Recanalization in cerebral ischemia

A register-based study

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Scientific environment

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List of abbrevations

AF	Atrial fibrillation
CI	Confidence interval
CT	Computed tomography
CRP	C-reactive protein
CTA	CT angiography
DWI	Diffusion-weighted imaging
ECASS	European Cooperative Acute Stroke Study
ECG	Electrocardiography
FDA	Food and Drug Administration
FLAIR	Fluid-attenuated inversion recovery
HT	Hemorrhagic transformation
ICA	Internal carotid artery
ICH	Intracerebral hemorrhage
LACS	Lacunar syndrome
MCA	Middle cerebral artery
M1	Proximal MCA
M2	Distal MCA
MNI	Major neurological improvement
MR	Magnetic resonance
MRA	MR angiography
MRI	Magnetic resonance imaging
mRS	Modified Rankin Scale

NIHSS	National Institutes of Health Stroke Scale
NINDS	National Institutes of Neurological Disorders and Stroke
NOR-SASS	Norwegian Sonothrombolysis in Acute Stroke Study
NOR-TEST	The Norwegian Tenecteplase Stroke Trial
OCSP	Oxfordshire Community Stroke Project
OR	Odds ratio
PACS	Partial anterior circulation syndrome
POCS	Posterior circulation syndrome
tPA	Tissue plasminogen activator
SICH	Symptomatic ICH
SITS	Safe Implementation of Thrombolysis in stroke
SITS-MOST	SITS-Monitoring Study
TACS	Total anterior circulation syndrome
TCD	Transcranial doppler
TEE	Transesophageal echocardiography
TIA	Transient ischemic attack
TOAST	Trial of Org 10172 in Acute Stroke Treatment

Introduction

Although representing approximately 2% of the total body weight, the human brain demands around 20% of the cardiac output when the body is at rest. As storage of oxygen, glucose and other substrates necessary for energy metabolism in the brain is limited, a continuous cerebral blood supply is of major importance. Consequently, the brain is extremely sensitive to even brief disruptions in blood flow. Focal ischemia occurs when a specific area of the brain suffers due to a critical reduction in blood flow. This reduction is often caused by an obstruction, typically a clot creating an occlusion of the cerebral arteries. Depending on the severity and location of the induced ischemia, neurological deficits may occur within short time. Persistent ischemia leads to death of cerebral tissue, cerebral infarction. The dissolution of the clot and reopening of the occluded vessel is called recanalization. Early recanalization may lead to reperfusion of ischemic tissue and reversibility of neurological deficits. Whether occurring spontaneously or induced by thrombolytic agents, recanalization represents an important goal of ischemic stroke treatment and is often critical in order to achieve a favorable outcome after cerebral ischemia.

Transient ischemic attack

Definition

Neurological deficits caused by cerebral ischemia may be reversible if recanalization is achieved and blood flow rapidly restored. Neurological deficits caused by ischemia typically include unilateral loss of motility, coordination, sensation or impaired ability to speak. Due to the prompt reversibility of symptoms, this disease is called transient ischemic attack (TIA). TIA may in this way be regarded as the ultimate successful clinical course of cerebral ischemia. Originally, TIA was defined as a "cerebral dysfunction of ischemic nature lasting no longer than 24 hours with a tendency to recur".[1, 2] In 1975, when this definition was formulated, there were no imaging techniques available on a routine basis to confirm the existence of cerebral

ischemia. The definition was therefore based on the assumption that the ischemia had resolved rapidly enough to only cause transient symptoms and no permanent brain injury. The 24-hour duration was chosen without supporting data.[2, 3] The definition of TIA proposed in 1975 is still in use today. We know, however, that the 24-hour time limit does not reflect the normal duration of these events. A study published two years after the original definition showed that the median duration of TIAs was 14 minutes for ischemia within the carotid artery territory and 8 minutes for posterior circulation territory.[4] Another study reported that 86% of those who had ischemic symptoms lasting longer than one hour still had persisting symptoms after 24 hours.[5] In a pooled analysis, 60% of TIAs lasted less than 1 hour, 71% less than 2 hours and 86% less than 6 hours.[6] These data indicate that the majority of TIAs are shorter than one hour in duration. In this context, the 24-hour time limit is misleading and does not reflect the normal duration of these events. With the development of better imaging techniques in stroke diagnostics we also know that a number of patients with an apparent TIA demonstrate ischemic lesions on neuroimaging. Patients may in other words have both TIA and cerebral infarction at the same time. These findings contradict the traditional concept of TIA as being transient and without any sign of infarction. This has led to a proposal of a new tissue-based TIA definition: "a transient episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischemia without acute infarction".[7]

This definition has been welcomed by many. The time limit has been removed and the difference between ischemic stroke and TIA is based on the evidence of infarction. This tissue-based definition is in harmony with the definitions of ischemic injuries to other organs. In ischemic heart disease, angina pectoris is not separated from myocardial infarction based on symptom duration but whether tissue damage is evident or not. Critics have, on the other side, argued that a new tissue-based definition will lead to different incidence rates of TIA and ischemic stroke depending on availability of brain imaging. MR diffusion-weighted imaging (DWI) is in this context especially relevant, considering its ability to detect ischemic damage.

Diffusion-weighted imaging and TIA

DWI is highly sensitive in detecting ischemic cerebral injury and the only imaging technique able to reliably demonstrate lesions within minutes after onset of cerebral ischemia.[8] The technique is based on the ability to detect self-diffusion of water, also known as Brownian motion. These movements are restricted in ischemic brain tissue due to the rapidly developing cytotoxic edema. Different sets of images are obtained in DWI, one or more with diffusion weighting and one without diffusion weighting (T2-sequence).[9] A dephasing and subsequent re-phasing of the spinning protons in water molecules are produced by a bipolar pair of diffusion-sensitizing magnetic field gradient pulses to the T2-sequence. A net displacement of a water molecule between these two pulses results in a signal loss in the image. This means that the signal loss is proportional to water movement. In ischemic tissue, water movement or diffusion is reduced. The lesion with reduced diffusion is identified as an area of signal increase compared to the hypointense normal brain parenchyma.

Patients with transient ischemic symptoms frequently demonstrate DWI lesions, even though neurological deficits are reversible.[10] Studies have shown ischemic lesions in 21-68% of patients with an apparent TIA.[11] Important questions arise with these results. Why do some patients with transient ischemic symptoms have DWI lesions while others have normal DWI findings? And is DWI lesion distribution different in DWI positive patients with transient symptoms as compared to those with persistent symptoms? Prior studies have shown that lesions are typically solitary and smaller in patients with transient symptoms as compared to those with persistent symptoms.[12] However, no studies have shown a specific predilection for DWI lesion location or distribution in patients with transient symptoms.[7] Some studies have compared patients with transient ischemic symptoms with or without DWI lesions, but with few consistent findings.[11] Clinical features, such as longer symptom duration, motor deficits and aphasia have been associated with DWI positivity in patients with an apparent TIA.[13-15] Other studies have also found an association with large artery

disease and cardioembolism, suggesting a higher chance of DWI lesions in patients with these stroke mechanisms.[16, 17]

DWI lesions and irreversible damage

It has been discussed whether DWI lesions really represent irreversible injury in the setting of TIA. If the answer is no, patients with transient symptoms and DWI lesions may still be classified as TIA using a tissue-based definition because both symptoms and DWI lesions are transient. Few studies have investigated reversibility of DWI lesions in patients with an apparent TIA. Three series have been performed, of which one study included 11 patients with transient ischemic symptoms and DWI lesions.[18] Follow-up MRI with T2 weighted imaging was performed within 2-9 days after symptom debut. All 11 patients with DWI lesions had corresponding lesions on follow-up. Another study included 20 patients with an apparent TIA and DWI lesions, of which 6 had MRI two to seven months after the event.[10] A total of 3 patients had corresponding lesions. The largest series included 33 patients with transient ischemic symptoms and DWI lesions who completed follow up MRI after approximately 10 months.[19] A total of 26 patients (79%) had infarctions corresponding to the original DWI abnormalities. The authors concluded that most of the DWI lesions represented irreversible damage and therefore supported a tissue-based TIA diagnosis. Animal studies have also demonstrated underlying histological tissue damage even though early DWI lesions reversed.[20, 21] It may thus be claimed that DWI positive patients with transient symptoms and normal follow-up T2 sequences still could be interpreted within the tissue-definition as ischemic stroke and not as TIA.

The link between TIA and ischemic stroke

TIA and ischemic stroke were previously considered as two entirely different conditions.[7] Health workers and the public often regarded TIA as a benign condition as compared to ischemic stroke, which was something serious. In recent years,

especially with the implementation of DWI into TIA- and stroke diagnostics, the link between TIA and ischemic stroke has proved to be closer than previously thought. These conditions are now by many considered as parts in a spectrum involving a serious state of cerebral ischemia. The majority of TIAs and ischemic strokes are caused by an occlusion where the transient nature of symptoms is the result of early recanalization and reperfusion. In contrast to ischemic stroke, TIA offers an opportunity to prevent permanent disability if the symptoms are taken seriously.

In total, 15-26% of patients with ischemic stroke have a history of TIA.[22] A majority of these patients experienced the TIA within short time before ischemic stroke onset. A total of 17% had TIA on the same day as the stroke, 9% on the day before and 43% at some point during the week before stroke onset. These observations highlight the risk of recurrent ischemic events after TIA. Attempts have been made to quantify the risk of ischemic stroke after TIA based on clinical observations, such as the $ABCD^2$ score.[23] The ABCD system was primarily developed to assist primary care physicians in triaging patients with suspected TIA. In $ABCD^2$, patients with an apparent TIA may score between 0 and 7 points based on the following factors: age ≥60 years (1 point), blood pressure ≥140/90 mm Hg (1 point), duration ≥60 minutes (2 points) or 10-59 minutes (1 point), symptoms with hemiparesis (2 points) or aphasia (1 point) and, finally, presence of diabetes mellitus (1 point). The 2-day risk of stroke range between 0% for the lowest scores (0-1) and 8.1% for the highest (6-7). The presence of DWI lesions in patients with transient symptoms is also strongly associated with an increased short-term risk of further vascular events. [24] This has led to the inclusion of DWI lesions in a new score developed for risk stratification in secondary care: the $ABCD^3$ score. [25]

The precision of these scores may be explained by the lower scores achieved in patients with mimics as compared to the higher scores of those with a true vascular etiology. Mimics represent 31-40% of TIA referrals to secondary healthcare institutions.[26, 27] As the gold standard for TIA remains the judgment of a vascular neurologist, the diagnosis of TIA is often subjective and difficult.[28] In this setting,

DWI proves itself as a useful tool to "catch" patients with a definite vascular etiology. Some of these patients could be interpreted as stroke mimics if DWI is not routinely performed in all patients with apparent TIA.

Ischemic stroke

Definition

The current World Health Organization definition of stroke was introduced in 1970 and is still in use today. It defines stroke as "rapidly developing clinical signs of focal (or global) disturbance of cerebral function, lasting more than 24 hours or leading to death, with no apparent cause other than that of vascular origin". [29] With the proposal of a tissue-based TIA definition, a new definition of ischemic stroke has also emerged as "an episode of neurological dysfunction caused by focal cerebral, spinal, or retinal infarction."[30] Infarction is here defined as cell death based on objective evidence of ischemic injury, such as pathological or imaging evidence, or clinical evidence of ischemic injury based on persisting symptoms ≥24 hours or until death where other etiologies are excluded. This broad definition includes clinical vascular symptoms ≥24 hours in addition to evidence of ischemic injury at any time, regardless of symptom duration. The updated definition is similar to the definition used in the present thesis where ischemic stroke was defined in accordance to the Baltimore-Washington Cooperative Young Stroke Study Criteria as "neurological deficits lasting more than 24 hours because of ischemic lesions or clinical TIA where neuroimaging showed infarction related to the clinical findings".[31]

Burden of ischemic stroke

Unlike TIA, ischemic stroke often leads to permanent neurological deficits and disability. Ischemic stroke has been rated as the third most common cause of death in the world and a major cause of disability requiring long-term institutionalization.[32] Patients with ischemic stroke are at highest risk of death within the first 30 days after symptom onset.[33] Higher age and comorbidities such as ischemic heart disease and

diabetes mellitus increase risk of poor outcome.[34] Outcome is also highly dependent on stroke location and volume. A complete middle cerebral artery infarction often has a worse outcome than an incomplete infarction within the same arterial territory. On the other hand, a strategic small lacunar infarction in the brain stem may have a far worse prognosis than a large supratentorial cortical infarction. Outcome after ischemic stroke is frequently measured by using the modified Rankin Scale (Appendix, figure 1). Favorable outcome is often categorized as mRS 0-1 or 0-2 on discharge or after 3 months, whereas a score of 6 means that the patient died. Mortality rates within 30 days range between 2.5% after lacunar infarction to 78% after malignant middle cerebral artery infarction.[35, 36] Death is most often caused by the stroke itself or cardiopulmonary complications.[37, 38]

In Norway, cerebrovascular disease is the most common cause for disability among elderly and comes after myocardial infarction and cancer as the most frequent cause of death.[39] The annual Norwegian incidence rate for first-ever and recurrent stroke was in 2007 estimated to 11000 and 3500, respectively.[39] This analysis included, however, intracerebral hemorrhage and subarachnoid hemorrhage. Age remains the most important risk factor for ischemic stroke. Approximately 60% of all strokes in Norway occur in patients who are older than 75 years.[40] An increased stroke incidence is expected in the near future due to the increased proportion of elderly in the population.[39] Other common risk factors for ischemic stroke include hypertension, diabetes, cigarette smoking, dyslipidemia, physical inactivity and conditions such as atrial fibrillation, internal carotid stenosis and ischemic heart disease. [41-45] Risk factors may differ according to stroke subtype.[43, 46]

Stroke symptoms and severity

Ischemic stroke is characterized by the sudden onset of focal neurological deficits. The specific type of neurological symptoms depends on the vascular territory affected. Anterior circulation occlusions typically produce contralateral facial and/or extremity weakness and sensory loss. Aphasia or neglect may also be present if the superficial cortex is affected. Symptoms of posterior circulation occlusions include

hemianopsia, ataxia, diplopia, dysarthria and vertigo in addition to unilateral weakness and sensory loss. Consciousness is mostly sustained in anterior circulation infarction, but may be impaired if the posterior circulation is affected, especially the basilar artery.

Stroke symptoms on presentation may be categorized and quantified. The Oxfordshire Community Stroke Project (OCSP) (Appendix, figure 2) classification categorizes stroke symptoms into four different syndromes: lacunar infarcts (LACI), total anterior circulation infarcts (TACI), partial anterior circulation infarcts (PACI) and posterior circulation infarcts (POCI).[47] The classification may prove useful in predicting stroke location and outcome, although etiology is not assessed. [48, 49]
A quantitative assessment of ischemic stroke symptoms is provided by the National Institutes of Health Stroke Scale (NIHSS) (Appendix, figure 3).[50] This scale includes 11 items with different scores where the total score may correlate with lesion volume and clinical outcome.[51] The NIHSS score is widely used in rating stroke severity and monitoring neurological development after ischemic stroke. However, limitations include higher scores for patients with left hemisphere strokes and poor interrater agreement in some of the components, such as grading limb ataxia.[52, 53]

Etiology and pathophysiology

The majority of ischemic strokes are caused by an arterial occlusion. More rarely, ischemic injury may be caused by hypoperfusion due to extra- or intracranial stenosis. This is especially relevant in severe carotid disease where watershed ischemia can be caused due to hemodynamic impairment.[54] New evidence suggests, however, that a significant proportion of these infarcts also may be caused by microembolism.[55]

The Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria is frequently used in describing stroke etiology and encompasses five major categories: large-artery disease, cardioembolism, small vessel disease, stroke of other determined cause and stroke of undetermined cause (Appendix, figure 4).[56] A German study

showed that approximately 15% of ischemic stroke patients had large-artery disease, 30% cardioembolism, 25% small vessel disease, 2% stroke of other determined cause and 40% unknown cause.[57] Large-artery disease is a more common cause in older patients, whereas younger patients have higher rates of other determined etiologies and undetermined etiology. [58]

Regardless of stroke etiology, ischemic brain injury is a common denominator. This is the result of blood perfusion below a critical threshold, which leads to energy depletion and eventually infarction. The acute arterial occlusion leads to an infarct core and a surrounding zone of ischemic penumbra. The central core consists of irreversibly damaged cells whereas the penumbral zone is supplied by sufficient blood to maintain structural integrity, even though the neurons remain dysfunctional.[59] The neurological deficits caused by the penumbra may be reversible if reperfusion can be achieved within a short time. If reperfusion fails, the penumbral zone will turn into infarct as well. The timing of infarction of the penumbral zone is dependent on residual blood flow, duration of ischemia and physiological factors, such as body temperature and serum glucose.[34] This time-window also represents the therapeutic window of opportunity in acute ischemic stroke in which recanalization can have a major clinical impact by saving neurons from irreversible destruction.

Recanalization

Recanalization hypothesis

Recanalization is the major therapeutic aim in patients admitted with acute cerebral ischemia. Rapid recanalization leading to reperfusion of threatened ischemic tissue improves clinical outcome as compared to no or too late recanalization.[60] This statement is called the “recanalization hypothesis”. The correlation between recanalization and clinical outcome was confirmed in a meta-analysis from 2007 including 53 studies and 2066 patients. [60]There was a four-fold increase in the odds of favorable outcome and a four-fold reduction in odds of death within 3 months if recanalization was achieved within 24 hours after stroke onset. The earlier

recanalization occurred, the higher were the chances for favorable outcome. Studies using Doppler monitoring have shown an association between early recanalization and dramatic neurological improvement.[61-63] Early improvement by ≥10 NIHSS points at 24 hours after symptom onset was associated with either complete or partial recanalization, whereas no clinical improvement or worsening indicated failed recanalization.[62] This major neurological improvement (MNI) may be considered as a useful surrogate marker for thrombolytic activity and successful recanalization.[64] Although the correlation between recanalization and favorable outcome has been established, recanalization is no guarantee for reperfusion and neurological improvement. This phenomenon of "futile recanalization" may occur if recanalization is achieved too late, i.e. if there is no penumbra left to salvage.[60] Recanalization of larger vessels may also result in inadequate reperfusion due to distal smaller occlusions originating from multiple embolic fragments of the dissolved primary occlusion. In addition, collateral circulation can weaken the recanalization-outcome correlation as neurological deficits may be minor if collateral vessels sufficiently supply threatened tissue in the presence of a larger occlusion.[65]

Recanalization and thrombolysis

Early recanalization is the incitement for thrombolytic therapy. Intravenous thrombolytic treatment with tissue plasminogen activator (tPA) was approved by the US Food and Drug Administration (FDA) in 1996 and is today routinely used as recanalizing treatment for ischemic stroke. TPA or Alteplase is a serine-protease, which converts plasminogen into plasmin.[66] Plasmin degrades fibrin and is thereby essential to the lysis of occluding thrombi, which mostly are made of fibrin in combination with platelets and erythrocytes. The relative proportions of thrombus components are thought to be based on clot origin. "Red" erythrocyte-and fibrin-rich clots are formed in areas with stagnant blood flow whereas "white" platelet-rich clots originate from areas of high flow, such as the arterial system.[67] Endogenous tPA is released from endothelial cells and contributes to the physiological balance between

thrombosis and thrombolysis. In the setting of an occluding thrombus, thrombolysis commences predominantly within the thrombus or at its surface.[68] Exogenously applied tPA is dependent on a certain amount of blood flow to reach the thrombus surface.[61] The following thrombolysis is a process where the clot is dissolved step-by-step. The first steps of clot dissolution allow blood perfusion further into the thrombus, which expose more binding sites for tPA and plasmin. This process may continue until complete clot break-up and recanalization is achieved under the pressure of arterial pulsations.

Thrombolysis with tPA

The National Institute of Neurological Disorders and Stroke (NINDS) study group demonstrated in 1995 efficacy of ischemic stroke treatment with tPA within 3 hours after symptom onset.[69] Patients receiving tPA had at least 30% better chance of favorable outcome at 3 months as compared to the placebo-group. Symptomatic intracerebral hemorrhage (sICH) occurred in 6.4% of patients treated with tPA. Efficacy of tPA administered in an extended time window of up to 6 hours was not shown in two following European trials: the European Cooperative Acute Stroke Study (ECASS) and ECASS II.[70, 71] However, a subsequent meta-analysis including >2500 stroke patients reported an odds ratio of 1.4 for favorable outcome if tPA was administered between 3 hours and 4.5 hours.[72] As a result, the ECASS III was designed to prospectively test efficacy and safety of tPA administered between 3 to 4.5 hours after stroke onset.[73] This study confirmed an improved outcome of patients treated with tPA as compared to placebo with a odds ratio of 1.3. A total of 2.4% had sICH. The difference in proportion of sICH between the NINDS trial and ECASS III may rely on the different definitions of sICH applied in each of these trials (table 1).

Table 1: Common symptomatic intracerebral hemorrhage definitions

Trial	*Definition*	*Ref*
NINDS	Any hemorrhage plus any decline in neurologic status	[69]
ECASS II	Blood at any site in the brain on CT, clinical deterioration or adverse events indicating clinical worsening or causing an increase in the NIHSS score of 4 points or more	[71]
ECASS III	Any apparently extravascular blood in the brain or within the cranium associated with clinical deterioration (defined by an increase in the NIHSS score of 4 or more points) or death, and that is identified as the predominant cause of the neurological deterioration	[73]
SITS-MOST	Local or remote parenchymal hemorrhage type 2* on the 22-36 hours post-treatment imaging scan, combined with a neurological deterioration of 4 points or more on the NIHSS from baseline or from the lowest NIHSS value between baseline and 24 h, or leading to death.	[74]

**Hemorrhagic infarction 1 (HI1) is defined as small petechiae along the margins of the infarct; hemorrhagic infarction 2 (HI2) as confluent petechiae within the infarcted area but no space-occupying effect; parenchymal hemorrhage (PH1) as blood clots in 30% or less of the infarcted area with some slight space-occupying effect; and parenchymal hemorrhage (PH2) as blood clots in more than 30% of the infarcted area with substantial space-occupying effect.*[71]

Outcomes of thrombolytic treatment may differ in clinical practice as compared to the setting of randomized trials. The multinational Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST) evaluated safety and efficacy in stroke patients treated with tPA in clinical routine settings within 3 hours after stroke onset.[74] The results confirmed the positive findings of previous randomized trials with similar rates of sICH and mortality. However, patients who did not meet the conservative pre-specified eligibility criteria were systematically excluded from the analysis.[75] This proportion of "off-label" tPA treated patients was not reported. It may thus be claimed that the results of SITS-MOST represent a too idealized clinical situation as compared to the reality in daily clinical practice.

Off-label thrombolysis

Although studies have demonstrated safety and efficacy of ischemic stroke treatment with tPA, the total numbers of treated patients in clinical practice have been low.[76] Different factors may explain this. A number of stroke patients are admitted to the hospital too late to reach the therapeutic time window, although one study showed that 50% of ischemic stroke patients may reach a hospital within the 3 hours[77] Treatment with tPA is approved within 3 hours after stroke onset according to Norwegian national guidelines (figure 1), although the current time-window has been extended to 4.5 hour in clinical practice, based on the ECASS III results.[78] If patients manage to arrive within this timeframe, several other contraindications remain which restrict the use of tPA. The narrow timeframe in combination with other contraindications make treatment with tPA only available for a fraction of the total number of acute ischemic stroke patients admitted. A study showed that approximately 75% of the total number of patients was excluded from thrombolytic treatment due to contraindications.[79] These contraindications originate from the study protocols of prior thrombolytic trials and were designed to include only patients with high likelihood of recovery after treatment.[80] Hence, most of the contraindications are expert opinions and not evidence-based. Earlier studies have shown increased rates of sICH in presence of frequent protocol violations, suggesting strict adherence to the guidelines in order to achieve best possible outcomes.[81] Other studies have, on the other hand, shown that administration of tPA may be safe in the presence of certain contraindications. Hence, off-label thrombolysis has turned into a controversial topic.

Figure 1: Norwegian contraindications to ischemic stroke treatment with tPA per September 2014.

Kontraindikasjoner:
Overfølsomhet overfor virkestoffet alteplase eller overfor et eller flere av hjelpestoffene.
Når det foreligger høy risiko for blødning, som ved:

- Signifikant blødningstilstand, enten pågående eller i løpet av de siste 6 md.
- Kjent hemoragisk diatese (blødningstendens).
- Pågående peroral antikoagulantiabehandling, for eksempel warfarin.
- Manifest eller nylig gjennomgått alvorlig eller farlig blødning.
- Tidligere kjent eller mistenkt intrakraniell blødning.
- Mistenkt subaraknoidalblødning eller tilstander etter subaraknoidalblødning forårsaket av aneurisme.
- Gjennomgått skade i sentralnervesystemet (for eksempel tumor, aneurisme, intrakraniell eller intraspinal operasjon).
- Nylig gjennomgått (siste 10 dager) ekstern hjertemassasje, fødsel eller punksjon av et ikke komprimerbart kar (for eksempel v. subclavia eller jugularis).
- Alvorlig, ukontrollerbar arteriell hypertensjon.
- Bakteriell endokarditt, perikarditt.
- Akutt pankreatitt.
- Dokumentert ulcererende sykdom i mave-tarmkanalen siste 3 md., øsofagusvariser, arteriell aneurisme, arteriell/venøs karmisdannelse.
- Neoplasme med økt blødningsrisiko.
- Alvorlig leversykdom, inklusive leversvikt, cirrhose, portal hypertensjon (øsofagusvariser) og aktiv hepatitt.
- Tørre kirurgiske inngrep eller alvorlig traume de siste 3 md.

I tillegg følgende kontraindikasjoner:
- Symptomer på iskemisk anfall begynt mer enn 3 t før infusjonens start eller tidspunkt for symptomdebut er ukjent.
- Mindre nevrologiske forstyrrelser eller symptomer som raskt bedres før infusjonens start.
- Alvorlig hjerneinfarkt bedømt klinisk (for eksempel NIHSS >25) og/eller ved passende bildeteknikk.
- Kramper ved hjerneinfarktets start.
- Tegn på intrakraniell blødning vist ved CT-bilde.
- Symptomer på mistenkt subaraknoidalblødning, selv ved normalt CT-bilde.
- Tilførsel av heparin i løpet av de foregående 48 t og en tromboplastintid som overstiger øvre normalverdi.
- Gjennomgått hjerneinfarkt og samtidig diabetes.
- Gjennomgått hjerneinfarkt de siste 3 md.
- Trombocyttall under 100 000/mm³.
- Systolisk BT >185 eller diastolisk BT >110 mmHg, eller aggressiv behandling (i.v. farmakoterapi) for å redusere BT til disse grensene.
- Glukosenivå <2,8 mmol/l eller >22,2 mmol/l

Videre når det gjelder behandling av barn, ungdom og eldre, gjelder følgende:
Actilyse er ikke beregnet til behandling av akutt hjerneinfarkt hos barn under 18 år eller eldre over 80 år.

Thrombolysis and sICH

SICH is the most feared complication of intravenous thrombolysis with tPA. Administration of tPA systematically alters hemostasis due to depletion of circulating fibrinogen, inactivation of coagulation factor V and VIII and impaired platelet function.[68] This impairment, in combination with ischemic injury to the blood-brain barrier, can lead to cerebral hemorrhage and neurological deterioration. Prior thrombolytic trials have defined sICH differently, especially concerning grades of neurological deterioration (table 1). Depending on which definition applied, rates of sICH range from 1.7% (SITS-MOST) to 6.4% (NINDS) in thrombolysed stroke patients.[69, 74] SICH following thrombolytic therapy is in general associated with poor outcome and high mortality rates. [82, 83] Clinical predictors for sICH include advanced age, increased blood pressure and serum glucose on admission, prior history of hypertension, high stroke severity, prolonged time from symptom onset to treatment and pre-stroke treatment with aspirin.[84, 85]

Augmenting thrombolysis – body temperature

Early recanalization has a substantial impact on outcome due to the salvage of penumbral tissue. Intravenous thrombolysis with tPA recanalizes approximately twice as many clots as spontaneous recanalization, yet less than half of all clots.[60] Up to 2/3 of patients with large artery occlusions may not achieve recanalization and a substantial proportion of thrombolysed stroke patients therefore remain disabled or dead.[86, 87] Endovascular intervention with intra-arterial thrombolysis or mechanical thrombectomy achieves higher recanalization rates, but not necessarily improved outcomes as compared to intravenous tPA alone.[88-90] As intravenous thrombolysis continues as first-line treatment for acute ischemic stroke, factors promoting recanalization and improved outcomes in tPA treated stroke patients are of great importance.[91]

Body temperature may represent one of these factors. Low body temperature or hypothermia is generally considered a potent neuroprotectant and may decrease

cerebral damage during ischemia.[92] Animal studies have shown increased numbers of surviving neurons after ischemia at lower temperatures and increased stroke volumes at higher temperatures.[93-95] Hypothermia has proved effective reducing neurological deficits after cardiac arrest in clinical trials.[96] The exact mechanisms of hypothermic neuroprotection is unknown, although the lower temperatures seem to mitigate neuronal damage at different levels in the ischemic cascade: prevention of blood-brain-barrier disruption and subsequent edema formation, reduced excitotoxic neurotransmitter release, lower metabolic rate and prevention of free radical production after reperfusion.[93, 97, 98]

Concordantly, higher body temperatures may result in unfavorable outcome after ischemic stroke, possibly due to increased metabolic demands and increased free radical production.[99] Body temperature is frequently increased in stroke patients and this increase may in some cases be caused by infection. Studies have shown an association between increased body temperatures within 24 hours after stroke onset and poor prognosis.[100-103] Most of these studies used temperature measurements up to 6 hours after stroke onset. Normalization of body temperature after ischemic stroke is therefore recommended, although there is no direct evidence to support this sort of treatment. A review of prior randomized trials could not find evidence to support the use of pharmacological or physical strategies to reduce temperatures in stroke patients.[92] A placebo-controlled trial reported no overall effect of paracetamol on outcome after ischemic stroke, although a post-hoc analysis showed an association between paracetamol administration and favorable outcome in patients with temperatures >37.0 ºC.[104]

Body temperature may play a different role in association with thrombolytic treatment. In vitro studies have demonstrated decreased lytic efficacy of tPA at lower temperatures.[105, 106] A study investigating the effect of hypothermia on clot lysis by tPA in human clot models showed no thrombolytic effect of tPA at 30º C as compared to controls without any thrombolytic agent.[105] Mean fractional clot loss was lower at 30-36 ºC than at 37 ºC in the models exposed to tPA. In support of these

findings, another in vitro study showed decreased clot lysis at lower temperatures when tPA was added to clot suspensions. [106] Other studies have indicated a beneficial effect of higher temperatures on thrombolysis.[107-109] Although not used anymore, fibrinolysis by streptokinase was increased at higher temperatures.[107] Heated tPA resulted in faster clot lysis in patients with acute lower limb ischemia receiving catheter-directed thrombolytic treatment.[108] A prior study from the Bergen NORSTROKE Registry demonstrated a beneficial effect of high body temperatures on admission in stroke patients treated with tPA, whereas lower temperature was associated with favorable outcome in acute stroke patients not treated with tPA.[109] The authors suggested that the clinical benefit of high body temperature on clot lysis outweighed the potential neuroprotective effect of lower body temperatures in the first hours of tPA treated stroke. This suggestion was, however, partially disproved in another analysis including >2000 tPA treated stroke patients from prior neuroprotection trials.[110] Outcomes were improved across temperatures from 35.5º C – 37.5 ºC, but lost significance at temperatures <35.5 ºC and >37.5 ºC. However, point estimates suggested an increasing beneficial effect in temperatures rising from 36.0 ºC to 37.5 ºC. In lack of new evidence, a beneficial effect of higher body temperatures on tPA treated stroke patients remains uncertain.

Other factors influencing thrombolysis

Other factors may also influence the rate of clot lysis and recanalization with tPA. Recanalization after 24 hours occurs spontaneously in approximately one quarter of all patients whereas the rate increases to ≈ 46% if treated with intravenous thrombolysis.[60] Recanalization with tPA seems to depend on vessel site and clot burden with lower recanalization rates in larger arteries.[111] Doppler controlled studies have shown a recanalization rate of 44%, 29% and 10% at 2 hours in tPA treated patients with distal middle cerebral artery occlusion, proximal middle cerebral artery occlusion and internal carotid artery occlusion, respectively.[111] This is likely explained by the increased clot volume in the more proximal sites, making it difficult for the administered tPA to penetrate the clot and achieve recanalization. Clot

etiology also has an impact on recanalization rates with tPA. Cardioembolic clots are more likely to be recanalized with intravenous thrombolysis as compared to clots of similar size originated elsewhere.[67] This may be explained by the high amount of fibrin in cardioembolic clots, which make these clots more suitable for fibrinolytic treatment.

Clot composition and the effect of tPA on clot lysis may also be influenced by external factors, such as cigarette smoking. Smoking is a well-known risk factor for cardiovascular events, such as myocardial infarction or ischemic stroke. This has partially been attributed to increased platelet activation and higher fibrin concentrations in smokers, causing the blood to become hypercoagulable.[112, 113] Smokers are therefore at higher risk of clot formation causing ischemic stroke. When stroke occurs, the clot may be thrombolysed faster with tPA due to the increased proportion of clot fibrin. This could lead to more rapid recanalization and better outcomes. In support of this theory, studies have shown improved myocardial perfusion and lower mortality rates in smoking patients with myocardial infarction treated with thrombolysis.[114, 115] This smoking-thrombolysis paradox has also been reported in stroke patients treated with tPA where smoking resulted in improved rates of recanalization and better prognosis.[116, 117] Other stroke studies have, however, failed to find these associations and attributed the beneficial effect of smoking to the low clinical risk profiles of these patients.[118-120]

List of publications

The thesis is based on the following papers:

I. Kvistad CE, Thomassen L, Waje-Andreassen U, Moen G, Logallo N, Naess H.
Clinical implications of increased use of MRI in TIA.
Acta Neurol Scand. 2013 Jul;128(1): 32-8.

II. Kvistad CE, Logallo N, Thomassen L, Moen G, Waje-Andreassen U, Naess H.
Diffusion-weighted lesions in stroke patients with transient symptoms – Where are they located?
Cerebrovasc Dis. 2014;38: 219-225

III. Kvistad CE, Logallo N, Thomassen L, Waje-Andreassen U, Brøgger J, Naess H.
Safety of off-label stroke treatment with tissue plasminogen activator.
Acta Neurol Scand. 2013 Jul;128(1): 48-53.

IV. Kvistad CE, Thomassen L, Waje-Andreassen U, Logallo N, Naess H.
Body temperature and major neurological improvement in tPA-treated stroke patients.
Acta Neurol Scand. 2014 May;129(5): 325-9

V. Kvistad CE, Oeygarden H, Logallo N, Thomassen L, Waje-Andreassen U, Naess H.
Is smoking associated with favourable outcome in tPA-treated stroke patients?
Acta Neurol Scand. 2014 Nov;130(5): 299-304

Aims of the thesis

1. To assess whether an increased use of DWI leads to a decreased proportion of tissue-based TIA diagnosis, the frequency of DWI lesions in patients with transient ischemic symptoms <24 hours and clinical characteristics in these patients as compared to those without DWI lesions. We hypothesized that an increased use of DWI would lead to a decreased proportion of TIA, a high proportion of DWI lesions in patients with transient ischemic symptoms <24 hours and that patients with DWI lesions would differ from those without DWI lesions regarding extent of performed diagnostic investigations and clinical characteristics. This hypothesis is discussed in paper I.

2. To assess whether location of DWI lesions in stroke patients with transient symptoms <24 hours differs from the location in those with persistent symptoms. We hypothesized a higher proportion of cortical DWI lesions in patients with transient symptoms. This hypothesis is discussed in paper II.

3. To assess frequency, safety and outcome of off-label stroke treatment with tPA. We hypothesized a high frequency of off-label treatment and no independent association between off-label treatment and rates of sICH or unfavorable outcome. This hypothesis is discussed in paper III.

4. To assess the relationship between body temperature and major neurological improvement in patients with cerebral ischemia treated with tPA. We hypothesized an independent association between higher body temperature and major neurological improvement. This hypothesis is discussed in paper IV.

5. To assess the relationship between smoking and outcome in acute ischemic stroke treated and not treated with tPA. We hypothesized an association between smoking and favorable outcome in stroke patients treated with tPA and no such association in acute stroke patients not treated with tPA. This hypothesis is discussed in paper V.

Material and methods

The Bergen NORSTROKE Study

Data for all papers were obtained from the Bergen NORSTROKE Study. The Bergen NORSTROKE Study prospectively registers patients admitted to the Department of Neurology, Haukeland University Hospital with ischemic stroke, TIA or ICH. The stroke centre at Haukeland University Hospital has a catchment area of approximately 150.000 inhabitants. In addition, patients with stroke aged <60 years from a neighbouring area (approximately 120.000 inhabitants) are admitted. The Bergen NORSTROKE Study started inclusion of patients in February 2006 and is still ongoing. Patient demography, prior medical history, clinical data, short-term outcomes and results from examinations, including radiological, cardiological and neurosonological findings are registered. Informed consent is obtained from the patient or legal representative before inclusion. The study has been approved by the regional ethics committee.

General management

Patients may be admitted directly to the hospital without prior medical examination if symptoms include persistent or transient acute neurological deficits. If symptoms started within 6 hours, patients are brought in by an emergency ambulance. Patients are clinically examined in the emergency department by a junior neurologist. The examination includes scoring with NIHSS and registration of physiological parameters, such as blood pressure and body temperature. From 2006 to 2009, body temperature was measured by an infrared tympanic device (LightTouch-LTX; Exergen Corp, Watertown, MA, USA). Since 2009, body temperature has been measured by using a temporal artery thermometer (Exergen Temporal Scanner; Exergen Corp). Blood samples, including haemoglobin, leucocytes, glucose, CRP, d-dimer and fibrinogen are obtained on admission.

After clinical examination, patients routinely undergo non-contrast CT. This is performed as quickly as possible if patients are candidates for recanalizing treatment. These patients are also routinely examined with CTA. Thrombolytic treatment is initiated in the CT lab and continued as the patient is transported to the stroke unit. Since 2008, patients with major occlusions have been offered treatment with endovascular intervention in addition to intravenous thrombolysis.

After arrival at the stroke unit, patients are monitored with frequent observations of physiological parameters and NIHSS scoring by a stroke nurse. Patients are regularly examined by a neurologist the next day after admission. Unless any contraindications are present, MRI and MRA are routinely performed on the day after admission in patients with suspected ischemic stroke or TIA. MRI capacity was, however, limited during the first years of the NORSTROKE Study. Not all patients with suspected TIA were therefore examined with DWI during this time period. DWI is performed as part of a routine MRI protocol for stroke patients on 1.5 Tesla Siemens Magnetom (Symphony, Erlangen, Germany). The DWI sequence is ep2d_diff:3scan_trace, with the following specification of parameters: field of view (FOV) 230 mm, slice thickness 5 mm, TR 3200 ms, TE 94 ms. Additional sequences were t2_flair_tra and ep2e_diff_3scan_trace_ADC. Duplex ultrasound examination of the extracranial arteries is regularly performed within the day after admission. If clinical history and findings indicate cardioembolic etiology, patients undergo echocardiography and 24-hour-Holter monitoring. Patients are mobilized early and referred to a multi-professional rehabilitation team as appropriate.

NORSTROKE Study registration

Data for the NORSTROKE Study is routinely registered on the day after admission by a stroke neurologist based on a predefined questionnaire. Patients with stroke mimics are not included in the NORSTROKE Study. Patient's age, sex and time of symptom onset are registered in addition to pre-morbid dependency and prior medical diseases. Pre-morbid dependency is based on premorbid residency and need for assistance. Prior medical diseases include: hypertension, considered present if

diagnosed by a physician before stroke onset; diabetes mellitus, present if glucose lowering diet or medication has been initiated before admission; atrial fibrillation, present if confirmed by ECG at any time prior to admission or during hospital stay. Registration of prior myocardial infarction, stroke or TIA is based on information from the patient, partner or relatives of the patient or medical journal. Smoking habits are separated into the following categories: current smoking, previous smoking and no smoking. Current smoking is defined as smoking at least one cigarette per day. Previous smoking requires cease of smoking at least one year before stroke onset. No smoking is considered present if the patient has never smoked. Premorbid medication is also registered in the NORSTROKE Study.

Clinical data on admission is registered and includes NIHSS score, blood pressure, pulse frequency and body temperature. Blood samples on admission, including haemoglobin, leucocytes, glucose, CRP, d-dimer and fibrinogen are registered. Based on type of neurological deficits on admission, patients are categorized into different stroke syndromes based on the OCSP classification. Stroke etiology is classified by the TOAST classification. This is based on clinical examination, neuroimaging results including ultrasound of extracranial arteries and cardiac examination. Registration of OCSP and TOAST has been performed by the same stroke neurologist during the entire study period (Halvor Næss).

Use and results of diagnostic work-up during the hospital stay, including CT and MRI are registered. If present, DWI lesions are classified into different groups depending on location; Cortical, lesions confined to the supratentorial cortex; mixed cortical-subcortical, lesions located both in the supratentorial cortex and subcortex; large subcortical, lesions located in the basal ganglia, internal capsule or corona radiate with a diameter ≥15 mm; lacunar, lesions located in the basal ganglia, internal capsule or corona radiate with a diameter <15 mm; cerebellar, lesions confined to the cerebellum; brain stem, lesions confined to the brain stem; multiple locations, lesions in more than one of the above defined areas (table 2). SICH on CT or MRI is defined as any intracerebral hemorrhage with any decline in neurological status. All MRI and

CT scans were reviewed and classified by the same stroke neurologist during the entire study period (Halvor Næss).

Table 2: Location of DWI lesions in the NORSTROKE Study

Variable name	*Corresponding areas of DWI lesion(s)*
Cortical	Supratentorial cortex
Mixed cortical-subcortical	Supratentorial cortex and subcortex
Large subcortical	Basal ganglia, internal capsule or corona radiate ≥15 mm
Lacunar	Basal ganglia, internal capsule or corona radiate <15 mm
Cerebellar	Cerebellum
Brain stem	Brain stem
Multiple	More than one of the above defined areas

NIHSS scores performed by stroke nurses or neurologists are registered along with the respective time points of the examinations during the hospital stay. NIHSS scores after 24 hours and 7 days (or at discharge, if discharged earlier) are used to assess clinical development in paper IV and III, respectively. In paper IV, major neurological improvement is defined as ≥8 point improvement in NIHSS score at 24 hours as compared to NIHSS score on admission. In paper III, NIHSS scores at day 7 or at discharge is compared to the NIHSS score on admission. Clinical improvement is here defined as an improvement of 4 points or more or NIHSS=0 at discharge. Clinical worsening is defined as a worsening of 4 points or more. Patients are considered clinical stable if they experience neither improvement nor worsening. All patients are scored with mRS on day 7 or at discharge, if discharged earlier. Mortality rates 30 days after discharge are extracted from the Norwegian Death Registry.

Statistics

Student`s *t*-test, Wilcoxon rank-sum test and Analysis of variance (ANOVA) are used

as appropriate for continuous variables. Fischer`s exact test and chi-square test are used for categorical variables. Logistic regression analyses are performed as appropriate by using stepwise backward elimination. Analyses are performed with the software “STATA/SE 11.0 for Windows” (Stata Corp, College station, TX, USA).

Summary of papers

Paper I: Clinical implications of increased use of MRI in TIA. Kvistad CE, Thomassen L, Waje-Andreassen U, Moen G, Logallo N, Naess H. *Acta Neurol Scand 2013 Jul;128(1): 32-8.*

Background: DWI is highly sensitive in detecting ischemic brain injury. With a new tissue-based TIA definition, we investigated whether an increased use of DWI resulted in a decrease in TIA diagnosis as compared to ischemic stroke. We also aimed to assess proportion and clinical characteristics of DWI positive patients with transient ischemic symptoms <24 hours as compared to DWI negative TIA patients.

Methods: Patients admitted with ischemic stroke or TIA were prospectively registered from 2006 to 2011 and the use of DWI annually recorded. Clinical characteristics, diagnostic work-up and etiology were registered in DWI positive patients with transient ischemic symptoms <24 hours and compared to those without DWI lesions.

Results: Use of DWI increased from 65% in 2006-2008 to 89% in 2009-2011 ($p<0.001$) and the proportion of TIA decreased from 12.2% to 8.3% ($p=0.002$). A total of 236 patients were included with transient ischemic symptoms, of which 113 patients (47.9%) had DWI lesions. Use of echocardiography ($p<0.001$) and 24-h Holter monitoring ($p<0.001$) was more frequent in DWI positive patients as compared to DWI negative patients. Lower age ($p<0.001$) and prior myocardial infarction ($p=0.029$) were independently associated with DWI lesions in patients with transient ischemic symptoms. There was a non-significant trend of prior paroxysmal atrial fibrillation being associated with DWI lesions ($p=0.089$).

Conclusion: An increased use of DWI resulted in a decrease in proportion of TIA. Although patients with transient ischemic symptoms and DWI lesions had a more extensive cardiac work-up, our results indicate an association between presence of DWI lesions and cardioembolic stroke mechanism.

Paper II: Diffusion-weighted lesions in stroke patients with transient symptoms – where are they located? Kvistad CE, Logallo N, Moen G, Thomassen L, Waje-Andreassen U, Naess H. *Cerebrovasc Dis. 2014;38: 219-225.*

Background: A number of patients with transient ischemic symptoms <24 hours have DWI lesions and are diagnosed as ischemic stroke and not TIA with the new tissue-based TIA definition. These patients experience complete neurological recovery within 24 hours, which may suggest successful vessel recanalization. We sought to see whether DWI location differed in stroke patients with transient symptoms hours as compared to those with persistent symptoms and hypothesized a higher proportion of cortical DWI lesions in patients with transient symptoms due to a possibly increased rate of recanalization in this group.

Methods: Patients admitted between 2006 and 2013 with acute ischemic stroke examined with DWI were included and classified according to DWI location into cortical, mixed cortical-subcortical, large subcortical, lacunar, cerebellar, brain stem or multiple locations in more than one of the above defined areas. Location of DWI lesions in patients with transient symptoms was compared to DWI location in stroke patients with persistent symptoms.

Results: A total of 972 patients with acute ischemic stroke were included, of which 142 (14.6%) patients had transient symptoms <24 hours. A larger proportion of patients with transient symptoms had cortical DWI lesions, whereas mixed cortical-subcortical location and lesions with multiple locations were more frequent in patients with persistent symptoms. Cortical DWI location was independently associated with transient symptoms when adjusted for confounders (OR 1.89, p=0.001).

Conclusions: Patients with transient symptoms <24 hours had more frequently cortical DWI lesions. This may be explained by a high rate of successful recanalization, resulting in upstream displacement of particles after recanalization and subsequent distal cortical DWI lesions.

Paper III: Safety of off-label stroke treatment with tissue plasminogen activator. Kvistad CE, Logallo N, Thomassen L, Waje-Andreassen U, Brøgger J, Naess H. *Acta Neurol Scand. 2013 Jul;128(1): 48-53.*

Background: Recanalizing treatment with tPA is limited to a small group of stroke patients due to a number of contraindications. Most of these contraindications are based only on expert opinion. We aimed to assess frequency, safety and outcome in patients treated off-label with tPA. We hypothesized a high proportion of patients being treated off-label with tPA and no independent association between off-label tPA treatment and sICH or unfavorable outcome.

Methods: Patients with ischemic stroke treated with tPA during 2006-2011 were prospectively registered. Rates of sICH, clinical improvement, short-term outcome and 30-day mortality were assessed in patients with contraindications to tPA and compared to the rates in thrombolysed patients without any contraindications or patients who had compatible contraindications and did not receive tPA.

Results: A total of 135 patients (50.9%) were treated off-label with tPA and 130 patients (49.1%) were treated without any contraindications. There were 134 patients with contraindications not treated with tPA. Rates of sICH and clinical improvement were similar in patients treated with tPA with or without contraindications, whereas short-term outcome was worse and mortality rates higher in tPA-treated patients with contraindications as compared to those without. Off-label treatment with tPA was not associated with unfavorable outcome or death when adjusted for age, sex and stroke severity on admission. A larger proportion of patients with contraindications treated with tPA experienced clinical improvement as compared to those with contraindications not treated with tPA, although outcome and mortality rates were similar.

Conclusions: Presence of contraindications to tPA did not independently predict unfavorable outcome or death. Off-label thrombolytic treatment may be safe and efficient in acute ischemic stroke.

Paper IV: Body temperature and major neurological improvement in tPA-treated stroke patients. Kvistad CE, Thomassen L, Waje-Andreassen U, Logallo N, Naess H. *Acta Neurol Scand. 2014 May;129(5): 325-9.*

Background: In thrombolytic stroke treatment a major goal is recanalization, of which major neurological improvement within 24 hours (MNI) represents a useful surrogate marker. Studies have suggested an increased thrombolytic effect of tPA at higher temperatures. We hypothesized an independent association between MNI and higher admission body temperatures in patients with acute cerebral ischemia treated with tPA.

Methods: Admission body temperatures of patients with cerebral ischemia treated with tPA between 2006 to 2012 were registered. MNI was defined as ≥8 point improvement in NIHSS score at 24 hours as compared to NIHSS score on admission. No significant improvement (no-MNI) was defined by either a worsening in NIHSS score or an improvement of ≤2 points at 24 hours in patients with an admission NIHSS score of ≥8 points. Patients with MNI and no-MNI treated with tPA were included.

Results: A total of 347 patients were treated with tPA, of which 32 patients (9.2%) had MNI and 56 (16.1%) no-MNI. Mean admission body temperature was higher in patients with MNI as compared to those with no-MNI (36.7 ºC vs. 36.3 ºC, p=0.004). Higher body temperature was independently associated with MNI when adjusted for confounders (OR 5.16, p=0.003).

Conclusions: Higher body temperature was independently associated with MNI in patients with acute cerebral ischemia treated with tPA. This may suggest a beneficial effect of higher body temperature on clot lysis and recanalization.

Paper V: Is smoking associated with favorable outcome in tPA-treated stroke patients? Kvistad CE, Oeygarden H, Logallo L, Waje-Andreassen U, Naess H. *Acta Neurol Scand. 2014 Nov;130(5): 299-304.*

Background: Smoking may lead to improved outcomes after thrombolytic treatment for myocardial infarction. Some studies have shown higher recanalization rates in smoking stroke patients as compared to non-smokers, although other studies have shown different results. We hypothesized an association between smoking and favorable short-term outcome in stroke patients treated with tPA and no such association in acute stroke patients not treated with tPA, suggesting a beneficial effect of smoking on thrombolysis with tPA.

Methods: Smoking habits in acute stroke patients admitted between 2006 and 2013 were registered and categorized into three different groups: current smoking, previous smoking and no smoking. Associations between smoking habits and short-term outcomes were assessed in stroke patients treated with tPA and stroke patients admitted within 6 hours after stroke onset and not treated with tPA.

Results: A total of 399 patients were treated with tPA, of which 94 were current smokers, 148 previous smokers and 157 non-smokers, whereas 424 patients were not treated with tPA, of which 90 were current smokers, 164 previous smokers and 170 non-smokers. There was an independent association between current smoking and favorable outcome in patients treated with tPA (OR 2.08, p=0.025), but not in patients not treated with tPA (OR 1.26, p=0.472).

Conclusion: Current smoking was independently associated with favorable outcome in tPA treated stroke patients, but not in acute stroke patients not treated with tPA. These findings are in support of a more effective thrombolysis with tPA in smokers.

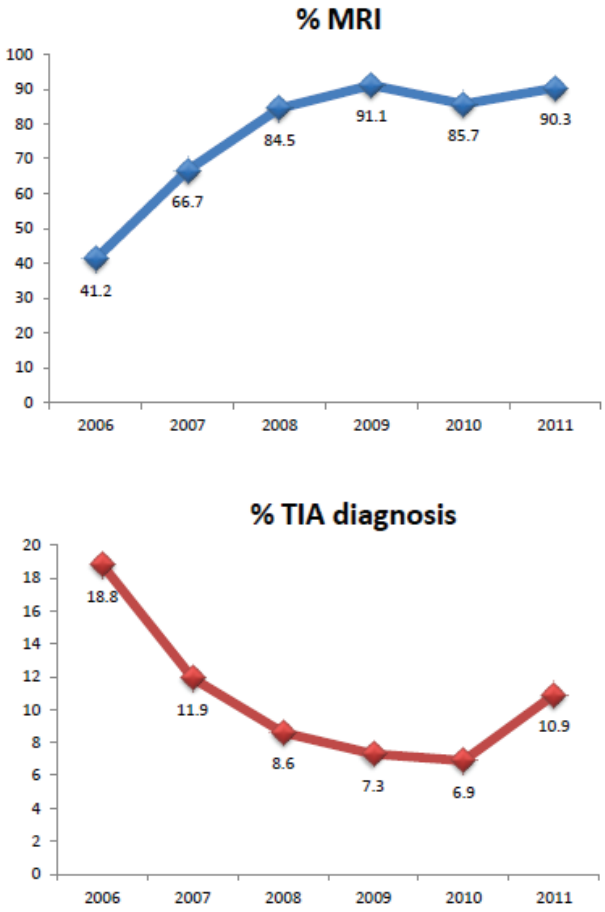
Discussion

TIA – The issue is tissue

With a tissue-based TIA definition, rates of TIA and ischemic stroke will depend on brain imaging availability and utility, especially on DWI considering its high sensitivity to ischemic injury. Our study confirms the strong relationship between use of DWI in patients with possible transient ischemic attack and rates of TIA using a tissue-based definition (figure 2) (paper I). This relationship occurs because a considerable number of patients with an apparent TIA have ischemic lesions on DWI. With a tissue-based TIA definition, these patients are characterized as ischemic stroke and not as TIA. In our population, approximately half of the patients with transient symptoms examined with DWI had ischemic lesions. This number is similar to that found in previous studies, although a recent meta-analysis pointed at a considerable variability of this proportion across different studies.[10, 11, 121, 122]

There is more than one explanation why some patients with transient symptoms demonstrate ischemic lesions on DWI while others do not. One explanation may be linked to recanalization. Spontaneous recanalization could lead to absence of ischemic injury and DWI lesions if full reperfusion is achieved within short enough time. In patients with transient symptoms and DWI lesions, a relatively late or incomplete recanalization may fail to prevent ischemic damage, yet prove sufficient to facilitate reperfusion and reverse stroke symptoms. The clots responsible for the DWI lesions could, in other words, be less inclined to undergo spontaneous recanalization as compared to the clots in patients without DWI lesions. This suggestion may be supported by our findings, which pointed at an independent association between cardioembolic stroke etiology and presence of DWI lesions. Cardioembolic clots are larger in size as compared to clots of other etiological origin and have been associated with more severe strokes.[123] As a consequence, these clots may less prone to recanalize spontaneously, resulting in higher chances of leaving ischemic footprints on DWI.

Figure 2: Proportion of MRI scans in patients with transient symptoms <24 h and proportion of TIA diagnosis as compared to ischemic stroke in percentage.



The absence of DWI lesions in some patients with cerebral ischemia may also be explained by collateral circulation. Reduced perfusion due to an occluding clot can promote blood flow through collateral vessels. Primary collateral pathways are represented by the arteries of the circle of Willis, while secondary pathways include the leptomeningeal vessels.[65] Patients with transient ischemia without DWI lesions may have benefitted from more potent collateral anastomoses averting ischemic damage whereas the robustness of collateral vessels in DWI positive patients proved insufficient to prevent ischemic damage. The theory of collateral circulation

preventing ischemic damage on DWI is speculative since data of collateral circulation was not registered.

Stroke mimics could offer another explanation to the differences between DWI positive and negative patients with transient stroke symptoms. It is sometimes difficult to distinguish between vascular and non-vascular etiologies in patients presenting with transient stroke symptoms. A positive DWI makes this decision easier. In these patients, the ischemic origin of the symptoms is more or less clear. It may be more difficult to separate a vascular event from disorders mimicking vascular events in patients with a negative DWI. Nevertheless, the gold standard of TIA remains the judgment of a vascular neurologist.[28] Stroke mimics are not registered in the NORSTROKE Study, yet a number of patients with stroke mimics labeled as TIA may have been difficult to avoid. And vica-versa, some patients with true TIA may have been diagnosed as stroke mimic with a negative DWI. These points should also be taken into account when studying the differences between DWI positive and negative patients with an apparent TIA. The younger age of patients with DWI lesions could be explained by this. Because age itself represents an important risk factor for vascular pathology, the clinician may have tended to label transient symptoms as TIA in older patients with negative DWI, but suspected stroke mimics in younger patients with negative DWI. This may have contributed to the higher age in DWI negative patients with transient stroke symptoms as compared to those with positive DWI. The relationship between prior myocardial infarction and presence of DWI lesions could also be explained by a dilution of the true ischemic events in the DWI negative group with stroke mimics. A history of coronary heart disease is a risk factor for ischemic cerebrovascular events but not necessarily for stroke mimic events.[43, 124, 125]All patients with DWI lesions had an ischemic event while some patients without DWI lesions could actually have had stroke mimics although labeled as true ischemic events. This could have led to a higher rate of causal ischemic stroke risk factors, such as ischemic heart disease, in the DWI positive group while the group of DWI negative patients had a lower rate of ischemic heart disease because this group in reality consisted of a proportion of stroke mimics where ischemic heart

disease is less prevalent. These points draw attention to the difficulty of comparing DWI positive and negative patients because a true vascular diagnosis is more certain in those with DWI lesions. The difficult TIA diagnosis highlights the importance of performing MR-DWI in these patients.

The importance of DWI in TIA

In TIA and ischemic stroke, therapeutic decisions depend on an accurate diagnosis and etiological classification. In this context, stroke mimics such as migraine or epileptic seizures are important differential diagnoses to TIA and minor strokes. Up to half of all TIA-referrals to stroke centers are stroke mimics.[126-128] As approximately 20% suffer an ischemic stroke within 3 months after a TIA, misclassifying TIA as stroke mimic could have dramatic consequences. Unlike TIA, stroke mimics is associated with an excellent cardiovascular prognosis.[129] To diagnose a stroke mimic as TIA would therefore also be a mistake with negative implications such as erroneous initiation of secondary cardiovascular prevention, incorrect patient information of long-term prognosis and delay of appropriate assessment of the true illness, which caused the apparent TIA. Magnetic resonance with DWI is very sensitive to even small areas of ischemic injury.[130] The importance of differentiating between TIA and stroke mimics is an important argument for DWI assessment in all patients with an apparent TIA.

DWI also has other values in TIA assessment, such as the recognition of ischemic patterns. DWI lesions in different vascular territories point at a cardiovascular cause of the ischemic event, while small lesions in the basal ganglia suggest lacunar stroke. This different display of DWI lesions may provide important information to stroke etiology and thereby ensure right treatment to the right group of patients. In addition, presence of DWI lesions also provides prognostic information. Studies have reported of an increased risk of subsequent ischemic stroke in patients with transient ischemic symptoms and DWI lesions as compared to those without DWI lesions. [13, 131, 132]

These prognostic differences also support the concept of a tissue-based TIA definition.

Location of DWI lesions in transient and permanent symptoms

Patients with DWI lesions due to cerebral ischemia may recover completely within short time or suffer more persistent neurological deficits. Previous studies have shown that DWI lesions in patients with transient symptoms are smaller as compared to those with persisting symptoms, yet few studies have looked into if DWI lesions are located differently in these two groups of patients.[7, 12] In our study, we found an independent association between cortical DWI location and transient symptoms with duration less than 24 hours (paper II). Indirectly, these findings are in concordance with other studies, which have reported a relatively high frequency of cortical cerebral dysfunction in patients with transient symptoms and DWI lesions, such aphasia.[14, 93, 122] A possible explanation may be linked to recanalization. Rapid neurological recovery, either spontaneous or mediated through thrombolytic treatment, is likely to be the result of recanalization and reperfusion. In the process of recanalization, the clot breaks up into fragments. These fragments are transported with the restored anterograde blood flow to distal cortical regions. Here, the fragments occlude smaller, cortical vessels. These occlusions could be large enough to cause cortical DWI lesions, but too small to produce persistent neurological deficits.

In opposition to this theory, only 43% of patients with transient symptoms and an occlusion on admission CTA had achieved complete recanalization on MRA the next day. Although only 14 patients were included in this specific analysis, the relatively low rate of recanalization in this group could be interpreted as a challenge to the link between recanalization and reversibility of neurological symptoms. However, also partial recanalization may lead to sufficient reperfusion and clinical improvement. Due to the small number of patients with an occlusion on admission CTA, only complete recanalization was registered in this study.

Neurological deficits caused by ischemia vary depending on which area the ischemia affects. Smaller subcortical lesions in the basal ganglia or brain stem may cause severe neurological symptoms due to injury of a large number of axons concentrated in white matter tracts.[133] Lesions of similar size located in the cortex could result in milder and less persistent symptoms due to the wider distribution of cortical functions in this area.[134] This could also offer a potential explanation of our results. In addition, studies have shown an increased perilesional reorganization and plasticity after cortical lesions, resulting in improved recovery.[135] However, our study showed a high rate of cortical DWI lesions in patients with reversible symptoms at 24 hours, a time frame probably too short for plasticity to take place.

Another explanation may be based on lesions size. Studies have shown a correlation between DWI lesion volume and neurological development and outcome[134, 136], although other studies have come to different conclusions.[137] The association between transient symptoms and cortical DWI lesions could thus be based on the smaller size of these lesions as compared to those located in other regions. The lack of DWI volume measurement is a limitation in our study. However, previous studies have shown an association between size of DWI lesions and stroke severity on admission.[134] We adjusted for stroke severity using NIHSS score on admission in our analyses and thereby partly compensated for the lack of volume data.

TIA- a dying breed?

With a tissue-based distinction between TIA and ischemic stroke, the diagnosis of TIA is dependent on a credible patient history of vascular origin and absence of ischemic damage on imaging. TIA will only be evident in patients where severity and duration of ischemia was sufficient to cause symptoms, but no infarcted tissue. As sensitivity of detecting ischemic injury increases, rates of TIA are thus bound to decrease in favor of ischemic stroke. In this context one might question if all DWI lesions should be considered as representing infarction. Infarction implies permanent injury, yet some studies have shown that DWI lesions can be reversible.[19] In spite of

this, a recent large, prospective study reported that DWI reversal is uncommon in patients with TIA or minor stroke and occurred only in 5.7% of the patients after 3 months in follow-up MR imaging with FLAIR (fluid-attenuated inversion recovery).[138] In addition, not all DWI lesions are necessarily of ischemic origin. Studies have shown DWI lesions in patients with different conditions, such as transient global amnesia, epileptic seizures and multiple sclerosis.[139-141] The ischemic origin of a DWI lesion in a patient with transient symptoms should thus not always be taken for granted.

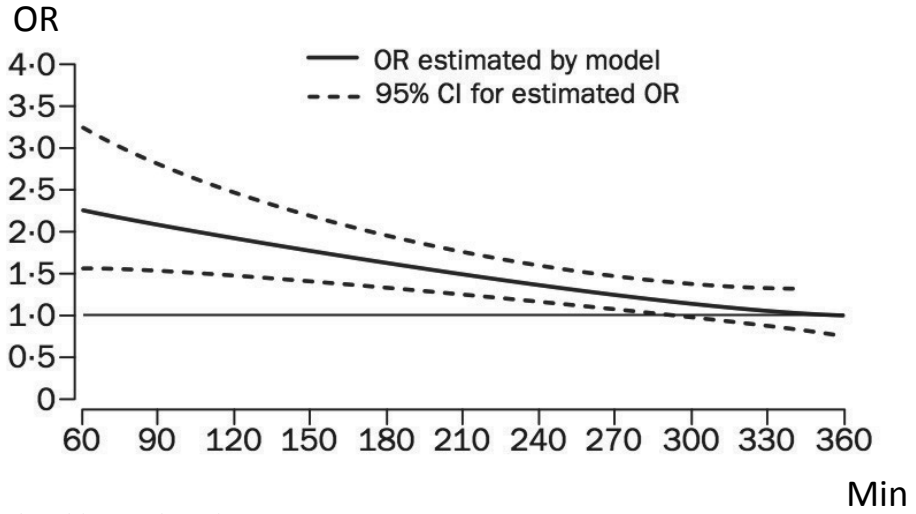
A different ischemic stroke population is another consequence of a tissue-based TIA definition. A large part of yesterday's patients with TIA are now registered as ischemic stroke due to DWI lesions on MRI. Because prognosis is more favorable in DWI positive patients who already have recovered from their symptoms, a general shift towards a better prognosis after ischemic stroke will be the consequence. This will, however, depend on local use of MRI and DWI, especially in patients with possible TIA. Methodological consequences and challenges in future stroke trials will also emerge. Modified Rankin scale score after 90 days have been used as primary outcome in major stroke trials for several years. A score of 0-1 or 0-2 have been considered as favorable outcome. This score may prove too inaccurate when patients previously diagnosed with TIA now are included in these trials as ischemic stroke patients. An increased number of patients will have to be included in order to achieve an acceptable power. With tissue-based TIA and stroke definitions, perhaps the time has come to replace the traditional definitions of outcome with other outcome parameters or methods.

Thrombolytic treatment

The failure of spontaneous recovery of ischemic neurological deficits may be caused by persistent occlusion. This supposition is the rationale for thrombolytic treatment in patients admitted with acute ischemic stroke symptoms. The beneficial effect of thrombolytic therapy is based on the augmentation of recanalization and reperfusion. In order to achieve clinical improvement after recanalization, the recanalization must

be achieved while there still is salvageable tissue. The clinical effect of thrombolytic treatment is in other words highly time dependent, which is demonstrated in figure 3.

Figure 3: The effect of tPA decreases with time



Adopted from Hacke et al. Lancet 2004: 363: 768-74.

This means that thrombolysis should be administered to eligible patients as soon as possible after hospital arrival. Under these circumstances the clinician has to balance the running time, with its potential loss of neuronal tissue, against the assessment of factors that may contradict thrombolytic treatment. Such factors include (a) uncertainty whether the symptoms are of ischemic origin, (b) if the symptoms could improve spontaneously without thrombolytic treatment or (c) if one or more contraindications to tPA are present. This assessment is important because (a) there is no benefit in treating a patient with stroke mimics or (b) a patient without stroke symptoms and (c) treating a patient with contraindications to tPA could increase the risk of sICH, which often outweighs the beneficial clinical effect of early recanalization.

In cases of (a), increasing evidence suggest that thrombolytic treatment in stroke mimics is safe. Across different studies, rates of stroke mimics erroneously receiving

thrombolysis varies between 2.8% to 21%, yet none of these patients suffered from sICH.[125, 142, 143] These findings indicate that thrombolytic treatment does not alter the frequently favorable natural prognosis in stroke mimics. Consequently, the general benefit of tPA is not reduced by the potential harm of thrombolysing patients with stroke mimics.

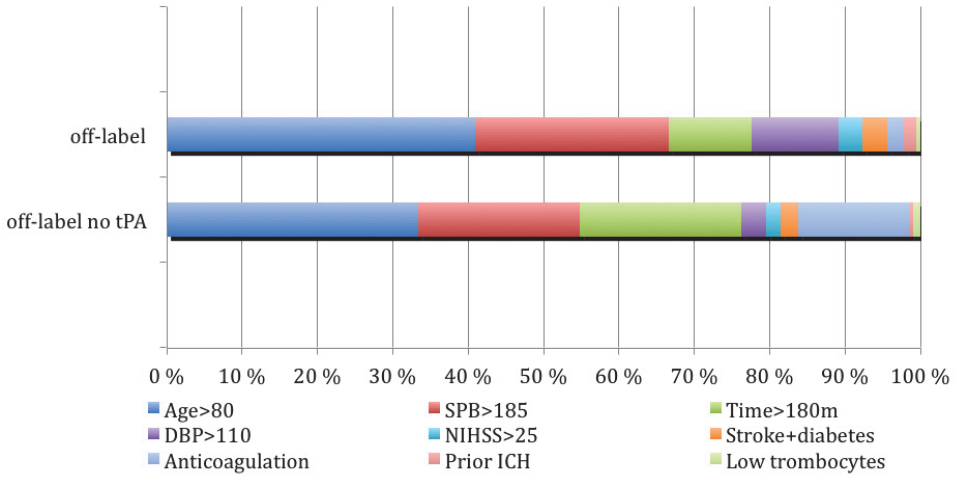
Clinicians also do not wish to treat patients with transient ischemic attacks where recanalization already has occurred and symptoms have reversed (b). A recent Norwegian study showed that thrombolysis was not administered in more than one third of admitted patients with acute ischemic stroke due to mild or rapidly improving symptoms.[144] The problem with rapidly reversing symptoms is that they may not improve completely. Although recanalization has occurred, fragments from the original clot may re-occlude distal arteries, causing remaining neurological deficits. It is also possible that a robust collateral circulation may temporarily compensate for an occlusion. Clinical deficits can be vague and too obscure to be detected in the setting of a pragmatic neurological examination in the emergency ward. Such deficits include neglect, dyscalculia, apraxia, gait disturbances and anosognosia. Symptoms not sufficiently apprehended by the NIHSS scale, such as deficits from the right hemisphere are also easily missed.[145, 146] Studies show that treating patients with minor stroke symptoms or regressing stroke symptoms may be safe and efficient.[147-149] These findings support an aggressive approach when it comes to patients with improving stroke symptoms and thrombolysis.

Another factor, and perhaps the most important one, is the presence of contraindications to trombolytic treatment (c). These are numerous and the systematic setup of contraindications listed in the national guidelines is appreciated by the clinician in the demanding setting of an acute stroke.[78] A number of contraindications to tPA are listed in these national guidelines, which may exclude a considerable proportion of patients from thrombolysis and thereby limit the general availability of this treatment. The listed contraindications are in general derived from earlier thrombolytic trials where patients with a presumed risk of cerebral hemorrhage or increased risk of unfavorable treatment results were excluded from participation. The

strict compliance of these guidelines may result in the exclusion of patients who potentially might benefit from thrombolytic treatment.

Our department has long experience in the administration of thrombolytic treatment and was the first center in Norway to routinely treat ischemic stroke patients with tPA. This experience could have resulted in a relatively liberal view on a number of the contraindications listed in the national guidelines. This is supported by our findings, which showed that approximately half of the patients treated with tPA had one or more contraindications to tPA (paper III). There was a similar number of patients with contraindications to tPA who did not receive thrombolytic treatment. The distribution of contraindications in patients treated and not treated with tPA are illustrated in figure 4.

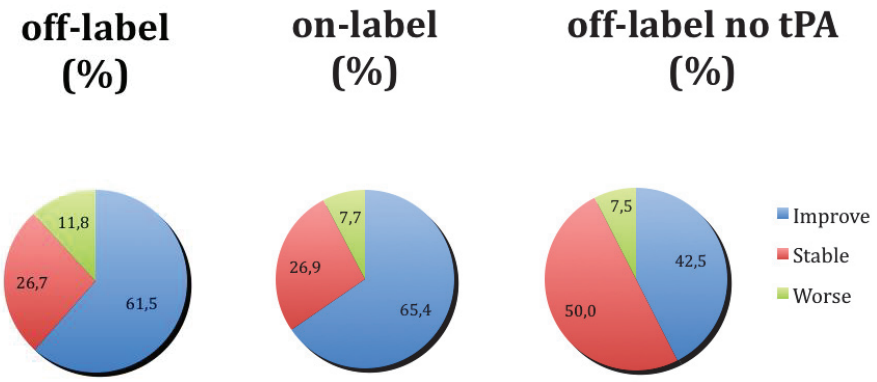
Figure 4: Distribution of contraindications in patients treated (off-label) and not treated with tPA (off-label no tPA).



There was no significantly increased risk of sICH in patients treated off-label with tPA as compared to those treated without any of the listed contraindications. Although rates of unfavorable outcome and mortality were higher in patients treated off-label, the presence of contraindications to tPA was not associated with worse prognosis when adjusted for confounders, such as age, sex and stroke severity on

admission. This points at a different cause for the unfavorable prognosis in patients treated off-label rather than the thrombolytic treatment itself. When off-label patients were compared to those who had contraindications and were not treated with tPA, there was a trend towards a beneficial effect of thrombolytic treatment. In addition, a higher proportion of patients treated off-label experienced neurological improvement during the hospital stay as compared to those who had contraindications and were not treated with tPA (figure 5).

Figure 5: Distribution of clinical improvement, stability or worsening between patients with contraindications treated with tPA (off-label), patients without contraindications treated with tPA (on-label) and patients with contraindications not treated with tPA (off-label no tPA).



These results must, however, be interpreted with caution. The non-randomized, retrospective design of the study makes it difficult to directly compare these groups of patients. The question to treat or not to treat with tPA is left to the clinical judgment of the clinician at charge. The decision is based on several factors such as prior diseases, clinical status and development and co-concomitant patient medication. The present contraindications in some patients not treated with tPA may not have been the direct cause of withholding thrombolytic treatment, rather an indirect cause tipping the balance in favor of no thrombolysis. A randomized,

placebo-controlled study could have eliminated this problem. Such a study may however be difficult to perform due to ethical issues.

Our results are in conformity with other similar studies looking either at separate or multiple contraindications to tPA (table 3).

Table 3: Studies of stroke patients treated off-label with tPA using similar contraindications as in our study in addition to minor stroke symptoms.

Authors	*Contra-indications*	*Inclusion period*	*N (off-label)*	*Conclusion*	*Ref*
Tanne et al.	Age ≥80	1995-1997	30	No evidence to support withholding tPA in patients aged ≥80	[150]
Engelter et al.	Age ≥80	1998-2003	38	Rates of favorable outcome and sICH similar in patients ≥80 and <80	[151]
Berrouschot et al.	Age >80	2000-2004	38	No increase in sICH, but outcome worse as compared to younger patients	[152]
Sylaja et al.	Age ≥80	2002-2005	270	No increased risk of sICH in patients aged ≥80	[153]
Ford et al.	Age >80	2002-2008	1831	Selected patients >80 years appropriate candidates for tPA. Poorer prognosis due to natural history	[154]
Mishra et al.	Age >80	2002-2009	3472	Increasing age associated with worse prognosis, but association between tPA and improved outcome is sustained in those >80	[155]
Henriksen et al.	Age >80	2007-2010	77	Age >80 associated with increased risk of sICH and death	[156]
IST-3 group	3-6 hours after onset and >80	2000-2011	507+817	In total, no difference tPA vs placebo. Effect of tPA as least as good for >80 as ≤80.	[157]
Mishra et al.	Prior stroke and diabetes	1998-2007	491	Better outcomes in thrombolysed patients with diabetes and/or prior stroke as compared to non-thrombolysed	[158]

Matuta et al.	Treatment with anticoagulants	2003-2010	91	INR levels <2 appear safe. Use of heparin appear to increase risk of sICH	[159]
Brunner et al.	Abnormal baseline coagulation	2006-2010	36	No increased risk of sICH in patients with abnormal baseline coagulation	[160]
Prabhakaran et al.	Anti-coagulation treatment prior stroke	2002-2009	13	More likely to experience sICH if treated with warfarin prior to stroke	[161]
Aleu et al.*	Multiple	1995-2006	273**	Risk of sICH in off-label thrombolysis not as high as presumed	[162]
Meretoja et al.	Multiple	1995-2008	499	Off-label therapy not associated with increased rates of sICH, nor with poorer outcome, except age >80	[80]
Lopez-Yunez et al.	Multiple	1996-1998	8	NINDS protocol violations are common and associated with sICH	[163]
Graham *	Multiple	1996-2003	523	Rates of sICH did not correlate with frequency of protocol violations. Mortality correlated with frequency of protocol violations.	[164]
Frank et al.*	Multiple	1998-2008	2755	Broad trend of more favorable outcome across all subgroups of contraindications	[165]
Cronin et al.	Multiple	2006-2010	80	Off-label therapy not associated with increased risk of sICH	[166]
Breuer et al.	Multiple	2006-2010	432	Off-label therapy not associated with increased risk of sICH	[167]
Mishra et al.	Admission NIHSS 1-4 and ≥ 25	1998-2007	8+64	No association between tPA and improved outcome outside NIHSS 5-24. However, small sample sizes at extremes of NIHSS scale	[168]
Strbian et al.	Minor stroke symptoms	1995-2010	58	No patients with NIHSS<2 (n=58) had sICH	[148]
Baumann et al.	Minor stroke/ regressing symptoms	2002-2005	19	Withholding of tPA because of early regression of symptoms may not be justified	[149]

Logallo et al.	Minor stroke symptoms	2006-2013	158	No increased risk of sICH, treatment with tPA associated with excellent outcome	[147]
Tsivgoulis et al.	Pre-treatment hypertension	1996-2005	63	Higher risk of sICH in patients with SBP >180 or DBP >110	[169]
Patel et al.	Major infarct on CT (>1/3 MCA territory)	1991-1994	38	Better prognosis with tPA treatment after adjusting for NIHSS on admission	[170]
Hacke et al.	3-4.5 hours after symptom onset	2003-2007	418	Improved clinical outcomes in thrombolysed patients as compared to placebo-group	[73]

*Meta-analysis

** Also included endovascular treatment

Especially two of these studies have considerably increased our knowledge of off-label thrombolytic stroke treatment. The ECASS-III trial showed in 2008 that tPA is safe and efficient in the time window of 3-4.5 hours after stroke onset.[73] This has led to clinical acceptance of thrombolytic treatment beyond 3 hours after stroke onset, even though national guidelines still advocate the 3 hour limit.[78] The IST-3 trial recently showed that patients older than 80 years have similar benefits of tPA treatment as those of younger age.[157] The study could, however, not show a clear clinical benefit of tPA administration between 4.5 – 6 hours. Other studies have found increased rates of sICH in patients treated off-label with tPA, including patients with anticoagulation treatment prior to stroke or hypertensive blood pressure before initiation of thrombolytic treatment.[161, 169] In contrast to these findings, a large retrospective study recently demonstrated improved outcomes of off-label tPA treatment in patients on anticoagulants with INR levels ≤ 1.7 as well as patients with hypertensive blood pressure before thrombolytic treatment.[165]

In total, our results combined with these prior findings indicate that some of the contraindications to tPA may be too conservative and that the strict adherence to these guidelines could preclude potentially life-saving treatment to eligible patients.

Future guidelines should consider updating its recommendations more accordingly to recent evidence and real-world experience.

A more efficient thrombolysis

When it comes to recanalization, endovascular intervention is more effective than intravenous thrombolysis alone. Approximately 43% of the occlusions are recanalized with intravenous tPA, largely depending on clot site and origin.[60] The recanalization rates of mechanical thrombectomy and intra-arterial thrombolysis are stipulated to 84% and 63%, respectfully. [60] However, three recent randomized trials comparing endovascular treatment to standard intravenous thrombolysis failed to show a clinical benefit of endovascular therapies, even though recanalization rates were higher in this group.[88-90] If recanalization is strongly associated with clinical outcome and endovascular treatment achieves higher recanalization rates, why did endovascular treatment fail to show a clinical benefit? There may be several explanations to this discrepancy, yet the most important factor may be time.[171] Initiation of endovascular therapy is time consuming. There is no benefit in recanalization if it occurs too late, regardless if the recanalization occurs through thrombectomy, thrombolysis or spontaneously. At least two therapeutic points can be derived from these disappointing results. Firstly, time is still crucial in acute ischemic stroke. This highlights the need for efficient and time-saving strategies to reduce door-to-needle time, including up-to-date guidelines regarding indications and contraindications to tPA. Secondly, as intravenous thrombolysis will continue to represent first-line treatment in ischemic stroke, research on increasing its efficiency is important. Advances have already been made in this field. Tenecteplase appears as a promising thrombolytic agent with a higher fibrin-specificity than tPA.[172] This drug has proved to be safe and more efficient than tPA in trials of selected stroke patients.[172-174] A phase III trial may confirm its superiority in a more general ischemic stroke population. Such a trial is currently being performed as a multi-center study in Norway (NOR-TEST).[175] Another way to potentiate the recanalizing effect of intravenous thrombolysis is by the use of ultrasound. This method is called

sonothrombolysis and the supplement of sonothrombolysis with intravenous thrombolysis has shown to increase rates of recanalization and improve outcomes in selected groups of stroke patients.[176] A trial of sonothrombolysis including a more general stroke population is currently being conducted in Bergen (NOR-SASS).

Higher temperature

Another way of achieving better recanalization rates and clinical improvement with intravenous thrombolysis may be based on temperature. Our findings point to a beneficial effect of higher body temperature as we found an increased body temperature being independently associated with major neurological improvement after 24 hours (paper IV). These results suggest an improved clot lysis and recanalization with tPA at higher body temperatures. This hypothesis is, however, not optimally addressed since imaging data of recanalization was not performed. Instead, major neurological improvement was used as a surrogate marker of successful recanalization. The use of major neurological improvement as a surrogate marker is in line with the close association between recanalization and dramatic neurological improvement found in Doppler-controlled studies.[62, 63, 177]

Our findings may strike as surprising and counter-intuitive considering the vast amount of evidence on low body temperature being neuroprotective.[178-180] A number of prior studies have looked into the relationship between body temperature and stroke outcome and many have found an association between high body temperature and poor outcome (table 4). There may, however, be two explanations for the discrepancy between these findings and our findings. Our study included patients admitted within the very first hours after stroke onset, whereas most previous studies have analyzed the association of body temperature measured beyond the first hours of ischemic stroke and patient outcomes. Body temperature may have a different impact on ischemic stroke outcomes in different time-windows. In the acute phase of ischemic stroke, a beneficial effect on clot lysis may outweigh the potential neuroprotective effect of lower temperatures.[109] Another important difference

between our study and some of the prior studies is thrombolytic treatment. All patients in our study were treated with intravenous tPA. Body temperature may have a different impact on outcome in patients treated with tPA as compared to those not treated with tPA. Prior in-vitro studies support this assumption, as the thrombolytic effect of tPA decreases with decreasing temperatures.[105, 106] Our results are also in conformity with another recent retrospective study where body temperatures of 37.0 °C or higher was associated with improved outcomes at 3 months in ischemic stroke patients treated with tPA, suggesting a larger benefit of intravenous thrombolysis at higher temperatures.[181]

Table 4: Studies of associations between body temperature and outcome in ischemic stroke.

Authors	*Hours onset-adm.*	*tPA*	*Inclusion period*	*N*	*Ischemic stroke / ICH*	*Conclusion*	*Ref*
Lees et al.	<3 h	Yes	1998-2007	1980	Ischemic	No evidence of influence of body temp. on tPA response. However, temp 37-37.5 higher effect of tPA than ≤35.5	[110]
Blinzler et al.	<3 h	Yes	2006-2009	320	Ischemic	Trend towards higher admission temp. in patients with early complete neurological recovery	[182]
Tiainen et al.	<4.5 h	Yes	1995-2008	985	Ischemic	Admission temp. higher in patients with good outcome.. Increasing temp. over 24 hours associated with worse prognosis	[183]
Reith et al.	<6 h	No	1991-1993	390	Both	For each 1 C° increase in temp, the relative risk of poor outcome rise by 2.2	[184]
Kammers-gaard et al.	<6 h	No	1991-1993	390	Both	Low temp. on admission predictor of good short-term outcome	[185]

Boysen et.al	<6 h	No	1998-2000	725	Both	Increased admission temp. no influence on outcome at 3 months. Temp. at 12 hours associated with poor outcome	[102]
Ridder et al.	<6 h	Yes	2003-2008	647	Ischemic	Baseline temp ≥37.0 C° associated with improved outcomes at 3 months	[181]
Hemmen et al.	<6 h	Yes	Pub. 2010	59	Ischemic	No clinical effect of endovascular cooling	[186]
De Georgia et al.	<12 h	56%	2001-2002	40	Ischemic	Endovascular cooling induced moderate hypothermia. Outcomes similar in cooling group and placebo group	[187]
Hertog et al.	<12 h	21%	2003-2008	1332	Both	No relation admission temp. and poor outcome. Increased temp. in first 24 hours associated with worse outcome	[103]
Hertog et al.	<12 h	22%	2003-2008	1400	Both	No overall effect of paracetamol on outcome. Post hoc showed beneficial effect in patients with temp 37-39 C°	[104]
Kasner et al.	<24 h	15%	1997-2000	39	Both	No clinical improvement of acetaminophen to afebrile patients	[188]
Hertog et al.*	<24 h	Partly	1997-2004	423	Both	No beneficial effect of pharmacological or physical temperature-lowering therapy	[92]
Castiollo et al.	<24 h	No	<1998	297	Ischemic	High body temperature associated with poor outcome	[101]

Wang et al.	No limit	No	1995-1997	509	Both	Hyperthermia associated with increased one year mortality. Hypothermia associated with reduction in in-hospital mortality	[189]

*meta-analysis

There are several studies confirming the neuroprotective effect of hypothermia on different brain injuries, including ischemic stroke.[96, 179, 190] There are also on-going phase III- trials investigating the efficacy of therapeutic cooling in ischemic stroke patients.[191] Perhaps a potential thrombolytic effect of higher temperatures can be combined with neuroprotective cooling of ischemic tissue? TPA may be heated before intra-arterial application, as performed in a study of intra-arterial treatment of lower limb ischemia. [108]Simultaneosly, the brain tissue itself could be exposed to hypothermia. In this way, the theoretical beneficial effect of increased temperature on clot lysis could be combined with the advantages of cooling therapy. Another approach may be to initiate hypothermic treatment once recanalization has been achieved, as demonstrated in a recent study where hypothermia after recanalization was independently associated with favorable outcome.[192] These possible modalities of future stroke therapy are of course speculative, but our results encourage untraditional reflections when it comes to temperature and ischemic stroke.

Smokers – A special group to thrombolyse?

Similar to the paradox of increased body temperatures improving outcomes in thrombolysed stroke patients, we showed that current smokers have improved outcomes after thrombolysis as compared to non-smokers (paper V). This phenomenon has also been reported in patients with myocardial infarction undergoing thrombolysis.[114, 115, 193] A likely explanation is that smoking leads to higher intra-arterial fibrin concentrations and thus formation of fibrin-rich clots.[112] These clots are

more susceptible to thrombolytic treatment with tPA and are therefore recanalized more efficiently, resulting in improved outcomes for thrombolysed smoking stroke patients. Some studies have found similar findings which support the results and hypothesis of our study.[116, 117] In a recent study, 148 patients treated with intravenous thrombolysis had MRA performed before and one day after thrombolytic treatment.[116] Although the number of smoking patients was low (n=32), smoking was independently associated with both recanalization and reperfusion in support of the "recanalization-hypothesis" of smokers. Others have attributed the improved outcomes of smokers to other mechanisms, such as the younger age of smokers.[118] Another explanation might be that smokers are earlier mobilized due to the urge to smoke. Our findings contradict both these assumptions. In our population, smoking patients were indeed younger as compared to non-smokers. However, age was adjusted for in multivariate analysis, which makes it less likely that age represents the only explanation to our results. We did not have any data regarding early mobilization of smokers, but all patients follow standard operating procedure and are mobilized early. Short-term mRS was used as outcome parameter in the present study and this could theoretically have influence our results as compared to other studies using long-term outcomes. However, we included a "control-group" of patients who were admitted within 6 hours after stroke onset and not treated with thrombolysis. In this cohort, there was no association of improved outcomes and current smoking. This supports the hypothesis of improved thrombolysis leading to favorable outcomes in smokers treated with tPA. The non-randomized design of the study does, however, not prevent bias in terms of differences between the thrombolysed group and non-thrombolysed group, making a direct comparison between these cohorts difficult.

If thrombolysis with tPA is more efficient in patients who smoke, the next question is how this can be translated into clinical guidelines exploiting this benefit. Due to lack of data, it is hard to recommend general changes in the treatment protocol of thrombolysis in smokers. Nonetheless, our results and prior findings speak in favor of a more aggressive standpoint in thrombolysing acute ischemic stroke patients who smoke. In clinical practice, the knowledge of current smoking in an acute ischemic stroke patient may tip the balance in favor of thrombolysis if the clinician is in doubt

whether to treat with thrombolysis or not. Another interesting point is the time-dependent clinical effect of tPA as shown in figure 3. Because the possible gain of thrombolytic treatment in smokers may be greater than in non-smokers, this graph could look different for smokers. The IST-III trial could not show a benefit of thrombolytic treatment in patients admitted between 4.5 – 6 hours after stroke onset.[157] Future trials including smokers treated within this extended time-window could reveal a clinical benefit for this specific patient group under similar circumstances. Our findings may encourage the initiation of such studies.

General limitations and strengths

Our study has some limitations. Firstly, although recanalization is a central theme in the present thesis, direct imaging regarding recanalization or reperfusion was not systematically assessed and therefore mainly not presented. In paper I and II, remission of stroke symptoms is considered to reflect recanalization, although this hypothesis cannot be confirmed with imaging. Obtaining imaging evidence of recanalization systematically is, however, difficult in this patient population as many patients with transient ischemic deficits experience their reversible symptoms before hospital admission. Secondly, data analysis was done retrospectively. Thirdly, whereas traditional studies present three-month outcomes, we only presented short-term outcomes. However, short-term outcomes are more directed to the stroke as such while potentially external factors such as infections, level of rehabilitation, family situation and recurrent strokes may influence long-term outcomes at three months. Strengths of the study include the use of a stroke registry where patients are prospectively included and data collected in a standardized manner with research quality.

Conclusions

If early recanalization occurs, stroke symptoms may be transient. Approximately half of all patients with transient ischemic symptoms have DWI lesions on MRI. With a tissue-based TIA definition, these patients should be diagnosed with ischemic stroke and not TIA. Thus, an increased use of MRI leads to a decrease in the proportion of TIA. Patients with DWI lesions are more thoroughly investigated with cardiac examinations. An independent association between presence of DWI lesions and prior myocardial infarction suggests a cardioembolic stroke mechanism in these patients.

Patients with transient ischemic symptoms have a different DWI distribution as compared to patients with persisting stroke symptoms. Transient ischemic symptoms are associated with cortical DWI lesions. The cortical location may be caused by recanalization, leading to upstream embolization of minor fragments from the original occlusion.

If the occlusion persists and ischemic symptoms fail to reverse spontaneously, recanalizing treatment with intravenous thrombolysis could be indicated. Approximately half of the patients treated with tPA have one or more formal contraindications to thrombolytic treatment. This off-label treatment with intravenous tPA may be safe and efficient despite presence of contraindications. The strict adherence to the conservative recommendations of national guidelines could deprive potentially eligible patients from crucial thrombolytic treatment.

In patients treated with tPA, a higher admission body temperature is associated with major neurological improvement after 24 hours, indicating a beneficial effect of higher body temperature on clot lysis and recanalization. This effect may outweigh the potential neuroprotective effect of lower body temperature in the acute phase of ischemic stroke treated with tPA.

Smokers treated with tPA have a more favorable outcome as compared to non-smokers. This association is not present in acute stroke patients not treated with tPA.

A likely explanation is that smokers have more fibrin-rich clots which respond more efficiently to thrombolytic treatment with tPA. These results suggest an aggressive point of view when it comes to treating smoking stroke patients with thrombolysis in order to achieve recanalization and a favorable outcome.

A tissue-based definition of ischemic stroke based on careful neuroimaging has turned the temporal evolution of ischemic stroke into a more pathophysiological direction. Acute stroke treatment should be harmonized with this perspective and may increase its efficiency if a more customized approach is adapted based on the pathophysiology of arterial clots and their recanalization.

Appendix

1. **The modified Rankin Scale (mRS)**
2. **The Oxford Community Stroke Project classification (OCSP)**
3. **National Institutes of Health Stroke Scale (NIHSS)**
4. **Trial of Org 10172 in Acute Stroke Treatment (TOAST)**

Modifisert Rankin Scale

Telefonisk oppfølging

Slagenheten
Nevrologisk avdeling
Haukeland Universitetssykehus

Pas.

Oppfølging

		3	6	12		dag	mnd	år
Oppfølging	måned	☐	☐	☐	**Oppfølging dato**			
Intervju med	pårørende	☐	pasient	☐	**Sykdomsstart**			
Bosituasjon	hjemme	☐	sykehjem	☐	**Evt. dødsdato**			

Modifisert Rankin scale (mRS)

kryss av	score	
☐	0	Ingen symptomer og ingen begrensninger i dagliglivet
☐	1	Lette symptomer, men i stand til å utføre alle vanlige aktiviteter *"Har han/hun problemer med å lese/skrive, snakke eller finne riktige ord, problemer med balanse, synsproblemer, nummenhet, svakhet, vanskeligheter med å svelge, eller andre symptomer som følge av slaget?"*
☐	2	Begrensninger i sosiale aktiviteter, men uavhengig i ADL *"Er det blitt en endring i hans/hennes arbeidsevne eller evne til å ta seg av andre, dersom dette var oppgaver før slaget?"* *"Er det blitt en endring i hans/hennes evne til å delta i tidligere sosiale aktiviteter eller fritidsaktiviteter?"* *"Har han/hun problemer i samvær eller er blitt isolert?"*
☐	3	Har behov for noe hjelp (instrumental ADL), men kan gå uten hjelp *"Er det nødvendig med hjelp til å lage et enkelt måltid, gjøre husarbeid, passe på penger, gjøre innkjøp eller reise med buss, bil nær hjemmet?"*
☐	4	Kan ikke gå uten hjelp, trenger hjelp i daglige aktiviteter (basic ADL), men trenger ikke kontinuerlig oppfølging og hjelp *"Er det nødvendig med hjelp til spising, daglig hygiene, bruk av toalettet, eller hjelp til å gå?"*
☐	5	Sengeliggende, inkontinent, avhengig av kontinuerlig hjelp *"Trenger pasienten kontinuerlig pleie og omsorg?"*
☐	6	Død

OCSP klassifikasjon

Slagenheten
Nevrologisk avdeling
Haukeland Universitetssykehus

Dato:

Pasient
Navn:
Født:

Scorer:

lars thomassen 04-2002

Klassifikasjon (velg én av de store boksene, små bokser er "arbeidsfelt")

☐ **LACS (Lacunar circulation syndrom)**

En av følgende funn skal foreligge:

- ☐ Ren motorisk hemiparese
- ☐ Ren sensorisk hemiforstyrrelse
- ☐ Sensomotorisk hemiparese
- ☐ Ataktisk hemiparese

☐ **TACS (Total anterior circulation syndrom)**

Følgende tre forutsetninger må foreligge:

- ☐ Høyere cerebral dysfunkjson (f.eks. afasi, dyskalkuli, neglect)
- ☐ Homonyme synsfeltutfall
- ☐ Motorisk og/eller sensorisk utfall i minst 2 av områdene ansikt-arm-ben

  Hvis bevissthet er redusert, testing av høyere cerebrale funksjoner eller synsfelttesting ikke er mulig, vurderes dette som at utfall foreligger

☐ **PACS (Partial anterior circulation syndrom)**

En av følgende forutsetninger må foreligge:

- ☐ To av de tre komponentene under TACS er tilstede
- ☐ Kun høyere cerebral dysfunksjon alene
- ☐ Sensomotoriske utfall i kun én ekstremitet eller i ansikt og hånd

☐ **POCS (Posterior circulation syndrom)**

En av følgende forutsetninger må foreligge:

- ☐ Ipsilaterale hjernenerveutfall og kontralaterale sensoriske/motoriske utfall
- ☐ Bilaterale sensoriske/motoriske utfall
- ☐ Forstyrrelse i konjugerte øyebevegelser
- ☐ Cerebellar dysfunksjon uten ipsilaterale sensoriske/motoriske utfall
- ☐ Isolert homonymt synsfeltutfall

NIH Stroke Scale

Slagenheten
Nevrologisk avdeling
Haukeland Universitetssykehus

Pasient

Sykdomsstart dato		NIHSS dato						
kl.		kl.						
1a	**Bevissthetsnivå** 0 = Våken 1 = Døsig, reagerer adekvat ved lett stimulering 2 = Døsig, reagerer først ved kraftigere/gjentatt stimulering 3 = Reagerer ikke, eller bare med ikke-målrettet bevegelse							
1b	**Orientering** (spør om måned + alder) 0 = Svarer riktig på to spørsmål 1 = Svarer riktig på ett spørsmål (eller ved alvorlig dysartri) 2 = Svarer ikke riktig på noe spørsmål							
1c	**Respons på kommando** (lukke øyne + knyte hånd) 0 = Utfører begge kommandoer korrekt 1 = Utfører en kommando korrekt 2 = Utfører ingen korrekt							
2	**Blikkbevegelse** (horisontal bevegelse til begge sider) 0 = Normal 1 = Delvis blikkparese (eller ved øyenmuskelparese) 2 = Fiksert blikkdreining til siden eller total blikkparese							
3	**Synsfelt** (bevege fingre/fingertelling i laterale synsfelt) 0 = Normalt 1 = Delvis hemianopsi 2 = Total hemianopsi 3 = Bilateral hemianopsi / blind							
4	**Ansikt** (vise tenner, knipe igjen øynene, løfte øyenbryn) 0 = Normal 1 = Utvisket nasolabialfure, asymmetri ved smil 2 = Betydelig lammelse i nedre ansiktshavdel 3 = Total lammelse i halve ansiktet (eller ved coma)							
5	**Kraft i armen** (holde armen utstrakt 45° i 10 sekunder) 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	ve hø						
6	**Kraft i benet** (holde benet utstrakt 30° i 5 sekunder) 0 = Normal (også ved "ikke testbar") 1 = Drifter til lavere posisjon 2 = Noe bevegelse mot tyngdekraften, drifter til sengen 3 = Ingen bevegelse mot tyngdekraften, faller til sengen 4 = Ingen bevegelse	ve hø						
7	**Koordinasjon / ataxi** (finger-nese-prøve / hæl-kne-prøve) 0 = Normal (også ved "ikke testbar" eller ved coma) 1 = Ataksi i arm eller ben 2 = Ataksi i arm og ben							
8	**Hudfølelse** (sensibilitet for stikk) 0 = Normal 1 = Lettere sensibilitetsnedsettelse 2 = Markert sensibilitetstap (også ved coma, tertraparese)							
9	**Språk /afasi** (spontan tale, taleforståelse, leseforståelse, benevning) 0 = Normal 1 = Moderat afasi, samtale mulig 2 = Markert afasi, samtale svært vanskelig eller umulig 3 = Ikke språk (også ved coma)							
10	**Tale / dysartri** (spontan tale) 0 = Normal 1 = Mild - moderat dysartri 2 = Nær uforståelig tale eller anartri (også ved coma)							
11	**"Neglect"** (bilateral simultan stimulering av syn og hudsensibilitet) 0 = Normal (også ved hemianopsi med normal sensibilitet) 1 = Neglect i en sansemodalitet 2 = Neglect i begge sansemodaliteter							
	Total NIHSS-Score							
	Undersøkerens signatur							

LTh / nevr / haukeland 21.04.2009

hustrykkeriet bestillingsnummer 202 3636

TOAST Classification

Nevrovaskulær seksjon
Nevrologisk avdeling
Haukeland Universitetssykehus

Dato:

Pasient

Navn:

Født:

Scorer:

halvor næss 04-2002

☐ **Aterosklerose (sannsynlig)**
- ☐ Ingen høy eller medium risiko kardial embolikilde (sykehistorie eller undersøkelser)
- ☐ Angiografi forenlig med diagnosen, eller Duplex halskar forenlig med diagnosen

☐ **Aterosklerose (mulig)**
- ☐ Ingen høy risiko kardial embolikilde (sykehistorie eller undersøkelser)
- ☐ Angiografi eller Duplex halskar ikke utført eller Duplex halskar forenlig med diagnosen, men angiografi inkonsistent

☐ **Kardial emboli (sannsynlig)**
- ☐ Høy eller medium risiko kardial embolikilde (sykehistorie eller undersøkelser)
- ☐ For medium risiko pasienter: ingen andre årsaker funnet
- ☐ Angiografi forenlig med diagnosen, eller Duplex halskar forenlig med diagnosen

☐ **Kardial emboli (mulig)**
- ☐ Høy eller medium risiko for kardial embolikilde (sykehistorie eller undersøkelser)
- ☐ For medium risiko pasienter: Ingen annen årsak funnet
- ☐ Angiografi ikke utført, eller Duplex halskar forenlig med diagnosen, men angiografi inkonsistent

☐ **Småkarsykdom (sannsynlig)**
- ☐ Ingen høy eller medium risiko for kardial embolikilde (sykehistorie eller undersøkelser). Ingen andre årsaker funnet
- ☐ Angiografi forenlig med diagnosen, eller Duplex halskar forenlig med diagnosen

☐ **Småkarsykdom (mulig)**
- ☐ Ingen høy risiko for kardial embolikilde (sykehistorie eller undersøkelser)
- ☐ Ingen andre årsaker funnet.
- ☐ Angiografi og Duplex halskar ikke utført eller Duplex halskar forenlig med diagnosen, men angiografi inkonsistent

☐ **Annen årsak (sannsynlig)**
- ☐ Fullstendige undersøkelser forenlig med årsaken
- ☐ Aterosklerose eller kardial emboli er utelukket

☐ **Annen årsak (mulig)**
- ☐ Undersøkelser (ikke fullstendige) forenlige med annen årsak

☐ **Ukjent årsak**
- ☐ Ingen mulig årsak
- ☐ To eller flere årsaker hvor ingen peker seg ut som mer sannsynlig

Veiledning (arbeidsfelt)

Klinikk
- ☐ Klinikk må være forenlig med subtype
- ☐ TIA i samme gebet taler for aterosklerose
- ☐ TIA i annet gebet taler for kardial emboli
- ☐ Angina pectoris eller perifer karsykdom taler for aterosklerose
- ☐ Systemiske embolier taler for kardial emboli
- ☐ Hypertensjon eller diabetes støtter småkarsykdom

Høy risiko kardial embolikilde
- ☐ Mekanisk ventil
- ☐ Atrieflimmer
- ☐ Sick Sinus Syndrom
- ☐ Akutt hjerteinfarkt < 4 uker
- ☐ Venstre ventrikkeltrombe
- ☐ Dilatert kardiomyopati
- ☐ akinetisk venstre ventrikkelsegment
- ☐ Venstre atriumtrombe
- ☐ Atriemyxom
- ☐ Endokarditt

Medium risiko kardial embolikilde
- ☐ Hjerteinfarkt > 4 uker, men <6 måneder
- ☐ Hjertesvikt
- ☐ Hypokinetisk venstre ventrikkelsegment
- ☐ Atrieflutter
- ☐ Biologisk ventil
- ☐ Mitralklaffprolaps
- ☐ Atrieseptumdefekt (ASD)
- ☐ Patent foramen ovale (PFO)
- ☐ Interatrialt septumaneurysme

Cerebral CT / MR (kan være negativ)
- ☐ skal ved småkarsykdom vise et lakunært infarkt < 1,5 cm sentralt i hemisfæren eller i hjernestammen
- ☐ skal ved aterosklerose eller kardial emboli vise infarkt kortikalt og/eller subkortikalt i hemisfæren eller infarkt tilsvarende en sirkumferensarterie i hjernestammen eller cerebellum
- ☐ Ved andre subtyper er det ingen spesifikke krav

Angiografi og Duplex ultralyd
- ☐ skal ved aterosklerose vise en stenose ≥ 50% eller ulcerasjon ≥ 2 mm i relevant arterie

Adams et al. Stroke 1993; 24: 35-41
Trial of Org 10172 in Acute Stroke Treatment

Source of data

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