Prehospital delay and patient knowledge in acute cerebrovascular disease

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Acknowledgements

As a fresh and inexperienced resident at the Department of Neurology, I was surprised to acknowledge that a large proportion of patients with suspected stroke arrived fairly late at the emergency department after symptom onset, and only occasionally patients were eligible for intravenous thrombolytic therapy. This disproportionate delay amazed me, because stroke is a condition of medical emergency in a similar manner as acute coronary syndrome, but stroke patients seemed to hesitate to contact health care professionals. The curiosity regarding the issue of prehospital delay in patients with acute stroke eventually led to the present thesis.

Without any previous experience in research, I am truly grateful to my supervisor, Ole Morten Rønning, having belief in me and providing me with the opportunity to be involved in clinical research. I appreciate his humble approach, guidance, constructive feedback and continuous support.

To start with, the research project involved blood flow measurement in intracranial arteries using a newly developed multifrequency, multigated transcranial Doppler instrumentation, and included two visits to Ulm, Germany. I would like to thank Professor David Russell, Professor Rainer Brucher, Sean Wallace and Nicola Logallo for their efforts, but ultimately, technical problems made it difficult to translate the in vitro experiments to a clinical setting.

We therefore opted to change focus to prehospital delay in acute stroke. My special thanks and gratitude go to Antje Sundseth for her enormous help and effort, and I deeply appreciate our close and rewarding collaboration. I am also grateful to my co-supervisor, Bente Thommessen, for her great support, contribution, guidance and enthusiasm.

The present work was carried out at the Department of Neurology, done part time during 2009 and 2013, and I thank Head of Department, Tormod Fladby, for his
support and encouragement. I would also like to thank all my colleagues at the Department of Neurology for their continuous support.

Another topic that interested me was the brain – heart connection. During this period, I also studied reasons for cardiac troponin elevation in patients with acute ischemic stroke. In the end, we chose not to include the results in the present thesis, as the topics are not closely connected. Nevertheless, I would like to thank Professor Torbjørn Omland, Gunnar Einvik and Pål Haugar Brekke for their contribution and help.

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I must admit that when working part time as a PhD candidate, neurologist with leadership responsibilities and emergency ward physician, the workload often exceeds 100%. I would like to thank my dear wife and best friend, Sahirah, for her patience, love and endless support. Thank you for your endurance and understanding during these years. And last but not least, I thank my four lovely boys, Ayaan, Yasin, Asim and Sahil, who have made me realize that, after all, you have, and will always have, the highest impact factor in my life.
### Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>ABCD</td>
<td>Age, blood pressure, clinical features, duration of symptoms</td>
</tr>
<tr>
<td>ABCD2</td>
<td>Age, blood pressure, clinical features, duration of symptoms, diabetes</td>
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<tr>
<td>ACS</td>
<td>Acute coronary syndrome</td>
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<tr>
<td>AHA</td>
<td>American Heart Association</td>
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<tr>
<td>AIS</td>
<td>Acute ischemic stroke</td>
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<td>ASA</td>
<td>American Stroke Association</td>
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<tr>
<td>BP</td>
<td>Blood pressure</td>
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<tr>
<td>CBF</td>
<td>Cerebral blood flow</td>
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<td>CBV</td>
<td>Cerebral blood volume</td>
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<td>CI</td>
<td>Confidence interval</td>
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<tr>
<td>CPSS</td>
<td>Cincinnati Prehospital Stroke Scale</td>
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<tr>
<td>CT</td>
<td>Computed tomography</td>
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<td>CTA</td>
<td>Computed tomography angiography</td>
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<tr>
<td>CTP</td>
<td>Computed tomography perfusion</td>
</tr>
<tr>
<td>DNT</td>
<td>Door-to-needle-time</td>
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<td>DWI</td>
<td>Diffusion-weighted imaging</td>
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<tr>
<td>ECASS</td>
<td>European Cooperative Acute Stroke Study</td>
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<tr>
<td>ECG</td>
<td>Electrocardiogram</td>
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<tr>
<td>ED</td>
<td>Emergency department</td>
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<tr>
<td>eGFR</td>
<td>estimated glomerular filtration rate</td>
</tr>
<tr>
<td>EMS</td>
<td>Emergency medical services</td>
</tr>
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<td>EUSI</td>
<td>European Stroke Initiative</td>
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<tr>
<td>FAST</td>
<td>Face, arm, speech, time (Face-arm-speech-test)</td>
</tr>
<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
</tr>
<tr>
<td>GP</td>
<td>General Practitioner</td>
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<td>ICH</td>
<td>Intracerebral haemorrhage</td>
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<td>INR</td>
<td>International normalized ratio</td>
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<td>Abbreviation</td>
<td>Description</td>
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<tr>
<td>IQR</td>
<td>Interquartile range</td>
</tr>
<tr>
<td>IST-3</td>
<td>International Stroke Trial 3</td>
</tr>
<tr>
<td>LACI</td>
<td>Lacunar infarction</td>
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<tr>
<td>LAPSS</td>
<td>Los Angeles Prehospital Stroke Screen</td>
</tr>
<tr>
<td>MCA</td>
<td>Medial cerebral artery</td>
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<tr>
<td>MRI</td>
<td>Magnetic resonance imaging</td>
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<tr>
<td>mRS</td>
<td>Modified Rankin Scale</td>
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<tr>
<td>MSU</td>
<td>Mobile stroke unit</td>
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<tr>
<td>MTT</td>
<td>Mean transit time</td>
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<tr>
<td>NECT</td>
<td>Non-contrast enhanced computed tomography</td>
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<td>NIHSS</td>
<td>National Institutes of Health Stroke Scale</td>
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<tr>
<td>NINDS</td>
<td>National Institute of Neurological Disorders and Stroke</td>
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<tr>
<td>OAC</td>
<td>Oral anticoagulant</td>
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<tr>
<td>OCSP</td>
<td>Oxfordshire Community Stroke Project</td>
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<tr>
<td>OR</td>
<td>Odds ratio</td>
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<tr>
<td>OTT</td>
<td>Onset to treatment time</td>
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<tr>
<td>PACI</td>
<td>Partial anterior circulation infarction</td>
</tr>
<tr>
<td>PCC</td>
<td>Prothrombin complex concentrate</td>
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<tr>
<td>PCP</td>
<td>Primary care physician</td>
</tr>
<tr>
<td>POCI</td>
<td>Posterior circulation infarction</td>
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<tr>
<td>rFVIIa</td>
<td>recombinant factor VIIa</td>
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<tr>
<td>rt-PA</td>
<td>Recombinant tissue plasminogen activator</td>
</tr>
<tr>
<td>SAH</td>
<td>Subarachnoid haemorrhage</td>
</tr>
<tr>
<td>SU</td>
<td>Stroke Unit</td>
</tr>
<tr>
<td>TACI</td>
<td>Total anterior circulation infarction</td>
</tr>
<tr>
<td>TCD</td>
<td>Transcranial Doppler</td>
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<tr>
<td>TIA</td>
<td>Transient ischemic attack</td>
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<tr>
<td>TOAST</td>
<td>Trial of Org 10172 in Acute Stroke Treatment</td>
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<td>WHO</td>
<td>World Health Organization</td>
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List of papers

I

II

III

IV
1 Introduction

1.1 Stroke definition and pathology
Stroke is a clinical syndrome, defined by the World Health Organization (WHO) as rapidly developed clinical signs of focal (or global) disturbance of cerebral function, lasting more than 24 hours or leading to death, with no apparent cause other than of vascular origin (1).

A transient ischemic attack (TIA) is defined as an episode of temporary and focal cerebral dysfunction of vascular origin, which is variable in duration, commonly lasting from 2 to 15 minutes, but occasionally lasting as long as a day (24 hours), leaving no persistent neurological deficit (2).

There are three pathological types of stroke; ischemic stroke (about 80-85%), intracerebral haemorrhage (ICH) (about 10-15%) and subarachnoid haemorrhage (SAH) (about 5%) (3, 4). This thesis will not deal with the latter.

An acute ischemic stroke (AIS) is caused either by atherothrombosis in precerebral or intracerebral arteries, or by an embolus originating from a proximal source, usually the heart or the precerebral arteries. The thrombus or embolus leads to partial or complete occlusion in a cerebral artery, resulting in reduced or abolished blood flow distal to the blockage. Reduced perfusion causes focal brain ischemia and infarction.

Normally cerebral blood flow (CBF) is maintained by cerebral autoregulation at about 50 mL blood/100 g brain/ min. At about 20 mL/100 g/min, neural function is compromised, but still recoverable. If CBF falls below 10 mL/100 g/min, irreversible neuronal damage (infarction) occurs. The concept of two CBF thresholds and an ischemic penumbra as an area of the brain, usually peripheral in location, surrounding the ischemic core, with reversible neuronal failure, was first described by Astrup et al in 1981 (5).

In the literature, ICH can also be referred to as haemorrhagic stroke, and is divided into traumatic and non-traumatic ICH. This thesis will deal with the latter. The
terms most often used for non-traumatic ICH are *primary ICH* and *spontaneous ICH*.

Primary ICH is caused by spontaneous rupture of a cerebral artery, causing bleeding into the brain parenchyma which leads to neuronal damage. The majority of patients have either pre-existing or newly diagnosed hypertension (6). The remaining patients may have vascular malformations, cerebral amyloid angiopathy or impaired coagulation (7). Reasons for secondary ICH may be oral anticoagulant (OAC) use, neoplasms, surgical intervention or the use of intravenous thrombolysis in ischemic stroke patients.

### 1.2 Stroke epidemiology

Stroke represents an important public health problem. In a study from 2009 (8), the annual stroke incidence rates (adjusted to the European population) were 141.3 per 100,000 in men and 94.6 per 100,000 in women, but there were considerable variations between different European regions. Stroke incidence has decreased by 42% in the past four decades in high-income countries (9).

Despite a trend of reduction in death rate in recent years, stroke remains the third most prevalent cause of death, after heart disease and all types of cancer combined, and the leading cause of morbidity and long-term disability (10, 11). The annual incidence of stroke in Europe is estimated to be 1.3 million, with a total annual cost of € 64.1 billion (12).

In Norway, approximately 15,000 strokes are expected annually, of whom 11,000 first-ever strokes, and the risk of stroke is higher for men than women (13). In the North Trøndelag Health Survey (14), the prevalence of stroke was 18.5 per 1000. In the age groups below 50 years, the prevalence was approximately 2 per 1000, increasing to 108 per 1000 in the age group over 80 years, underlining the fact that stroke mainly is a disease among the elderly. Because of demographic changes with an aging population, estimates indicate an increasing incidence of stroke and stroke-related burden in the future (15). In Norway, stroke incidence is expected to
increase about 50% within the next 20 years because of the increased proportion of the population in the older age groups (16).

1.3 Diagnosis of stroke
The initial diagnosis of acute stroke remains a clinical diagnosis. Stroke and TIA are characterized by acute onset and evolution of symptoms attributed to a focal brain lesion. Typical symptoms include muscle weakness, sensory loss, facial paresis, dysarthria and homonymous hemianopia. In addition, strokes affecting the cerebral cortex may lead to aphasia, apraxia, agnosia and neglect.

The National Institute of Neurological Disorders and Stroke (NINDS) (17) has highlighted the following five stroke warning signs: i) sudden numbness or weakness of face, arm, or leg, especially on one side of the body; ii) sudden confusion, trouble speaking or understanding speech; iii) sudden trouble seeing in one or both eyes; iv) sudden trouble walking, dizziness, loss of balance or coordination; and v) sudden severe headache with no known cause.

Symptom severity should be assessed by formal stroke scales (18), preferably the National Institutes of Health Stroke Scale (NIHSS) (19).

Since the clinical presentation varies, it may sometimes be difficult to diagnose acute stroke. In a recently published systematic review (20), 74% of the patients admitted with suspected stroke had a final diagnosis of stroke or TIA. The five most frequent non-stroke diagnoses were seizure, syncope, sepsis, migraine and brain tumours. These and other diseases mistaken for stroke are often referred to as stroke mimics. In the opposite case, strokes could be mistaken for other diseases, and are referred to as stroke chameleons.

1.4 Imaging
Both AIS and ICH are characterized by acute onset of focal symptoms. A computed tomography (CT) scan of the brain in the Emergency department (ED) is a quick
and effective investigation, and should be done in all patients admitted with suspected stroke. A non-contrast enhanced CT (NECT) scan will reliably detect acute haemorrhages, but a normal scan does however not exclude an acute infarction. Hence, the main purpose of a NECT scan in a patient with suspected stroke is to distinguish between ischemic and haemorrhagic stroke, and to rule out other central nervous system lesions (i.e. tumours, abscesses). Regarding intravenous thrombolytic therapy, a NECT remains sufficient for identification of contraindications to intravenous thrombolytic therapy.

Other methods which are useful in acute stroke imaging are CT angiography (CTA) and perfusion-weighted CT (CTP). A CTA provides potentially important information about the presence of extracranial and intracranial vessel occlusion or stenosis. On CTP, the ischemic core and penumbra can be estimated using parameter maps of CBF, cerebral blood volume (CBV) and mean transit time (MTT).

In patients with ICH, repeated CT scans may be necessary if the patient deteriorates. In addition, a contrast-enhanced CT and CTA should be considered to help identify patients at risk for hematoma expansion and to evaluate for underlying structural lesions (21).

A magnetic resonance imaging (MRI) is more sensitive to the presence of ischemia, and the diffusion-weighted imaging (DWI) has emerged as the most sensitive and specific imaging technique for acute infarction, even at very early time points (22, 23), but because of limited MRI-resources at most institutions, a NECT remains the most practical initial brain imaging test. MRI has an important role in selected patients, e.g. patients with transient or improving symptoms, and to rule out stroke mimics.

1.5 Diagnostic tests and further investigation
In addition to imaging, several tests should be performed shortly after admission (18). Biochemical analyses should include blood glucose, electrolytes, creatinine...
and estimated glomerular filtration rate (eGFR), complete blood count with platelet count, cardiac markers (preferably cardiac troponin) and international normalized ratio (INR), and a 12-lead electrocardiogram (ECG) should be recorded on all patients with suspected stroke.

Carotid Doppler ultrasound is a cost-effective screening investigation for imaging the carotid bifurcation and measuring blood velocities in order to detect vessel abnormalities (24), and should be performed during hospitalization. Further, transcranial Doppler (TCD) ultrasonography can be used to detect intracranial occlusions and stenoses. Interestingly, continuous TCD has been shown to augment thrombolytic therapy (25).

1.6 Ischemic stroke classification
There are several stroke classification systems. Two frequently used classification systems are the Trial of Org 10172 in Acute Stroke Treatment (TOAST) (26) and the Oxfordshire Community Stroke Project (OCSP) (27).

TOAST was introduced in 1993 to improve subclassification of ischemic stroke according to aetiological mechanism. There are 5 subtypes in the TOAST classification; large-artery atherosclerosis, cardioembolism, small-vessel occlusion, other determined aetiology and undetermined aetiology. Aetiology identification is important because it will influence the acute treatment, further investigation and secondary prevention.

The OCSP classifies ischemic strokes according to topographic localization, and is of prognostic value. There are 4 subtypes: total anterior circulation infarction (TACI), partial anterior circulation infarction (PACI), posterior circulation infarction (POCI) and lacunar infarction LACI.)
1.7 TIA and stroke risk
Patients with TIA require special attention, as the risk of stroke within 48 hours after TIA has been reported to be 3-5% (28, 29). TIA has *per se* a good outcome without new persisting deficits, but because of the elevated risk of early ischemic stroke, TIA is an important warning sign. Several different risk scores have been developed in an attempt to stratify the short-term and long-term risk of stroke after a TIA. The ABCD score (Age, Blood pressure, Clinical features and Duration of symptoms) (30) is a simple score for 7-day risk of stroke. Further, a refined score called ABCD2 (the four variables from the ABCD score plus Diabetes) (31) was introduced, predicting 2-day, 7-day and 90-day stroke risk. The ABCD and ABCD2 scores are frequently used in research and in clinical settings (32), as they use easily assessable clinical variables.

1.8 Treatment of acute ischemic stroke
Four interventions have been proven to improve outcome in AIS; management of patients in specialized Stroke Units (SUs), intravenous thrombolysis, the use of aspirin within 24 to 48 hours after stroke onset and hemispheric decompressive surgery for malignant oedema (18, 33). A comprehensive guideline for early management of patients with AIS by the American Heart Association (AHA) and the American Stroke Association (ASA) was recently published (18) and includes detailed recommendations based on current evidence.

1.9 Time is brain
The “time is brain” paradigm is now well established in acute stroke care, and emphasizes that neuronal tissue is rapidly lost as a stroke progresses. The ischemic penumbra is the target for therapeutic interventions since effective treatment can prevent an irreversible neuronal damage, thus leading to neurological improvement and recovery. In patients suffering a large-vessel acute ischemic stroke, 1.9 million neurons are destroyed each minute, and the ischemic brain ages 3.6 years each hour without treatment (34).
1.10 Thrombolytic therapy for acute ischemic stroke
The use of intravenous thrombolysis in AIS was first reported by Sussmann and Fitch (35) in 1958. Three patients were treated with fibrinolysin, and one patient showed clinical improvement. Anecdotal cases and pilot studies followed the next decades (36). Still, intravenous thrombolytic therapy with recombinant tissue plasminogen activator (rt-PA) was first approved by the US Food and Drug Administration (FDA) in 1996, based on the positive results of the NINDS rt-PA Stroke Study in 1995 (37). The trial showed that 0.9 mg/kg alteplase administered intravenously within 3 hours of symptom onset resulted in improved clinical outcome (at least 30% more likely to have minimal or no disability) at 3 months compared to placebo. Treatment with rt-PA was approved in most European countries, including Norway, in 2002.

A pooled analysis from six randomized placebo-controlled trials (including the NINDS study) which included 2775 stroke patients (38), confirmed the beneficial effect of intravenous rt-PA and extended previous findings by showing an association between outcome and different time intervals of onset of symptoms to start of treatment time (OTT). Interestingly, odds of a favourable 3-month outcome decreased as OTT increased; odds ratio (OR) 2.8 for 0-90 minutes, 1.6 for 91-180 minutes, 1.4 for 181-270 minutes, and 1.2 for 271-360 minutes in favour of the patients treated with rt-PA (figure 1).

Figure 1. Model estimating odds ratio for favourable outcome at 3 months in rt-PA-treated patients compared with controls by OTT. From Hacke et al (38), reprinted with permission from Elsevier. Copyright 2004.
In 2008, the European Cooperative Acute Stroke Study (ECASS) III trial (39) provided evidence that rt-PA administered between 3 and 4.5 hours was safe and effective. An updated pooled analysis (40) confirmed favourable 3-months outcome in patients treated with alteplase within 4.5 hours.

Recently, the third International Stroke Trial (IST-3) has provided evidence that thrombolysis with alteplase within 6 hours does not affect survival, but does lead to clinically relevant improvements in functional outcome and health-related quality of life that are sustained for at least 18 months (41).

A systematic review published in 2010 (42) showed that rt-PA seems to be cost-effective for the management of AIS, and might reduce the associated healthcare costs as well as patient disability.

1.11 Endovascular interventions
A number of techniques and devices have been studied or are under study in different trials. Intra-arterial thrombolysis (43, 44) or mechanical thrombectomy (45, 46) seems beneficial for treatment of selected patients with major ischemic strokes caused by occlusion of the medial cerebral artery (MCA), both patients who have contraindications to the use of intravenous thrombolysis and patients who have not responded to intravenous thrombolysis (47, 48).

1.12 Thrombolysis rate
Although treatment with intravenous thrombolytic therapy is considered safe and effective, only 3-8.5% of patients with AIS receive this treatment (49-51). There are several explanations for the low thrombolysis rate. In a systematic review of identifying barriers to delivery of thrombolysis for acute stroke (52), important barriers were: i) the patient or family did not recognize symptoms of stroke or seek urgent help; ii) the general practitioner (GP), rather than an ambulance, was called first; iii) the paramedics and ED staff triaged stroke as non-urgent; iv) delays in neuroimaging; v) inefficient process of in-hospital emergency stroke care; vi)
difficulties in obtaining consent for thrombolysis, and vii) physicians’ uncertainty about administering thrombolysis. In addition, uncertainty about the accurate time of symptom onset, wake-up strokes and numerous contraindications may limit the use of rt-PA. Great effort is made to shorten in-hospital delay and to develop efficient SUs. Still, delayed arrival is one of the most common reasons for not treating stroke patients with rt-PA (53, 54).

1.13 Treatment for intracerebral haemorrhage
Patients using OACs with elevated INR should correct the INR as rapidly as possible. Intravenous vitamin K requires hours to correct the INR (55). Prothrombin complex concentrates (PCC) are plasma-derived factor concentrates containing factors II, VII, IX and X, and are increasingly recommended because of the ability to rapidly normalize INR in patients taking OACs (21, 56). PCCs have therefore emerged as the initial therapy for life-threatening OAC-associated haemorrhages.

The effect of recombinant factor VIIa (rFVIIa) in noncoagulopathic patients has been studied in two randomized trials (57, 58), given within four hours after symptom onset. There was an increase in thromboembolic risk and no clear benefit, thus rFVIIa is not recommended in unselected patients (21).

Regarding acute blood pressure (BP) lowering, the European Stroke Initiative (EUSI) writing committee recommend treatment in patients i) with known history of hypertension and systolic BP > 180 mmHg and/ or diastolic BP > 105 mmHg (target BP 170/100 mmHg), and ii) without known hypertension and systolic BP > 160 mmHg and/ or diastolic BP > 95 mmHg (target BP 150/90 mmHg) (59). AHA/ASA guidelines (21) recommend treatment if systolic BP > 180 mmHg. In a recently published study (60), intensive BP treatment (target systolic BP < 140 mmHg) compared to guideline-recommended treatment showed a positive trend (p = 0.06) regarding outcome (death or major disability after 90 days) in patients with ICH within the last six hours, and could be the beginning of a paradigm shift in acute ICH management.
For most patients, the usefulness of early surgery for acute ICH remains uncertain (21), but there are some exceptions, such as patients with superficial haemorrhages, cerebellar haemorrhages and clinical deterioration, or brainstem compression and/or hydrocephalus from ventricular obstruction.

1.14 Prehospital delay in acute stroke
Prehospital delay is defined as the time interval from onset of symptoms to admission to hospital. Further, prehospital delay can be subdivided into a decision delay and a transport delay. Decision delay (also referred to as patient delay) is the time interval from onset of symptoms to the point when the first contact with medical assistance occurs, while transport delay is the time interval from the first medical contact to ED arrival.

Because of the narrow time window, delayed arrival is one of the most common reasons for not treating ischemic stroke patients with rt-PA (52, 54). Studies focusing on prehospital delay have shown that between 23-51% of patients arrive at the hospital within 3 hours after symptom onset (61-64). In a comprehensive review of studies examining delay in acute stroke published since 2000, median prehospital delay was between 3 and 4 hours (65). There has been an annual decline of 6% in hours per year since the first study was published in 1981 (66), but this decline of prehospital delay has slowed in recent years (65). Similarly, nearly 27% of the of the patients arrived within 3.5 hours in the “Get With The Guidelines” Stroke program, and the proportion of early arriving patients with AIS did not increase significantly from 2003 to 2009 (51).

Prehospital delay is longer for stroke than for acute coronary syndrome (ACS) (67, 68), although there is a pathophysiological overlap between the two conditions. One of the main reasons is that pain is a symptom in the majority of patients with ACS, whereas pain is rarely associated with stroke. Equally important is the difference in symptom distribution. Patients with stroke will potentially have significant deficits,
such as aphasia, reduced consciousness or cognitive impairment, preventing them from seeking help and thereby increasing the prehospital delay.

An important proportion of the prehospital delay consists of the time interval from symptom onset to seeking medical assistance, i.e. decision delay. Several factors are related to decision delay, such as failure to recognize stroke symptoms, not regarding symptoms as serious because of a lack of knowledge, a wait-and-see attitude, a hope that symptoms will resolve, and hesitation to contact emergency medical services (EMS). In addition, the awareness that stroke is a medical emergency varies among health-care professionals (69). Contacting the EMS and arrival by ambulance is strongly related to shorter prehospital delay (52, 70). Standardization of stroke education modules and protocols is recommended in order to facilitate recognition of stroke and provide sufficient prehospital stroke care by the EMS (71), and assessment tools such as the Los Angeles Prehospital Stroke Screen (LAPSS) (72, 73) and the Cincinnati Prehospital Stroke Scale (CPSS) (74) are highly recommended for prehospital health care professionals.

### 1.15 In-hospital delay in acute stroke

In-hospital delay can be defined in various ways, such as the time interval from admission (ED arrival) to being evaluated by a doctor (ED physician or neurologist), to initiation of a CT scan, to CT interpretation, to SU admission or to rt-PA administration. Regarding the latter, the phrase “door-to-needle time” (DNT) is often used. An organized protocol for the emergency evaluation of patients with suspected stroke is recommended, and the goal should be a complete evaluation and to begin rt-PA treatment within 1 hour of ED arrival (18). Different in-hospital measures and ED “stroke fast tracks”/ “stroke codes” are effective in reducing in-hospital delay, and in a study from Finland (75) DNT was annually reduced, from median 105 minutes in 1998 to 20 minutes in 2011.
1.16 Stroke knowledge
Although stroke is a common cause of death and disability, knowledge regarding stroke seems to be poor in the general population (76-78). Early admission implies symptom recognition and attributing the symptoms to acute stroke. The awareness of stroke being a condition of medical emergency in a similar manner as an ACS is lacking (68).

Stroke knowledge can be divided into: i) knowledge of stroke symptoms and signs, and: ii) knowledge of stroke risk factors. Knowledge of stroke symptoms is important in order to recognize an acute stroke and consequently result in rapid hospitalization, i.e. transfer symptom knowledge into recognition and action, thus reducing the prehospital delay. Knowledge of stroke risk factors is equally important, as raised awareness is important in both primary and secondary prevention so that individuals can alter their risk factor profile and thereby reduce the risk of a cerebrovascular event or other cardiovascular events, which have the same risk factor profile.

Information about stroke could be gained from family and friends, mass media, health care professionals or other sources (79).

The ability to name stroke symptoms or risk factors is poor but variable in different studies, partly depending on whether the questions are open-ended or close-ended (76). However, studies exploring trends in stroke knowledge have found significant improvement in public knowledge (80-82). Nevertheless, in a systematic review from the UK, symptom recognition did not reduce time to presentation, and for the majority of patients, the GP was the first medical contact (83).

1.17 Public education campaigns
Public education campaigns designed to improve recognition of stroke symptoms and the need for early EMS contact have been initiated in several countries in various ways. Rapid response to symptoms is essential to reduce prehospital delay,
thus improve the thrombolysis rate and consequently improve outcome after stroke, reducing long-term disability (84).

Mass media campaigns are expensive, and their cost-effectiveness is debatable. A systematic review of mass media interventions aimed to improve emergency response to stroke (85), concluded that campaigns aimed at the public may raise the awareness of stroke symptoms but unfortunately do have limited impact on behaviour. Other studies have also shown no impact of educational campaigns on stroke awareness (80, 86), or a decline in awareness a few months after the end of a campaign (87, 88). Some creative campaigns are the “kids identifying and defeating stroke project” (89) and the “beauty shop stroke education project” (90), educating school children and beauticians, respectively, in stroke recognition.

The Face Arm Speech Time (FAST) campaign (91, 92) has been initiated in several countries, also in Norway (93) (figure 2). The mnemonic combines three of the major stroke signs (facial weakness, arm weakness and speech disturbance), which cover 90% of strokes (74), and focuses on the importance of time. In a study from South London (63), differences in prehospital delay and thrombolysis rates were determined for the period immediately before and after the FAST mass media campaign. Unfortunately, no differences were observed between the proportion of patients arriving early or receiving intravenous thrombolytic therapy post-campaign in comparison with pre-campaign. A review of the effectiveness of public stroke educational interventions (94) concluded that different community settings can be used to successfully deliver affordable stroke educational interventions, that the message delivered must be clear and easy to remember, and that television proved to be the medium that yielded the most positive feedback.

There are divergent findings regarding the role of health care professionals in stroke education (95-97).
Figure 2: The Norwegian version of FAST, from helsenorge.no, FAST-regelen (source: Helse-Vest RHF) (93)
2 Aims

2.1 General aim
Late presentation to hospital is a major reason for the low thrombolysis rate in AIS. In addition, there is a growing perception of ICH as a condition of emergency in a similar manner as AIS. The general aim of this thesis was to explore factors related to prehospital delay and patient knowledge in a Norwegian population with acute cerebrovascular disease.

2.2 Specific aims
- To assess the time interval and path from symptom onset to admission, and to explore factors associated with prehospital delay.
- To identify the most important factors relating to decision delay and the decision to call the EMS as the first medical contact.
- To assess whether there is a correlation between prehospital and in-hospital delay.
- To explore the knowledge of stroke symptoms and risk factors in stroke patients, to identify factors related to knowledge, and to assess whether previous stroke knowledge influences decision delay, prehospital delay and EMS use.
- To explore reasons for not treating ischemic stroke patients admitted within the time window with thrombolytic therapy, and reasons for delayed admission, i.e. reasons for the low thrombolysis rate in AIS.
3 Materials and methods

3.1 Study design and subjects
A prospective, cross-sectional hospital-based study focusing on prehospital delay was conducted during a 1-year period (from April 15, 2009, to April 1, 2010), at the Stroke Unit, Department of Neurology, Akershus University Hospital.

Patients aged 18 years or older, with a diagnosis of AIS, ICH or TIA were included. Exclusion criteria were: in-hospital strokes, SAH and other final diagnoses than stroke or TIA (stroke mimics). In the case of multiple admissions during the study period, only the first admission was included.

We opted to include patients with AIS, ICH and TIA because it is often not possible to distinguish between these events before admission.

Demographic data and the presence of stroke risk factors were obtained. Aetiology was determined according to the TOAST classification (26) and topography according to the OCSP criteria (27).

Stroke severity was assessed by the neurologist on call in the ED using the 11-item Norwegian version of NIHSS (19) (appendix 1). In those cases where the NIHSS was not scored in the ED, the score was estimated retrospectively from chart review by KWF, AS or BT, which has shown a high degree of reliability and validity (98). Global functioning was assessed by the modified Rankin Scale (mRS) (99).

For patients with wake-up strokes, the time of awakening was considered as the time of symptom onset. For patients with uncertain accurate time of symptom onset (patients unable to seek help because of severe symptoms, speech difficulties or reduced consciousness), the time when they were identified was considered as the time of symptom onset, because it represents the time when medical help could be sought. There was no upper time limit for prehospital delay.

Early decision was defined as decision delay $\leq$ 1 hour.
The decision to treat ischemic stroke patients with intravenous thrombolysis was made by the treating neurologist based on clinical evaluation including our SU’s guideline of inclusion characteristics and absolute and relative contraindications (appendix 2).

A structured questionnaire was completed by KWF or AS for every patient, and information was obtained within 72 hours after admission by interviewing the patient and/or relatives, and by reviewing the medical records.

In order to explore the knowledge of stroke symptoms and risk factors, patients had to answer two open-ended questions by spontaneous naming: “Which stroke symptoms do you know?” and “Which stroke risk factors do you know?”. Stroke symptoms were defined according to NINDS (17). Knowledge of stroke symptoms was defined as being able to identify both “numbness or weakness of the face, arm or leg” and “confusion or trouble speaking or understanding speech”, as “facial weakness”, “arm weakness”, and “speech disturbance” are the key elements of FAST (91).

Knowledge of stroke risk factors was defined as knowing at least two of the three stroke risk factors hypertension, smoking and diabetes, as they are important, well-documented and modifiable risk factors linked to stroke and other cardiovascular diseases (100).

Previous stroke knowledge was assessed by asking the patients if they had received any information about stroke before admission (open-ended question). If they answered in the affirmative to that question, they were asked from which source the information was obtained.

In addition, reasons for not treating with thrombolytic therapy were identified from the medical records, and reasons for late arrival were recorded, as patients were asked about the main reason for the delay (open-ended question).

Patients with AIS, in whom the accurate time of symptom onset was known, were dichotomized into an “eligible group” (prehospital delay of ≤ 3.5 hours) and a “non-
eligible group” (prehospital delay of > 3.5 hours). The cut-off of 3.5 hours was preferred because 1 hour is considered as the upper limit of in-hospital delay (101, 102), including neurological examination, imaging, laboratory analysis, transport within the hospital and, if necessary, correcting the blood pressure.

Figure 3 shows the patient subgroups included in the four papers in the present thesis.

**Figure 3: Patient subgroups in papers I-IV.**

### 3.2 Statistical analyses

Continuous variables were tested for normality using normality Q–Q plots and Kolmogorov–Smirnov analyses. Comparisons between groups were performed with Mann–Whitney U test for continuous variables because most variables were not normally distributed, and Pearson’s $\chi^2$-test or Fisher’s exact test (where appropriate) for categorical variables. Several multivariable linear and logistic regression analyses were performed. The prehospital delay time was not normally distributed, thus logarithmically transformed in the linear analysis. Associations are presented as ORs with the corresponding 95 % CIs.
In all analyses, a two-tailed p-value < 0.05 was used as a cut-off for statistical significance. All statistical analyses were performed using SPSS (Statistical Package for the Social Sciences) statistical software versions 18 and 20 (SPSS Inc, Chicago, IL).

Detailed descriptions of statistical considerations are presented in each paper.

### 3.3 Ethical considerations

The study was approved by the Regional Committee for Ethics in Medical Research and by the Data Protection Authorities. All participants or their first degree relatives gave their oral, informed consent.
4 Summary of results

4.1 Paper I
Median prehospital delay was 3.0 hours (179 minutes; interquartile range [IQR] 77-542). The most common first medical contact was to call the EMS (231 patients; 52.5%). A total of 101 (23.0%) patients called a primary care physician (PCP), 102 (23.2%) patients visited a PCP and 6 (1.4%) came directly to the ED. In all, 310 (70.5%) patients arrived by ambulance. Among these, 217 (70.0%) had only one medical contact (phone call to the EMS) before admission. A total of 50.0% of patients had prehospital delay <3 hours, while 55 (12.5%) patients arrived after 24 hours.

In the multivariate linear regression analysis, high NIHSS score (p < 0.001), transport by ambulance (p < 0.001) and lower age (p = 0.048) were significantly associated with early admission. In the multivariate logistic regression analysis using the 6 hours cut-off, transport by own means (OR 0.27, 95% confidence interval [CI] 0.17-0.42) and mild symptoms expressed as low NIHSS scores (OR 0.92, 95% CI 0.88-0.97) were significantly associated with late admission (OR for prehospital delay < 6 hours).

4.2 Paper II
Median decision delay was 2.0 hours. Decision delay accounted for 62.3% of prehospital delay (median value). Moderate (NIHSS score 8-16; OR 4.16, 95% CI 1.86-9.30) or severe symptoms (NIHSS score ≥ 17; OR 10.38, 95% CI 2.70-39.90) and living together (OR 1.84, 95% CI 1.02-3.43) were associated with decision delay of ≤ 1 hour. The presence of stroke risk factors was not related to early decision.

Moderate (OR 6.31, 95% CI 2.79-14.29) or severe symptoms (OR 8.44, 95% CI 2.64-26.98) were associated with calling the EMS as the first medical contact. Of the patients who were able to answer, 69.5% confirmed that they had received
information about stroke from one or more sources, but previous stroke knowledge did not affect an early decision or EMS use.

4.3 Paper III
The accurate time of symptom onset was known in 145 of 290 (50.0%) patients. Of these, 72 (49.7%) patients arrived later than 3.5 hours. In all, 22 (7.6%) patients were treated with intravenous thrombolytic therapy with rt-PA. Of these, 16 patients had known time of symptom onset, and all were in the eligible group. Six patients with uncertain time of symptom onset were treated with thrombolytic therapy, as they were all last seen well 4.5 hours or less before rt-PA administration.

The three most common reasons for not treating eligible patients (known time of symptom onset and arriving within 3.5 hours) were: minor symptoms (22.8%); clinical improvement from symptom onset to admission (17.5%) and; uncertainty about the diagnosis (12.3%). The major reasons for delayed admission after 3.5 hours of symptoms onset were: patients did not attribute their symptoms to stroke (25.4%); a wait-and-see attitude, hoping symptoms would resolve (25.4%) and; patients who chose to wait for the GP’s office to open (14.3%).

The time from symptom onset to admission was strongly correlated to the time from admission to being evaluated by a nurse (Spearman’s $\rho = 0.34$, $p < 0.001$), from admission to being evaluated by a doctor (Spearman’s $\rho = 0.52$, $p < 0.001$), and from admission to initiation of a CT scan (Spearman’s $\rho = 0.48$, $p < 0.001$).

4.4 Paper IV
In all, 203 of 287 (70.7%) patients knew at least one stroke symptom. Knowledge of both numbness/ weakness and speech difficulties as stroke symptoms (42.9% of the patients) was associated with lower age (OR 0.96, 95% CI 0.94-0.99), higher education (OR 2.25, 95% CI 1.17-4.30), and having received information about stroke at an earlier stage (OR 7.74, 95% CI, 3.82-15.67). All three elements of FAST were recognized by 16.7% of the patients.
In all, 43.2% of the patients were able to name at least one stroke risk factor. None of those with previous cerebrovascular disease identified this as a risk factor. Knowing at least two of the three stroke risk factors smoking, hypertension and diabetes (13.9% of the patients) was associated with lower age (OR 0.94, 95% CI 0.92-0.97).
5 Discussion

Despite being a common cause of mortality and morbidity, symptom recognition and early admission remains a major issue in acute stroke care. Treatment with intravenous thrombolytic therapy is considered safe and effective, but only a small proportion of patients presenting with AIS receive this treatment because of the narrow time window. Knowledge of stroke symptoms seems to be varying, and there is a lack of the ability to translate knowledge into appropriate course of action.

To be able to reduce the burden of stroke, several strategies must be applied. One approach is to try to reduce the stroke incidence, which could be undertaken by implementing good primary and secondary prevention measures at an individual and population level (78). In addition, patients suffering a stroke must be provided the best available therapy in order to improve outcome. Because of the narrow time window for rt-PA treatment, patients need to attend hospital as soon as possible, which requires adequate knowledge of stroke symptoms and risk factors, and the ability to translate knowledge into action.

5.1 Prehospital delay
The median prehospital delay was 3.0 hours (mean 14.2 hours), and a total of 50% of the patients were admitted within 3 hours. The findings regarding the prehospital time interval are similar to other studies examining prehospital delay (64, 103-107). Some studies have been truncated at 24 (103) or 48 hours (64, 107), and by not excluding extreme values, the stroke delay times (especially mean values) may be affected. Our results are in line with the review by Evenson et al (65), which summarizes that the 50th percentile for delay occurs between 3 and 4 hours, thereby excluding many patients from being considered for intravenous thrombolytic therapy and likely contributing to longer subsequent in-hospital delay.

Stroke severity was significantly related to prehospital delay, with patients having more severe strokes, described by a higher NIHSS score on admission, arriving faster. NIHSS and other stroke scales (e.g. Scandinavian Stroke Scale) have been
used to measure stroke severity, and have been related to prehospital delay previously (64, 104, 106, 108).

Transport by ambulance was also significantly related to shorter prehospital delay, as described before (103, 109). Lower age barely reached significance level, but previous results regarding age and prehospital delay are diverging (64, 106). Gender and educational level were found to be unrelated to prehospital delay, as reported previously (103, 110, 111). A history of previous cerebrovascular disease did not affect time to admission. Most previous studies have not found any association between previous stroke and prehospital delay (104, 106, 112, 113), while some studies report such an association (64, 114).

Over half of the patients called the EMS as their first medical contact. Only 1.4% of the patients came directly to hospital, which is generally rare in Norway. Figure 4 shows the various prehospital paths from symptom onset to admission (from paper I). Few studies have assessed the prehospital path from symptom onset to admission in detail (115). Interestingly, of all the patients who first called a PCP, 62% of the patients thereafter visited the PCP before admission, i.e. their symptoms were not interpreted as serious or acute, and they were advised to visit the PCP rather than contacting the EMS as the next medical contact. Furthermore, 59% of the patients who first contacted or/ and visited a PCP, came to the hospital by own means and not by an ambulance, even though the PCP suspected that the patients suffered a stroke. On the other hand, only 6.1% of the patients who first contacted the EMS were not transported directly to the hospital by an ambulance. There could be several possible explanations to these results. First, EMS personnel answering emergency calls may have more experience and training, thus may easier detect stroke symptoms than the personnel answering calls to the PCP, often medical secretaries or nurses. In addition, patients calling a PCP may have milder symptoms than those calling the EMS, hence more difficult to relate the symptoms to stroke. Additionally, because of limited ambulance resources, the PCPs may opt to use other transport modalities than an ambulance. Alternatively, which is more
worrying, is if a high proportion of PCPs do not consider stroke as a condition of medical emergency.

![Prehospital path from symptom onset to admission.](image)

**Figure 4. Prehospital path from symptom onset to admission.** From paper I, reprinted with permission from BMJ Publishing Group Ltd. Copyright 2013.

### 5.2 Decision delay and the use of the EMS

The median decision delay was 2.0 hours when patients with uncertain time of symptom onset were excluded, a time interval also reported by others (105, 110, 116). Mosley et al (117) reported 53 minutes as median decision delay, but included only patients admitted by ambulance. In the multivariable model, only the presence of moderate (NIHSS score 8-16) and severe symptoms (NIHSS score ≥ 17) and living together were associated with early decision. In all, 36% of the patients had a decision delay of one hour or less in our study, whiles others have reported 24-54% (110, 111, 116, 117). Decision delay accounted for 62% of the prehospital delay. In a study from Taiwan, Chang et al (116) reported a proportion of 45%. Both these
figures indicate that about half of the prehospital delay is related to hesitation in seeking medical assistance after symptom onset.

As for prehospital delay, factors such as educational level and a history of cerebrovascular disease did not influence decision delay. It is therefore important that patients hospitalized for cerebrovascular disease receive proper information during hospitalization about stroke risk factors, typical symptoms, and the need for urgent and appropriate action in the case of a new cerebrovascular event because current awareness seems to be insufficient. The information given should emphasize the presence of an effective treatment that can improve outcome and reduce disability but which is highly time dependent. Relatives should also receive this information as bystanders often are involved in the decision making after symptom onset (62, 110, 118).

About 2/3 of the patients arrived to the hospital by ambulance. Previous studies have focused on factors related to the patients arriving at the ED by ambulance (64, 103, 104), but it is equally important to emphasize the importance of contacting the EMS as the first medical contact. Median decision delay and prehospital delay was 53 and 95 minutes, respectively, in patients who contacted the EMS as the first medical contact, compared to 270 and 505 minutes in patients with other types of first medical contact. Only the presence of moderate and severe symptoms was associated with EMS contact. Our findings are in line with a review of stroke education (118), which concluded that there was no association between previous cerebrovascular disease and EMS use.

In a randomized trial from Saarland, Germany (119), patients with suspected stroke received treatment in a mobile stroke unit (MSU; a specialized ambulance with a CT scanner, point of care laboratory and telemedicine connection) or at the hospital. The median time from alarm to treatment decision was reduced from 76 minutes (IQR 63-94; hospital group) to 35 minutes (IQR 31-39) in the MSU group, but there were no significant differences in the proportion of patients receiving intravenous thrombolytic therapy. Recently, results of a pilot study of an ongoing project (Pre-Hospital Acute Neurological Treatment and Optimization of Medical care in Stroke
[PHANTOM-S]) in Berlin, Germany were published (120), and the MSU was staffed with a neurologist, paramedic and radiographer. A total of 23 of 45 (51%) of the patients received rt-PA. Although interesting, larger trials are needed before implication, and importantly, the cost effectiveness of MSUs is debatable.

5.3 In-hospital delay
Prehospital delay was strongly correlated to the time when the patients were evaluated by a nurse, a doctor and imaging, thus implying an association and dependency between pre- and in-hospital delay. Shorter median time from ED admission to CT scan for patients arriving less than 3 hours after symptom onset (121) and by the EMS (103) have been reported previously. Ideally, prehospital delay should not influence in-hospital delay, as there are carefully designed protocols concerning acute stroke care. Nevertheless, early arrival seems to enhance the perception of urgent assessment, and our and previous results imply opportunities for improvement. Rapid and streamlined management requires appropriate ED infrastructure and continuous educational efforts and different practical measures, and should apply to both patients eligible and not eligible for thrombolysis. Examples of such measures are EMS involvement and education, direct hospital prenotification, bolus rt-PA administration on the CT table, CT priority and rapid neurological evaluation on CT table (75). In our hospital, many of these measures have been implemented after the present study, resulting in significantly reduced in-hospital delay and DNT (unpublished data) compared to the data in this thesis.

5.4 Reasons for exclusion from thrombolysis
Only 25% of the patients with AIS were eligible for intravenous thrombolytic therapy, i.e. in which the accurate time of symptom onset was known in addition to arrival within 3.5 hours. In this group, the thrombolysis rate was 22%, compared to 7.6% in the whole study group of ischemic stroke patients, which is in line with the proportions reported previously (50). Interestingly, 9.2% of the patients with
uncertain time of symptom onset were also treated with rt-PA, as the time when they were last seen well was known and $\leq 4.5$ hours on rt-PA administration. This illustrates the importance of obtaining information about when the patient was last seen well if the accurate time of symptom onset is not known. The same applies for wake-up strokes, such as patients having an afternoon nap.

Absolute and relative contraindications against rt-PA therapy accounted for a minor proportion of reasons for excluding patients from such therapy, as over half of the eligible patients were excluded due to uncertainty about the diagnosis, minor symptoms or clinical improvement. The benefit of treating AIS patients with mild or rapidly improving symptoms with intravenous thrombolytic therapy is debatable, as results are diverging (122, 123), and large randomized clinical trials are needed.

5.5 Patient knowledge

Patients were asked if they had received information about stroke before admission, as an indicator of previous stroke knowledge, and 70% of the patients confirmed that they had received information from one or more sources. However, patients may have mistaken perceptions of what “information” means. Previous stroke knowledge was not associated with decision delay or prehospital delay, and the results indicate that patients’ own perception of their stroke knowledge may be inaccurate as their knowledge is not related to shorter decision delay or prehospital delay, that is, the ability to translate knowledge into action. As in previous studies (82, 95), mass media and family/ friends were the most frequently cited sources of information.

Only 17% of the patients were able to name all the three FAST-elements “facial weakness”, “arm weakness” and “speech disturbance”, and only 14% of the patients were able to identify at least two of the three risk factors smoking, hypertension and diabetes. Importantly, none of the patients with previous cerebrovascular disease recognized it as a risk factor, as previously described (124).
Lower age, higher education and having received information about stroke at an earlier stage were related to adequate knowledge of stroke symptoms, while only lower age was related to adequate knowledge of stroke risk factors. The majority of previous studies have found a decrease of knowledge with age and a positive association between education and knowledge (118).

Studies examining stroke knowledge changes over time (80, 81) found significant improvement in stroke symptom knowledge, but the proportions were still low, and the knowledge of risk factors remained nearly unchanged.

5.6 **Strengths and limitations**

All patients in the hospital’s well-defined catchment area hospitalized for stroke are admitted to the present hospital regardless of severity. Hence the study should represent the general population of stroke. In addition, all patients with suspected TIA are admitted and evaluated by a neurologist in the ED and subsequently admitted to the SU, and not assessed at an outpatient clinic. No public campaigns regarding stroke were conducted before or during the study period. No patients refused participation.

Some patients could not be included because they had been discharged before registration and interview, likely to be patients with mild or transient symptoms. Patients with severe symptoms (AIS or ICH) who were rapidly transferred to Neurosurgical Department, Oslo University Hospital were also lost. We did not assess whether worsening before admission or different symptom distribution could influence the prehospital delay. Importantly, distances and travel times (transport delay) were not noted, which may affect the prehospital time interval.

Regarding stroke knowledge, because of the exclusion of 35% of the patients due to speech or language difficulties, reduced consciousness or cognitive impairment, the responder-group may not reflect the whole stroke population.

An additional important limitation is the lack of follow-up and outcome measures.
5.7 Methodological considerations
Because of the hospital’s well-defined catchment area and the fact that all patients hospitalized for stroke are admitted to our hospital regardless of severity, selection bias is likely avoided, even if the study does not include all patients in the study period.

The final diagnosis of stroke or TIA was made by the treating neurologist based on the WHO definition (1). A NECT was routinely undertaken in all patients, but additional imaging (CT, MRI) was performed at the discretion of the treating neurologist.

Although prehospital delay is defined as the time from symptom onset to arrival at the ED or the hospital, there are methodological differences between studies and no consensus as to how time intervals are reported. The lack of a unanimous definition, especially for symptom onset, affects the prehospital delay intervals reported in different studies. For patients with wake-up strokes, we considered the time of awakening as the time of symptom onset, whereas others have used the time the patient fell asleep (103, 106, 116). For patients with uncertain accurate time of symptom onset, the time when they were identified and the symptoms first noticed was considered as the time of symptom onset. There was no upper limit for prehospital delay in our study, but some studies have excluded patients admitted e.g. after 24 or 48 hours. These considerations imply that it is difficult to compare the results from different studies because of different definitions of prehospital delay.

An important factor in observational studies is a potential recalling bias regarding information from patients and/or family members that cannot be found in medical records, in this case particularly the exact time of different actions or events. Furthermore, subtle cognitive deficits and denial in the acute phase of stroke may have contributed to recalling bias.

Information was usually obtained the day after admission, but in patients who were admitted during the weekend, it could take up to 72 hours before information was
obtained. Therefore, patients may have gained in-hospital information on stroke before the interview (information bias), which reflects that the actual level of stroke knowledge may be lower than that reported.

Regarding knowledge of stroke symptoms and risk factors, 35% of the patients were excluded as they were not able to answer the questions due to speech or language difficulties, reduced consciousness or cognitive impairment, and there were significant differences between the responder group and the non-responder group, creating a selection bias. However, it is less likely that the non-responders had better stroke knowledge, as they were significantly older and had a lower educational level than the responders (lower age was related to adequate stroke symptom and risk factor knowledge, and higher education to stroke symptom knowledge).

Regarding the level of stroke knowledge, the use of open-ended questionnaires may result in an underestimation, while close-ended questionnaires may lead to an overestimation. Again, there is little standardization as to how define stroke knowledge. In some studies, being able to name a certain number of symptoms or risk factors was defined as adequate knowledge, while other studies required specific combinations of symptoms or risk factors. Comparisons with other studies are therefore challenging.

An open-ended approach is challenging because of the need to analyse and group answers to different categories. This process involves judgment decisions, and the results may be biased by this decision process. On the other hand, when closed-ended questions are used, the act of asking the questions will indicate what the answer could be. This was addressed in an article by Rowe et al (125), assessing knowledge of stroke symptoms and risk factors, using both approaches. Interestingly, 7-24% and 77-95% of the respondents correctly identified stroke symptoms using open-ended and close-ended questions, respectively, and this discrepancy highlights the methodological challenges.
6 Conclusions and implications for further research

The present thesis has focused on factors related to prehospital delay and knowledge of stroke symptoms and risk factors. Conclusions:

- A large proportion of patients with acute cerebrovascular disease do not reach the ED in time to be considered for treatment with thrombolysis due to prehospital delay.
- The optimal prehospital path in acute cerebrovascular disease should be to notify the EMS immediately after symptom onset and subsequent transport to the ED by ambulance in order to minimize the prehospital delay.
- Stroke severity, type of transport and age are related to prehospital delay
- Decision delay in acute cerebrovascular accounts for more than half of the prehospital delay.
- Previous stroke knowledge and the level of education do not affect decision delay.
- A large proportion of patients with ischemic stroke are not treated with intravenous thrombolysis because of mild or rapidly improving symptoms, and because they arrive too late as they do not attribute their symptoms to stroke or have a wait-and-see attitude.
- There is a correlation between prehospital and in-hospital delay.
- Knowledge of stroke symptoms and risk factors is insufficient.

We hope that the papers included in this thesis will contribute to draw attention to the prehospital part of acute stroke care. Great effort is made to shorten in-hospital delay and to develop efficient SUs. The awareness among EMS personnel that stroke is a medical emergency has increased considerably in recent years. Still, delayed arrival is one of the most common reasons for not treating ischemic stroke patients with rt-PA. In addition, there is a growing perception of ICH as a condition of emergency in a similar manner as AIS. Prehospital delay is longer for stroke
than for ACS, although there is a pathophysiological overlap between the two conditions. There should be more focus on the “time is brain” paradigm to accentuate acute stroke as a condition of medical emergency in a similar manner as ACS is.

The findings in this thesis could be useful for health care professionals involved in prehospital and in-hospital stroke care (EMS personnel, paramedics, GPs, emergency physicians, stroke nurses and stroke physicians). In addition, the findings could be of interest for politicians, health bureaucrats and other policy makers, along with different patient interest groups, as acute stroke is an important and increasing public health problem. The results can be used to develop new strategies to raise the attention and awareness of early hospital admission.

Data from the papers in this thesis can be used in different information campaigns. One approach could be an intervention study with an in-hospital educational program aimed at stroke patients and their relatives during admission, and evaluation of the intervention after a certain period of time. Educational programs could also be aimed at the general population or at specific groups.

This thesis has demonstrated that the prehospital path is complex. Future studies should explore the prehospital phase in more depth, including first contact (relatives, neighbour, health care professionals, others) and the role of bystanders. Decision delay can be further divided in i) symptom onset to symptom recognition, ii) symptom recognition to the decision to seek medical attention, and iii) decision to seek medical attention to the first medical contact.

In different parts of Norway, transport delay will vary due to geographical differences, and multicentre studies are needed to assess decision delay and patient knowledge. Studies of how patients or bystanders present stroke symptoms and how health care professionals respond to the information given by the patients or bystanders would also be of great interest.

Finally, future prospective studies should be combined cross-sectional and cohort studies, and should include different follow-up and outcome measures.
7 References


8 Errata

Paper I

In the “Subjects and Methods” section, the specified study period is incorrect (15 April 2008 to 1 April 2009). The correct study period was from 15 April 2009 to 1 April 2010.
## Appendix

### 9.1 Appendix 1: Norwegian version of NIHSS

#### NIH Stroke Scale (NIHSS)

<table>
<thead>
<tr>
<th>Task</th>
<th>Description</th>
<th>Score</th>
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| **1a Bevissthetsnivå** | 0 = Våken  
1 = Desig, reagerer adekvat ved lett stimulering  
2 = Desig, reagerer først ved kraftigere/gjentatt stimulering  
3 = Reagerer ikke, eller bare med ikke-målrettet bevegelse |  |  |
| **1b Orientering** | 0 = Svarer riktig på to spørsmål  
1 = Svarer riktig på ett spørsmål (eller ved øyegang dysartri)  
2 = Svarer ikke riktig på noe spørsmål |  |  |
| **2 Blikkbevegelse** | 0 = Normal  
1 = Delvis blikkpåse (eller ved øyenmuskelpåse)  
2 = Fiksirt blikkdreining til siden eller total blikkpåse |  |  |
| **3 Synsfelt** | 0 = Normalt  
1 = Delvis hemianopsi  
2 = Total hemianopsi  
3 = Bilateral hemianopsi / blindness |  |  |
| **4 Ansikt** | 0 = Normal (også ved "ikke testbar")  
1 = Drifter til lavere posisjon  
2 = Noe bevegelse mot tyngdekraften, drifter til sengen  
3 = Kun små muskelbevegelser, faller til sengen  
4 = Ingen bevegelse |  |  |
| **5 Kraft i armen** | 0 = Normal (også ved "ikke testbar")  
1 = Drifter til lavere posisjon  
2 = Noe bevegelse mot tyngdekraften, drifter til sengen  
3 = Ingen bevegelse |  |  |
| **6 Kraft i benet** | 0 = Normal (også ved "ikke testbar")  
1 = Drifter til lavere posisjon  
2 = Noe bevegelse mot tyngdekraften, drifter til sengen  
3 = Ingen bevegelse |  |  |
| **7 Koordinasjon / ataxi** | 0 = Normal (også ved "ikke testbar")  
1 = Ataksi i arm eller ben  
2 = Ataksi i arm og ben |  |  |
| **8 Hudfølelse** | 0 = Normal  
1 = Lettere sensibilitetsnedsettelse  
2 = Markert sensibilitetsnedsettelse (også ved coma, tetraparese) |  |  |
| **9 Språk / afasi** | 0 = Normal  
1 = Moderat afasi, samtale mulig  
2 = Markert afasi, samtale svært vanskelig eller umulig  
3 = Ikke språk (også ved coma) |  |  |
| **10 Tale / dysartri** | 0 = Normal  
1 = Mild - moderat dysartri  
2 = Nær uforståelig tale eller anartri (også ved coma) |  |  |
| **11 "Neglect"** | 0 = Normal (også ved hemianopsi med normal sensibilitet)  
1 = Neglect i en sansemodalitet  
2 = Neglect i begge sansemodaliteter |  |  |

**Total NIHSS-Score**

| undersøkerens signatur | 63 |
9.2 Appendix 2: Thrombolysis guideline, Akershus University Hospital

REPERFUSJONSBEHANDLING VED AKUTT HJERNEINFARKT

Intravenøs trombolyse

**Indikasjon:** Iskemisk hjerneinfarkt. Akutt oppståtte fokale nevrologiske utfall.

**Tidsvindu:** Behandlingsstart < 4,5 timer etter ictus

**Absolutive kontraindikasjoner:**
- Intrakraniell blødnings, utbredte infarktforandringer (> 1/3 av mediagebet)
- BT > 185/110 tross i.v. behandling
- Marevan med INR ≥ 1.7, behandling med Pradaxa/Xarelto siste

**Relative kontraindikasjoner (må veies opp mot risiko ved å ikke gi trombolyse):**
- Fragmin/Heparin siste 48 timer - ikke gi trombolyse ved høydose behandling!
- Tidligere hjerneblødnings/SAH, kjent AVM/tumor cerebri/større aneurysmer
- Hjerneinfarkt eller CNS-kirurgi siste 2 mndr
- Pågående/nylig gjennomgått blødningssto
- Større kirurgi/traume siste 14 dager
- Graviditet, fødsel siste 10 døgn, punksjon ikke-komprimerbart kar siste 10 døgn
- Trombocyter < 100
- Glukose < 2.8 eller > 22.0 (korrigér først glukose, vurder trombolyse etterpå igjen)
- Disseksjon av store kar (aorta, carotis communis) – gjelder ikkje interna el. vertebralis
- Bakteriell endokarditt/perikarditt. Akutt pankreatitt, alvorlig leversykdom, aktiv hepatitt.

**Faktorer som er assosiert med økt blødningsrisiko:**
- Forhøyet glukose, kjent diabetes, høy NIHSS-score, høy alder, tidligere ASA-bruk,
- kjent hjertesvikt, lang tid mellom symptomdebut og behandling

**Varslingsrutiner:**
- Alle trombolysekandidater meldes til trombolysetelefon 60100 for konferering
- → Spør etter: fødselsnr, symptomer og debuttidspunkt, forventet ankomst sykehus
- Ansvarshavende sykepleier i mottak tlf 60090 rekvirerer trombolyseteam
- → sett samtale over eller ring opp 60090

**Trombolysekandidat – De 10 regler**
1. Møt på Akutmottak til angitt klokkeslett, motta rapport fra ambulanse
2. Undersøk pasienten raskt (< 10 min). Sjekk kontraindikasjoner.
3. Ring radiolog tlf 64111 for å bekrefte ø.hj. CT
4. Ring trombolysepleier
5. Informer pasient eller pårørende
6. Gjenta NIHSS og sjekk BT. Ikke vent på svar på angio eller perfusjon
7. Gi bolus. Trombolysepleier gir infusion
8. Ved okkludert distale interna/proksimale media/basilaris varsles OUS Rikshospitalet
   Ring først intervensionsradiolog 951 59 246, så nevrolog 916 25 634
9. Husk navnelapp i trombolyseboken
10. Pust ut
Radiologiske undersøkelser:
Alle pasienter med mistanke om hjerneslag innenfor 4,5 timer skal ha ø.hj. CT caput.
Actilyse gis så snart CT har utelukket blødning – ikke vent på svar på angio/perfusjon!

TIA-pasienter og pasienter som åpenbart ikke har hjerneslag, meldes ut av trombolysesløyfen
CT angio er nødvendig for å avgjøre om pasienten kan få endovaskulær behandling
CT angio kan derfor droppes hvis intervension ikke er aktuelt (se nedenfor)
Relative kontraindikasjoner for CT angio:
Graviditet, kjent nyresvikt, hypertyreose, behandling med Metformin
CT perfusjon er nyttig for å avgjøre om indikasjon for trombolyse ved
Usikker debut, usikker klinik eller trombolyse ut over 4,5 timer

Behandling av BT > 185/110 før og under trombolyse:
1. Stopp Actilyseinfusjon
2. Ro rundt pasienten
3. Kateteriser hvis full blære
4. Gi medikamentell behandling
   - Furosemid 20-40 mg i.v., kan gjentas
   - Trandate 10-20 mg i.v., gis over 1-2 min (rytmekontroll!), kan gjentas etter 5 min
   - Stesolid 2,5-5 mg i.v. (ved angst)
   - Ketorax 5 mg i.v. (ved smerter)
   - Trandateinfusjon: 200 mg (2 amp á 20 ml) blandes med 160 ml NaCl (→ 1 mg/ml),
     infusjonshastighet 0,5 ml/min (30 ml pr. time). OBS rytmeovervåkning.

Alarmsymptomer: Stopp Actilyseinfusjon og ta ny cerebral CT umiddelbart ved
   - Økende utfall (NIHSS ≥ 2 poeng)
   - Hodepine
   - Kvalme, oppkast
   - Bevissthetsnedsettelse

Endovaskulær behandling (i.a. trombolyse, trombektomi, stent)

Indikasjon: Iskemisk hjerneinfarkt med betydelige utfall (parese, afasi) og påvist arterieokkl.
   Gjelder distale interna, proksimale media (M1/M2), basilaris
Tidsvinduer: Carotis interna og cerebri media 6-8 timer, basilaris 9-12 timer
Absolusste kontraindikasjoner: Alvorlig demens, langtkommet kreft
Relativ kontraindikasjon: Høy alder (85-90)
Ring OUS Rikshospitalet, først intervensjonsradiolog 951 59 246, så nevrolog 916 25 634.
Overfør CT-bilder. Sørg for rask overflytting (rød respons).

Relevante telefonnumre

Akuttmottak 60090  Trombolyse-spl 69670
Radiolog 64111  Nevrologisk bakvak 69642
Radiograf 62318  Nevrologisk forvak 69639
Intervensjonsradiolog OUS Rikshospitalet: mobil 951 59 246
Nevrolog OUS Rikshospitalet: mobil 916 25 634

Ahus - Behandlingslinje Hjerneslag utredning og behandling  dok-ID 21408  oktober 2012
10 Papers
Full title: Reasons for low thrombolysis rate in a Norwegian ischemic stroke population

Short title: Low thrombolysis rate in ischemic stroke

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Keywords: stroke, thrombolysis, recombinant tissue plasminogen activator, ischemic stroke
ABSTRACT

Background/Aims: A minor proportion of patients with acute ischemic stroke (AIS) receive treatment with intravenous thrombolysis. We aimed to explore reasons for not giving thrombolysis and to determine if there was a correlation between prehospital and in-hospital delay in a Norwegian ischemic stroke population.

Methods: Prospective study including patients with AIS during a 1-year period. Time intervals for prehospital and in-hospital delay, reasons for not treating with thrombolytic therapy in patients admitted within the time window and reasons for late arrival were recorded.

Results: In all, 290 patients were included, and 7.6% were treated with intravenous thrombolysis. The most frequent reasons for not treating eligible patients were: minor symptoms (22.8%), clinical improvement (17.5%) and uncertainty about the diagnosis (12.3%). Patients’ reasons for delayed admission were: not attributing their symptoms to stroke (25.4%), a wait-and-see attitude (25.4%), and choosing to wait for the GP’s office to open (14.3%). Prehospital delay was strongly correlated to in-hospital delay (p<0.001).

Conclusions: A large percentage of patients with AIS are not treated with thrombolysis because of mild or rapidly improving symptoms, and because patients arrive too late to the hospital. Absolute and relative contraindications account for a minor proportion of reasons for excluding patients.
INTRODUCTION

Treatment with intravenous thrombolytic therapy with recombinant tissue plasminogen activator (rt-PA) is considered safe and effective for patients with acute ischemic stroke (AIS) when administered within 4.5 hours of symptom onset [1, 2], but should be given as early as possible, even within the narrow time window [3]. However, only 3-8.5% of the patients with AIS receive this treatment [4-6].

There are several explanations for the low thrombolysis rate [5]. Numerous contraindications related to comorbidity limit the use of rt-PA. In addition, the time interval from symptom onset to admission to hospital is a major problem, as many patients arrive too late at the emergency department (ED) to be considered for intravenous thrombolytic therapy. Patients with wake-up strokes or uncertainty regarding the accurate time of symptom onset are not treated unless they were last seen well less than 4.5 hours before initiation of intravenous thrombolytic therapy.

Some of the main reasons for prehospital delay include lack of symptom recognition and low level of public awareness [7]. Even in-hospital delay may contribute to low thrombolysis rate [8], and few studies have explored how prehospital delay influences in-hospital delay [9].

The primary aim of the present study was to explore reasons for not giving thrombolysis and their impact on the thrombolysis rate in a Norwegian ischemic stroke population. In addition, we wanted to determine if there was a correlation between prehospital and in-hospital delay.
SUBJECTS AND METHODS

Data for this study were collected as part of a prospective, cross-sectional study on prehospital delay in patients with acute stroke or transient ischemic attack (TIA) conducted during a 1-year period (April 2009 to April 2010) at the Stroke Unit, Department of Neurology, Akershus University Hospital, Norway. In the case of multiple admissions during the study period, only the first admission was included. Details of the study design have been described in detail previously [10]. Patients with a final diagnosis of TIA (n = 100) and intracerebral hemorrhage (n = 50) were excluded in the present study.

Patient characteristics (age, sex and presence of stroke risk factors) were obtained from medical records and interview of the patients and/or the next of kin. The National Institutes of Health Stroke Scale (NIHSS) [11] was used to assess stroke severity on admission. Etiology was determined according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification [12] and topography according to the Oxfordshire Community Stroke Project (OCSP) criteria [13]. The use of Emergency Medical Services (EMS) was recorded.

The accurate time of symptom onset was categorized as i) known; ii) uncertain (patients unable to seek help because of severe symptoms, speech difficulties or reduced consciousness); and iii) unknown in the case of wake-up strokes. For patients with uncertain time of symptom onset, the time when they were identified was considered as the time of symptom onset. For patients with wake-up stroke, the time when they woke up was considered as the time of symptom onset.

Time intervals were recorded i) from symptom onset to admission (i.e. prehospital delay); ii) from admission to being evaluated by a nurse; iii) from admission to being examined by a doctor; and iv) from admission to initiation of a computed tomography (CT) scan. All patients were evaluated by the attending neurologist in the ED.
Patients in whom the accurate time of symptom onset was known, were dichotomized into an “eligible group” (prehospital delay of \( \leq 3.5 \) hours) and a “non-eligible group” (prehospital delay of \( > 3.5 \) hours). The cut-off of 3.5 hours was preferred because 1 hour is considered the upper limit of in-hospital delay \([14, 15]\), including neurological examination, imaging, laboratory analysis, transport within the hospital and, if necessary, blood pressure regulation. In patients with uncertain time of symptom onset and wake-up strokes, the time when they were last seen well was considered as the time of symptom onset when considering treatment with intravenous thrombolytic therapy.

In the eligible group, reasons for not treating with rt-PA were identified from the medical records and categorized. In the case of multiple reasons for exclusion from thrombolytic therapy, the main reason emphasized by the physician in the ED was recorded. In the non-eligible group, reasons for late arrival were recorded and categorized, as patients were asked to designate the main reason for their delay (open-ended question).

Time intervals are presented as median values and interquartile ranges (IQRs). Comparisons between groups were performed with Mann–Whitney U test for continuous variables, and Pearson’s \( \chi^2 \)-test or Fisher’s exact test (as appropriate) for categorical variables. Spearman’s rank correlation analysis was used to assess the relationship between the prehospital and in-hospital time intervals.

Statistical analysis was performed using SPSS statistical software version 20 (SPSS Inc., Chicago, IL).

Oral, informed consent was obtained. The study was approved by the Regional Committee for Ethics in Medical Research and by the Data Protection Authorities.
RESULTS

In all, 290 patients with AIS were included in the study. Median age was 75 years (IQR 66-82), and 137 (47.2%) were female. Patient characteristics are presented in Table 1. Median NIHSS on admission was 4 (IQR 2-8). The patient enrollment flow chart is outlined in Figure 1.

Known time of symptom onset

The accurate time of symptom onset was known in 145 (50.0%) patients. Of these, 72 (49.7%) patients arrived later than 3.5 hours. Eligible patients had higher NIHSS score on admission (5 [IQR 2-12] versus 2 [IQR1-5], p < 0.001) and arrived more frequently by EMS (90.4% versus 51.4%, p < 0.001) compared to non-eligible patients. Stroke topography distribution was significantly different (p = 0.009), and eligible patients had a higher frequency of total anterior circulation infarctions. There were no other significant differences regarding patient characteristics (Table 1).

Reasons for not treating eligible patients (known time of symptom onset and arriving within 3.5 hours) with thrombolytic therapy with rt-PA, are listed in Table 2. The three most frequent reasons were: minor symptoms (22.8%), clinical improvement from symptom onset to admission (17.5%) and uncertainty about the diagnosis (12.3%).

In the non-eligible group, reasons for delayed admission more than 3.5 hours of symptom onset are listed in Table 3. The major reasons were that patients did not attribute their symptoms to stroke (25.4%) and a wait-and-see attitude, hoping symptoms would resolve (25.4%). In addition, 14.3% of the patients chose to wait for the general practitioner’s (GP’s) office to open.

Intravenous thrombolysis
In all, 22 (7.6%) patients were treated with intravenous thrombolytic therapy with rt-PA (Figure 1). Of these, 16 patients had known time of symptom onset, and all were in the eligible group. Six patients with uncertain time of symptom onset were treated with thrombolytic therapy, as they were all last seen well 4.5 hours or less before rt-PA administration. In addition, four patients with uncertain time of symptom onset were last seen well 3.5 hours or less when admitted, but these patients did not receive thrombolysis because of infarction on CT scan (n = 3) or minor symptoms (n = 1).

**In-hospital delay**

Median prehospital delay in the whole study group (n = 290) was 193 (IQR 78-543) minutes. Median time from admission to being evaluated by a nurse, being examined by a doctor and initiation of a CT scan was 12 (IQR 5-25), 49 (IQR 21-103) and 119 (IQR 55-195) minutes, respectively.

The time from symptom onset to admission was strongly correlated to the time from admission to being evaluated by a nurse (Spearman’s $\rho = 0.34$, $p < 0.001$), from admission to being examined by a doctor (Spearman’s $\rho = 0.52$, $p < 0.001$), and from admission to initiation of a CT scan (Spearman’s $\rho = 0.48$, $p < 0.001$).

In the subgroup of patients with known time of symptom onset, there were significant differences between eligible and non-eligible patients regarding evaluation by a nurse ($p = 0.001$), examination by a doctor ($p < 0.001$) and initiation of a CT scan ($p < 0.001$). The results are summarized in Table 4.
DISCUSSION

In the present study, we have identified some of the main reasons for the low rate of intravenous thrombolytic therapy in a Norwegian ischemic stroke population.

Only 25.2% of the patients with AIS were eligible for intravenous thrombolytic therapy, i.e. in which the accurate time of symptom onset was known in addition to ED arrival within 3.5 hours. In this group, the thrombolysis rate was 21.9%, compared to 7.6% in the whole study group of ischemic stroke patients, which is in line with the proportions reported previously [5]. Interestingly, 9.2% of the patients with uncertain time of symptom onset were also treated with thrombolysis in this study, as the time when they were last seen well was known and equal to or less than 4.5 hours on rt-PA administration. This illustrates the importance of obtaining information about when the patient was last seen well when the accurate time of symptom onset is not known. The same applies for wake-up strokes, such as patients having an afternoon nap, although none of the patients with wake-up stroke were treated with intravenous thrombolysis in this study.

Absolute and relative contraindications to rt-PA therapy accounted for a minor proportion of reasons for excluding patients from such therapy, as over half of the eligible patients were excluded due to uncertainty about the diagnosis, minor symptoms or clinical improvement. The latter two are often referred to as “mild or rapidly improving symptoms” (MRIS) [16, 17] or “too good to treat” (TGT) [18, 19], and accounted for 40.3% of the eligible patients not treated with rt-PA. Previous studies have highlighted favorable outcomes in AIS patients categorized as MRIS/ TGT treated with rt-PA [20, 21], and the safety of intravenous thrombolytic therapy in stroke mimics and neuroimaging-negative cerebral ischemia has also been demonstrated [22]. The benefit of treating AIS patients categorized as MRIS/ TGT is debatable, as results are diverging. In a study from Switzerland [16], 75% of the patients with
MRIS admitted within 6 hours of symptom onset and not receiving thrombolysis had favorable outcome after 3 months (modified Rankin Scale $\leq 1$), whereas a small subgroup of patients (those with proximal vessel occlusions and NIHSS $\geq 10$) could have benefited from thrombolysis. However, Smith et al [18] reported that 27% of the patients categorized as TGT and thus excluded for treatment with rt-PA, were unable to be discharged home, whereas Willey et al [19] reported an increase in NIHSS from admission to discharge in only 2.4% of the TGT patients.

In patients arriving late, over half of the patients did not attribute their symptoms to stroke or they had a wait-and-see attitude, hoping the symptoms would resolve. Interestingly, 1 in 7 patients waited for the GP’s office to open, thus critically prolonged the prehospital delay. If delay could have been avoided in the late arriving patients, the number of patients eligible for thrombolysis would have nearly doubled (increased from 73 to 145). Unfortunately, recent public educational campaigns have had little prolonged effect on patient behavior in response to acute stroke [23, 24]. Given that stroke patients fail to recognize or do not understand the seriousness of their symptoms, reducing prehospital delay will be challenging. Mass media campaigns are expensive, and the public knowledge seems to diminish some months after the end of the campaigns [25]. It is of great importance that educational campaigns focus on how to make the public translate stroke knowledge into action, and there is a need to evaluate the efficacy of different campaign models.

In a recently published study including 58,353 patients treated with rt-PA [26], faster time from symptom onset to treatment was associated with reduced in-hospital mortality, reduced symptomatic intracranial hemorrhage and increased discharge to home, thus emphasizing the “time is brain” paradigm in acute stroke care, as an estimated 2 million neurons die per minute until reperfusion is achieved [27].
Delay in admission to hospital after the onset of stroke symptoms is one of the most important reasons for the poor utilization of intravenous thrombolytic therapy with rt-PA [7], and the majority of the ischemic stroke population remains ineligible for this treatment due to the narrow time window. Previous studies have shown that between 23-51% of the patients arrive at the hospital within 3 hours after symptom onset [28-30]. Tong et al [6] showed that 26.8% of the patients arrived within 3.5 hours in the “Get With The Guidelines” Stroke program, and that the proportion of early arriving patients with AIS did not increase significantly from 2003 to 2009.

In a German study [31], the median time between ED admission and imaging was 108 minutes, and a prehospital delay of less than 3 hours was associated with shorter in-hospital delay. In the present study, the median time from admission to initiation of a CT scan was 119 minutes, and prehospital delay was correlated to the time until the patients were evaluated by a nurse, examined by a doctor and imaging, thus implying an association and dependency between prehospital and in-hospital delay. Shorter median time from ED admission to CT scan has also been reported for patients arriving by the EMS [32]. Ideally, prehospital delay should not influence in-hospital delay, as there are ED protocols concerning acute stroke care. Nevertheless, early arrival seems to enhance the perception of urgent assessment and the results from this and other studies imply opportunities for improvement. Rapid and streamlined management requires appropriate ED infrastructure and continuous educational efforts, and should apply to both patients eligible and not eligible for thrombolysis.

Our study has some limitations, most importantly the lack of follow-up and outcome measures. In the study design, we chose to use the time when patients with uncertain or unknown time of symptom onset were identified or woke up, respectively, because it represents the time when medical help could be sought. Other studies have used the time when the patient was last seen well [32, 33], which gives a higher median prehospital delay
time. In addition, the small sample size implies that the results should be interpreted with caution. Also of interest, the median NIHSS on admission was relatively low in our stroke population (median score 4), and patients with low NIHSS scores tend to be the ones who do not receive thrombolytic treatment.

CONCLUSIONS

In this study, a large proportion of patients with ischemic stroke were not treated with intravenous thrombolytic therapy because of mild or rapidly improving symptoms, and because they arrived too late because they did not attribute their symptoms to stroke or had a wait-and-see attitude. There was a correlation between prehospital and in-hospital delay. Randomized clinical trials are needed to clarify whether patients categorized as MRIS/ TGT should receive intravenous thrombolytic therapy. In addition, educational campaigns should focus on how to make the public translate stroke knowledge into action.

Conflict of interests/disclosures: None.

REFERENCE LIST


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### TABLES

**Table 1. Patient characteristics**

<table>
<thead>
<tr>
<th></th>
<th>All patients</th>
<th>Eligible patients (*)</th>
<th>Non-eligible patients (**)</th>
<th>p (*** )</th>
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</thead>
<tbody>
<tr>
<td><strong>Total</strong></td>
<td>290</td>
<td>73</td>
<td>72</td>
<td></td>
</tr>
<tr>
<td><strong>Age (years)</strong></td>
<td>75 (66-82)</td>
<td>73 (64-81)</td>
<td>73 (66-81)</td>
<td>0.34</td>
</tr>
<tr>
<td><strong>Female</strong></td>
<td>137 (47.2)</td>
<td>35 (47.9)</td>
<td>32 (44.4)</td>
<td>0.67</td>
</tr>
<tr>
<td><strong>Medical history</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>92 (31.7)</td>
<td>22 (30.1)</td>
<td>20 (27.8)</td>
<td>0.75</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>103 (35.5)</td>
<td>27 (37.0)</td>
<td>22 (30.6)</td>
<td>0.41</td>
</tr>
<tr>
<td>Hypertension</td>
<td>209 (72.1)</td>
<td>55 (75.3)</td>
<td>50 (69.4)</td>
<td>0.43</td>
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<tr>
<td>Hypercholesterolemia</td>
<td>162 (55.9)</td>
<td>42 (57.5)</td>
<td>37 (51.4)</td>
<td>0.46</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>90 (31.0)</td>
<td>20 (27.4)</td>
<td>15 (20.8)</td>
<td>0.36</td>
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<tr>
<td>Diabetes mellitus</td>
<td>53 (18.3)</td>
<td>13 (17.8)</td>
<td>17 (23.6)</td>
<td>0.39</td>
</tr>
<tr>
<td>Smoking</td>
<td>73/267 (27.3)</td>
<td>17/71 (23.9)</td>
<td>16/70 (22.9)</td>
<td>0.88</td>
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<tr>
<td>Arrival by EMS</td>
<td>217 (74.8)</td>
<td>66 (90.4)</td>
<td>37 (51.4)</td>
<td>&lt;0.001</td>
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<tr>
<td>NIHSS</td>
<td>4 (2-8)</td>
<td>5 (2-12)</td>
<td>2 (1-5)</td>
<td>&lt;0.001</td>
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<td>TOAST</td>
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<td>0.210</td>
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<tr>
<td>Cardioembolic</td>
<td>80 (27.6)</td>
<td>22 (30.1)</td>
<td>12 (16.7)</td>
<td></td>
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<tr>
<td>Large artery</td>
<td>51 (17.6)</td>
<td>17 (23.3)</td>
<td>15 (20.8)</td>
<td></td>
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<tr>
<td>Small vessel</td>
<td>99 (34.1)</td>
<td>20 (27.4)</td>
<td>37 (51.4)</td>
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<tr>
<td>Other/ undetermined</td>
<td>60 (20.7)</td>
<td>14 (19.2)</td>
<td>8 (11.1)</td>
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<td>OCSP</td>
<td>TACI</td>
<td>PACI</td>
<td>POCI</td>
<td>LACI</td>
</tr>
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<td>------</td>
<td>------</td>
<td>------</td>
<td>------</td>
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</tr>
<tr>
<td></td>
<td>36 (12.4)</td>
<td>124 (42.8)</td>
<td>34 (11.7)</td>
<td>96 (33.1)</td>
</tr>
<tr>
<td></td>
<td>13 (17.8)</td>
<td>29 (39.7)</td>
<td>10 (13.7)</td>
<td>21 (28.8)</td>
</tr>
<tr>
<td></td>
<td>2 (2.8)</td>
<td>29 (40.3)</td>
<td>8 (11.1)</td>
<td>33 (45.8)</td>
</tr>
<tr>
<td></td>
<td>0.009</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(*) Time of symptom onset known, prehospital delay of $\leq 3.5$ hours

(**) Time of symptom onset known, prehospital delay of $> 3.5$ hours

(***) Comparing eligible and non-eligible patients

EMS, Emergency Medical Services; LACI, lacunar circulation infarction; NIHSS, National Institutes of Health Stroke Scale; OCSP, Oxfordshire Community Stroke Project; PACI, partial anterior circulation infarction; POCI, posterior circulation infarction; TACI, total anterior circulation infarction; TOAST, Trial of Org 10172 in Acute Stroke Treatment;
Table 2. Reasons for not giving intravenous thrombolytic therapy with rt-PA in patients admitted within 3.5 hours of symptom onset

<table>
<thead>
<tr>
<th>Reason</th>
<th>Count (Percentage)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>57</td>
</tr>
<tr>
<td>Minor symptoms/too good to treat</td>
<td>13 (22.8)</td>
</tr>
<tr>
<td>Clinical improvement</td>
<td>10 (17.5)</td>
</tr>
<tr>
<td>Uncertainty about diagnosis</td>
<td>7 (12.3)</td>
</tr>
<tr>
<td>Comorbidity</td>
<td>5 (8.8)</td>
</tr>
<tr>
<td>Severe symptoms</td>
<td>5 (8.8)</td>
</tr>
<tr>
<td>Anticoagulation, INR ≥ 1.7</td>
<td>4 (7.0)</td>
</tr>
<tr>
<td>CT scan: infarction</td>
<td>4 (7.0)</td>
</tr>
<tr>
<td>Age</td>
<td>3 (5.3)</td>
</tr>
<tr>
<td>GI hemorrhage ≤ 3 months</td>
<td>2 (3.5)</td>
</tr>
<tr>
<td>Major surgery ≤ 14 days</td>
<td>1 (1.8)</td>
</tr>
<tr>
<td>Not documented</td>
<td>3 (5.3)</td>
</tr>
</tbody>
</table>

CT, computed tomography; GI, gastrointestinal; INR, international normalized ratio; rt-PA, recombinant tissue plasminogen activator
Table 3. Reasons for prehospital delay in patients admitted after 3.5 hours of symptom onset

<table>
<thead>
<tr>
<th>Reason</th>
<th>Count (Percentage)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>63*</td>
</tr>
<tr>
<td>Not attributing symptoms to stroke</td>
<td>16 (25.4)</td>
</tr>
<tr>
<td>Wait-and-see, hoping symptoms will resolve</td>
<td>16 (25.4)</td>
</tr>
<tr>
<td>Waiting for GP’s office to open</td>
<td>9 (14.3)</td>
</tr>
<tr>
<td>Waiting for relatives to come and help</td>
<td>8 (12.7)</td>
</tr>
<tr>
<td>Not been able to seek medical assistance because of symptoms</td>
<td>4 (6.4)</td>
</tr>
<tr>
<td>Regarding symptoms to have another specific cause</td>
<td>4 (6.4)</td>
</tr>
<tr>
<td>Having perception of coming quickly</td>
<td>4 (6.4)</td>
</tr>
<tr>
<td>Other reasons</td>
<td>2 (3.2)</td>
</tr>
</tbody>
</table>

*72 patients in total, but 9 patients were not able to answer because of aphasia, reduced consciousness or cognitive impairment.

GP, general practitioner
**Table 4.** In-hospital time intervals in patients with known time of symptom onset

<table>
<thead>
<tr>
<th></th>
<th>Prehospital delay ≤ 3.5 hours</th>
<th>Prehospital delay &gt; 3.5 hours</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evaluation by a nurse</td>
<td>8 (2-17)</td>
<td>15 (6-28)</td>
<td>0.001</td>
</tr>
<tr>
<td>Examination by a doctor</td>
<td>20 (8-50)</td>
<td>80 (43-115)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Initiation of a CT scan</td>
<td>51 (34-113)</td>
<td>138 (91-190)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Time intervals are presented as median with interquartile range.
FIGURES

Figure 1. Flow chart of patient enrollment; time according to emergency department admission

ICH, intracerebral hemorrhage; rt-PA, recombinant tissue plasminogen activator; TIA, transient ischemic attack
Factors related to knowledge of stroke symptoms and risk factors in a Norwegian stroke population

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Running title: Stroke knowledge in a Norwegian stroke population

Key words: stroke patients – knowledge – stroke symptoms – stroke risk factors – predictors
Abstract

Background: Previous studies have identified insufficient knowledge of stroke symptoms and risk factors in the general population and among stroke survivors. The purpose of this study was to investigate knowledge of stroke symptoms and risk factors in a Norwegian stroke population, and to identify factors associated with good knowledge.

Methods: This prospective study included patients with acute transient ischemic attack, ischemic stroke and intracerebral hemorrhage. Knowledge of stroke symptoms and risk factors was explored by asking open-ended questions. Bivariate and multivariate regression analyses were performed to identify factors related to good knowledge.

Results: In total, 287 patients (mean age ± SD, 70.0 ± 12.9 years) were able to answer the open-ended questionnaire. In all, 71% and 43% knew at least one stroke symptom and one risk factor, respectively. Knowledge of both numbness/weakness and speech difficulties as stroke symptoms (43% of the patients) was associated with lower age (OR, 0.96; 95% CI, 0.94-0.99), higher education (OR, 2.25; 95% CI, 1.17-4.30), and having received information on stroke at an earlier stage (OR, 7.74; 95% CI, 3.82-15.67). Knowing at least two of the three stroke risk factors “smoking”, “hypertension” and “diabetes” (14% of the patients) was associated with lower age (OR, 0.94; 95% CI, 0.92-0.97).

Conclusions: Knowledge of stroke symptoms and risk factors in patients with acute cerebrovascular disease seems to be insufficient. Further educational efforts are needed, as better knowledge may improve stroke prevention and increase the number of patients available for thrombolysis.
Introduction

The burden of cerebrovascular disease can be reduced by providing optimal acute care in stroke units, including time-dependent reperfusion therapy. Intravenous thrombolytic therapy within the time window of 4.5 hours of stroke offers beneficial effect in selected patients with acute ischemic stroke (AIS). Admission to the hospital within this narrow time window presupposes the patients’ recognition of stroke symptoms and the knowledge of the necessity of rapid hospitalization. However, the lack of stroke awareness often results in delayed admission, making thrombolysis only accessible for a minor proportion of the patients. Furthermore, the population’s knowledge of risk factors of cerebrovascular disease is essential to improve their own risk profile in order to prevent stroke.

Both in the general population and in stroke patients, a number of studies regarding knowledge of stroke symptoms and risk factors have been performed in the 1990s and early 2000s, i.e. at the beginning of the thrombolysis era. Knowledge of stroke was generally poor, especially in those at highest risk. One would expect that long-lasting increased media focus on public health, increased awareness of own health, and widespread access to health information had contributed to improved knowledge and awareness of stroke. However, more recent studies indicate that knowledge of stroke still is insufficient.

The aims of the present study were to explore the current knowledge of stroke symptoms and risk factors in a Norwegian population with acute cerebrovascular disease, and to identify factors associated with good knowledge.

Methods

The present study is part of a prospective trial on prehospital delay in patients with acute transient ischemic attack (TIA) or stroke admitted to the stroke unit of the Department
of Neurology, Akershus University Hospital, during a 1-year period. No public campaigns regarding stroke were conducted before or during the study period.

Patients ≥18 years with a suspected TIA or stroke (AIS or intracerebral hemorrhage (ICH), first-ever or recurrent), were included. Stroke was defined according to the World Health Organization as ‘rapidly developing clinical signs of focal (at times global) disturbance of cerebral function, lasting more than 24 h or leading to death with no apparent cause other than that of vascular origin’. Patients with subarachnoid hemorrhage, in-hospital TIA/stroke, and those discharged with a diagnosis other than TIA/stroke were excluded.

All patients were interviewed by AS or KWF within 72 hours of admission to the hospital, using a standardized, structured questionnaire, consisting of both close-ended and open-ended questions. Both the patients and their relatives could answer the close-ended questions, while the open-ended questions had to be answered by the patients themselves. Those unable to answer the questions due to speech or language difficulties, reduced consciousness or cognitive impairment were excluded.

Close-ended questions concerned the patients’ background: age, sex, educational level (primary/secondary vs higher education [university or university college]), living arrangement (living in a household of at least two residents vs living alone), and the presence of stroke risk factors: hypertension (on treatment with anti-hypertensive drugs), hypercholesterolemia (on treatment with lipid-lowering drugs or total cholesterol >5mmol/l or LDL cholesterol >3mmol/l), cardiovascular disease (previous myocardial infarction or angina pectoris, congestive heart failure), atrial fibrillation (paroxysmal or persistent), diabetes (on treatment with oral anti-diabetic drugs or insulin), smoking, and previous cerebrovascular disease (TIA or ischemic or hemorrhagic stroke). Further, we recorded the type of the cerebrovascular accident. On admission, stroke severity was assessed by the 11-item version of the National
Institutes of Health Stroke Scale (NIHSS), and global functioning was evaluated using the modified Rankin Scale (mRS).

Knowledge of stroke symptoms and risk factors

In order to explore the knowledge of stroke symptoms and risk factors, patients had to answer two open-ended questions by spontaneous naming: “Which stroke symptoms do you know?”; and “Which stroke risk factors do you know?”. According to the National Institute of Neurological Disorders and Stroke (NINDS), stroke symptoms were defined as following: (1) sudden numbness or weakness of face, arm, or leg, especially on one side of the body; (2) sudden confusion or trouble speaking or understanding speech; (3) sudden trouble seeing in one or both eyes; (4) sudden trouble walking, dizziness, or loss of balance or coordination; or (5) sudden severe headache with no known cause. In addition to the established stroke risk factors (hypertension, smoking, heart disease [cardiovascular disease including atrial fibrillation], diabetes, hypercholesterolemia, previous cerebrovascular disease, and alcohol overuse), the following were considered as risk factors: higher age, family history of cardiovascular disease, obesity, poor diet, and physical inactivity.

In the present study, adequate knowledge of stroke symptoms or risk factors was considered to be more than just being able to mention any kind of stroke symptom or risk factor. In previous studies, the correct recognition of 3 of 5, or 4 of 6 stroke warning signs was considered as sufficient stroke symptom knowledge. We defined adequate knowledge of stroke symptoms as being able to identify both “numbness or weakness of the face, arm or leg” and “confusion or trouble speaking or understanding speech” as stroke symptoms, as hemiparesis, paresthesia and speech abnormalities are the most common symptoms in acute ischemic stroke, and “facial weakness”, “arm weakness”, and “speech disturbance” are the key elements of the Newcastle Face Arm Speech Test (FAST).
Adequate knowledge of stroke risk factors was defined as knowing at least two of the three stroke risk factors “hypertension”, “smoking” and “diabetes”, as they are well-documented modifiable risk factors, and as more than half of all ischemic strokes in the population can be attributed to them.

Finally, the patients were asked whether they had received any kind of information on stroke at an earlier stage or not.

Ethics

The Regional Committee for Medical and Health Research Ethics and the Data Protection Authorities approved the study. All patients gave their oral informed consent.

Statistical Analysis

The statistical analyses were performed using SPSS version 18.0 (SPSS Inc., Chicago, IL) and 5% was the level of significance. Categorical variables are presented as frequencies and percentages, and continuous variables as means and standard deviations (SD) for normally distributed data, and medians and interquartile ranges (IQR) for non-parametric data. Between-group differences for categorical variables were determined by $\chi^2$ statistics or Fisher exact test, as appropriate, for normally distributed continuous variables by unpaired two-sample $t$-tests, and for non-parametric continuous variables by Mann-Whitney $U$ test.

To identify factors related to adequate knowledge of stroke symptoms and risk factors, logistic regression analyses were performed. Candidate variables in the binary model were: age, sex, educational level, previous cerebrovascular disease, having at least one stroke risk factor, living arrangement, and having received information on stroke at an earlier stage. Variables reaching a significance level of $P<.20$ were subjected to the multivariate analysis.
Stepwise elimination was performed, removing variables with a significance level of $P \geq .05$. Results are presented as odds ratios (OR) and 95% confidence intervals (CI).

**Results**

In total, 440 patients were included in the study. Of these, 153 patients (34.8%) were not able to answer the open-ended questions of the questionnaire (non-responder group), leaving 287 patients (65.2%; responder group). The characteristics of the two groups are summarized in Table 1. Compared to the non-responders, the responders were younger ($P = .003$), had a lower prevalence of cardiovascular disease ($P = .01$) and atrial fibrillation ($P = .004$), had milder strokes (lower NIHSS and mRS score on admission: $P < .001$), and the cause of hospitalization was more often TIA ($P < .001$) and less often ICH ($P < .001$).

**Knowledge of stroke symptoms**

Of the 287 responders, 203 (70.7%) knew at least one stroke symptom. In all, 191 (66.6%) patients identified the stroke symptom “numbness or weakness of the face, arm or leg”, and 131 (45.6%) the stroke symptom “confusion or trouble speaking or understanding speech”, while 123 (42.9%) were able to identify both stroke symptoms. Only 48 patients (16.7%) knew the three FAST-elements “facial weakness”, “arm weakness” and “speech disturbance”.

From the binary logistic regression analyses (Table 2), the variables age, educational level, living arrangement, and having received information on stroke at an earlier stage were entered into the multivariate model, in addition to sex. After stepwise elimination of non-significant variables, knowledge of stroke symptoms was associated with lower age (OR, 0.96; 95% CI, 0.94-0.99; $P = .001$), higher education (OR, 2.25; 95% CI, 1.17-4.30; $P = .02$),
and having received information on stroke at an earlier stage (OR, 7.74; 95% CI, 3.82-15.67; \(P<.001\)).

**Knowledge of stroke risk factors**

In all, 124 patients (43.2%) were able to name at least one stroke risk factor. Smoking and hypertension were the two most commonly cited stroke risk factors with 22.3% and 19.5%, respectively (Table 3). Forty patients (13.9%) were able to identify at least two of the three risk factors “smoking”, “hypertension” and “diabetes”, and only five patients (1.7%) knew all three.

The proportion of patients having a particular stroke risk factor and identifying it as such is shown in Table 4. A significantly higher percentage of those with the risk factors smoking, diabetes and heart disease identified these as risk factors compared to those without these risk factors. None of those with previous cerebrovascular disease identified this as a risk factor.

Performing binary logistic regression, the candidate variables age, educational level, having at least one stroke risk factor, living arrangement, and having received information on stroke at an earlier stage reached \(P<.20\) (Table 2). In multivariate regression analyses, also including sex, only lower age (OR, 0.94; 95% CI, 0.92-0.97; \(P<.001\)) was associated with adequate knowledge of stroke risk factors.

**Discussion**

The results of the present study indicate lacking knowledge of stroke symptoms and risk factors in patients hospitalized with acute TIA or stroke. Two-thirds of the patients identified numbness or weakness as stroke symptom, while less than half identified speech disturbances. Only one in six was able to name all the three FAST-elements “facial
weakness”, “arm weakness” and “speech disturbance”. Roughly four out of ten patients knew at least one stroke risk factor, where smoking and hypertension were most frequently mentioned. The proportion of those with a certain risk factor and identifying it as such was low. Lower age, higher education and having received information on stroke at an earlier stage predicted adequate knowledge of stroke symptoms, while only lower age was related to adequate knowledge of stroke risk factors.

The existing studies on knowledge of stroke symptoms and risk factors have used various definitions of good or adequate knowledge, i.e. the number of symptoms or risk factors respondents had to identify. Furthermore, some used open-ended questions, which may have led to an underestimation of the population’s knowledge, while others used close-ended questions, which probably gave an overestimation. Hence, a direct comparison with each other and our study is difficult.

Hemiparesis, paresthesia and speech abnormalities are the most common symptoms in acute ischemic stroke, and were most often mentioned in our study, which is in line with previous findings. In an Australian study, those making the call for ambulance assistance were asked which symptoms of the stroke event they recalled. Only recalling at least two of the three stroke symptoms “limb weakness”, “facial weakness”, and “speech problems” was associated with stroke recognition and showed a trend towards calling for ambulance assistance. Stroke knowledge seems to be more than just being able to identify any kind of stroke symptom, and comprises also recognition of the cerebrovascular event and appropriate action by calling an ambulance immediately. In the present study, only 43% of the patients were able to name both numbness/weakness and speech disturbances, when asked for stroke symptoms, and not more than 17% knew all three FAST-elements. The level of knowledge was equally poor in previous studies, where between 9% and 28% of the respondents could name 3 or more established stroke warning signs.
using close-ended questions, only 65% of the subjects correctly identified at least 4 out of 6 stroke symptoms.\textsuperscript{13}

Regarding knowledge of stroke risk factors, only 43% of our patients could name at least one risk factor, which is in the lower range of what has been reported in the literature previously (40-79%).\textsuperscript{4, 6, 8-10, 14, 15, 28, 30} Both hypertension and smoking were mentioned by one in five of our patients. In previous studies using open-ended questions, hypertension was named by 20-51% of the respondents,\textsuperscript{4, 6, 8-10, 15, 28} and smoking by 19-39%.\textsuperscript{4, 8-10, 15, 28} Despite the use of close-ended questions in another study, not more than 75% of the subjects identified hypertension as a stroke risk factor, and only 30% smoking.\textsuperscript{27} Interestingly, our patients more often mentioned alcohol overuse, obesity and poor diet as stroke risk factors than the established risk factors diabetes, heart disease and previous cerebrovascular disease, which is in line with previous results where heart disease and diabetes were among the least mentioned risk factors.\textsuperscript{4, 6, 8, 9, 28, 31} The number of respondents able to identify more than one stroke risk factor is discouraging (25-50%).\textsuperscript{6, 8-10}

Only a small proportion of our patients with certain stroke risk factors identified them as such. This is considered a major problem, as awareness of own risk profile is a precondition for risk changing behavior, and thus prevention of stroke. Health care professionals should have ample opportunities to inform about stroke and its risk factors, as patients with risk factors, i.e. those at highest risk of stroke, are assumed to be in regular contact with the health care system. According to Samsa et al., having been informed about one’s own stroke risk by a physician was associated with the understanding of an increased stroke risk, which again was related to a higher compliance with stroke preventive measures.\textsuperscript{32} In the same study, nearly 60% of the patients with previous stroke were unaware of their increased stroke risk.\textsuperscript{32} Importantly, none of our patients with previous cerebrovascular disease recognized it as a stroke risk factor, as previously also described by Carroll et al.\textsuperscript{4} and
in fact, prior cerebrovascular disease was neither associated with better knowledge of stroke symptoms or risk factors, which is in accordance with Hickey et al.\textsuperscript{27} The health care system’s information to patients with previous TIA or stroke seems to be insufficient. Our results indicate equally poor knowledge of both stroke symptoms and risk factors as in previous studies, which is somewhat unexpected, as the Norwegian population is generally highly educated.\textsuperscript{33}

In the present study, lower age was associated with better knowledge of both stroke symptoms and risk factors, as described previously.\textsuperscript{6, 8, 9, 16} Others, however, did not find any age effect at all,\textsuperscript{27} or only regarding either knowledge of stroke symptoms\textsuperscript{13} or risk factors.\textsuperscript{4, 30} Greenlund et al revealed better recognition of stroke symptoms in middle-aged respondents\textsuperscript{11} and Schneider et al found those younger than 35 years having less stroke knowledge,\textsuperscript{9} which could be explained by low general disease interest in a presumed healthy population. This may also be why in a general population with a mean age of 40 years those older than 60 years had better knowledge of stroke risk factors.\textsuperscript{31}

Education is likely to influence the knowledge of stroke symptoms and risk factors, and previous studies have shown better knowledge in those with higher education.\textsuperscript{8, 9, 15, 16, 31} However, we only found an effect on stroke symptom knowledge. Similar to several previous studies,\textsuperscript{6, 10, 13, 16, 27} we could not reveal any significant association between sex and knowledge of stroke symptoms or risk factors.

Better knowledge of stroke symptoms was predicted by having received any kind of information on stroke at an earlier stage. Thus, educational efforts are needed to increase awareness of stroke symptoms. Mass media campaigns have shown to improve knowledge of warning signs of stroke, but may be less effective in those over 65 years.\textsuperscript{27} Information must be tailored to the audience. As knowledge declines after the end of educational campaigns,\textsuperscript{34} continuous\textsuperscript{34} or long intermittent campaigns\textsuperscript{35} might be more effective. Furthermore, the
choice of information campaign type is essential, as television advertising seems to increase knowledge, whereas newspaper advertising does not.\textsuperscript{36} There are divergent findings on the role of health care professionals in stroke education, varying from being the main source of information in some parts of the population\textsuperscript{8} to being less important.\textsuperscript{4,6,10,15} Regardless of that, professionals should get more involved in educating patients, especially those at highest risk of stroke. Educational efforts should include both information on treatment of modifiable stroke risk factors and thus prevention of stroke, and information about stroke symptoms and appropriate action in the event of stroke.

It is uncertain whether and to what extent the population’s knowledge of stroke and its risk factors can be increased in the future. Probably there is an upper limit on how much information can be remembered. According to Kleindorfer et al and Reeves et al, knowledge of stroke risk factors remained nearly unchanged over a 5 year period despite slightly higher educational level of the subjects and educational efforts over time.\textsuperscript{14,28} Moreover, having knowledge and recognizing stroke does not imply proper action in the case of stroke.\textsuperscript{5,6,29,37}

The strength of the present study was the hospital’s well-defined catchment area with admission of all patients with acute TIA or stroke to the stroke unit. Furthermore, no patients refused participation. Nevertheless, because of the exclusion of 35\% of the patients due to speech or language difficulties, or reduced consciousness or cognitive impairment, our responder-group does not reflect the whole stroke population. It is however less likely that the non-responders had better stroke knowledge, as they had a lower educational level and were significantly older than the responders. All study participants were interviewed within 72 hours of admission to the hospital and may have got in-hospital information on stroke before the interview, which reflects that the actual level of stroke knowledge may have been even lower than what we report. On the other hand, using an open-ended questionnaire may have resulted in an underestimation of the knowledge of stroke symptoms and risk factors. Finally,
cognitive deficits and denial in the acute phase of stroke may have contributed to the poor level of knowledge in the present study.

In conclusion, the present study revealed insufficient knowledge of stroke symptoms and risk factors in a Norwegian population hospitalized with acute TIA or stroke. Further efforts to improve knowledge are required. Better knowledge of stroke symptoms might contribute to an increased number of patients available for thrombolysis, whereas better knowledge of risk factors and awareness of the own risk profile may result in improved compliance with the recommended risk factor treatment and behavioral changes, and thus prevention of stroke.

Acknowledgement: None.
References


### Tables

**Table 1. Baseline characteristics**

<table>
<thead>
<tr>
<th></th>
<th>All</th>
<th>Responder group</th>
<th>Non-responder group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=440</td>
<td>N=287</td>
<td>N=153</td>
</tr>
<tr>
<td>Age, y, mean±SD</td>
<td>71.4±13.0</td>
<td>70.0±12.9</td>
<td>73.9±12.8</td>
</tr>
<tr>
<td>Male sex, n (%)</td>
<td>245 (55.7)</td>
<td>167 (58.2)</td>
<td>78 (51.0)</td>
</tr>
<tr>
<td>Living in a household of at least two residents, n (%)</td>
<td>254/434 (58.5)</td>
<td>170 (59.2)</td>
<td>84/147 (57.1)</td>
</tr>
<tr>
<td>Higher education, n (%)</td>
<td>86/346 (24.9)</td>
<td>71/273 (26.0)</td>
<td>15/73 (20.5)</td>
</tr>
</tbody>
</table>

| Stroke risk factors, n (%)           |            |                 |                     |
| None                                 | 37/438 (8.4) | 26 (9.1)        | 11/151 (7.3)        |
| Previous TIA/stroke                  | 145 (33.0)  | 97 (33.8)       | 48 (31.4)           |
| Hypertension                         | 295 (67.0)  | 190 (66.2)      | 105 (68.6)          |
| Hypercholesterolemia                 | 245 (55.7)  | 169 (58.9)      | 76 (49.7)           |
| Cardiovascular disease               | 149 (33.9)  | 85 (29.6)       | 64 (41.8)           |
| Atrial fibrillation                  | 111 (25.2)  | 60 (20.9)       | 51 (33.3)           |
| Diabetes                             | 71 (16.1)   | 42 (14.6)       | 29 (19.0)           |
| Smoking                              | 104/403 (25.8) | 71/286 (24.8) | 33/117 (28.2) |

<p>| NIHSS score on admission, median (IQR) | 3 (1-8) | 2 (0-5) | 9 (3-20) |
| mRS score on admission, median (IQR)   | 2 (1-4) | 2 (0-3) | 4 (3-5) |</p>
<table>
<thead>
<tr>
<th>Stroke type, n (%)</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>TIA</td>
<td>100 (22.7)</td>
<td>80 (27.9)</td>
<td>20 (13.1)</td>
</tr>
<tr>
<td>AIS</td>
<td>290 (65.9)</td>
<td>190 (66.2)</td>
<td>100 (65.3)</td>
</tr>
<tr>
<td>ICH</td>
<td>50 (11.4)</td>
<td>17 (5.9)</td>
<td>33 (21.6)</td>
</tr>
</tbody>
</table>

Abbreviations: AIS, acute ischemic stroke; ICH, intracerebral hemorrhage; IQR, interquartile range; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; SD, standard deviation; TIA, transient ischemic attack.
**Table 2. Binary logistic regression of factors associated with knowledge of stroke symptoms and risk factors**

<table>
<thead>
<tr>
<th>Knowledge of stroke symptoms*</th>
<th>Knowledge of stroke risk factors†</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>OR (95% CI)</strong></td>
<td><strong>OR (95% CI)</strong></td>
</tr>
<tr>
<td><strong>P value</strong></td>
<td><strong>P value</strong></td>
</tr>
<tr>
<td>Age</td>
<td>0.95 (0.93-0.97)</td>
</tr>
<tr>
<td>Male</td>
<td>0.81 (0.51-1.30)</td>
</tr>
<tr>
<td>Education, higher</td>
<td>2.99 (1.71-5.25)</td>
</tr>
<tr>
<td>Previous TIA/stroke</td>
<td>0.75 (0.45-1.23)</td>
</tr>
<tr>
<td>Having at least one stroke risk factor‡</td>
<td>0.62 (0.27-1.38)</td>
</tr>
<tr>
<td>Living in a household of at least two residents</td>
<td>1.63 (1.00-2.63)</td>
</tr>
<tr>
<td>Previous information on stroke</td>
<td>9.03 (4.62-17.64)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; OR, odds ratio; TIA, transient ischemic attack.

* Knowledge of both “numbness/weakness of the face, arm or leg” and “confusion, trouble speaking or understanding speech”.

† Knowledge of at least two of the three risk factors “smoking”, “hypertension” and “diabetes”.

‡ Hypertension, hypercholesterolemia, cardiovascular disease, atrial fibrillation, diabetes, smoking, previous TIA/stroke.
### Table 3. Number of patients identifying stroke risk factors

<table>
<thead>
<tr>
<th>Stroke risk factors</th>
<th>Responder group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
</tr>
<tr>
<td>Smoking</td>
<td>64 (22.3)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>56 (19.5)</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>29 (10.1)</td>
</tr>
<tr>
<td>Alcohol overuse</td>
<td>28 (9.8)</td>
</tr>
<tr>
<td>Obesity</td>
<td>27 (9.4)</td>
</tr>
<tr>
<td>Poor diet</td>
<td>24 (8.4)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>23 (8.0)</td>
</tr>
<tr>
<td>Heart disease*</td>
<td>20 (7.0)</td>
</tr>
<tr>
<td>Physical inactivity</td>
<td>20 (7.0)</td>
</tr>
<tr>
<td>Heredity</td>
<td>16 (5.6)</td>
</tr>
<tr>
<td>Age</td>
<td>2 (0.7)</td>
</tr>
<tr>
<td>Previous cerebrovascular disease</td>
<td>1 (0.3)</td>
</tr>
</tbody>
</table>

* Cardiovascular disease including atrial fibrillation.
Table 4. *Number of patients with a particular stroke risk factor identifying it as such*

<table>
<thead>
<tr>
<th>Stroke risk factor</th>
<th>Patients with risk factor identifying it as such</th>
<th>Compared with those without risk factor</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>P value</td>
</tr>
<tr>
<td>Smoking, n=71</td>
<td>30 (42.3)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Hypertension, n=190</td>
<td>39 (20.5)</td>
<td>.54</td>
</tr>
<tr>
<td>Diabetes, n=42</td>
<td>8 (19.0)</td>
<td>.01</td>
</tr>
<tr>
<td>Heart disease*, n=119</td>
<td>13 (10.9)</td>
<td>.03</td>
</tr>
<tr>
<td>Hypercholesterolemia, n=169</td>
<td>13 (7.7)</td>
<td>.11</td>
</tr>
<tr>
<td>Previous cerebrovascular disease, n=97</td>
<td>0 (0)</td>
<td>1.00</td>
</tr>
</tbody>
</table>

* Cardiovascular disease including atrial fibrillation.