but this did not lead to a change in significance. The OCT duration and high-priority transport to the hospital were the most important determinants for both end points (ODT and OTT).

## 5.5 FIRE ENGINE SUPPORT AND OST IN PREHOSPITAL STROKE CARE (II)

The ambulance dispatch was as expected made more frequently using stroke code and a high priority in the patient group that was managed by ambulance and fire engine crews together. The patients in this group were heavier than those managed by ambulances alone but did not differ in terms of GCS or building floor height. Despite that the fire engine support practically tripled the number of EMS

**Table 17.** Comparison of patients managed by ambulances and fire engine crews and ambulances only.

Variable	Ambulance + fire engine	Ambulance only	p-value
Patients, n	45	32	
Body weight, kilograms	84 ± 16	76 ± 13	0.017
Glasgow coma score, points	15 (14-15)	15 (13-15)	0.671
Building floor of the location, height	1 (0-3)	0 (0-1)	0.006
High priority dispatch, %	100.0	53.1	<0.001
Dispatch code stroke, %	91.1	34.3	<0.001
Personnel on the scene, n	6 (5-7)	2 (2-2)	<0.001
Onset-to-dispatch time, min	25 (7-67)	19 (6-41)	0.368
Ambulance response time, min	7 (5-10)	8 (5-11)	0.340
On-scene time, min	21 (18-26)	24 (20-32)	0.073
Transport time, min	8 (6-12)	9 (6-13)	0.457
Dispatch-to-door time, min	38 (33-46)	41 (35-53)	0.109
Onset-to-door time, min	68 (48-106)	69 (48-97)	0.713

Patient weight is given as mean ± standard deviation and all other variables using median (interquartile range) unless stated otherwise.

personnel on the scene, no change in the OST or other prehospital time intervals was observed (Table 17). The patients were compared in terms of short and long OST (Table 18). Only the use of stroke code in ambulance dispatch was associated independently with a short (<22 minutes) OST [odds ratio 3.952 (95% CI 1.279-12.207)].

**Table 18.** Comparison of patients with short and long OSTs.

Variable	OST <22 minutes	OST ≥22 minutes	p-value
Patients, n	33	44	n/a
Weight, kilograms	78 ± 15	82 ± 15	0.273
Fire engine on the scene, %	69.6	50.0	0.104
Personnel on the scene, n	5 (3-6)	4 (2-6)	0.564
Building floor of the location, height	0 (0-2)	0 (0-0)	0.901
Dispatch code stroke, %	81.8	56.8	0.027
Dispatch using high priority, %	90.9	72.7	0.079
Onset-to-dispatch time, min	17 (7-81)	23 (8-56)	0.943
Ambulance response time, min	7 (4-10)	7 (5-10)	0.653

Patient weight is given as mean ± standard deviation and other variables using median (interquartile range) unless stated otherwise. OST= on-scene time.

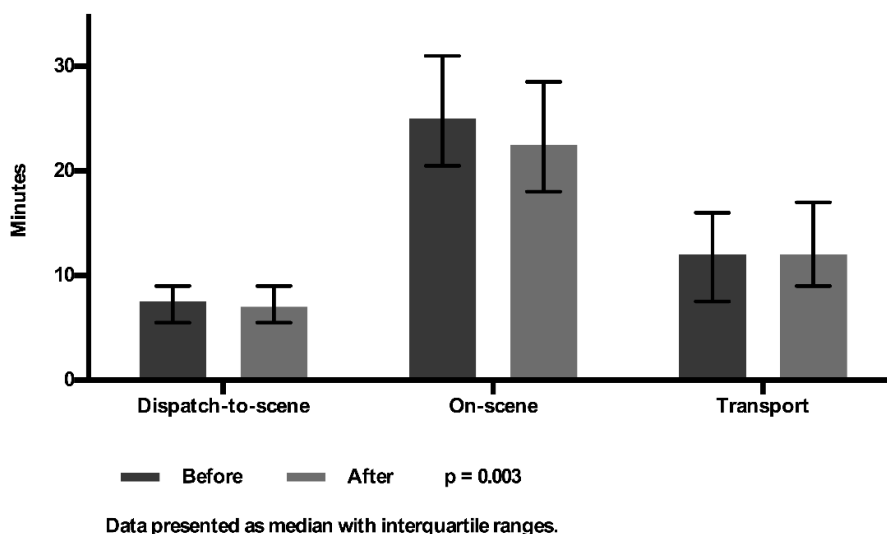
## 5.6 EMS TRAINING PROGRAMME TO DECREASE THE OST (IV)

In 2015, 141 patients (age  $65 \pm 17$  years, 47.5% male) were registered before and 148 (age  $66 \pm 16$  years, 50.7% male) after the implementation of the training package. The groups did not differ in terms of patient age, sex, frequency of physician's telephone consultations, or number of ALS-trained crews ( $p > 0.1$ ), but the training programme was found to be followed by a decrease in the OST by 10% (Table 19, Figure 5). However, this did not translate into net savings in the overall time from dispatch to door hospital arrival, which remained at 45 minutes (Table 19). Consultation with a prehospital emergency physician or a neurologist via telephone was associated with a longer OST in the univariate comparisons and multivariable regression model, whereas ALS training of the EMS personnel promoted a shorter OST when compared to BLS-trained crews. Participation in the training programme showed a strong trend toward shorter OST durations (Tables 20 & 21).

**Table 19.** Comparison of patients registered before and after the training package implementation.

Variable	Before (n=141)	After (n=148)	p-value
ALS-trained ambulance crew, %	57.4	59.5	0.811
Dispatch-to-scene time, min	7.5 (5.5–9.0)	7.0 (5.5–9.0)	0.853
On-scene time, min	25.0 (20.5–31.0)	22.5 (18.0–28.5)	0.003
Ambulance transport time, min	12.0 (7.5–16.0)	12.0 (9.0–17.0)	0.417
Dispatch to hospital arrival, min	45.0 (41.5–54.0)	44.5 (38.0–52.0)	0.152
Physician consulted, %	51.8	45.3	0.291
Hospital diagnosis stroke or TIA, %	51.4	61.4	0.099
Recanalization therapy given, %	20.0	21.1	0.886
IVT only	16.4	14.3	
EVT only	2.1	1.4	
IVT + EVT	1.4	5.4	

All time intervals presented using median (interquartile range). OST= on-scene time, IVT= intravenous thrombolysis, EVT= endovascular treatment.



**Figure 5.** Comparison of three central prehospital time intervals measured before and after the training period.

**Table 20.** Comparison of study patients with short and long scene times.

Variable	OST≤24 min (n=142)	OST>24 min (n=146)	p-value
Age, years	64 ± 16	68 ± 17	0.079
Ambulance crew ALS-trained, %	64.1	53.4	0.073
Training package received, %	57.0	45.9	0.061
Ambulance response time, min	7.5 (5.5–9.0)	7.0 (5.5–9.0)	0.757
Dispatch-to-patient time, min	9.5 (7.5–11.5)	9.5 (7.5–11.5)	0.506
Ambulance transport time, min	13.5 (10.0–17.5)	11.0 (7.0–15.0)	<0.001
Dispatch-to-door time, min	41.0 (35.0–45.5)	50.5 (43.5–56.0)	<0.001
Physician consulted, %	42.3	54.8	0.035

Age in years using mean ± standard deviation and all time intervals using median (interquartile range). ALS= advanced life support, OST=on-scene time.

**Table 21.** Variables independently associated with on-scene time duration in binary logistic regression analysis

Variable	p-value	Odds ratio (95% confidence interval)
Ambulance crew only BLS-trained	0.026	1.760 (1.070-2.895)
Patient's older age	0.065	1.014 (0.999-1.029)
Physician not consulted	0.016	0.546 (0.333-0.893)
Stroke training package not received	0.074	1.550 (0.959-2.505)

BLS= basic life support.

## 6 DISCUSSION

### 6.1 THE DURATION OF THE PREHOSPITAL TIME INTERVALS (I-IV)

Previous studies have usually measured the total prehospital delay, or focused on a single prehospital time interval or a local stroke protocol. (Morris et al. 2000, Chang et al. 2004, Abdullah et al. 2008) The definition and nomenclature of the different time intervals has also varied. The results from different settings using different management protocols are incomparable. In this study, a sequential approach was used for the first time to 'dissect' the prehospital chain of care. This study is novel because it analysed a substantial single-center sample of consecutive stroke patients receiving IVT unlike earlier studies (Adams et al. 1999, Morris et al. 2000, Chang et al. 2004, Turan et al. 2005). When compared to earlier published results from the same hospital setting, the in-hospital delays had significantly improved and favourable prehospital time intervals were observed throughout the study period. The median ODTs varied between 62 and 82 minutes and the OTTs between 112 and 146 minutes depending on the studied year and the severity of stroke symptoms.

However, the study also demonstrated that the prehospital delays in the chain of recovery for stroke remained essentially unchanged and the substantially shortened OTT was the result of a simultaneous decrease in DTT during the period of operational reorganization. (Tables 10 & 11) The fraction of 'gained time' was 25% of the OTT and it was accompanied by a 60% increase in the number of patients treated with rtPA during a period when the total number of stroke patients remained unchanged. The sheer increase in the proportion of thrombolized patients at our ED indicates that the reorganization of the stroke chain of survival for in our hospital area was indeed successful (Lindsberg et al. 2006).

The proportional growth of ODT within OTT in our setting over the years emphasizes the focus on EMS operation. More detailed scrutiny aimed to find potential room for improvement in the current dispatch and prehospital protocols. Similar sequential analysis of the prehospital time intervals was used. A further analysis of the prehospital time intervals confirmed that the delayed activation of the EMS remains the dominant holdup time component in the stroke chain of survival (Table 15). However, similar to stroke severity, the delayed decision to seek help (OCT) was non-modifiable from the perspective of the EMS system. Because 'ad hoc' community outreach education campaigns tend to achieve only transient results

and have a high cost (Hodgson et al. 2007), better stroke knowledge should perhaps be achieved by integrating its education into social programmes and the school systems instead of depending on patient associations and citizen organisations to disseminate that information. Moreover, stroke knowledge and how to identify the patient's condition might not be factors as important in EMS activation as the caller's palpable sense of urgency (Mikulík et al. 2008, Skolarus et al. 2011).

Although the emergency phone call duration of less than three minutes was not a surprising finding, the call-to-dispatch time was shown to be more than 50% longer than that recommended by the Emergency Response Centre Administration (a Finnish authority) (Table 15). This may reflect the time-consuming nature and associated difficulties of dealing with 'stroke calls'. The ambulance response times remained at 8 minutes or below at all times which is in compliance with the current Finnish EMS guideline for high priority calls. Ambulance transport times of usually less than 20 minutes fits in well with the distances, traffic and speeds used in Finnish city-based EMS systems. However, OST duration was found to have increased by 4 minutes without obvious changes in the prehospital protocol between 2003 and 2012 (Tables 10 & 15).

The key-point behind the success of the acute stroke management philosophy in HUH has been 'to do as little as possible after the patient has arrived at the ED and as much as possible before that' (Meretoja & Kaste 2012). Such emphasis could have 'frontloaded' and caused some inevitable delays to the OST. This might also explain why the OST has shown a tendency to increase when the DTT at HUH has been pushed below 20 minutes (Meretoja et al. 2012). The OST in the late arrival and treatment groups of study III were 2 minutes longer, which it was thought, could indicate a decreased sense of urgency in cases in which the OCT was long to begin with (Tables 16 & 17). The OST accounted for approximately 40% of the EMS operational time, although the ambulance crews should have operated using a 'load and go' management approach.

Although OSTs as low as 15 to 18 minutes have been successfully achieved by both American and Danish investigators (Patel et al. 2014, Simonsen et al. 2014), those reports did not discuss the duration of in-hospital delays nor the OTT. Caution is required when comparing and interpreting the results from different EMS systems since an excessively tight time limit for the OST might result in inferior quality of patient examination and reporting. This does not remove the delay but rather transfers it to the ED process. However, special attention should be focused on patient cases with a very long OST (>25 minutes) to help identify possible bottlenecks in existing prehospital protocols. Hospital-based feedback to the EMS staff has been shown to be an effective method to help ensure that the personnel act according to the guidelines (Choi et al. 2014).

## **6.2 STROKE RECOGNITION BY THE EMDS AND AMBULANCE CREWS (III)**

The EMDs used the stroke code in more than two-thirds of the cases and high-priority dispatch in more than 80% of the time. The ambulance crews successfully identified over 90% of the acute stroke patients, and the simultaneous use of high-priority transport remained at only a small fraction below 90% (Table 15). These figures are among the highest reported for both emergency call processing (Kothari et al. 1995, Buck et al. 2009, Krebs et al. 2012, Jones et al. 2013) and prehospital stroke care. However, even for these eventually recanalized patients there still remains some room for improvement as the assignment of calls to high priority and stroke code status in dispatch and transportation did not reach 100%.

A rigid code-specific algorithm is not used in the Finnish EMS system when determining the dispatch code and priority. This flexibility allows the dispatcher enough freedom to decrease delays when the caller spontaneously provides the key information. On the other hand, the additional time used in the dispatch process may have contributed to the relatively high frequency in the use of stroke code and high priority in ambulance dispatch which might have eventually benefited patient transportation. Consequently, striving towards even greater expedition of call processing by dispatchers might not boost performance. The shortening of the initial telephone interviews could, in fact, degrade diagnostic accuracy.

The EMS had a high reporting rate for all FAST criteria, which reflects knowledge of prehospital stroke care in this study setting. Stroke recognition was high despite there being substantial proportion of posterior circulation stroke (9%). Although patients were frequently transported using stroke code and high priority, documented prenotification of the ED was found in slightly over 60% of the reports. However, the prenotification is an essential part of the prehospital protocol, thus this percentage of prenotification was most likely the result of inadequate (written) reporting practices.

## **6.3 PREDICTORS OF EARLY HOSPITAL ARRIVAL, EARLY TREATMENT AND GOOD OUTCOME (I & III)**

An important observation supporting earlier findings was that increasing stroke severity considerably decreased OCT, onset-to-dspatch time or more commonly 'call delay' (Table 11) (Chang et al. 2004, Turan et al. 2005). In addition, study I indicated that the differences in ODT caused by stroke severity were mainly concentrated in the call delay and OST components. Although it is rational that more alarming symptoms would prompt one to seek more immediate medical attention, the time-limiting step

is that either the patient retains the capacity to recognize the symptoms and call for help herself or himself or more commonly a bystander acts on behalf of the patient. Similarly, the more severe the symptoms are, the more time-consuming it would be to secure the airway, breathing, and circulation on the scene before transport. However, ALS-level emergency procedures actually have been required in only a few percent of all stroke cases (Petchy et al. 2014) and severely stricken patients still arrive at hospital significantly earlier than those with milder symptoms (Table 13). This strengthens the overall conception that symptom severity and the early decision to seek help are the most important patient-dependent time determinants of the ODT or 'prehospital delay'.

The results of study III further highlighted the components of the prehospital phase that assign stroke patients to early and late management groups. Although the call-to-dispatch time was associated with early hospital arrival and treatment (Tables 15 & 16), only minute-delays could be attributed to it. An interesting finding was that the dispatcher's suggestion to call back in case of worsening state was associated with shorter OTT. This could be because the dispatcher's intuition managed to single out some of those potentially severely ill patients who should be treated fast by EMS on the scene and rushed to the ED. On the other hand, the long OCT was the single most important determinant of both early hospital arrival and treatment in study III (Tables 15 & 16). Moreover, prompt operation on the scene and use of high-priority transport were key operational success features for routing patients to the early categories of hospital arrival and recanalization treatment. Interestingly, using high-priority dispatch, the stroke code or prenotification to the ED were not found to promote early hospital arrival or early recanalization treatment. However, it must be remembered that the present sample was limited to patients who had successfully received stroke treatment. Moreover it is especially important that the critical role of the emergency call processing in the initiation of the chain of survival must not be undermined. After the regression analysis, the unilateral arm weakness was the only FAST-symptom associated with early treatment (Tables 15 & 16), which suggests that a classic anterior circulation stroke is well recognized by the EMS.

Although the effect of a shorter OTT was found to be predictive of a favourable outcome in large pooled analyses (Hacke et al. 2004, Emberson et al. 2014), study I was the first to suggest that shortened DTT alone may be an independent predictor of a favorable functional outcome. This finding itself must be interpreted with great caution, as the study did not compare outcomes in our patients to those in patients before the ED restructuring process, but rather it describes a longitudinal evolution of the OTT. Similar observations have been made in the > 70 000 patients studied in the 'Get with the Guidelines' quality improvement initiative in the United States (Fonarow et al. 2014). Based on these results it seems that all efforts to reduce OTT are likely to improve the overall postintervention outcome as later suggested (Meretoja et al. 2014).



## 6.4 IMPROVING THE PREHOSPITAL CHAIN OF CARE (II & IV)

Continuous monitoring of stroke quality metrics and implementation of quality improvement activities are essential to the efficient functioning of a comprehensive stroke centre. The collected information should be used to stimulate ongoing quality management in line with the steps of the Deming cycle (plan, do, check, act). In HUH, motivated by the first European randomized controlled trials of the rtPA, the investigators first reported the first cycle (1998–2001) of the ‘prelabel’ IVT service for acute stroke (Lindsberg et al. 2003) and later the second guided quality assurance cycle (1999–2004) principally to improve in-hospital delays (Lindsberg et al. 2006). After study I confirmed that a DTT reduced to 32 minutes was associated with improved patient outcomes (Table 13), the process led to a well-known optimization of DTT below 20 minutes by 2011 in Helsinki (Meretoja et al. 2012), which allowed ultra-early recipients (OTT <70 minutes) of IVT to gain the most independence (Strbian et al. 2010).

The OST was subjected to detailed scrutiny in studies II & IV due to its significant proportion of the ODT (Figure 4), its increasingly long duration and variance seen throughout the years and the severity of stroke (Tables 10 & 15). Study II was the first to introduce the use of fire engine crews to support ambulances in prehospital stroke care. This approach is typical of Finnish EMS systems particularly in out-of-hospital cardiac arrest (Väyrynen et al. 2008), but few reports on its effectiveness exist. The fire engines were found to respond promptly and their deployment practically tripled the number of personnel managing the patient on the scene, but the measured OST did not differ when compared to the conventional and standard prehospital management by two-person ambulance crews. Using the fire engines as a part of the prehospital stroke protocol inevitably increased the units’ workload and utility costs, and also hindered them from responding to fire and other types of rescue calls in their area. In multivariate regression analysis, the ambulance dispatch using the stroke code was the only variable associated with a short (<22 minutes) OST. It is important to note that although patients’ high GCS, mean body weight, and easily accessible location near the street level all favoured a short on-scene stay, the overall median OST measured in this study was still well over 20 minutes (Tables 17 & 18).

Study IV highlighted the possibility of decreasing the OST significantly with a dedicated training programme that targeted existing, experienced EMS personnel. Although several components of the prehospital chain of thrombolysis candidates are dictated by the surrounding ephemeral and prevailing conditions (ie. rush hour traffic), the workflow of the on-scene management remains modifiable and includes adjustable performance task variables. Study II merely aimed at increasing the number of EMS personnel on the scene, the ground-breaking initiative in study

IV was to give special emphasis to the attitude and ‘sense of urgency’ for the EMS personnel on the scene in addition to raising awareness of the elapsed overall time –not merely stroke knowledge and recognition. The study demonstrated that a low-cost education programme for ambulance crews can affect their decisions about physician consultations and influence the composition and thereby reduce the duration of the OST. The study also identified novel modifiable elements in the prehospital chain. The reduction of 10% achieved in the OST was associated with the higher training level of the ambulance crews and fewer physician consultations. Less time on the scene did not lead to premature rushing of patients into ED, because 10% more patients that reached the hospital with the diagnosis of cerebral ischemia ( $P < 0.1$ ) received recanalization therapy with at least the same frequency. Therefore, training the EMS staff of imperatives stemming from the time-dependent ischemic pathophysiology may create a time-saving opportunity. Regardless of the geographical position, rural or metropolitan, the OST contains a considerable modifiable time-saving potential. However, a repetitive training programme is challenging to include in the congested training scheme of EMS personnel; all of whom also have to manage a capricious palette of injured and critically ill patients on a daily basis. Suspected acute stroke cases in Helsinki currently comprise only 3% of the task load of the EMS. Therefore, the overall results are reassuring, even though decreasing system-based delays must be implemented as a continuous dynamic process.

## 6.5 LIMITATIONS

The study has some limitations. Foremost, all the studies I-IV were register-based and represented single-centre samples. The patient selection focused on either thrombolysis candidates (suspected acute stroke) (II, IV) or patients that successfully received recanalization treatment (I, III). The study design lacked a control group and the sample size was limited for multi-variable analysis using several predictor variables.

The sample in study II was limited to prehospital data only. The calls managed by ambulance crews without fire engine support were less often dispatched using a high priority or the stroke code which could have resulted in longer prehospital time intervals. The severity of stroke symptoms was not measured, partly due to the fact that dedicated symptom severity scales, such as the NIHSS are not readily available in a prehospital setting. Finally, the study was based on patients with suspected stroke but whose hospital diagnoses, in-hospital delay, and treatment data were not available to the investigators. The possible benefit gained from the use of additional manpower on the scene therefore remained questionable after the study. However, the significance of the number of EMS personnel on the scene

might become more evident in a metropolitan settings where people reside in tall apartment buildings and the emergency vehicles cannot drive near the patient's location (Graham et al. 2009). Another important aspect is the phenomenon of increasing patient obesity which is not only associated with increased morbidity but also practical difficulties in emergency procedures and moving the patients from the scene (Wiesener et al. 2008).

In study III, patients who were not considered for recanalization and nonstroke patients assigned with the stroke code in the EMS system (false positives) could not be included. The FAST criteria record had a number of missing values and often represented more than one symptom category simultaneously, which possibly reduced their weightings as predictors. Alternatively, the natural evolution of stroke symptoms may have included fluctuation of FAST symptoms by the time the patients reached the ED and the neurologist's examination.

The small sample size in study IV might explain why the obvious decrease in the OST did not directly translate into reduced dispatch-to-hospital time, although the latter did associate with reduced OST (Table 20).

## 6.6 FUTURE CONSIDERATIONS

The stricken person's hesitancy or disability to seek help remains an unwavering problem, which burdens the whole chain of survival. Patient-dependent delays can only be influenced by promoting awareness of stroke symptoms in the general public to increase the number of prompt emergency calls. A novel approach to this problem may be provided by the increasing popularity of various social media platforms in the World Wide Web. However, this type of coverage is often based on expert opinion rather than a controlled campaign. Similarly, the extensive media coverage given to renowned surviving patients has also helped to make the disease and its warning symptoms more common to the public (YLE News 15.6.2016) Social media may also have an increasing role in medical education and training programs aimed at EMS staff. Social media has been successfully used to share free medical education through the Free Open-Access Medical Education (FOAMED) -initiative in the emergency medicine community. (Nickson 2014) However, no studies currently exist regarding the role of social media in the public education on health-related issues or the training of medical professionals.

Prehospital stroke recognition can still be improved by repetitive and further training of EMDs and EMS professionals. Evaluating mild, atypical or fluctuating symptoms and posterior circulation stroke remain important challenges. An increasingly important aspect of stroke recognition in the prehospital phase will be the sub-group of stroke patients with an LVO that require mechanical thrombectomy. Although several identification algorithms have been studied, the

results have to this date been significantly inferior to prehospital stroke recognition in general. On the other hand, the increasing knowledge of stroke and neurological symptoms in the EMCCs and EMS systems have also increased the sensitivity to using the stroke code. Stroke neurologist have noticed an increase in the number of thrombolysis candidates but also false positives seen at the ED. This can be especially harmful when several patients arrive at short intervals and they have to wait for the neurologist's examination and assessment.

Recently, it has been suggested that EMS performance in acute stroke care could be further improved by executing some of the common emergency procedures (i.e. intravenous cannula placement) and the neurologist consultation during ambulance transport (Simonsen et al. 2014). However, travel time to the hospital often amounts to only a small and fixed proportion of the total prehospital delay period in highly dependable EMS systems (Tables 10, 15, 17 & 19). Emergency procedures performed in a moving vehicle can jeopardize both the patient and the EMS personnel (i.e. the lack of safety belts, accidental needle-sticks) and should be avoided. When the transport time is expected to be long (>1 hour), especially in cases where the possibility of LVO is considered, helicopter transport may be an important method to save time when direct transport to a comprehensive stroke centre is the most favourable option (Jauch et al. 2013). Similarly, a 'drip-and-ship' method may be used in arranging interhospital transport between primary and comprehensive stroke centres (Sheth et al. 2015). In drip-and-ship, the rtPA bolus is given at primary hospital, with a possible telemedicine consultation by a stroke neurologist, and continued as an infusion during ambulance transport to the comprehensive stroke centre. This strategy may save important minutes and still enable timely IVT administration to a higher number of patients than centralisation of all the patient flow to a comprehensive stroke centre directly. Moreover, patients with LVO can be transferred to receive definitive care (Holodinsky et al. 2017, Milne et al. 2017). Finally, the importance of a prenotification to alert the in-hospital stroke team and enable the direct referral to imaging studies and laboratory exams should not be forgotten.

The fastest median OTT in acute stroke to date has been achieved by using a mobile stroke unit. The mobile stroke unit concept might become more accessible in EMS systems worldwide when the neurological assessment can be done remotely by telemedicine neurologist as recently suggested. This would also dramatically decrease the unit's operational costs (Taskinen 2016, Wu et al. 2017). However, the recent developments in stent-retriever techniques have promoted the use of advanced diagnostic imaging but these are currently only available at fully-equipped hospitals. Moreover, the implementation of prehospital thrombolysis has not been shown to improve the patient's functional outcome when compared to standard hospital care. (Kunz et al. 2016) Further research is therefore required before prehospital stroke therapies are more widely implemented.

The EMS retains important potential for the utilization of novel diagnostic methods and neuroprotective drugs. Earlier studies have been able to show that the feasibility of prehospital blood sampling, drug administration and implementation of management strategies has been proven to be excellent. The development of point-of-care blood analysis to identify a specific biomarker for either ischaemic stroke or haemorrhage, which could become an elegant way to streamline suspected stroke patients to definitive treatment as early as in the field (Mattila et al. 2016). Similarly, the development of a neuroprotective drug or a treatment providing additional time in the tight time window of recanalization could be quickly implemented in the field instantly benefiting a whole patient population.

The most significant challenge may be the difficulty of prehospital emergency-related research; informed consent, randomisation and that the implementation of new features to existing prehospital protocols are frequently questioned by ethics review boards and the current legislation on medical research.

## **7 CONCLUSIONS**

This was the first study to analyse sequentially the composition of the prehospital phase and to measure the performance of Finnish EMDs and ambulance crews in acute stroke recognition and management. Sequential analysis revealed that the prehospital time intervals were among the shortest and the rate of stroke recognition among the highest hitherto reported. The results provide important information for the international development of the prehospital chain of stroke care. Sequential analysis of the pretreatment delay and the development of systematic improvement strategies together with the ambulance crews, EMS physicians and neurologists are methods that can be utilized in different hospital settings and EMS systems.

### **7.1 ANSWERS TO STUDY QUESTIONS**

#### **7.1.1 WHAT IS THE TEMPORAL COMPOSITION OF THE PREHOSPITAL PHASE OF THE STROKE CHAIN OF SURVIVAL IN THE HUH AREA?**

In a sequential analysis, the prehospital phase consisted of emergency call delay (either OCT or onset-to-dispatch time depending on study design), call-to-dispatch time, ambulance response time, OST and transport time. The OST was found to be the longest phase of prehospital operation comprising up to 40% of the entire ODT in the early hospital arrival patient population. However, the OCT was the most important determinant of early versus late hospital arrival and treatment. More severe stroke symptoms were associated with shorter OCT and OST duration.

#### **7.1.2 HOW DO THE EMDS AND PARAMEDICS PERFORM IN IDENTIFYING 'THROMBOLYSIS CANDIDATES' IN THE HUH AREA?**

The EMDs identified over 65% and the paramedics over 90% of the patients receiving recanalization therapy. Moreover, the EMDs dispatched over 80% of the ambulances using high priority regardless of the code used which describes a heightened sense of urgency in acute neurologically suspicious symptoms. Ambulance crews used high priority patient transport for nearly 90% of the cases which is indicative of the difficulty in perceiving the treatment window and symptom severity. This percentage of high priority transport is among the highest reported for both emergency call processing and prehospital stroke care.

### **7.1.3 IS SUCCESSFUL STROKE RECOGNITION DURING THE EMERGENCY PHONE CALL AND PREHOSPITAL ASSESSMENT ASSOCIATED WITH EARLY HOSPITAL ARRIVAL AND TREATMENT?**

Using the stroke code in ambulance dispatch was not associated with early hospital arrival nor treatment in patients receiving recanalization therapy. However, this was a selected patient sample and in the vast majority of cases high priority dispatches and transports were routinely used, which effectively mask the possible time benefit acquired when using the stroke code. However, the ambulance dispatch using the stroke code in study II was associated with a decreased OST.

### **7.1.4 CAN FIRE ENGINE CREWS BE UTILIZED TO PREVENT DELAYS IN PREHOSPITAL STROKE MANAGEMENT?**

The fire engines were found to respond promptly and their use for supporting ambulances of prehospital care more than doubled the manpower managing the patient on the scene. However, the measured OST did not differ when compared to standard prehospital management by ambulance crews alone. Using the fire engines as a part of the stroke protocol inevitably increased the units' workload and utility costs, and also hindered them from responding to simultaneous fire-rescue calls in their area. The possible benefit gained from the use of the additional personnel on the scene remained questionable after the study.

### **7.1.5 CAN OST BE DECREASED BY SYSTEMATICAL TRAINING OF EMS STAFF?**

The low-cost education programme had a measurable influence on OST reduction. The OST of thrombolysis candidates decreased by 10% from 25 to 22.5 minutes after comparing the EMS performance before and after the training programme implementation. ALS training of the ambulance crews was associated with a shorter OST and the decision to consult a physician via telephone was reflected by longer OST. The training package also showed a tendency to decrease the need for the physician's consultation.

## **7.2 CLINICAL IMPLICATIONS**

This study demonstrates that delays in the care of acute stroke patients can be shortened by using systematic, critical assessment of routines in the prehospital milieu. The emphasis must be on identifying and eliminating all possible bottlenecks in the chain of recovery. Seamless teamwork between the EMS and the ED staff

is one of the key objectives in forming a successful, streamlined chain of survival for acute stroke. When the early OTT window of 120 minutes is missed, the mean additional delay stems from the patient-dependent OCT by over 40 additional minutes. Assuming that this delay cannot be further improved by honing the standard operational procedures, the largest remaining additional delay is OST, which accounts for an important proportion of the OTT especially in the early arriving patient group. Increasing the prehospital personnel resources on the scene was not found to decrease the OST or the ODT but using a multi-modal training programme that involved the whole EMS staff did indeed provide favourable results.

However, the ultimate objective is not to strive solely for high stroke sensitivity during emergency call processing or the shortest possible OST during EMS operation. The key to a successful prehospital chain of care is to ensure that all parts of the chain support and complement each other and the time used is also well spent.



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## **ORIGINAL PUBLICATIONS**