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The MIDNOR TIA study

Doctoral thesis

NTNU
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NORSK SAMMENDRAG:

Transitorisk iskemisk anfall (TIA) – Risiko for hjerneslag og bruk av kliniske og biologiske markører for vurdering av risiko

Årlig rammes ca. 12 000 mennesker i Norge av hjerneslag. Det finnes et vidt spekter av mulige utfall etter et hjerneslag – fra de små hjerneslagene uten sikre følgetilstander, til de store hjerneslagene som kan ha alvorlige konsekvenser for pasientene, deres pårørende, og for samfunnet.

Transitorisk iskemisk anfall (TIA) er en tilstand med kortvarige slagsymptomer hvor symptomene går over innen kort tid, og som oftest allerede innen én time. I dagligtalen omtales det ofte som «hjernedrypp», eller bare «drypp». TIA anses ofte som et forvarsel, eller alarmsignal, om et kommende større hjerneslag, og derfor er det utført en del studier internasjonalt på denne tilstanden gjennom de senere årene. Tilsvarende store prospektive multisenterstudier er imidlertid ikke blitt gjennomført i Norge eller Skandinavia.
Det overordnede formålet med denne avhandlingen var å øke kunnskapen om pasienter med TIA i vår region. Mer spesifikt ønsket vi å kartlegge risiko for å få et manifest hjerneslag etter TIA. Det er tidligere utviklet risikoskår for TIA-pasienter basert på ulike kjennetegn ved pasientene, og vi ønsket å evaluere nytten av disse risikoskårene hos TIA-pasienter. Vi ønsket å undersøke om disse skårene bør ha en plass i risikovurdering og behandling av TIA-pasienter ved legekontorer, legevakter og i sykehusene.

Vi gjennomførte en prospektiv observasjonsstudie ved åtte sykehus i Midt-Norge, i nært samarbeid med henvisende fastleger og legevakter. Fem hundre og syttisju pasienter ble inkludert. I første del av studien ble pasientene fulgt opp i ett år, og deretter fram til fem år etter inklusjon. Det ble samlet inn en rekke grunnlagsdata om hver pasient. Hos enkelte ble det tatt utvidede blodprøver til den regionale biobanken for ytterligere analyser. Både data fra telefonoppfølging og fra kvalitetsregister ble brukt for å estimere risiko for hjerneslag etter TIA.

Risiko for hjerneslag etter TIA viste seg å være svært lav, både like etter, og innen ett og fem år etter hendelsen. Slagrisikoen var vesentlig lavere enn i tilsvarende eldre studier, men på samme nivå som i en del nyere studier fra store sentra i andre land. Det tyder på at kvaliteten på behandlingen av TIA i Midt-Norge er god. For de pasientene som i henhold til risikoskåringen hadde høy risiko for hjerneslag, var risikoen noe høyere enn for lavrisikopasientene, men forskjellene var i vår studie ikke signifikante. I en mindre subgruppeanalyse av inflammatoriske biomarkører i blod, fant vi ingen sammenheng mellom nivåer av disse prøvene og risiko for slag eller andre vaskulære hendelser etter TIA.

Vi konkluderte med at for å begrense risikoen for hjerneslag etter TIA så mye som mulig, bør man i stedet for å lene seg på ulike risikoskår, sørge for rask, grundig og helhetlig utredning i spesialisthelsetjenesten for alle pasienter hvor det er mistanke om gjennomgått TIA. Selv om langtidsrisiko for vaskulære hendelser reduseres etter ett år, har TIA-pasienter også deretter en kontinuerlig økt risiko.

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MIDNOR TIA

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Summary

Every year millions of people suffer stroke worldwide, and stroke is the second-leading cause of premature death and disability. In Norway, approximately 12 000 people suffer a stroke annually. There is a wide specter of consequences of stroke – ranging from transient symptoms to strokes leading to total functional dependency and death.

Transient ischemic attack (TIA) is defined as an acute loss of focal brain or monocular function with symptoms lasting shortly, often less than one hour. TIA is considered a warning sign for a subsequent stroke. While there have been performed large prospective studies on patients with TIA internationally, there is a lack of such studies in Norway and Scandinavia.

The overall aim of this thesis was to increase the knowledge about TIA patients in our region. More specifically we wanted to investigate the risk of having a subsequent, established stroke after TIA. Different risk scores for TIA patients based on certain clinical traits have been developed the last two decades, and we wanted to evaluate these risk scores in our TIA patients, and to establish what role these scores could have in assessment of these patients in the primary and secondary health care.

We performed a prospective observational study in eight hospitals in the region of Central Norway, in close collaboration with the general practitioners and the primary health care system. Five hundred and seventy-seven patients were included and were followed up until five years after inclusion. Broad baseline data and data from investigations were gathered. In some of the patients expanded blood test to the regional biobank were taken. Telephone follow-up data and data from quality registries were used in assessing the risk of stroke after TIA.

The risk of stroke after TIA turned out to be low in our population, both shortly after the TIA and within one and five years. The stroke risk was noticeably lower than in older studies, but similar to that found in newer studies. There was an association between higher risk scores and increased stroke risk after TIA, but not at a significant level. In a small subgroup analysis

of inflammatory biomarkers, we found no association between levels of these and the risk of stroke and other cardiovascular events after TIA.

We conclude that, in order to reduce stroke risk after TIA as much as possible, instead of using risk scores, we should strive for fast, thorough and comprehensive investigation and treatment in the secondary health services for every patient with a suspected TIA.

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Abbreviations

AUC	Area under the curve
CI	Confidence intervals
CRP	C-reactive protein
CT	Computed tomography
DALY	Disability-adjusted life years
DAPT	Dual antiplatelet treatment
DWI; DW-MRI	Diffusion-weighted imaging; diffusion-weighted magnetic resonance imaging
ESRS	Essen stroke risk score
HR	Hazard ratio
ICC	Intraclass correlation coefficient
ICD-10	10th revision of the International Statistical Classification of Diseases and Related Health Problems
IQR	Interquartile range
LDL cholesterol	Low-density lipoprotein cholesterol
LiLAC	Life-long after cerebral ischemia trial
mRS	Modified Rankin Scale
NIHSS	National Institutes of Health Stroke Scale
OR	Odds ratio
RCT	Randomized controlled trial

ROC	Receiver operating characteristics curve
RRE-90	Recurrence risk estimator at 90 days
SD	Standard deviation
SPI (I/II)	Stroke prognosis instrument (I/II)
TIA	Transient ischemic attack
WHO	World Health Organization

List of Papers

This thesis is based on the following papers, which will be referred to in the text by their Roman numeral (I-III):

I Fredrik Ildstad, Hanne Ellekjær, Torgeir Wethal, Stian Lydersen, Janne Kutschera Sund, Hilde Fjærtoft, Stephan Schüler, Jens Wilhelm Horn, Geir Bråthen, Ann-Grete Midtsæther, Åse Hagen Morsund, Marja-Liisa Lillebø, Yngve Müller Seljeseth, Bent Indredavik. Stroke risk after transient ischemic attack in a Norwegian prospective cohort. *BMC neurology* 2019; 19: 2. 2019/01/05.

II Fredrik Ildstad, Hanne Ellekjær, Torgeir Wethal, Stian Lydersen, Hild Fjærtoft, Bent Indredavik. ABCD3-I and ABCD2 scores in a TIA population with low stroke risk. *Stroke Research and Treatment*, vol. 2021, Article ID 8845898, 8 pages, 2021.

III Fredrik Ildstad, Hanne Ellekjær, Torgeir Wethal, Stian Lydersen, Thor Ueland, Tom Eirik Mollnes, Pål Aukrust, Bent Indredavik. Five-year risk of cardiovascular events after transient ischemic attack – results from a prospective cohort. Submitted to *Acta Neurologica Scandinavica* on September 6, 2021.

1 Introduction

The age-standardized rates of stroke mortality have decreased worldwide in the past three decades, while the absolute number of people who have a stroke every year, stroke survivors, deaths related to complications, and the overall global burden of stroke are increasing.[1] Stroke is the second-leading cause of premature death and disability, and approximately a third of stroke survivors are functionally dependent at 1 year.[2] Moderate rises in TIA incidence has been reported in the same period.[3, 4]

There is an increased risk of stroke after TIA. *Without treatment*, stroke risk has been shown to be as high as 20% at 3 months, with the highest risk occurring already within the first two days.[5-7] Earlier studies have shown that up to 25% of ischemic strokes are preceded by transient ischemic symptoms.[89] TIA could therefore be considered a "red flag" and a critical opportunity to quickly find and treat the underlying cause in order to prevent a devastating stroke. Several prospective studies on the association between TIA and stroke have been performed internationally, and some retrospective or single-center studies have been performed in Scandinavia,[10, 11] but there has been a lack of large prospective observational studies on this patient group in Norway and in Scandinavia.

Also, different risk scores for defining mode of assessment and treatment of different risk categories of TIA patients have been developed and validated in studies in other countries. In the present thesis, methods and results from a large prospective TIA study from the region of Central Norway is presented, in relation to existing literature relevant for comparison. Both the risk of subsequent stroke and other cardiovascular events after TIA, and what role certain clinical and biological risk markers have in this patient population are discussed.

2 Background

2.1 Historical perspective

The first vague descriptions of transient neurological symptoms in medical literature can be traced back to the 17th century. In these descriptions symptoms representing focal deficits were not clearly distinguished from non-specific symptoms of a more global nature such as fainting or headache.[12, 13] The so called "cerebral softening", or loss of brain parenchyma at pathology, was until the middle of the 19th century believed to be caused by an inflammatory process. After having established that this was rather caused by occlusion of cerebral arteries, transient episodes of cerebral ischemia were recognized increasingly often in the next decades.[14, 15] In 1914 Hunt pointed out the role of "the carotid arteries in the causation of vascular lesions of the brain" and described "attacks of threatened hemiplegia and cerebral intermittent claudication".[16]

The term *transient ischemic attack* was introduced in 1954 and 1956 during the first two Princeton Cerebrovascular Disease conferences.[17] At these conferences different terms were considered: intermittent vascular insufficiency, recurrent focal cerebral ischemic attacks, ischemic recurrent attacks, transient cerebral ischemia and transient ischemic attacks. During the second conference neurologist Miller Fisher, who is credited with describing the clinical syndrome of TIA, presented an extensive definition of what he for the first time dubbed TIA, which "may last from a few seconds up to several hours, the most common being a few seconds up to 5 or 10 minutes".[18]

The real origin of the term "Transient Ischemic Attack" is described in "C. Miller Fisher: An appreciation" in a *Stroke* edition of 2013 citing Miller Fisher himself: *«…Here I have patients who have a blocked carotid and had transient blindness in the opposite eye [opposite to the subsequent stroke], and it meant that carotid disease causes trouble - I knew that by then - and that there are warning spells. Transient blindness was a warning that a stroke was coming. That was the birth of transient ischemic attacks. I didn't give it that name at that time, but then I went to veteran's hospitals on Sunday and spoke to relatives of people with*

strokes. And just one after another [they reported] warnings before the stroke came. So, within a few months I had found out about carotid disease, that it is associated with transient blindness, and that there are transient warning symptoms of different kinds before the big stroke comes. ...I used different terms for about a year and [then] decided on transient ischemic attack. A neurologist in Texas somewhere was at a meeting and he put up a slide and for transient ischemic attack, he didn't have room to put it all in one place, so he [wrote] "TIAs." That gave me the idea to shorten it to TIA. I told Ray Adams and - this is not complimentary - I told him that I had finally decided to call the warning spells TIAs. And he said, "It'll never fly." Just like that.»[19]

2.2 Definition of TIA

Since the early part of twentieth century, a variety of definitions of TIA involving duration of symptoms and signs have been used. A widely used definition during the last decades has been the diagnostic criteria from the World Health Organization (WHO) from 1976: *An acute loss of focal brain or monocular function with symptoms lasting less than 24 hours and that is thought to be caused by inadequate cerebral or ocular blood supply as a result of arterial thrombosis, low flow, or embolism associated with arterial, cardiac, or hematological disease.*[20]

TIA is distinguished from stroke on the basis of a 24-hour cutoff for resolution of symptoms. However, during the last two decades the WHO definition has been challenged since the 24-hour cutoff is arbitrary rather than being based on clinical, imaging, or pathological criteria. Also, the 24-hour cutoff does not reflect the fact that the majority of TIAs last for less than 60 minutes.[21] An alternative definition for TIA was introduced in 2002. It was proposed as comprising a transient episode of neurological dysfunction caused by focal brain or retinal ischemia *without evidence of acute infarction on brain imaging*.[22] This definition of TIA has both been welcomed and critiziced.[23] It has the problem that brain imaging does not correlate particularly well with pathological infarction: brain imaging may be normal in clinically definite stroke, silent infarction may occur, and the sensitivity of imaging is highly dependent on both imaging method and area of the brain being examined. As brain imaging technology

advances rapidly, it also means that what is defined as TIA will change (see Table 1 – based on “Transient Ischemic Attack and Stroke – Diagnosis, Investigation and Treatment” by G. Lau, S. Pendlebury, P. Rothwell).

When reviewing the literature, most studies with TIA patients (including the randomized controlled trials (RCTs)) use a clinical definition.[24] This shows that a clinical definition is still the most widely used definition in research and clinical practice, which also makes it possible to generalize the findings of these studies. In our TIA study, and in this thesis, the conventional TIA definition based on symptoms or signs lasting less than 24 hours, is being used.

Table 1. Advantages and disadvantages of conventional, time-based and imaging-based definitions of transient ischemic attack

Definition	Advantages	Disadvantages
Conventional definition	Diagnosis can be made at assessment	Diagnosis based on an arbitrary cut point of no physiological or prognostic significance
	Comparisons with previous studies using the conventional definition possible	Diagnosis based on patient recall, susceptible for recall bias
Imaging based definition	Based on patho-physiological endpoint and emphasizes prognostic importance of cerebral infarction	Diagnosis based on interpretation of imaging, which is likely to vary between individuals and centers; also, sensitivity of imaging techniques is likely to increase with time
	Majority of transient ischemic attacks last less than 60 minutes	Pathophysiological significance of changes on new imaging techniques not fully understood
	Encourages use of neuroimaging	Classification of events lasting more than 1 hour without infarction unclear
	Consistent with the distinction between unstable angina and myocardial infarction	Diagnosis cannot be made in center where no imaging (MRI) is available

2.3 Definition of stroke

A stroke is defined by WHO as rapidly developing symptoms and/or signs of focal, and at times global (applied to patients in deep coma and to those with subarachnoid hemorrhage), loss of brain function, with symptoms lasting more than 24 hours or leading to death, with no apparent cause other than that of vascular origin.[20]

There are three main pathological types of stroke: ischemic, primary intracerebral hemorrhage and subarachnoid hemorrhage. In Norway, of those patients admitted to hospital with stroke, 85% of the cases are comprised of ischemic strokes, 12% of intracerebral hemorrhages, and 3% of subarachnoid hemorrhages.[25]

2.4 Burden of stroke

Stroke is the second most common cause of death worldwide.[2, 26, 27] Mortality data however underestimate the true burden of stroke since, in contrast to coronary heart disease and cancer, the major burden of stroke is chronic disability rather than death. The Global Burden of diseases, Injuries, and Risk Factors Study, one of the most comprehensive observational epidemiological studies to date, reported that from 1990 to 2017 although stroke incidence, prevalence, mortality and disability-adjusted life year rates declined, the absolute number of people who developed new stroke, died, survived or remained disabled from stroke has almost doubled.[28] In 2017, there were globally 11.9 million incident, 104.2 million prevalent, 6.2 million fatal cases of stroke, and 132.1 million disability-adjusted life years (DALYs) were lost due to stroke. Approximately a third of stroke survivors are functionally dependent at 1 year. Stroke also causes secondary medical problems, including dementia, depression, epilepsy, falls, and fractures. The bulk of the global stroke burden during the last decades is in low- to middle-income countries.[29] This is partially due to a disproportionate higher incidence of hemorrhagic stroke in these countries. Also, diseases related to infections and malnutrition have been replaced by non-communicable diseases such as stroke. Increased smoking rates and increasing use of processed foods with more fat and salt has probably also contributed.[30]

In stroke and TIA research, the expression of "minor stroke" is often used. There is however no accepted definition for what constitutes minor stroke.[31] The distinction between minor and major stroke is sometimes based on the National Institute of Health Stroke Scale (NIHSS) at assessment of ≤ 3 or a score of ≤ 2 on the modified Rankin Scale (mRS) at 1 month. In line with the new tissue-based definition of TIA some also consider transient symptoms with a small ischemic brain lesion on imaging as a minor stroke, and further, due to the same clinical manifestations and management as TIA, consider these two clinically together.[9, 32] In our study we made a clear distinction between TIA, and minor and major stroke, including only patients with TIA according to the WHO definition into the study.

2.5 Epidemiology of TIA

The epidemiology of TIA is more challenging than stroke epidemiology since patients with TIAs are more heterogeneous and present to different clinical services, if they present to medical attention at all.[33] The incidence rate of new cases of TIA can most reliably be assessed in prospective population-based studies since hospital-based studies are subject to referral bias (the incidence rate: the number of new cases of a condition per unit time per unit population at risk, in this context expressed as the number of new cases per 1,000 population at risk per year).[34]

In the population-based Oxford Vascular Study (OXVASC), in a population of 93,000 defined by registration in nine general practices in Oxfordshire, UK, the incidence of definite, first-ever-in-a-lifetime TIA was 0.5/1,000 person-years. When including also possible TIA and recurrent TIA, the incidence was 1.1/1,000. In the same material, when taking into consideration all referrals to a TIA clinic including definite, probable and suspected events (with an eventual non-neurovascular diagnosis), and minor stroke, the incidence was 3.0/1,000.[35]

In another population-based cohort study (Framingham Heart Study) from 1948 to 2017, the estimated TIA incidence was 1.19/1,000 person-years, and when comparing the incidence of the earlier period from 1948 to 1985 with the most recent period from 2000 to 2017, the incidence remained unchanged.[36] Previous population-based cohorts have reported lower TIA incidence rates ranging from 0.42/1,000 person-years to 0.83/1,000 person-years.[37-39] A more recent population study in Sweden reported a TIA incidence of 0.74/1,000 person-years, and interestingly, similarly to the Framingham Heart Study, found no decline in incidence over time when comparing with previous studies.[40] Some studies have even found a moderate rise when comparing incidence in the 1980s with the 1990s and 2000s.[3, 4]

Constant or moderately rising TIA incidence rates over time maybe reflects changes in public health awareness, with people being more likely to seek medical attention for transient neurological symptoms. Additionally, better secondary prevention may have caused a shift from severe forms of cerebrovascular disease to less severe forms. As a result, TIA and suspected TIA are a common presentation to both primary and secondary health care services.

2.6 Clinical features and differential diagnosis of TIA

While TIAs are very rarely caused by hemorrhage,[41] the pathophysiology and causes of acute cerebral ischemia in TIA is the same as in stroke. The ischemia is due to locally decreased blood flow to the brain, or the retina of the eye, causing focal neurological symptoms, or transient visual disturbances.[42] Decreased blood flow result from either embolism into a cerebral supply artery (from the great proximal vessels, extracranial or intracranial arteries affected by atherosclerosis, or from the heart), or they can also be caused by occlusion of small perforating arteries. The majority of TIAs are probably caused by arterial embolism and occlusion.[43] Resolution of symptoms within a short time probably occurs by spontaneous lysis or distal passage of the occluding thrombus or embolus, or by compensation through collateral circulation restoring perfusion into the ischemic brain area. Less common are TIAs caused by low-flow distal to a severely stenosed or occluded artery in the neck, for instance related to a fall in blood pressure after antihypertensive medication, after standing or sitting up quickly or during cardiac arrhythmia.[44] These rarely observed episodes might have an

atypical presentation as symptoms may develop over several minutes, there may be irregular shaking or dystonic posturing of the extremities contralateral to the cerebral ischemia, or there may be certain visual disturbances.[45]

The key rule for recognizing a TIA is that symptoms of TIA should, in most cases, mimic known stroke syndromes, and so be "focal" and relatable to a certain arterial territory. In approximately 80% of TIAs carotid arteries are involved, and in 20% the vertebrobasilar.[46] Defining the arterial territory may be straightforward where there are cortical symptoms such as dysphasia, or brainstem symptoms such as diplopia. However, because the motor and sensory pathways are supplied by both vascular systems at different points in their course, it is not always possible to distinguish which territory is involved. One study found that the agreement between the clinical diagnosis of vascular territory in patients with TIA or minor stroke made by three neurologists compared with the near "gold standard" of lesion location on diffusion-weighted magnetic resonance imaging (DW-MRI or DWI) was only moderate, with kappa statistics varying from 0.48 to 0.54 for each neurologist. Interobserver agreement on territory ranged from 0.46 to 0.60.[47]

Symptoms of TIA are sudden, and an abrupt onset of maximal symptoms predict a final diagnosis of definite TIA.[48] Motor symptoms are the most common, including weakness, clumsiness and a feeling of heaviness on one side of the body.[49] Unilateral sensory symptoms are often described as numbness or deadness. Speech disturbances are common, both aphasia and dysarthria, or both. Transient monocular blindness, also called amaurosis fugax, affects the upper or lower half, or all the vision of one eye. Transient monocular ischemia can also cause partial visual loss, such as blurring or dimming. Symptoms of retinal ischemia may be very short-lived. Table 2 shows a list of transient neurological symptoms, divided by probability of representing a TIA.

If more than one body part is involved, the symptoms usually start simultaneously in all parts, persist for a while, and then gradually wear off. TIAs typically begin with *negative symptoms*, indicating a loss or reduction of central nervous system neuron function (e.g., loss of power, sensation, vision), in contrast to positive symptoms (e.g., pain, paresthesia, flashing lights, zigzag shapes) often occurring in nonvascular transient episodes. Vertigo, diplopia,

dysphagia, unsteadiness, tinnitus, amnesia, and drop attacks may be caused by posterior circulation ischemia, but if these symptoms occur in isolation, the diagnosis of TIA should only be considered when other possibilities are excluded. Although patients with non-focal symptoms of syncope or presyncope (light-headedness, fainting, blackouts) are sometimes referred for assessment of possible TIA, loss of consciousness is only very rarely a symptom of stroke or TIA.[50]

There is no test to definitely confirm a TIA. The gold standard remains a thorough clinical assessment as soon as possible by an experienced physician. The diagnosis relies heavily on the patient's account of their symptoms, and on the clinician's interpretation of these symptoms. A diagnosis of TIA is supported by sudden onset and definite focal symptoms in the history, and evidence of vascular disease on examination. TIAs are rare in young people without vascular risk factors. Owing to the transient nature of the symptoms of TIA, the differential diagnoses differ from that of stroke. Some conditions and syndromes are particularly frequently misdiagnosed as TIA and are often referred to as TIA "mimics", for instance migraine with aura, seizures (e.g., parietal-lobe epilepsy), syncopes, and anxiety related attacks. In Table 3 are listed some clinical features differing definite TIAs from these often considered most common "mimics". Other causes of transient focal neurological attacks are labyrinthine disorders, metabolic (hypo- or hyperglycemia, hypercalcemia, hypokalemia, hyponatremia), cerebral amyloid angiopathy with amyloid spells, peripheral nerve root lesions, multiple sclerosis, myasthenia, structural intracranial lesions (tumor, chronic subdural hematoma, vascular malformation, giant aneurysm).

Table 2. Overview of common and less common symptoms of TIA

Most common symptoms
Half-sided weakness in one or two limbs and the face
Half-sided sensory deficit in one or two limbs and the face
Aphasia or dysarthria
Monocular blindness (amaurosis fugax) or visual-field defect (homonymous hemianopia)
Less common symptoms (at least two of these symptoms combined increases probability)
Diplopia
Balance problems, incoordination of limbs
Vertigo, dizziness
Dysphagia
Probably not a TIA
Confusion
Transient loss of consciousness
Amnesia
Partial sensory deficit
Unusual cortical visual symptoms (e.g., bilateral positive visual phenomena)

Table 3. Overview of some of the characteristics of TIA and TIA mimics

	Demographic	Neurological symptoms	Associated symptoms	Timing
TIA	Older age Vascular risk factors	Negative symptoms, usually maximal at onset Does not migrate Alteration in consciousness almost never occurs	Headache may occur	Sudden onset, gradual offset, often duration < 1 hour
Migraine	Young age More common in women	Positive symptoms, spreading at onset Visual symptoms most common Symptoms may evolve into another modality Alteration of consciousness seldom	Headache usually afterwards with migrainous features	Usually up to thirty minutes, sometimes longer
Syncope	Any age, often younger More common in women	Faint or light-headed Vision may darken Loss of awareness	Sweating, pallor, nausea, rapid recovery to full alertness	Seconds to less than a minute
Anxiety / functional	Younger More common in women	Isolated sensory symptoms common	May be preceded by emotional or psychosocial stressors	Recurrent, stereotyped
Seizures	Any age	Positive symptoms, including limb jerking, dystonic posturing, head turning Loss of awareness and amnesia unless simple partial seizures. Postictal negative symptoms (e.g, Todd's paresis)	Tongue biting, incontinence, muscle pains, exhaustion or disorientation, headache	Usually less than two minutes

2.7 Management of TIA

2.7.1 Assessment of TIA

From at physiologic perspective, TIA and stroke represent different ends of an ischemic continuum. However, there is no qualitative difference between TIA and stroke, anything that causes an ischemic stroke may also cause a TIA. Therefore, the management of a patient suspected of having had a TIA, is similar to that of a stroke patient.[51]

The diagnosis of TIA depends primarily on the quality and quantity of information available at the time of assessment. Clinical history is essential in diagnosing a TIA. After clarifying the patient's symptoms, the circumstances of the event should be determined. Was the onset sudden or gradual? What was the patient doing at the time? Have the symptoms occurred before? Patients vary in reliability in reporting the events they have experienced, so even an experienced physician may find it challenging to make a certain diagnosis based on the history and physical examination alone. Even stroke experts do not agree about which clinical events are in fact TIAs.[52, 53] Also, in some studies up to 60% of patients referred to a TIA clinic will not have a final diagnosis of TIA.[48, 54] Identification of possible TIA mimics is an important stage in the assessment of patients with transient neurologic symptoms. A diagnosis of a TIA mimic will impact treatment decisions and provides reassurance when the diagnosis is something more benign.

After a thorough clinical history has been taken, a neurologic and cardiac examination should be completed. An electrocardiogram (ECG) and cardiac telemetry monitoring should be performed to evaluate for atrial fibrillation. In patients in whom the cause of the TIA is unclear after the initial investigations, further evaluations may include prolonged cardiac monitoring (Holter monitoring or an implantable cardiac monitoring device) and echocardiography. Transesophageal echocardiography to detect cardiac structural abnormalities such as patent foramen ovale, valvular disease, and atrial thrombus as a source of cerebral embolism may be performed if it will alter management decisions. Blood pressure, pulse rate, and oxygen saturation should be obtained. Routine blood work should be done,

including complete blood count, glycated hemoglobin, blood glucose, lipids, electrolytes, sometimes coagulation screen and other tests as clinically indicated.[24, 55, 56]

The preferred neuroimaging test for patients with a suspected TIA is DW-MRI (DWI).[9, 55, 57] This should be performed as early as possible after the TIA.[58] The sensitivity in detecting brain ischemia is much higher than that with computed tomography (CT).[59, 60] In some studies, in up to 50% of patients with suspected TIA according to the time-based definition, a bright spot indicating ischemia is found on DWI.[9, 22, 61-64] Although CT of the head generally cannot be used to diagnose ischemia, when DWI imaging is not available, CT should be performed to rule out alternative causes.

In most TIA patients, extracranial arteries should be routinely assessed with the use of carotid duplex ultrasound. CT angiography, and MRI angiography, could be alternative modalities of assessment, both for clarifying the degree of carotid stenosis detected with carotid duplex ultrasound, and when there is suspicion of symptomatic stenosis or occlusions in intracranial arteries.

2.7.2 Treatment of TIA

Two hallmark TIA studies published in 2007 showed up to an 80% reduction in stroke risk after TIA with the early implementation of secondary stroke prevention strategies.[65, 66] Recognition and rapid assessment and management of TIA offers the greatest opportunity to prevent disabling stroke.

In patients with a non-cardioembolic TIA event, aspirin (acetylsalicylic acid) is the most effective treatment to reduce the risk of recurrent stroke during the first 3 months.[67] A loading dose of 300 mg should be administered as soon as possible after TIA symptoms, preferably before admission or on arrival for urgent care.[32] Dual antiplatelet therapy with aspirin and clopidogrel for 10 to 21 days after TIA, and then mono antiplatelet therapy, has been shown to reduce subsequent stroke rates,[68] and is considered by many experts to be the standard of

care.[55] Patients with atrial fibrillation, or other cardioembolic causes of the ischemic event, should be started on anticoagulation. In patients with ipsilateral, significant carotid stenosis, carotid endarterectomy is performed, if no other etiologies are considered to be more likely. Based on studies proving that aggressive lowering of low-density lipoprotein (LDL) cholesterol levels reduces cardiovascular risks after acute coronary syndrome and ischemic stroke, most patients with TIA are treated with statins (target LDL cholesterol < 1.8 mmol/L, <70 mg per deciliter).[69] Blood pressure-lowering medications are initiated if indicated (target < 140/90 mmHg, or <130/80 in patients with diabetes and small-vessel disease). In patients with known or newly diagnosed diabetes mellitus, a glycated hemoglobin-level of < 53 mmol/mol (< 7%) is targeted. Generally, patients should be encouraged to do lifestyle interventions, such as smoking cessation and physical exercise, and counseling regarding diet and weight loss is given, if needed.

2.8 Methods of determining prognosis in TIA

When a diagnosis has been made, the *prognosis* - the likely course or outcome when having this diagnosis or put more stringent - the absolute risk of poor outcome - is an issue that is important both for the patient and the treating physician. Simple prognostic studies of groups of patients can provide useful information on the average risk of poor outcome and could potentially also provide data that can be used to inform decisions about treatment on an individual level. If possible, treatments should always be targeted at those individuals who are likely to benefit. On the other hand they should be avoided in those with little chance of benefit of the treatments, or in whom the risks of complications of treatments outweighs the expected benefit.[34]

A *prognostic model* is the mathematical combination of two or more patient or disease characteristics to predict outcome. Alternative terms for prognostic models that are used in research and in clinical situations are *prognostic indexes, risk scores, probability models, risk stratification schemes, or clinical prediction rules*.[34, 70] To be useful, they must be shown to predict clinically relevant outcomes reliably. This means that they must derive from a representative cohort in which outcome has been measured accurately, and they must go

through both internal and external validation.[71, 72] A risk score should also ideally be simple enough to be memorized and calculated without the need for a calculator. Prediction models are usually developed using logistic regression or Cox regression, and the samples size needed depends on the number of outcomes, and not the number of patients.[73] The variables in the model should be chosen based on reasonable clinical criteria, and potential interactions between the predictive value of particular variables should be avoided.

Several prognostic models, or risk scores, have been developed to predict the individual short- and long-term risk of stroke following an initial episode of stroke or after stroke *or* TIA. Examples of these scores are the ESRS and RRE-90,[74, 75] which were developed solely from stroke cohorts. Others were developed from a combination of TIA and stroke patients, like SPI-I and SPI-II,[76, 77] Dutch TIA score and LiLAC score.[78, 79]

In the 1990s the Hankey score was derived from at cohort of 469 TIA patients and evaluated prospectively over an average period of 4.1 years. The major outcome events were a stroke, coronary event, stroke, myocardial infarction, or vascular death. It used 8 prognostic factors to determine a 5-year risk percentage. These factors included age, gender, affected region (amaurosis fugax, carotid as well as vertebrobasilar TIAs), frequency of TIA, peripheral vascular disease, left ventricular hypertrophy, and residual neurological signs.[80] In two independent validation cohorts (UK-TIA aspirin trial and Oxfordshire Community Stroke Project), the reliability of Hankey score was good for lower-risk patients, but it overestimated risk in the higher risk group.[81] Also, the complexity of this score makes the usefulness questionable.

A decade later, two other post-TIA risk scores were developed. The California risk score was derived from a retrospective cohort of 1707 patients identified by emergency department physicians as having TIA to predict the 90 day risk of stroke.[5] The ABCD score was derived from a population-based cohort of 209 patients of the Oxfordshire Community Stroke Project with a probable or definite TIA to estimate the 7 day risk of stroke, and it was validated in a similar cohort of 190 patients in the Oxford Vascular Study.[82]

By unifying the original California and ABCD scores, the *ABCD2 score* was developed to predict short-term (2, 7, and 90 days) risk of stroke among patients with TIA, and was meant primarily for use in triaging patients in primary and secondary care.[83] The score is based on information that is easily obtained, and is an acronym for the clinical parameters of *A*ge, *B*lood pressure, *C*linical symptoms, *D*uration of symptoms, and presence of *D*iabetes. Many studies have validated the ABCD2 score, with conflicting results regarding accuracy for both short- and long-term stroke prediction.[84-99] Nevertheless, this risk score has previously been implemented in several TIA guidelines.[9, 100]

Further on, several studies have tried to improve the performance of the ABCD2 score by adding additional variables, resulting in different variations of the score. ABCD2 + MRI , the Clinical- and Imaging-based prediction of stroke risk after TIA (CIP Model) and the ABCD2-I scores were created by adding different weighting of DWI imaging to the ABCD2 score.[101-103] The ABCD3 score was derived from ABCD2 score by assigning 2 points for dual TIA, and the *ABCD3-I score*[104] by assigning 2 points for at least 50% stenosis on carotid imaging and another 2 points for abnormal DWI. Validation results of the ABCD3-I score have also been conflicting.[105-112] The items of the ABCD2 score and its main variations are summarized in Table 4.

Prognostic models, or risk scores, based on demographic and clinical parameters, might be at risk of bias, and might not be accurate enough to allow reliable decision-making.[113, 114] Blood-based biomarkers might provide additional information that could be used for estimating the risk of recurrent stroke, or other cardiovascular events after TIA or stroke. Previous studies have reported on the prognostic value of various biomarkers related to different disease pathways, such as inflammation, thrombosis and cardiac function, for cardiovascular event and death, in subjects both with and without pre-existent cardiovascular disease.[115-120] Several biomarkers, including C-reactive protein (CRP), interleukin-6 (IL-6), and D-dimer, have been shown to predict long-term risk of cardiovascular evens in primary prevention populations.[121, 122] Studies investigating the prediction value of biomarkers for recurrent vascular events or death after TIA or stroke, however, have been conflicting.[123-139]

Table 4. ABCD2 score and its variants with items and definitions

Item	Definition	ABCD2[§]	ABCD2-I	ABCD3	ABCD3-I[§]
Age	≥ 60 years[‡]	0 or 1	0 or 1	0 or 1	0 or 1
Blood pressure	≥ 140/90 mmHg	0 or 1[†]	0 or 1[†]	0 or 1[†]	0 or 1[†]
Clinical features	Speech impairment without weakness Unilateral weakness	1 2	1 2	1 2	1 2
Duration	< 10 min 10-59 min ≥ 60 min	0 1 2	0 1 2	0 1 2	0 1 2
Diabetes	Diabetes present[‡]	0 or 1	0 or 1	0 or 1	0 or 1
Dual TIA	TIA prompting medical attention, plus at least on other TIA in the preceding 7 days	NA	NA	0 or 2	0 or 2
Imaging – carotid	≥ 50 % stenosis of ipsilateral carotid artery[‡]	NA	NA	NA	0 or 2
Imaging - brain	Acute DWI hyperintensity[‡]	NA	0 or 3	NA	0 or 2
Total range		0-7	0-10	0-9	0-13

NA: not applicable

[†]Coded as 1 if either systolic blood pressure ≥ 140 or diastolic blood pressure ≥ 90 mmHg

[‡]Coded as 0 if definition not fulfilled

[§]Clinical scores investigated in this thesis

2.9 Prognosis after TIA

From the 1950s on a risk of stroke after TIA of 1% to 2% at 7 days and 2% to 4% at 1 month were usually reported.[140, 141] These rates were however probably underestimates because of the long delay before patients were included into these hospital-based studies and clinical trials. Any patient who had a major stroke during this period were excluded.

In the 1990s and beginning of the 2000s several studies started to indicate a high rate of subsequent stroke after TIA,[5, 7, 37, 82, 83, 142-144] with a 7-day risk of recurrent stroke up to 10%. Already in the middle of the 90s guidelines for the management of TIA recommended a timely evaluation of patients with TIA,[145] and some years later supplements to these guidelines emphasized different medical and surgical treatment.[146] Furthermore, the findings from the Oxford Vascular Study group from 2000 to 2007 (the EXPRESS study),[65] and the SOS-TIA study,[66] confirmed the importance of urgent TIA management, especially among patients with vascular risk factors. In line with this, management of TIA has gained significant attention during the past 25 years. Several studies and meta-analysis have during the last two decades shown a reduction in the rate of subsequent stroke after a TIA.[36, 147-149]

Less is known regarding the long-term risk of stroke and other cardiovascular events after TIA, and the clinical and demographic factors that determine this risk. In a large multicenter TIA registry study, it was found that the risk of stroke and cardiovascular events continues to rise steadily in the long term, suggesting that patients with TIA remain at high risk beyond the early phase.[150] In Scandinavia, up to date no large, prospective multicenter TIA studies, either on short- or long-term risk after TIA, have been performed.

2.10 Summary and rationale for the thesis

The burden of stroke continues to rise worldwide, and transient ischemic attack is a major herald of stroke. There are studies showing an increasing incidence of TIA, and there is some evidence that patients with TIA remain at high risk beyond the early phase. Studies on prognostic models for post-TIA risk of stroke and other cardiovascular events are conflicting, and their role in TIA management is unsure. Large prospective, multicenter cohort studies on stroke risk after TIA, involving the use of common prognostic models, have not been performed in Scandinavia to date. Since stroke patients in Norway and other Scandinavian countries differ from stroke populations in many other countries by having lower post-stroke mortality,[151] it is timely to assess the risk of vascular events in such a population. Also, modern treatment regimens and alteration in risk factors in the population make it necessary to come up with new estimates of what risk lies in having had a TIA.

3 Aims of the thesis

The overall aim of this thesis was to increase knowledge about patients who have had a transient ischemic attack in our region of Central Norway, exploring their risk factors, their short-, medium- and long-term risk of stroke and other cardiovascular events, the role of the most common clinical risk scores, and in a subgroup also assessing the prognostic value of blood biomarkers.

The PhD thesis consists of three papers, and the specific aims of each were:

Paper I: The primary aim was to find the cumulative stroke risk within 1 week, 3 months and 1 year after TIA. The secondary aim was to evaluate the predictive value of the dichotomized ABCD2 score, low-risk 0-3 versus high-risk 4-7.

Paper II: The primary aim was to investigate the predictive accuracy of the ABCD3-I score. Secondary, we aimed to compare this score with the ABCD2 score in short- (within 3 months) and medium-term (1 year) risk stratification. We also wanted to examine whether the ABCD3-I score performed better in populations with a low risk of stroke after TIA.

Paper III: The primary aim was to examine the risk of new cardiovascular events within 5 years after TIA. The primary outcome was a composite of stroke, acute coronary syndrome, and death from cardiovascular causes. Our secondary aim was to find baseline predictors of long-term vascular events, and to examine if inflammatory biomarkers could be used as prognostic markers of future cardiovascular events in TIA patients.

4 Material and methods

4.1 Study design and setting

The thesis is based on our TIA study MIDNOR TIA, which was a prospective, multicenter study performed in the stroke units of all eight hospitals in the geographical and administrative region of Central Norway, which consists of two counties: Trøndelag and Møre og Romsdal. The region has currently (2021) 736 668 inhabitants, and this constitutes about 14% of Norway's total population of approximately 5.4 million. The hospitals involved are situated in Volda, Ålesund, Molde, Kristiansund, Orkdal, Trondheim (St. Olavs hospital), Levanger, and Namsos. In St. Olavs hospital, which is a university hospital, at that time the neurological department treated TIA and stroke patients aged below 60 years, and the stroke unit in the medical clinic treated those above 60 years. In the other hospitals the stroke care was either done in stroke units run by neurologists, specialists in internal medicine and geriatrics, or in a collaboration between these.

Patients were consecutively enrolled from October 2012 to July 2014. Only St. Olavs hospital had an out-patient service for acute TIA diagnostics and treatment, but most patients were treated as in-patients. In total, 577 patients were enrolled into the study. The duration of the inclusion period was according to what was planned in the study protocol. Figure 1 illustrates the study design.

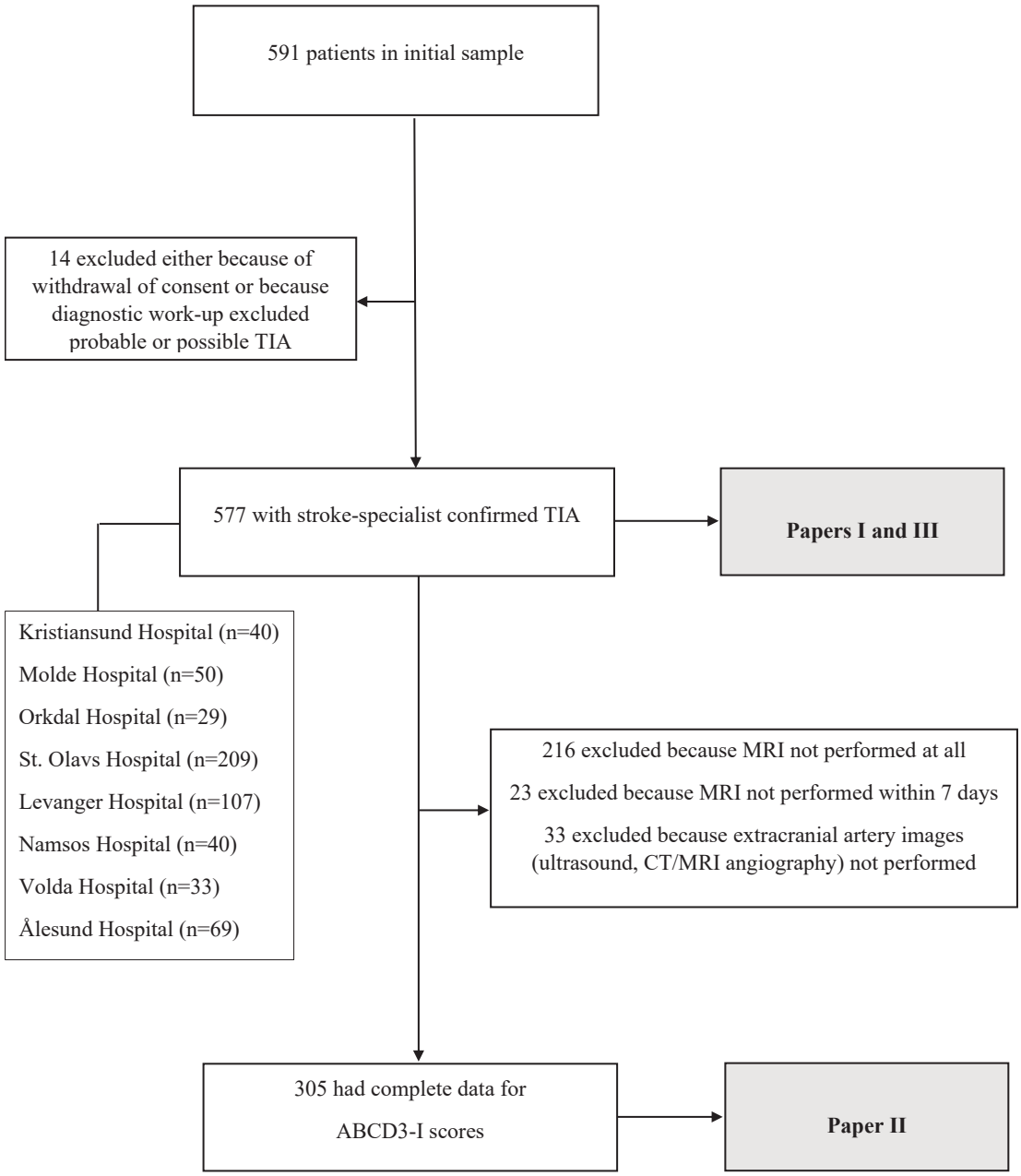

Figure 1. Overview of the study design

4.2 Preparations for the study and diagnostic evaluation

MIDNOR TIA was a hospital-based TIA risk study, and not a population-based study to estimate the incidence of TIAs in the population. However, to enroll as representative TIA patients as possible, thus reducing potential referring bias, we implemented two measures in the few months before initiating inclusion. Firstly, we sent a brochure to all the general practitioners and other referring physicians in the region, informing about the study in general, and specifying the most typical symptoms of a TIA. A similar brochure, again specifying common symptoms of TIA and symptoms usually not representing TIA, was sent to all physicians in the emergency departments and stroke units at all involved hospitals. Secondly, we sent an information letter to all home care nursing facilities, asking the personnel to refer patients reporting of having had symptoms suspicious of TIA during the recent days, to their general practitioner on the day of notification.

Stroke physicians performed inclusion according to criteria of eligibility. In most cases this was done after in-person assessment on the hospital ward, and in a few cases in the outpatient clinic. Physicians involved in patient enrollment were experienced regarding assessment of TIA and stroke patients. They were instructed in enrolling patients who had a probable, or a possible TIA, the last one referring to patients where other causes of transient neurological symptoms were less likely than an ischemic cause.

4.3 Study participants

Eligibility criteria specified prior to initiating study enrollment are summarized in Table 5.

Table 5. Eligibility criteria

Probable / possible TIA (based on patient history, neurologic and general clinical examination, brain imaging, and other investigations)
Resident of Central Norway
Age between 18 and 90 years
Possible to enroll within 2 weeks from index TIA
Modified Rankin Scale ≤ 3 and living at home
Informed consent

4.4 Data collection and assessment of outcome

Trained research nurses appointed at each center prospectively registered detailed baseline data using standardized web-based case report forms. The study group agreed on a standardized diagnostic work-up based on current national guidelines for assessment of TIA. As a minimum this contained a thorough patient history, a neurologic and general physical examination, blood tests, ECG, and cardiac telemetry if available. Further, either MRI or CT, and carotid Doppler ultrasound or CT angiography, was required among the investigations. The ABCD2 score reported in paper I was prospectively recorded in standardized paper forms that explicitly listed each item of the score. The ABCD3-I score reported in paper II was

calculated after the study completion by assigning additional two point for dual TIA, two points for stenosis on carotid imaging, and two points for positive diffusion-weighted imaging.

In the first part of the study recurrent strokes within 1 week, 3 months and 1 year after the TIA that prompted medical attention, was recorded by telephone follow-up at each time point. This was also done by the research nurses. All registered strokes within the time points of 1 week, 3 months, 1 year and 5 years were confirmed by using data from the Norwegian Stroke Registry, which is the national quality registry for stroke care established by law. Data from the Norwegian Cardiovascular Disease Registry was used for registering deaths and carotid surgery in the 1-year follow-up, and for the outcomes of acute coronary syndrome, death by cardiovascular causes, and all cause-mortality within 5 years.

4.5 Definitions

Ahead of enrollment several definitions were specified:

In our study we used the conventional, time-based definition of TIA: *an cute loss of focal cerebral or ocular function lasting less than 24 hours*.[20] As for TIA, we also used the WHO criteria of stroke which includes both ischemic and hemorrhagic strokes.[152]

Carotid stenosis was defined as ≥ 50% narrowing in the lumen of the internal carotid artery that could be responsible for the transient episode. The index TIA was defined as the most recent TIA leading the patient to seek medical help. Dual TIA was defined as the occurrence of at least one other TIA during the 7 days before the index TIA. The blood pressure measurement used for the ABCD2- and ABCD3-I assignment was the first ever recorded after the onset of the TIA. A positive DWI was defined as ≥1 areas of high signal intensity interpreted as acute ischemic lesions. The abnormal DWI findings were diagnosed by radiologists, in most cases neuroradiologist. In the extended 5-year follow-up the definition of death from cardiovascular causes was based on the 10th revision of the International Statistical

Classification of Diseases and Related Health Problems (ICD-10) and included fatal ischemic, hemorrhagic or unspecified strokes, acute coronary syndrome, heart failure, cardiac arrest, pulmonary embolism, deep venous thrombosis and aortic disease.

4.6 Clinical management

The clinical management followed the current national treatment guidelines for TIA, which was in line with other national and international guidelines.[153] Referring physicians were informed to administer aspirin bolus dose of 300 mg as soon as possible after the transient event. In many patients, aspirin was continued in combination with other antiplatelet treatment (most often dipyridamole), except for the cases where atrial fibrillation or other cardioembolic etiology gave indication for anticoagulation therapy. Vascular risk factors such as hypertension, hypercholesterolemia, and diabetes were assessed, and treated according to guidelines. Supplemental lifestyle advice was given. Patients with symptomatic, significant carotid stenosis were treated with endarterectomy, if no contraindications were present. The follow-up of secondary prevention was performed by the patients' general practitioners.

4.7 Estimation of power

The ABCD2 score was derived from the California score and ABCD score (total n=1916). These original scores were validated in four independent groups of patients (total n=2893) diagnosed with TIA in emergency departments and clinics in defined populations in the US and UK. In the validation study of these two combined scores (n=4809),[83] an ABCD2 score of 0-3 (1628/4809 – 34%) gave a stroke risk within 1 week of < 1%, and a score of 4-7 (3181/4809 – 66%) gave a stroke risk of > 5%. With significance level 0.05 and power 80% we calculated a requirement of 564 patients.

In paper II we validated the ABCD3-I score, which requires completeness of additional history information (presence of dual TIAs or not) and results from diagnostic investigations (of extracranial arteries and DWI). The power estimation did not take into account potential missing data for any items in this score. Likewise, we did not perform any power calculations for the subgroup analysis of blood biomarkers in paper III. The goal was to achieve additional blood samples from as many of the included patients as possible, but the capacity and staff in the investigating stroke unit, put a restriction on the number of tests.

4.8 Statistical procedures

Demographic and baseline data:

Descriptive statistics were used to report the demographic and baseline data. Continuous variables were given as means with standard deviations (SD), and categorical variables were presented in frequencies and percentages.

Statistical program packages used for all analysis:

IBM SPSS Statistics version 23-25 were used for most analysis. Additionally, the Roger Newson's program Somers' D[154] in Stata 15 was used to compute an equivalent to the AUC when analyzing the risk scores in paper 2.

4.8.1 Paper I

We used Kaplan-Meier analysis to determine the cumulative stroke-free survival after TIA within 1 week, 3 months and 1 year. Log rank test was used to assess for statistical differences in stroke-free survival between the ABCD2 groups. Non-stroke related deaths were treated as censoring events. To test the predictive ability of the ABCD2 score, we used a receiver operating characteristics curve (ROC), quantifying the areas under the curve (AUC). Perfect prediction of in this context a clinical risk score, produces an AUC of 1.0, whereas

prediction that is no better than chance produces an AUC of 0.5. Confidence intervals (CI) for binomial proportions were calculated using the Wilson score method.[155] To further analyze the ABCD2 score we performed a Cox proportional hazards regression analysis to calculate hazard ratios (HRs), comparing ABCD2 high-risk scores (4-7) with low risk (0-3), using the low-risk group as the reference category.

4.8.2 Paper II

For testing and comparing the predictive ability of the ABCD2 and ABCD3-I scores, the Roger Newson's program Somers' D was used to compute the Harrell's C, which is an equivalent to the AUC. The values found were for the rest of the paper consequently referred to as the AUC. As in paper I, we performed Cox proportional hazards regression analysis to calculate HRs, using the low-risk ABCD3-I group as the reference category. We also performed a Cox regression analysis with the covariates positive DWI, dual TIA, and carotid stenosis one at a time to identify to what degree these additional features in the ABCD3-I score contributed to the predictive value of the score.

4.8.3 Paper III

The long-term cumulative incidence of the composite outcome consisting of stroke, acute coronary syndrome, and cardiovascular death, was estimated by Kaplan-Meier plots. The log rank test was used to assess for statistical differences in event-free survival for baseline risk factors. In the composite outcome, if more than one event occurred, the event occurring closest in time to the index TIA was used, and all causes of death other than by stroke and other cardiovascular events were treated as censoring events. Events that occurred after the 5-year follow-up period were not included in the analyses. Predictors of outcome events were assessed using univariable and multivariable Cox proportional hazard regression analysis. All variables, regardless of significance value, were included into the multivariable analysis.

In the subgroup analysis of serum biomarkers, a Cox proportional hazard regression analysis (adjusted for age) was used to calculate odds ratios (OR) and 95% CI per unit increase in biomarker for the dependent binomial outcomes of recurrent stroke and the composite outcome of stroke, acute coronary syndrome, and cardiovascular death. To reduce the level of confounding, all patients with CRP above 10 mg/L were analyzed for comorbidities involving increased immune response. On this basis six patients were excluded from the final analysis (two because of ongoing urinary tract infections, one because of ongoing vasculitis, one because of active seronegative rheumatoid arthritis, one with newly diagnosed esophageal cancer, and one because of recent orthopedic surgery). In the few cases where the biomarker results were below detection values, we imputed random values between 0 and the lower detection number.

4.9 Ethical concideration

The MIDNOR TIA study was approved (REC no. 2012/1224) by the Regional Committee of Medical and Health Research Ethics of Møre og Romsdal and Trøndelag, Norway (REC Central, Faculty of Medicine and Health Sciences, Norwegian University of Science and Technology). All the subjects gave written informed consent before inclusion in the original 1-year follow-up study. Upon performing the 5-year follow-up study, the Regional Ethics Committee gave additional approval for using collected baseline data and quality registry data from the time of the qualifying event and 5 years onward. Permission to take additional serum and plasma samples at baseline for storage in the regional biobank, was given in the original approval. The Norwegian Institute of Public Health (Folkehelseinstituttet) is the data controller for the registries used in the study, and according to the acceptance from REC Central gave permission to use data from the Norwegian Cardiovascular Disease, hereunder Norwegian Stroke Registry and Norwegian Myocardial Infarction Registry. Approval to use data from these registries for the 5-year follow-up publication was given in November 2020 (REC no. 28560).

Patients were informed that assessments, and treatments would be done according to current guidelines for TIA patients,[153] and that the only difference in practice for included patients would be receiving a telephone call from a study nurse at 1 week, 3 months, and 1 year after enrollment.

5 Summary of the papers

5.1 Paper I

Stroke risk after transient ischemic attack in a Norwegian prospective cohort

From October 2012 to July 2014, we performed a prospective, multicenter study enrolling 577 patients with a TIA within the previous 2 weeks. Our aim was to assess stroke risk at 1 week, 3 months and 1 year after TIA, and to determine the predictive value of the dichotomized $ABCD^2$ score (0-3 vs 4-7) at each time point. We used data obtained by telephone follow-up and registry data from the Norwegian Stroke Registry. The mean time from TIA onset to hospital admission was 17 hours, and 493 patients (85.4%) were examined by a stroke specialist within 24 hours after symptom onset. In all, five patients had a stroke within 1 week (all strokes within 1 week occurred within the first 2 days), 19 patients within 3 months, and 31 patients within 1 year, corresponding to a cumulative incidence of stroke of 0.9%, 3.3% and 5.4%, respectively. The cumulative incidence within the same time points for the high-risk ABCD2 group (score 4-7) was 1.1%, 4.0%, and 6.7%, and for the low-risk group (score 0-3) 0.5%, 1.9% and 2.9%. The accuracy of the $ABCD^2$ score provided by *c*-statistics at 7 days, 3 months and 1 year was 0.62 (95% CI, 0.39-0.85), 0.62 (95% CI, 0.51-0.74) and 0.64 (95% CI, 0.54-0.75), respectively.

In conclusion, we found a lower stroke risk after TIA than reported in earlier studies. We also concluded that $ABCD^2$ score did not reliably discriminate between low and high-risk patients, suggesting that it may be less useful in populations with a low risk of stroke after TIA.

5.2 Paper II

ABCD3-I and ABCD2 scores in a TIA population with low stroke risk

In the second paper our aim was to evaluate the ABCD3-I score and to compare it with the ABCD2 score in short- (1 week) and medium-term (3 months; 1 year) stroke risk prediction. In our prospective TIA cohort consisting of 577 patients, a subset of 305 patients had complete data for both risk scores. We calculated the AUC statistics of the ABCD3-I score and compared this with the ABCD2 score. Telephone follow-up and registry data were used for assessing stroke occurrence. Within 1 week, 3 months and 1 year, 1.0% (n=3), 3.3% (n=10) and 5.2% (n=16) experienced a stroke, respectively. The AUCs for the ABCD3-I score were 0.72 (95% CI, 0.54 to 0.89) at 1 week, 0.66 (95% CI, 0.53 to 0.80) at 3 months and 0.68 (0.95% CI, 0.56 to 0.79) at 1 year. The corresponding AUCs for the ABCD2 score were 0.55 (95% CI, 0.24 to 0.86), 0.55 (95% CI, 0.42 to 0.68), and 0.63 (95% CI, 0.50 to 0.76).

The ABCD3-I score had limited value in short-term prediction of subsequent stroke after TIA, and it did not reliably discriminate between low and high-risk patients in long-term follow-up. The ABCD2 score did not predict subsequent stroke accurately at any time point. Since there is a generally lower stroke risk after TIA during the last years, the benefit of these clinical risk scores and their role in TIA management seems limited.

5.3 Paper III

Five-year risk of cardiovascular events after transient ischemic attack – results from a prospective cohort

The background for the third paper was the fact that there are few contemporary, prospective studies reporting on the long-term risk of stroke and other cardiovascular events after transient ischemic attack (TIA). In our long-term follow-up study our primary aim was to examine the risk of new cardiovascular events within 5 years after TIA. The primary outcome was a composite of stroke, acute coronary syndrome, and cardiovascular death. We used data from the Norwegian Cardiovascular Disease Registry. Secondary, we aimed to identify baseline predictors of long-term cardiovascular events, including inflammatory biomarkers in a subgroup analysis consisting of 112 subjects. The primary outcome occurred in 108 patients (18.7%), of which 69 patients (12.0%) had a stroke and 47 (43.5%) events were registered during the first year after TIA. Increasing age (HR 1.05; 95% CI, 1.03 to 1.08), male sex (HR 1.82, 95% CI 1.16 to 2.85), hypertension (HR 1.67; 95% CI 1.04 to 2.67) and acute infarction on brain imaging (HR 1.84; 95% CI 1.17 to 2.91) were significant predictors for the primary outcome. In the subgroup analysis, none of the blood inflammatory biomarkers were associated with cardiovascular events.

Even if the risk of cardiovascular events was highest during the first year after TIA, and relatively low during the next years, the risk kept steady throughout the follow-up period. This emphasizes the importance of continuing long-term secondary preventive treatment after TIA. The sample size of the subgroup analysis of inflammatory biomarkers was small, but the results still give us reason to believe that such biomarkers are probably not important as prognostic markers of cardiovascular disease in TIA patients.

6 General discussion

6.1 The main results of the thesis

The overall purpose of our prospective study and this thesis was to collect and follow a cohort of TIA patients over time to estimate their short-, medium- and long-term risk of subsequent stroke and other cardiovascular events, and to evaluate clinical risk scores and biological markers for predicting prognosis after TIA.

First, this thesis has found that the risk of stroke after TIA in a hospital-based setting where almost all patients were assessed in a specialized stroke units shortly after the transient event, is low. Rapid assessment and intervention in specialized stroke centers are presumed to be the key factors behind the low stroke risk in our study, and the decreasing post-TIA stroke risk observed internationally during the last decades.

Second, we showed that the most widely used TIA risk stratification rules, the ABCD2 and the ABCD3-I scores, had limited value in prediction of subsequent stroke in both short- and long-term follow-up. The scores were able to identify patients with very low risk of stroke after TIA. However, since the high-risk group also had relatively low risk of stroke, and since low-risk patients also can have underlying high-risk pathology, these clinical risk scores do not seem to have a central role in the organization and assessment of TIA patients.

Third, we found that the risk of major cardiovascular events, and especially stroke, was highest during the first year after TIA, and then the risk remained steady over the next years.

Finally, we found no association between levels of blood inflammatory biomarkers taken in the acute phase after TIA, and stroke and other cardiovascular events within 5 years.

In the following section an integrated discussion of the results of the thesis is given, considering methodological issues, and results from other relevant studies.

6.2 Methodological considerations

This thesis builds on prospective, observational data from a cohort of patients with suspected TIA. Except from telephone follow-up by study nurses at certain time points, and usual care according to current treatment guidelines, there were no specific interventions.

Design

The prospective observational cohort study design used in our study has the advantage of being close to clinical practice. Cohort studies allow for assessing associations between exposures and new cases of the outcome (or several outcomes) over time, to get incidence rates and relative risks. They are able to assess associations, but they cannot establish cause and effect, like randomized controlled trials can.[156] They can be accurate in regards to the information collected about exposures, endpoints, and confounders. Main disadvantages of cohort studies are loss to follow-up, validity issues due to systematic error, and that they are time consuming. And there are random errors, like in other study designs. Prospective cohort studies are considered the gold standard among observational studies.[157]

Validity

Although the prospective design is a major strength of our study, a general challenge of observational research is validity. Validity of a research study refers to a lack of systematic error.[158] Validity is commonly separated into two types: internal validity and external validity. Internal validity refers to the strength of inferences from the study - if the study has measured what it had originally planned on measuring. Did the "exposure" (independent variable) cause a difference in the outcome or was a difference in the outcome caused by systematic error, such as selection bias, confounding factors or missing data?[159] It is essential to have internal validity in order to establish external validity, which refers to the degree to which the study results can be generalized to other populations.[158] The highest level of external validity occurs when the results also can be generalized to other environments and other times.[160]

6.2.1 Internal validity of MIDNOR TIA study

The main methodological issues that could threaten the internal validity of our study are certain types of bias, precision related to sample size, and confounding factors.

Selection bias

The selection of subjects to study is important in all research. The probability of the event of interest occurring may be strongly related to how the sample was obtained. Selection bias takes place when the selection of individuals, groups or data for analysis is not random. The association between the exposure and the disease is dissimilar for the participants and the non-participants, resulting in the sample examined not being representative of the population intended to be studied.[158] There are some potential sources of selection bias in our TIA study, of which the main focus of the following section will be on the *study setting, timing of enrolment, diagnostic accuracy and loss to follow-up.*

Study setting

The MIDNOR TIA study was hospital-based, meaning that all patients of the cohort were enrolled after having been assessed by stroke physicians in the hospitals. This can imply selection bias, as for instance some very mild or short lasting TIAs might not have come to medical attention or were treated by the general practitioner without referral to the hospital. Also, there could have been underreporting of transient symptoms from frail, elderly patients living at home. Referral rates to the hospital can also vary geographically and over time and make comparison between studies less reliable. Measures were taken before starting enrolment in MIDNOR TIA to achieve a demographically and clinically representative TIA cohort. Brochures with information about the study, specifying the most typical symptoms of TIA were sent to all general practitioners and other referring physicians in the region, to all physicians in the emergency departments and stroke units at all involved hospitals, and to all home care nursing facilities. The baseline demographic and vascular risk factor characteristics in our study were comparable to other TIA stroke prediction studies, as shown in Table 6

where baseline data from our study are compared with a recent systematic review of 68 TIA risk studies with 223 866 patients performed between 1971 and 2019.[147]

Table 6. Comparison of baseline characteristics between MIDNOR TIA and a systematic review of 68 post-TIA risk studies

Baseline characteristic	MIDNOR TIA (n= 577) (%)	Systematic review, Shahjouei et al., 2020 (n= 223 866) (%)
Age in years, mean ± SD	70.5 (11.0)	68 (5.0)
Male	56.7	45.0
Hypertension	53.9	56.7
Former stroke	15.1	12.0
Former myocardial	11.6	11.8
Diabetes mellitus	11.4	21.8
Atrial fibrillation	13.7	15.1
Hypercholesterolemia	37.4	18.0
Carotid artery stenosis	9.2	5.3
Smoking	16.3	9.6

There are fewer patients with diabetes mellitus in our cohort, but also higher proportions of hypercholesterolemia, carotid artery stenosis and active smoking, and the mean age is slightly higher. The cohort of MIDNOR TIA seems to have baseline vascular risk factors and demographic characteristics that are similar to previous studies in the research area.

Timing of enrolment

Patients with TIA are at risk of subsequent stroke especially early after the attack.[5, 161] Therefore, to estimate early risk of stroke after TIA, potential patients must be recruited as rapidly as possible after the event so that stroke following very early after TIA are included. Previously, some studies of the prognosis of TIA ascertained patients some weeks or even months after the transient event, and therefore underestimated the immediate risk of stroke.[162]

Nine out of ten patients in our study were enrolled by a stroke specialist within 24 hours after the event. Two percent of all patients were enrolled between 1 and 2 weeks after the event. In the small number of patients seen by a stroke specialist after 24-48 hours, there was only one stroke. When trying to exclude these patients from the calculations the stroke rates changed only minimally.

There are previous studies showing that 20-25% of ischemic stroke are preceded by TIA, most of them during the hours and days immediately before the stroke.[8] In recent years, data from the Norwegian Stroke Registry show that 10-12% of strokes are preceded by TIA. One can argue that enrolling such patients in a TIA study could have increased the stroke rates. This, however, would be an unusual TIA study design approach making the analysis of the usefulness of prediction scores and the effect of rapid assessments and initiation of medical treatment, less applicable.

Diagnostic accuracy

As discussed previously, the TIA diagnosis itself can be subject to bias since it is based on clinical information and not on any specific diagnostic test. The diagnosis heavily relies on patient's account of their symptoms (subject to recall bias), and the clinician's interpretation of them. Several studies have demonstrated poor agreement between physicians to define the likelihood of a TIA, not only between referring physicians and stroke specialists, but also among specialists interviewing the same patients.[52, 163-167]

To keep the study inclusion, diagnostic assessments, and treatment as close to a "real-life" clinical scenario as possible our study protocol stated that patients with "probable" and "possible" TIAs were eligible for inclusion - the last category referring to patients where other causes of transient neurological symptoms were less likely than an ischemic cause and therefore were put on secondary prophylactic treatment.

Even though all referring physicians were well informed of our study and of TIA in general before and during study inclusion, and physicians involved in ascertainment and recruitment of patients were mostly stroke specialists, after completion of enrolment we could not rule out that some of the subjects did not represent real TIAs. To further estimate the accuracy of the TIA diagnoses of the included patients, we did a post-hoc analysis in a sample of patients (n=30) in our cohort, testing for agreement on the TIA diagnosis. Inter-rater agreement was analyzed as follows:

Thirty patients were drawn at random from the 577 patients. These were rated by 4 raters, one neurologist (BT) and three physicians specialized in internal medicine (BI, HE, FI). All of them had several years of experience with TIA and stroke patients. The raters had access to the hospital discharge summary of each patient. Each rating was categorical, with the three categories "probable TIA", "possible TIA", and "likely not TIA". We used a two-way random effect model with patient and rater as random factors. In this design, the raters are crossed with individuals (not nested within individuals), hence, these are crossed random effects. Stata was used for analysis.[168]

There are 3 variance components in the results:

Between patients: $0.28080=0.52990^2$

Between raters: $0.00389=0.06239^2$

Residual: $0.18178=0.42636^2$

The total variance is the sum of these. The between rater, within individual intraclass correlation coefficient estimate (ICC) is:

$$\frac{Patient\ variance}{Patient\ variance + Rater\ variance + Residual\ variance} =$$

$$\frac{0.2808}{0.2808 + 0.0039 + 0.1818} = 0.602$$

Table 7. Distribution of ratings in the different likelihood categories for each patient

Patient serial number (n=30)	No. of rates		
	Probable TIA	Possible TIA	Likely not TIA
12	4	0	0
20	3	1	0
72	3	1	0
79	4	0	0
117	0	3	1
126	4	0	0
139	1	3	0
146	4	0	0
147	0	3	1
172	0	2	2
174	0	3	1
176	4	0	0
177	4	0	0
181	4	0	0
183	4	0	0
184	2	2	0
212	4	0	0
234	4	0	0
260	4	0	0
280	1	3	0
292	1	0	3
338	1	0	3
341	0	2	2
342	4	0	0
375	4	0	0
396	4	0	0
431	1	3	0
437	3	1	0
476	4	0	0
505	2	2	0

Table 7 shows distribution of the ratings for each patient, and Table 8 for each rater. We see that the variation between the patients is large and the variation between the raters is small. This agrees with the fact that the between patient variance estimate is substantially larger than the between rater variance estimate.

Table 8. Proportions of rates for each likelihood category for each rater

Rater No.	Rating (%)		
	Probable TIA	**Possible TIA**	**Likely not TIA**
1	53.3	33.3	13.3
2	66.7	20.0	13.3
3	73.3	16.7	10.0
4	66.7	26.7	6.7
Total	65.0	24.2	10.8

An ICC (which is approximately equal to Cohen's quadratic weighted kappa) of 0.602 is regarded as a moderate to good interrater agreement. The sample of patients constituted about 5% of the entire cohort but probably gives a good representation of the patients. According to this analysis about 10% of patients are categorized as "likely not TIA", and about 90% are "probable" or "possible TIA". One must take into consideration that the raters were not blinded for the diagnosis, as the patients assessed in this analysis were already recruited in the study.

The analysis suggests that our cohort did not consist only of patients with symptoms due to transient ischemic attacks, and this form of selection, or misclassification bias might be regarded as an important limitation of our study. We could have done a similar analysis of

diagnoses in the entire cohort, but neither time nor capacity of the study staff at that moment allowed for this. Still, a cohort consisting of nearly 90% probable TIAs might well be considered being a representative TIA cohort.

Loss to follow-up

Loss to follow-up is important in determining a study's validity because patients lost to follow-up can have a different prognosis than those who complete the study. During and soon after having enrolled 591 patients at the end of the inclusion period, 7 patients withdrew their consent. A review of the electronic patient journal for all patients was performed (FI) and resulted in another 7 patients being excluded from the study because they were regarded as "definitely not" TIAs (e.g., symptoms lasting >24 h). One might consider these patients as "lost to follow-up" (attrition bias). As we did not perform any analysis of data from these patients, we do not know if they differed in demographic or clinical characteristics. However, since the number of excluded patients was very small, it probably did not have an effect on the primary and secondary aims of our study. During the rest of the study period there were no other patients abandoning the study through withdrawal of consent. During the primary follow-up period up to 1 year, 7 patients died of causes other than stroke and these were treated as censoring events. Within 5 years a total of 52 patients died from non-cardiovascular causes and were likewise treated as censoring events.

Selection bias in Paper II and III

In addition to the mentioned sources of selection bias concerning the entire cohort which all three papers are based on, two other situations concerning paper II and III should be mentioned.

In the analysis of the ABCD3-I score in paper II, 272 patients were excluded from the analyses because DWI was performed too late or not at all, or because extracranial imaging was not done. These patients were older and had generally higher load of vascular risk factors than the 305 patients included in the analysis, and this could have led to biased results. At the

same time, there were several similarities between these two groups: Excluded patients had proportions of dual TIAs similar to the included patients, and patients that did undergo carotid artery imaging had similar rates of carotid stenosis as the included patients. Important also, there were no significant differences in subsequent stroke rates between the groups. Therefore, excluding a part of the cohort due to lack of investigational data, probably did not introduce a relevant selection bias. Also important, the baseline clinical characteristics of the included patients were similar to those of comparable post-TIA stroke prediction studies.

In paper III, additional serum and plasma samples were collected and stored in a regional biobank before being analysed for potential inflammatory biomarkers. The capacity and staff in the recruiting stroke units put a restriction on the number of tests that were taken, and we ended up with samples from 112 patients. The majority of samples were taken at St. Olavs hospital or Levanger hospital. It is uncertain if this could have biased the biomarker results. However, baseline demographic and vascular risk factor data of the sampled patients were very similar to that of the entire cohort. Also, data from the health registries was the only source for identifying cardiovascular outcome events in paper III. This might have led to underreporting, since patients enrolled in the registries are hospitalized. However, most patients with cardiovascular events are hospitalized, and the Norwegian Cardiovascular Disease Registry is well-functioning with coverage above 90%.

Information bias

Information bias may arise from questionnaires, interview- or instrumental procedures that do not measure what they are intended to measure because of inaccurate diagnostic procedures or incomplete or incorrect data sources. The term misclassification is used if subjects are placed in wrong exposure or disease categories. Missing data may also bias study results.[169-171] In prospective cohorts, information bias can be easy to elude, because measures may be taken during the design by including all variables in registration forms, in order not to miss variables of interest.

We had trained research nurses that used both registration paper forms (see appendix) and eventually web-based case report forms for final registration of data. Baseline data were collected mainly from the electronic patient journal, and no registrations were based on questionnaires. To get an impression of the quality of the registration process, we did a review of about 10% of the case report forms (50 patients), showing good consistency between data in the patient's journal and the variables registered in the study case report forms. It is however unavoidable that some errors and inaccuracies were made in registering data variables.

There are some other potential sources of information bias in our study: When recording the ABCD2 score prospectively it was supposed to be assigned by the stroke physician enrolling the patient. We did not register if, or in how many patients the assignment finally was done by the study nurse at the site, but this could have been the case in some recordings. The interrater reliability of the ABCD2 score, even between specialists, has been shown to be only moderate.[172] Further, the ABCD3-I score assessed in paper II was calculated *retrospectively* after study completion by assigning two points for dual TIA, two points for stenosis on carotid imaging and two points for positive DWI. This might also have increased the risk of errors in registration of data, as these scores were developed with prospective assignment in mind. Also, the blood pressure measurement used for the ABCD2 assignment was supposed to be the first ever recorded after the onset of the TIA, and in most cases, this would be the blood pressure recorded in the emergency department. However, we did not register when the blood pressure assigned to the score had been measured.

As stated earlier, the possibility of having enrolled TIA mimics in our study could be regarded as both a type of selection and misclassification bias. However, the clinical outcomes of ischemic or hemorrhagic stroke, other cardiovascular events and all-cause mortality were specified prior to enrolment starting. Outcomes occurring within 1 year were recorded through telephone follow-up and diagnoses were confirmed by using data from the Norwegian Cardiovascular Disease Registry. The diagnoses of this registry and the associated Norwegian Stroke Registry and Norwegian Myocardial Infarction Registry are based on ICD-10. There was good consistency between data retrieved from telephone follow-up and registry data. The 5-year follow-up study used the same registries for outcome data. The study was therefore not likely prone to bias due to misclassification of outcome variables.

Reclassification of DWI positive TIAs as stroke can potentially reduce the incidence of subsequent stroke in TIA prognostic studies, since the DWI negative TIAs have been shown to have a lower stroke risk than DWI positive TIAs.[173] However, all physicians involved in study enrolment were according to the study protocol informed to use the time-based TIA definition.

When following up patients by phone during the first year at time points 1 week, 3 months and 1 year, a few patients were not reached (31 patients at 1 year), hence some follow-up data were missing for these subjects. Some other data variables were also randomly missing, for instance time for onset of TIA symptoms, or time at admission to hospital. In these few cases the missing data were extracted from the patient record. Baseline data were close to complete for all enrolled patients. There were no missing ABCD2 scores, and the primary outcome of subsequent stroke was retrieved from registry data (with coverage above 90%) for all patients. In paper III, in the few cases where the inflammatory biomarker results were below detection values, we imputed random values between 0 and the lower detection number. The study results were not likely threatened by missing data.

Confounding factors

Confounding is often referred to as a "mixing of effect" wherein the effects of the exposure under study on a given outcome are mixed in with the effects of an additional factor (or several factors) resulting in a distortion of the true relationship.[174] Observational studies may be biased by unknown confounders, and while we can assess associations in our TIA study, we should not easily assume causality.

Generally, in stroke research key vascular risk factors such as age, smoking, diabetes, and hypertension, are often adjusted for because stroke outcomes including mortality vary according to them. All the baseline clinical and demographic characteristics of the patients in our study can be considered potential confounders since they are related to both the TIA event and the outcome events of stroke and other cardiovascular events. We regarded age as the

most important potential confounder in our study. The risk estimates of stroke and other cardiovascular events presented in paper I and III were cumulative incidences, and therefore did not need any adjusting for confounders. In paper II we did a Cox proportional hazard regression analysis with the covariates positive DWI, dual TIA, and carotid stenosis one at a time to identify to what degree these additional features in the ABCD3-I score contributed to the predictive value of the score. These were all adjusted for by age.

In the analysis of associations between baseline risk factors and the composite outcome of stroke, acute coronary syndrome, or cardiovascular death within 5 years after TIA in paper III, all baseline characteristics could be seen as potential confounders. We first assessed the predictors of outcome events by using univariable Cox proportional hazard regression analysis. Then all variables assessed to be of clinical relevance (which were all) were included in the multivariable analysis, regardless of significance value.

In the analysis of inflammatory biomarkers in paper III, infections and inflammatory conditions could represent confounding factors. To reduce the level of such confounding, all patients with CRP above 10 mg/L were analysed for comorbidities involving increased immune response. We excluded six patients from the final analysis due to ongoing infections, vasculitis, rheumatoid arthritis, cancer, or recent surgery. In the final analysis of biomarkers, we used Cox proportional hazards regression and, again, adjusted for the most evident potential confounder, age.

A limitation of our study is that we did not collect information about adherence to secondary prevention in the follow-up period, nor did we have any data on long-term treatment effects of for instance blood-pressure-lowering and lipid-lowering medications. Neither did we have a control group to compare with. This implies that there could be unknown confounding factors in our study that we were not able to adjust for.

Random error

In addition to the challenges of our study concerning possible sources of systematic error, random error – or the precision of the study, also needs to be discussed. Precision refers to lack of random error or random variation in a study's estimates.[158] It is closely related to the sample size and the statistical power of the study.

The power calculation of our study was based on the validation study of the ABCD2 score (n=4809) where a score of 0-3 gave a stroke risk within 1 week of <1% and a score of 4-7 gave a stroke risk of >5%.[83] With significance level 0.05 and power 80% we calculated a requirement of 564 patients.

In our study there were few subsequent strokes in the follow-up period, not only in the low-risk ABCD2 group, but also in the high-risk group. As described earlier, the data concerning the ABCD2- and the ABCD3-I scores showed an association between higher scores and increased stroke risk at all time points during follow-up. However, since there were very few outcome events – the study was underpowered – any significant differences could not be demonstrated. The proportion of subjects with the outcome will impact the efficiency and thus precision of the study estimates, and in our study the confidence intervals of the AUC values and the hazard ratios of the Cox proportional hazards regression analysis showed wide confidence intervals. The study therefore was prone to type II error, i.e., the probability that we incorrectly failed to reject the *null hypothesis* – in other words, that we might have missed some statistical differences that really were there.[175]

In the subgroup analysis of inflammatory biomarkers, we did not perform any power calculations as the goal was to achieve additional blood samples from as many of the included patients as possible, but the capacity and staff in the investigating stroke unit, put a restriction on the number of tests. Again, the hazard ratios of the univariable Cox proportional hazards regression analysis showed relatively wide confidence intervals, reflecting low precision.

In conclusion, our study seems to have been impacted by bias to some degree. Due to sample size and power issues, it seems to have also been affected by random errors. That said, the

study was well designed and well performed, and generally it seems to have achieved to study what it had originally planned on measuring. We therefore judge the study to have quite good internal validity.

6.2.2 External validity of MIDNOR TIA study

External validity is the degree to which the conclusions in a study would hold for other persons in other places and at other times. One indication that a study has good external validity is if the sample is representative. The most common loss of external validity in observational research comes from the fact that studies often employ small samples obtained from a single geographical location or facility.[156] Can the results from the MIDNOR TIA study apply to other hospital-based settings treating TIA patients – are they generalizable?

The MIDNOR TIA study was a relatively large prospective, multicenter study in which all the local hospitals of the region collaborated. The region of Central Norway is a quite large, well-defined geographical region with nearly three-quarters of a million inhabitants. Broad inclusion criteria were used and there was high adherence to current guidelines for assessment and treatment of TIA and stroke patients. As showed previously, the baseline demographic and vascular risk factor characteristics in our study were comparable to other TIA stroke prediction studies. As most TIA studies identified in the literature, our also used the clinical, time-based definition. This shows that the clinical definition is still the most widely used definition in research and clinical practice, which is important for generalizing the findings of these studies.

Surely, the best way to demonstrate external validity of research results is to replicate results in populations, places, and time periods. The MIDNOR TIA study (paper I and III) has contributed to estimates of risk of stroke and other cardiovascular events after TIA, that are in line with other recent TIA studies. Accordingly, the external validity can be considered good for hospital-based TIA services (either inpatient- or outpatient-based) that deliver rapid

assessment and treatment of TIA patients. We must however underline shortcomings related to power of our study: Both in paper I, II and paper III, the sample size was too small to draw very robust conclusions regarding the ABCD2 score, the ABCD3-I score and inflammatory biomarkers, respectively, and we would be cautious about concluding on external validity for these aspects of the study.

6.3 Discussion of the main results and clinical implications

6.3.1 Paper I

The main findings of paper I were low stroke risks 1 week, 3 months and 1 year after TIA. The stroke risks were lower than reported in cohorts used to develop and validate the ABCD2 score and in several previous TIA cohorts.[83, 143, 176] However, the estimated stroke risks are in line with the results of more recent studies,[7, 177] including studies evaluating the effect of rapid assessment and initiation of preventive treatment for TIA patients.[36, 65, 66, 147, 178]

Almost all patients in our study were hospitalized. To what extent this itself contributed to the low stroke risk is unclear. The vast majority of patients, regardless of belonging to the low-risk or high-risk group, were evaluated by a specialist shortly after the event (9 of 10 within 24 hours). In the rapid assessment studies, the EXPRESS study[65] and the SOS-TIA study,[66] in which patients were assessed and treated in dedicated out-patient TIA clinics, the very low subsequent stroke rates (80% relative stroke risk reduction at 90 days) were attributed to the systematized rapid assessment and treatment initiation.

Early administration of aspirin has been identified as a key intervention. A pooled subgroup analysis from 3 clinical trials of aspirin versus placebo in 8561 participants with mild ischemic strokes who were randomized within 2 days of symptom onset found that aspirin was associated with lower rates of stroke at 14-day follow-up compared with placebo (0.89%

versus 1.74%; HR, 0.51 (95% CI, 0.34 to 0.75).[67] Early antiplatelet treatment may be the main contributor to the low event rate of ischemic stroke during the first days after TIA. In our study almost 90% of the patients were treated with aspirin, either alone or in combination with other antiplatelet drugs (some patients were on anticoagulant therapy). Aspirin is simple and low-cost treatment that can be initiated urgently after a TIA, independent of the organization of TIA management on an outpatient or in-patient basis. We informed the referring physicians to administer aspirin bolus dose of 300 mg as soon as possible after the transient event. We did not, however, record which patients got this treatment before being seen by a stroke physician, and this strategy has neither been formally evaluated in other studies.

Further on, dual antiplatelet treatment (DAPT) has shown good results in two rather recent studies. In the CHANCE (Clopidogrel in High-Risk Patients with Acute Non-Disabling Cerebrovascular Events) trial, 5170 participants in China with TIA and minor stroke who presented within 24 hours of symptom onset were randomized to receive DAPT consisting of clopidogrel plus aspirin or aspirin monotherapy. At 90 days, recurrent ischemic and hemorrhagic stroke events occurred in 8.2% of participants in the DAPT group versus 11.7% in the aspirin monotherapy group (HR, 0.68 (95% CI, 0.57 to 0.81).[179] The POINT (Platelet Oriented Inhibition in New TIA and Minor Ischemic Stroke) trial performed in North America, Europe, Australia, and New Zealand enrolled 4881 participants within 12 hours of TIA or minor stroke symptom onset who were randomized to receive DAPT or aspirin monotherapy. The POINT trial was stopped early due to greater efficacy of DAPT for preventing stroke at 90 days (5.0% versus 6.5% occurrence; HR, 0.75 (95% CI, 0.59 to 0.95), but major bleeding was increased in the DAPT group compared with aspirin alone (0.9% versus 0.4%; HR, 2.32 (95% CI, 1.10 to 4.87).[180] Pooled analysis of these two trials showed that DAPT was associated with lower rates of recurrent stroke (6.5% versus 9.1%; HR, 0.70 (95% CI, 0.61 to 0.81) without increase in intracranial bleeding. This association of DAPT with stroke risk reduction was largest in the first 21 days but was not observed after 21 days,[181] suggesting that the optimal DAPT duration to maximize benefit and minimize bleeding risk is 3 weeks. These trials included only TIA patients regarded to be of high-risk defined by an ABCD2 score ≥4, and we know less about the effect of this treatment in patients with low-risk ABCD2 score. The results were presented after the initiation of our study and have later been implemented in clinical practice.[24, 55]

We did not find the ABCD2 score to be useful in stratifying between high- and low-risk groups. In the low risk ABCD2 group there were very few strokes. Only 1 of 206 patients with an ABCD2 score of ≤3 experienced a stroke within 1 week. Consequently, a low ABCD2 score still indicates a very low stroke risk. At the same time, patients with a high ABCD2 score also had a low risk of stroke. Although there were approximately twice as many strokes in the high versus the low-risk group at each time point, we did not find significant differences in our analyses, and as discussed earlier this can probably partly be explained by lack of statistical power. The ROC analyses showed insufficient discriminating value of the ABCD2 score both when applied 1 week, 3 months and 1 year after stroke. We also did not find sufficient discriminating values when testing for other cut-off values (0-5 vs 6-7 and 0-2 vs 3-7). As shown in earlier studies, patients with low ABCD2 score may have underlying severe pathology, like atrial fibrillation and internal carotid stenosis, and even though these might not be considered to be high-risk conditions during the first couple of days after TIA, it still underscores the benefit from thorough and rapid diagnostic evaluation regardless of risk score.[7]

In conclusion, in our study TIA patients had a very low risk of stroke, and rapid assessment and intervention are likely the main reasons for the low stroke risk. Our results also indicate that the ABCD2 score may be less applicable to discriminate between high and low stroke risk groups in populations with a low risk of subsequent stroke after TIA. In clinical practice, this implies that all TIA patients regardless of their ABCD2 score value should be assessed and treated rapidly, either this is done in an in-patient or out-patient setting. This is also supported by recent publications and guidelines.[182, 183]

6.3.2 Paper II

In paper II we validated the usefulness of the ABCD3-I score to predict the 1-week, 3-month, and 1-year risk of stroke after TIA.

We found an association between the higher ABCD3-I scores and increased stroke risk at each time point, both with the use of the AUC values for ABCD3-I and Cox proportional hazards regression analyses comparing the medium- and high-risk with low-risk ABCD3-I score. This is in line with several previous TIA risk studies investigating this risk score.[106, 107, 184-186] However, due to very few strokes registered, the precision was low with AUC statistics showing very wide confidence intervals. Within the first week, only 3 out of 233 patients (1.3%) with a moderate to high-risk ABCD3-I score ≥4 experienced a stroke. The corresponding numbers for the entire follow-up period of 1 year for the same group were also low – 15 out of 233 patients (6.4%). In the low-risk group (score 0-3) there were no registered strokes within 1 week and 3 months, and only 1 stroke within 1 year. Again, our results were probably affected by lack of statistical power due to the low rates of outcome events.

We found that the ABCD2 score was not able to predict stroke after TIA in this cohort. The AUC values for the ABCD3-I score were higher than that of the ABCD2 score, but only significantly for stroke recurrence at 1 week. Though many studies have pointed out the increased discrimination ability of the ABCD3-I score, there is little evidence on how this score could be implemented in a clinical setting and used in practice. The ABCD3-I score was developed to improve risk scoring accuracy in a specialist setting. It was not intended to be used in the prehospital settings, as DWI and carotid artery imaging is generally not available to community-based clinicians who make referrals. Our regression analysis on the additional components in the ABCD3-I score supports the relation between positive DWI after TIA and the risk of future strokes, and we agree that such investigation should be done, if available. But the availability of DW-MRI varies greatly between hospitals, regions, and countries. In our TIA population, almost all patients underwent rapid TIA assessment, including DWI and extracranial artery investigations, and were medically treated according to guidelines. Consequently, further progression in investigations or treatment did probably not differ greatly between the low- and high-risk groups. This may reduce the usefulness of the ABCD2 and ABCD3-I scores and contribute to explaining why the scores do not discriminate better between the low- and high-risk groups.

I conclusion, the ABCD3-I score had limited value in a short-term prediction of subsequent stroke after TIA, and the ability to predict stroke deteriorated further during long-term follow-up. Since there were very few outcome events, and we did not have enough power to detect

significant differences in stroke risk between high- and low-risk scores, our results must be interpreted with caution. They still give an indication that this clinical risk score is less beneficial to discriminate between the high- and low-stroke-risk groups in populations with a general low risk of stroke after TIA. It seems like the best approach to TIA patients is to carefully consider each of the components of the investigated scores through rapid assessment and initiation of treatment, rather than using dichotomized scores.

6.3.3 Paper III

In paper III we described the long-term rates of cardiovascular events including stroke, acute coronary syndrome, and cardiovascular mortality during a 5-year follow-up period. We found that the cumulative incidence of total cardiovascular event and stroke were 18.7% and 12.0%, respectively giving an average annual risk of 3.7% and 2.4%, respectively. Approximately half of the cardiovascular events as well as strokes occurred during the first year after TIA. Even though beyond one year after TIA the annual rate of cardiovascular events and stroke was relatively low, it remained constant.

Our 5-year cardiovascular event rates are similar to those reported in comparable large post-TIA risk studies, which show relatively highest risk of subsequent strokes and other cardiovascular events during the first year, and then constant annual event rates not diminishing over time,[36, 150, 187-190] and even increasing towards 10-15 years after TIA.[189]

In multivariable analyses we found that patients with new cardiovascular events were likely to be older males with hypertension and acute infarction on brain imaging. Lower risk of cardiovascular events after TIA in women than in men has been shown in other studies.[191] Age was a strong predictor of cardiovascular events and death with a 5% increase in outcome risk for each year. There is strong evidence for an association between undertreated hypertension and cardiovascular events including stroke,[36] and the association seems to persist in contemporary TIA cohorts. This study demonstrates the importance of blood pressure as an important risk factor for subsequent stroke in TIA patients and the need for

ambitious monitoring and aggressive treatment of blood pressure. Diabetes mellitus is established as an important risk factor for cardiovascular disease, but diabetes did not predict cardiovascular events in our study. This may be due to the fact that the proportion of diabetes patients in our cohort was rather low, and that those who had diabetes were relatively well treated at the time of their TIA (median HbA1c 7.2 mmol/l, SD ± 1.3). Similar explanations can probably be used for carotid stenosis and atrial fibrillation, which also were not predictive of cardiovascular events in our analyses. Over half of the patients with significant carotid stenosis underwent carotid endarterectomy within 2 weeks of their TIA. Additionally, nearly 9 of 10 of all patients were on lipid-lowering medication at discharge and nearly all patients received antithrombotic medication, with a potential to stabilize a carotid stenosis. Similarly, nearly all patients with atrial fibrillation were on anticoagulation therapy at discharge. Also, it should be mentioned that validation studies of post-TIA risk scores have not found an increased predictive stroke risk accuracy by taking atrial fibrillation into account.[192, 193]

There is conflicting evidence regarding the predictive ability of DWI positives for stroke recurrence in the long-term evaluation.[194, 195] In our study, DWI was performed in two-thirds of the patients, and almost all recognized acute infarctions on brain imaging were found on this modality. A positive DWI predicted both the composite outcome and stroke separately. Importantly, a positive DWI was predictive of subsequent stroke, not only at one year, but also for strokes occurring during the entire period until 5 years. It is reasonable to conclude that an acute ischemic lesion after TIA should be regarded as a clinical important event comparable with acute MI and stroke.

In a subgroup analysis we wanted to investigate whether inflammatory biomarkers could predict subsequent stroke, acute coronary syndrome, and cardiovascular death within 5 years after TIA. Of the twelve inflammatory biomarkers tested in Cox proportional hazards regression analyses, no associations between neither the primary composite outcome nor stroke were revealed. Neither were there any associations between the inflammatory markers and the presence of previous cardiovascular events (other than TIA) at baseline, a high ABCD2 risk score of 4-7, a positive DWI scan and/or carotid stenosis. Inflammatory markers have been associated with a poor functional outcome and clinical complications after stroke, and a marker of a poor prognosis after cardiovascular events in general.[129, 136, 196] However, there are considerable methodological variations between studies[197] and there is conflicting

evidence of their prognostic usefulness and incremental value over established prognostic markers. Analyses of inflammatory markers in the acute phase of TIA may be problematic. It is not clear if their prognostic value is during the acute phase or in the stable phase after TIA. Even if TIA is a clinical event, it may be too small to trigger an enhanced inflammatory response, and some TIAs may not be true cerebrovascular ischemic events but rather caused by other neurological conditions or represent TIA mimics. Nonetheless, our findings do not support the use of inflammatory biomarkers in the risk assessment following TIA.

To conclude, the risk of cardiovascular events, and especially stroke, was highest in the first year after TIA. Even though the risk of cardiovascular events was lower during the next years, and the general long-term prognosis for TIA patients seems to be quite good, the risk remained steady over the next years. In clinical practice, these findings underscore the importance of both early initiation of and long-term continuation of secondary preventive treatment after TIA. This combination of urgent diagnosis and treatment, improved secondary prevention and presumably also a reduction of risk factors in the population probably explain the observed reduction in the risk of stroke and other cardiovascular events after TIA during the last decades.[65, 66, 147, 198, 199]

6.4 Future research

The issues addressed in this thesis reveals areas that should be further investigated:

- It is still not fully known which is the optimal healthcare setting to treat TIA. Large RCTs should compare different models of TIA care, including triage strategies, to see which of them is the most useful and cost effective in preventing stroke and other cardiovascular events.

- As we have emphasized through our TIA study, patients recognizing TIA symptoms and urgently contacting health services seems to be crucial in prevention of further cardiovascular events. Future research should evaluate which public health strategies are the most effective in recognizing TIA symptoms.

- Age was as expected a strong predictor of cardiovascular events and death after TIA. There is a lack of data on optimal secondary prevention approaches in very old adults, and future research should seek to establish optimal treatment regimens for this patient category.

- During the last decades the bulk of the global burden of stroke is in low- to middle-income countries. There is a lack of TIA studies performed in these countries. Future research should assess how to manage TIA patients to reduce the risk of stroke and other cardiovascular event in such resource-limited settings, including the utility of telemedicine in TIA management.

- Since the interrater agreement on the diagnosis of TIA is low, and a diagnosis of a TIA mimic will impact treatment decisions - and since there is no test to definitely confirm a TIA - future research should explore the additional diagnostic value of biological biomarkers identifying transient cerebrovascular ischemic events.

7 Conclusions

The conclusions of the research questions stated in the aims of this thesis are:

- There were low risks of stroke both 1 week, 3 months and 1 year after TIA. The estimated stroke risks were lower than in older TIA studies, but in line with the results of more recent studies. Rapid assessment and intervention are likely the main reasons for the low stroke risk.

- The ABCD2 score was not useful in stratifying between high- and low-risk groups. In the low risk ABCD2 group there were very few strokes. At the same time, patients with a high ABCD2 score also had a low risk of stroke, and this score therefore seems to be less applicable in populations with a general low risk of subsequent stroke after TIA.

- The ABD3-I score had limited value in stratifying between low- and high-risk TIA patients within 1 week in our cohort of TIA patients with a general low risk of subsequent stroke, and the predictive ability deteriorated further during follow-up until 1 year. The ABCD2 score did not predict subsequent stroke accurately at any time point.

- In the 5-year follow-up study we found that the cumulative incidence of a composite outcome of cardiovascular events consisting of stroke, acute coronary syndrome and cardiovascular death was 18.7%. The cumulative incidence of stroke was 12.0%. Approximately half of the cardiovascular events and strokes occurred during the first year after TIA. Even though the risk of cardiovascular events was lower during the next years, and the general long-term prognosis for TIA patients seems to be quite good, the risk remained steady over the next years. The all-over favorable prognosis in our study population might indicate that both the acute treatment and the follow-up has been of high quality.

- We found that increasing age, male sex, hypertension, and acute infarction on brain imaging were significant predictors for the long-term primary composite outcome of stroke, acute coronary syndrome, and cardiovascular death.

- There was no association between levels of blood inflammatory biomarkers taken in the acute phase and cardiovascular events within 5 years. Our findings do not support the use of inflammatory biomarkers in the risk assessment following TIA.

8 References

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Paper I

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RESEARCH ARTICLE Open Access

Stroke risk after transient ischemic attack in a Norwegian prospective cohort

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Abstract

Background: Transient ischemic attack (TIA) is a risk factor of stroke. Modern treatment regimens and changing risk factors in the population justify new estimates of stroke risk after TIA, and evaluation of the recommended $ABCD^2$ stroke risk score.

Methods: From October, 2012, to July, 2014, we performed a prospective, multicenter study in Central Norway, enrolling patients with a TIA within the previous 2 weeks. Our aim was to assess stroke risk at 1 week, 3 months and 1 year after TIA, and to determine the predictive value of the dichotomized $ABCD^2$ score (0–3 vs 4–7) at each time point. We used data obtained by telephone follow-up and registry data from the Norwegian Stroke Register.

Results: Five hundred and seventy-seven patients with TIA were enrolled of which 85% were examined by a stroke specialist within 24 h after symptom onset. The cumulative incidence of stroke within 1 week, 3 months and 1 year of TIA was 0.9% (95% CI, 0.37–2.0), 3.3% (95% CI, 2.1–5.1) and 5.4% (95% CI, 3.9–7.6), respectively. The accuracy of the $ABCD^2$ score provided by *c*-statistics at 7 days, 3 months and 1 year was 0.62 (95% CI, 0.39–0.85), 0.62 (95% CI, 0.51–0.74) and 0.64 (95% CI, 0.54–0.75), respectively.

Conclusions: We found a lower stroke risk after TIA than reported in earlier studies. The $ABCD^2$ score did not reliably discriminate between low and high risk patients, suggesting that it may be less useful in populations with a low risk of stroke after TIA.

Trial registration: Unique identifier: NCT02038725 (retrospectively registered, January 16, 2014).

Keywords: TIA (Transient Ischemic Attack), Stroke, $ABCD^2$ score, Risk factors, Prognosis

Background

Stroke is a major cause of disability and death worldwide. Transient ischemic attack (TIA) has the same etiology as stroke, and patients with a TIA have been shown to be at high risk of a subsequent stroke although the stroke risk varies in different studies depending on study population and methodology [1, 2].

Several clinical risk scores have been developed to identify TIA patients with high and low early stroke risk in order to triage the patients in primary and secondary care. The $ABCD^2$ score from 2007 has achieved particular prominence [3]. The score is based on clinical information that is easily obtained, consisting of age, blood pressure, type of symptoms, duration of symptoms and presence of diabetes (Table 1). Validations of the $ABCD^2$ score have given conflicting results regarding accuracy for both short and long term stroke prediction [4, 5]. However, it remains the most widely used risk score in TIA patients, and several guidelines recommend that patients with a high $ABCD^2$ score (4–7), indicating high risk of stroke, should receive specialist assessment within 24 h after the onset of TIA, while for patients with a low score (0–3) specialist assessment within a few days after TIA is considered sufficient [6–8].

Prospective cohort studies on stroke risk after TIA stratified by the $ABCD^2$ score, have not been performed

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Table 1 $ABCD^2$ score

Characteristics		Score
Age	≥60 years	1
Blood pressure	> 140/90 at presentation	1
Clinical symptoms	Unilateral weakness	2
	Speech disturbance without weakness	1
Duration of symptoms	> 60 min	2
	10–59 min	1
Diabetes	Presence of diabetes	1

in Scandinavia. Since stroke patients in Norway and other Scandinavian countries differ from stroke populations in many other countries by having lower post-stroke mortality [9], it is timely to assess if TIA patients also differ when it comes to stroke risk and survival. Moreover, modern treatment regimens and alteration in risk factors in the population make it necessary to estimate the risk of stroke after TIA and evaluate whether the recommended $ABCD^2$ risk score is still useful in identifying TIA patients at the highest stroke risk. The primary aim was to establish a large prospective cohort of TIA patients to find the cumulative stroke risk within 1 week, 3 months and 1 year after TIA. Secondary, we evaluated the predictive value of the dichotomized $ABCD^2$ score 0–3/4–7. Additionally, 1 year follow-up data on endarterectomy for symptomatic carotid stenosis, and case fatality, was recorded.

Methods

Study design and patient selection

In a prospective, multicenter study, named MIDNOR TIA, TIA patients were consecutively enrolled from October, 2012, to July, 2014. All eight hospitals in the geographical and administrative region of Central Norway recruited patients, of which seven were community hospitals and one a university hospital. Only the university hospital had an out-patient service for acute TIA diagnostics and treatment. TIA patients eligible for enrollment were residents of Central Norway aged 18 to 90 years, they were evaluated by a stroke specialist within 2 weeks of their TIA, and living at home with a modified Rankin Scale of ≤3.

Data collection and follow-up

Stroke physicians performed inclusion according to eligibility criteria after in-person assessment on the hospital ward, or in a few cases in the outpatient clinic, and then recorded the $ABCD^2$ score in standardized paper forms that explicitly listed each component of the score. A standardized diagnostic work-up contained as a minimum a thorough patient history, a physical examination, blood tests, ECG, a brain MRI or CT, and carotid Doppler ultrasound or CT angiography. Trained research nurses appointed at each center prospectively registered detailed baseline data using standardized web-based case report forms. Subsequent stroke (ischemic and hemorrhagic) within 1 week, 3 months and 1 year after the index TIA, was recorded by telephone follow-up at each time point. Additionally, all registered strokes were confirmed by using data from the Norwegian Stroke Register, which is the national quality registry for stroke care established by law. Data from the Norwegian Cardiovascular Disease Registry was used for registering deaths and carotid surgery in the 1 year follow-up period.

Definitions

TIA was defined as an acute loss of focal cerebral or ocular function lasting less than 24 h according to the diagnostic criteria from the World Health Organization (WHO) [10]. The TIA leading the patient to seek medical help, was defined as the index TIA. The WHO criteria were also used for stroke [11].

The blood pressure measurement used for the $ABCD^2$ assignment was the first ever recorded after the onset of the TIA, and in most cases it was recorded in the emergency department. Carotid stenosis was defined as a ≥ 50% narrowing of the symptomatic internal carotid artery on carotid imaging, and the diagnosis of atrial fibrillation was based on at least one confirmative ECG prior to or during the investigation.

Clinical management

The clinical management followed the current treatment guidelines for TIA [12]. Patients were treated with an antiplatelet agent, mainly aspirin, as soon as possible after the TIA. Hypercholesterolemia, hypertension, atrial fibrillation and diabetes were treated according to current guidelines, supplemented with lifestyle advices. Patients with symptomatic, significant carotid stenosis were in the absence of contraindications treated with endarterectomy. Follow-up of secondary prevention was performed by the patients' general practitioners.

Statistical analysis

In a large, previous study [3] of TIA patients ($n = 4809$), an $ABCD^2$ score of 0–3 (1628/4809–34%) gave a 1 week stroke risk of < 1% and a score of 4–7 (3181/4809–66%) gave a stroke risk of > 5%. Based on these results, we calculated a requirement of 564 patients in the present study (significance level 0.05 and power 80%).

Kaplan-Meier analysis was used to determine the cumulative incidence of stroke, and the log rank test was used to assess for statistical differences in stroke-free survival between the $ABCD^2$ groups. Deaths from other causes than stroke were treated as censoring events. The predictive ability of the $ABCD^2$ score was quantified by the areas under the curve (AUC) of a receiver operating

characteristics curve (ROC). Confidence intervals (CI) for binomial proportions were calculated using the Wilson score method. We performed Cox proportional hazards regression analysis to calculate hazard ratios (HRs), using the low-risk $ABCD^2$ group as the reference category.

Descriptive statistics for continuous variables are given as means with standard deviations (SD), and for categorical variables as frequencies and percentages. Statistical analyses were performed using IBM SPSS Statistics (version 23).

Results

Originally 591 patients were enrolled, but 7 patients later withdrew their consent. Another 7 patients were excluded, either because symptoms lasted for more than 24 h ($n = 1$), or because the diagnostic work-up excluded the diagnosis of TIA ($n = 6$). Thus, the final study population included 577 patients.

Table 2 summarizes the baseline characteristics, the clinical features and the main investigations of the study population. The mean (SD) age of the patients was 71.5 years (11.0). Four hundred and eighty-nine patients (84.7%) were above 60 years of age and 56.7% were male. A total of 467 subjects (82.5%) experienced their first ever TIA. Four hundred and ninety-one patients (85.4%) were examined by a stroke specialist within 24 h and 525 patients (91%) within 48 h after symptom onset. Only 27 (4.7%) were evaluated at the outpatient clinic, whereas the majority of patients were hospitalized. Median length of hospital stay was 2 days. Speech difficulties, motor weakness and sensory deficits were the most commonly reported symptoms. Forty-eight of 520 (9.2%) patients who had intra- and extracranial imaging performed had a symptomatic carotid stenosis. All patients were examined with brain imaging, either with a CT scan (97.7%) or a diffusion-weighted MRI (DWI-MRI) (62.6%), or both, and all patients were evaluated with either ECG or 24-h Holter ECG, or both.

Stroke risk and case fatality

Five patients had a stroke within 1 week, 19 patients within 3 months, and 31 patients within 1 year, corresponding to a cumulative incidence of stroke of 0.9, 3.3 and 5.4%, respectively. Twenty-seven (87.1%) of the 31 recurring strokes within 1 year were ischemic strokes, and 4 were intracranial hemorrhages.

All strokes within 1 week occurred within the first 2 days after the TIA. The 5 patients experiencing a stroke within 1 week had $ABCD^2$ scores of 3, 4, 4, 6 and 6, respectively (mean score 4.6). One of them had atrial fibrillation and one had a symptomatic carotid stenosis, both of these had $ABCD^2$ score of 6. Of all included patients, 9.6% versus 10.2% had carotid stenosis and 11.7%

Table 2 Baseline characteristics, clinical features and main investigations of the study population

Variable	n (%)	
Age in years, mean ± SD	70.5 ± 11.0	
Age > 60 years	489 (84.7)	
Male	327 (56.7)	
Evaluation within 24 h. of TIA onset	493 (85.4)	
Medical history		
Former TIA	101 (17.5)	
Former ischemic stroke	87 (15.1)	
Former myocardial infarction	67 (11.6)	
Diabetes mellitus	66 (11.4)	
Hypertension	311 (53.9)[a]	
Hypercholesterolemia	216 (37.4)[b]	
Current smoker	94 (16.3)	
Former smoker	222 (38.5)	
Modified Rankin score		
0	282 (48.9)	
1	195 (33.8)	
2	79 (13.7)	
3	21 (3.6)	
Clinical features		
Speech disturbances	277 (48)	
Hemiparesis of arm	193 (33.4)	
Hemisensory loss	134 (23.2)	
Hemiparesis of leg	115 (19.9)	
Hemiparesis of face	115 (19.9)	
Hemianopsia	36 (6.2)	
Amaurosis fugax	21 (3.6)	
Diplopia	19 (3.3)	
Investigations		
Brain CT	564 (97.7)	
Acute infarction	13/564 (2.3)	
Brain DWI-MRI	361 (62.6)	
Acute infarction	97/361 (26.9)	
Extracranial imaging	520 (90.1)	
Significant stenosis or occlusion	48/520 (9.2)	
ECG and/or 24-h Holter ECG	577 (100)	
Newly diagnosed and known atrial fibrillation and flutter	79/577 (13.7)	
Medication	At baseline	At discharge
Aspirin	162 (28.1)	179 (31.0)
Other antiplatelet agent	12 (2.1)	36 (6.2)
Aspirin + other antiplatelet agent	59 (10.2)	284 (49.2)
Anticoagulation	56 (9.7)	91 (15.8)
Blood-pressure lowering agent	311 (53.9)	356 (61.7)
Lipid-lowering agent	216 (37.4)	483 (83.7)

[a]Using blood pressure-lowering medication
[b]Using lipid-lowering medication

versus 14.8% had atrial fibrillation in the low and high risk group, respectively.

In all, 26 of 48 patients with significant, symptomatic carotid stenosis underwent carotid endarterectomy. During the entire follow-up period of 1 year 10 (1.7%) of the patients died and three of them by hemorrhagic strokes.

ABCD^2 score and stroke risk

In all, 64.3% ($n = 371$) had a high risk ABCD^2 score 4–7. The median ABCD^2 score was 4 (IQR 3–5). Figure 1 shows the Kaplan-Meier curves of patients surviving free from stroke from the time of presenting TIA within 1 week, 3 months and 1 year, stratified according to ABCD^2 score 0–3 and 4–7. The low risk group shows a higher probability of stroke free survival than the high risk group, although the difference is not statistically significant ($p = 0.46$ at 1 week, $p = 0.18$ at 3 months, $p = 0.051$ at 1 year, log rank test).

The distribution of the ABCD^2 score with the corresponding stroke rates at each time point is shown in Table 3. In patients with ABCD^2 score 0 or 1 no strokes occurred at any time point, and for score 2–3 only one stroke within a week. However 19.4% ($n = 6$) of all strokes for the whole period occurred in patients with ABCD^2 score 2–3. The risk of stroke tended to increase with a higher ABCD^2 score, with the risk at 1 year ranging from 0% (score of 0 and 1) to 13.2 and 10.5% (score of 6 and 7, respectively).

The area under the ROC curve was 0.62 (95% CI = 0.39 to 0.85, $p = 0.36$) at 1 week, 0.62 (95% CI = 0.51 to 0.74, $p = 0.065$) at 3 months, and 0.64 (95% CI = 0.54 to 0.75, $p = 0{,}008$) at 1 year (Fig. 2). A cox regression analysis comparing high ABCD^2 score (4–7) with low (reference) score (0–3) showed hazard ratios of 2.22 (95% CI, 0.25 to 19.88, $p = 0.48$), 2.11 (95% CI, 0.7 to 6.35, $p = 0.19$) and 2.37 (95% CI, 0.97 to 5.77, $p = 0.058$) at 1 week, 3 months and 1 year, respectively.

Discussion

Stroke risk

We found a low stroke risk after TIA in our study. Both early and late stroke risks were lower than reported in cohorts used to develop and validate the ABCD^2 score [3], and in several previous TIA cohorts. The pooled stroke risk at 7 days in a meta-analysis published in 2007 reporting from 17 TIA studies performed between 1981 and 2007 was 5.2% [1], 5-fold the risk we found in our study. In the Oxfordshire study the 1 year stroke risk was 11.6% [13], more than two times the stroke risk we found within 1 year. However, the estimated stroke risks in our cohort are in line with the findings in more recent studies [2, 14], including studies evaluating the effect of rapid assessment and initiation of preventive treatment for TIA patients [15–17]. This trend towards a lower stroke recurrence probably reflects both a more rapid evaluation by stroke specialists and improved treatment and secondary prevention strategies implemented for TIA patients during the recent years. In Scandinavia these findings parallel the improved outcome for stroke patients [9], reflecting high quality of initial assessment, treatment and follow-up of both stroke and TIA patients. Differences in socioeconomic status, health economics and health care organization between countries might have an influence on the varying stroke risks found in TIA studies. Performing large TIA studies in different countries provides valuable information on the current post-TIA stroke risk.

To what extent the high hospitalization rate in our study contributed to the low stroke risk is unclear. The aim of the present study was not to compare out-patient and in-patient TIA services. However, in the rapid assessment studies, the EXPRESS study [15] and the SOS-TIA study [16], in which patients were assessed and treated in dedicated out-patient TIA clinics, the very low subsequent stroke rates were attributed to the

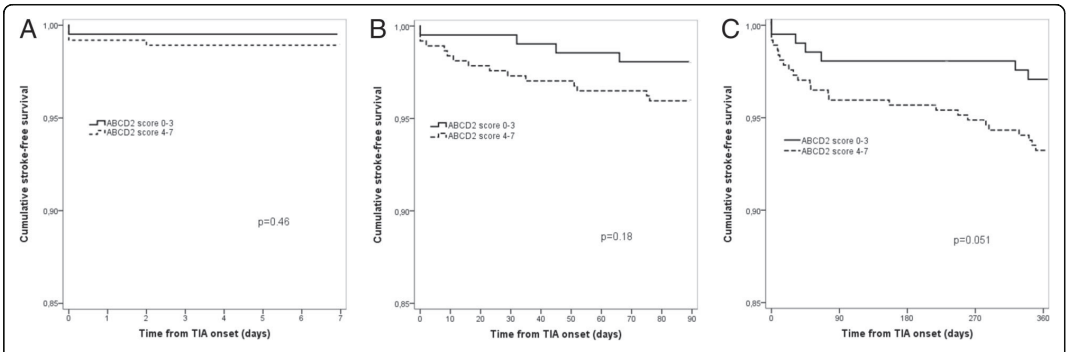

Fig. 1 Kaplan-Meier plots of patients surviving free from stroke from time of presenting TIA within 1 week (**a**), 3 months (**b**) and 1 year (**c**) stratified according to ABCD^2 score 0–3 and 4–7. Log rank tests for differences between the groups

Table 3 The 1 week, 3 months and 1 Year Risks of Stroke According to Each Stratum of the $ABCD^2$ Score and Dichotomized Score, with Corresponding AUC Levels for each Time Point

$ABCD^2$ score	Patients, n (%)	Stroke events (% of patients)		
		< 1 week	< 3 months	< 1 year
0	7 (1.2)	0	0	0
1	15 (2.6)	0	0	0
2	62 (10.8)	0	0	1 (1.6)
3	122 (21.1)	1 (0.8)	4 (3.3)	5 (4.1)
4	177 (30.7)	2 (1.1)	6 (3.4)	10 (5.6)
5	107 (18.5)	0	3 (2.8)	4 (3.7)
6	68 (11.8)	2 (2.9)	6 (8.8)	9 (13.2)
7	19 (3.3)	0	0	2 (10.5)
< 4	206 (35.7)	1 (0.5)	4 (1.9)	6 (2.9)
≥4	371 (64.3)	4 (1.1)	15 (4.0)	25 (6.7)
Total	577 (100)	5 (0.9)	19 (3.3)	31 (5.4)
AUC[a] (95% CI)		0.62 (0.39–0.85)	0.62 (0.51–0.74)	0.64 (0.54–0.75)

[a]AUC = Area Under the Curve

systematized rapid assessment and treatment initiation. Similarly, in our study, the vast majority of patients, regardless of belonging to low risk or high risk group, were evaluated by a specialist shortly after the event (9 of 10 within 24 h). Only 2% of the patients were enrolled between 1 and 2 weeks after the event. In the small number of patients who were enrolled after 24–48 h from symptom onset, there was one stroke. Excluding these patients from the calculations changes the stroke risks only minimally.

Furthermore, a meta-analysis of 12 randomized trials of aspirin versus control in secondary prevention after TIA or ischemic stroke, identified early administration of aspirin as a key intervention [18]. This may be the main contributor to the low event rate of ischemic stroke during the first days after TIA. In the TIA studies of the meta-analysis from 2007 [1], treatment with aspirin varied considerably, ranging between 47 and 90%. In our study 80.2% of the patients were treated with aspirin, either alone (31%), in combination with dipyridamole (43.7%) or in combination with clopidogrel (5.5%). Aspirin is a simple and low-cost treatment that can be initiated urgently after a TIA, independent of the organization of TIA management on an out-patient or in-patient basis. In contrast, the beneficial effect of other initiated treatments, like antihypertensive and lipid-lowering medication, occurs over time. Promising results regarding dual antiplatelet therapy with aspirin and clopidogrel have been found in two recent studies on stroke risk after TIA or minor stroke [19, 20]. The results however were presented after the initiation of our study, and their clinical implementation need to be validated further.

We acknowledge that neurological symptoms in some enrolled patients might have been caused by non-ischemic conditions, causing a weakening of the association between

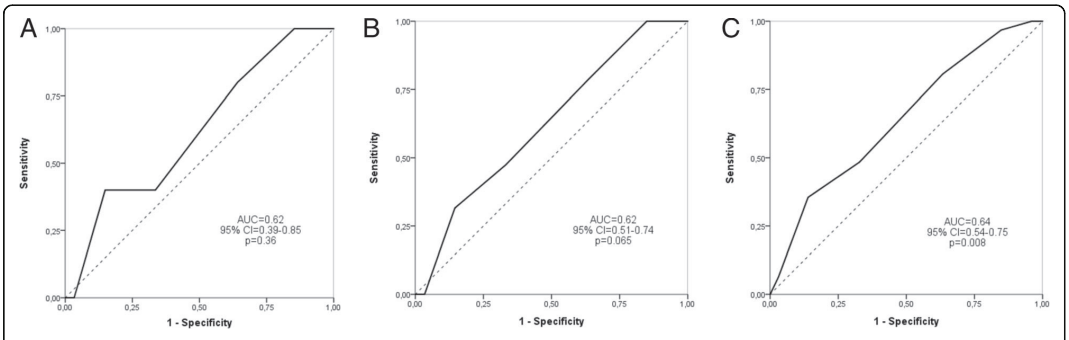

Fig. 2 Receiver operating characteristics curves (ROC) for predictive value of $ABCD^2$ score within 1 week (**a**), 3 months (**b**) and 1 year (**c**). AUC = Area Under the Curve)

TIA and stroke risk. However, low risk of stroke explained by misclassification is not likely due to inclusion performed by trained stroke physicians with several years of experience with TIA and stroke patients. Secondly, the $ABCD^2$ distribution in our study, with about two thirds of the patients having a high risk score of 4 or more, and a median score of 4, was not towards a lower risk than TIA populations in previous cohorts [3–5]. Thirdly, reclassification of DWI-MRI positive TIAs as stroke can potentially reduce the incidence of subsequent stroke in TIA prognostic studies, since the DWI negative TIAs have been shown to have a lower stroke risk than DWI positive TIAs [21]. All physicians involved in study inclusion were informed to use the time-based TIA-definition. Finally, the mean time from onset to hospital admission was only 17 h, which indicates an appropriate follow-up from TIA onset for most patients and thus prevented loss of stroke-events during the first few days when the risk of stroke after TIA is regarded as high [22].

$ABCD^2$ score

In the low risk $ABCD^2$ group there were very few strokes, so a low $ABCD^2$ score still indicates a very low stroke risk. However a new and interesting finding was that patients with a high $ABCD^2$ score also had a low risk of stroke. Although there were approximately twice as many strokes in the high versus the low risk group at each time point, we did not find significant differences in the Kaplan-Meier analysis. The hazard ratios of 2.1 to 2.4 confirm the same trend towards higher stroke occurrence in the high risk group, but again these were non-significant differences. Furthermore ROC analyses showed insufficient discriminating value of the $ABCD^2$ score both when applied 1 week, 3 months and 1 year after stroke.

Only 1 of 206 patients with an $ABCD^2$ score of ≤3 experienced a stroke within 1 week. However, as shown in earlier studies, patients with low $ABCD^2$ score may have underlying severe pathology, like atrial fibrillation and internal carotid stenosis, which underscores benefit from rapid diagnostic evaluation regardless of risk score [16, 23]. In the present study there were no significant differences in the prevalence of carotid stenosis and atrial fibrillation in the low- and high risk group.

Strengths and limitations

The strength of the study is the prospective design with the use of standardized diagnostic criteria. The study was conducted in a well-defined geographical region in close collaboration with all the local hospitals and primary health care system. The high adherence to current guidelines regarding assessment and treatment make it a "real-life" clinical scenario, meaning that these findings can be generalized and applied in a broader health-care setting.

The main limitation of our study is the lack of power caused by the low rate of strokes. With a larger cohort we might have been able to show significant differences between the two risk groups. The power calculation was, however, based on current knowledge of post-TIA stroke risk and cannot be considered a methodological error. The fact that our study is not population-based can imply selection bias, as for instance some very mild or short lasting TIAs might not have come to medical attention, or were treated by the general practitioner without referral to the hospital. It is, however, likely that the majority of these patients constitute a low risk group and would have resulted in an even weaker association between TIA and subsequent stroke if included in the analyses. As in most studies, missing data are unavoidable, but the outcome variables were confirmed by using well-functioning national quality registries, and there were no missing $ABCD^2$ scores.

Conclusions

In our study TIA patients had a very low risk of stroke, indicating that the health services in our region offer TIA patients management of high quality. Urgent assessment and intervention are likely the main reasons for the low stroke risk.

Low $ABCD^2$ score predicted very low risk of stroke. However, patients with a high score also had a low risk of stroke. Due to the low numbers of stroke, the study did not have sufficient power to detect significant differences in stroke risk between patients with high and low $ABCD^2$ score. Our results can still indicate that the $ABCD^2$ score may be less applicable to discriminate between high and low stroke risk groups in populations with a low risk of stroke after TIA. Patients with a low score also can have severe underlying pathology, hence rapid evaluation seems to be the key factor for optimizing the outcome in all TIA patients.

Abbreviations

AUC: Areas under the curve; CI: Confidence intervals; DWI: Diffusion-weighted imaging; HR: Hazard ratios; IQR: Interquartile range; ROC: Receiver operating characteristics curve; TIA: Transient ischemic attack

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Availability of data and materials
Deposition of patient level data in a public repository was not specified in the study protocol, which was approved by the ethics committee before the study began. Patient-level data will be available on request, provided that the Regional Ethics Committee gives approval.

Author's contributions
BI, HE and TW contributed to conception and design of the study. BI and FI were involved in gaining ethical approval. FI performed all analyses after discussions with and statistical input from SL. FI wrote the first draft of the manuscript. SS, JWH, GB, AGM, ÅHM, MLL, YMS, BI, HE and FI were responsible for patient recruitment, assessment and data collection at their respective hospitals. JKS contributed to follow-up of patients. HF was responsible for data from the Norwegian Stroke Register. All authors reviewed and edited the manuscript and approved the final version of the manuscript.

Ethics approval and consent to participate
The study was approved (REC no. 2012/1224) by the Regional Committee of Medical and Health Research Ethics of Møre og Romsdal and Trøndelag, Norway (REC Central, Faculty of Medicine and Health Sciences, Norwegian University of Science and Technology). Permission to use data from the Norwegian Cardiovascular Disease Registry, hereunder the Norwegian Stroke Register, was granted by the Norwegian Institute of Public Health. Written informed consent was obtained from all subjects before study inclusion.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

Publisher's Note

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Paper II

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Research Article

ABCD3-I and ABCD2 Scores in a TIA Population with Low Stroke Risk

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Objectives. We aimed to evaluate the ABCD3-I score and compare it with the ABCD2 score in short- (1 week) and long-term (3 months; 1 year) stroke risk prediction in our post-TIA stroke risk study, MIDNOR TIA. *Materials and Methods*. We performed a prospective, multicenter study in Central Norway from 2012 to 2015, enrolling 577 patients with TIA. In a subset of patients with complete data for both scores ($n = 305$), we calculated the AUC statistics of the ABCD3-I score and compared this with the ABCD2 score. A telephone follow-up and registry data were used for assessing stroke occurrence. *Results*. Within 1 week, 3 months, and 1 year, 1.0% ($n = 3$), 3.3% ($n = 10$), and 5.2% ($n = 16$) experienced a stroke, respectively. The AUCs for the ABCD3-I score were 0.72 (95% CI, 0.54 to 0.89) at 1 week, 0.66 (95% CI, 0.53 to 0.80) at 3 months, and 0.68 (0.95% CI, 0.56 to 0.79) at 1 year. The corresponding AUCs for the ABCD2 score were 0.55 (95% CI, 0.24 to 0.86), 0.55 (95% CI, 0.42 to 0.68), and 0.63 (95% CI, 0.50 to 0.76). *Conclusions*. The ABCD3-I score had limited value in a short-term prediction of subsequent stroke after TIA and did not reliably discriminate between low- and high-risk patients in a long-term follow-up. The ABCD2 score did not predict subsequent stroke accurately at any time point. Since there is a generally lower stroke risk after TIA during the last years, the benefit of these clinical risk scores and their role in TIA management seems limited. *Clinical Trial Registration*. This trial is registered with NCT02038725 (retrospectively registered, January 16, 2014).

1. Introduction

Patients with transient ischemic attacks (TIA) are at risk of subsequent strokes, especially early after the attack [1, 2]. Therefore, urgent assessment and intervention is essential in preventing strokes in patients with TIA [3, 4]. Accurate identification of patients at highest risk of stroke after TIA has been considered important in the clinical evaluation and management of these patients. In the last two decades, clinical scores have been established to estimate the stroke risk following a TIA, with the ABCD2 and the ABCD3-I scores being the best validated ones (see Table 1). The ABCD2 score was originally developed to aid nonspecialists in community-based referring settings in management of TIA patients [5]. The ABCD3-I score was developed for use in secondary care and includes information from initial diagnostic investigations [6].

In our prospective TIA study, MIDNOR TIA, we found a lower stroke risk after TIA than reported in earlier studies [7]. The ABCD2 score was able to identify patients with very low risk of stroke, but did not reliably discriminate between low- and high-risk patients, suggesting that it may be less useful in populations with a general low risk of stroke after TIA. The primary aim of the present study was to investigate the predictive accuracy of the ABCD3-I score and secondary to compare it with the ABCD2 score in short- and long-term

Table 1: ABCD2 and ABCD3-I scores.

	ABCD2 score	ABCD3-I score
Age ≥ 60 years	1	1
Blood pressure ≥ 140/90 mmHg	1	1
Clinical features		
Speech impairment without weakness	1	1
Unilateral weakness	2	2
Duration		
10-59 min	1	1
≥60 min	2	2
Diabetes present	1	1
Dual TIA (TIA leading patient to seek medical help plus at least on other TIA in the preceding 7 days)	NA	2
Imaging: ≥50% stenosis of ipsilateral internal carotid artery	NA	2
Imaging: acute MRI-DWI hyperintensity	NA	2
Total range	0-7	0-13

NA: not applicable; TIA: transient ischemic attack; DWI: diffusion-weighted imaging.

risk stratification, and to test whether the ABCDI-3 score performed better in populations with a low risk of stroke after TIA.

2. Materials and Methods

2.1. Study Design and Participants. This is a prospective multicenter study enrolling patients with TIA; the methods of which have been described in detail previously [7]. In brief, all eight hospitals in the region of Central Norway recruited patients from October, 2012, to July, 2014, with a follow-up until July, 2015. Experienced stroke physicians performed inclusion, in most cases on the hospital ward. All patients underwent a standardized diagnostic work-up containing brain and vascular imaging in addition to a detailed patient history, physical examination, blood tests, and cardiac rhythm monitoring. By a telephone follow-up, trained study nurses recorded subsequent stroke (ischemic and hemorrhagic) within 1 week, 3 months, and 1 year after the index TIA. To confirm registered strokes, we used data from the Norwegian Cardiovascular Disease Registry, which includes the Norwegian Stroke Register. All patients were managed according to current treatment guidelines for TIA [8].

Recording of the ABCD2 score was done prospectively as this was the primary aim of the original study, while the ABCD3-I scores were calculated after the study completion by assigning two points for dual TIA, two points for stenosis (≥50%) on carotid imaging, and two points for positive diffusion-weighted imaging MRI (DWI). A positive DWI was defined as ≥1 areas of high signal intensity interpreted as acute ischemic lesions. The abnormal DWI findings were diagnosed by radiologists, in most cases neuroradiologist. Carotid stenosis was defined as a ≥50% narrowing in the lumen of the internal carotid artery that could be responsible for the neurological symptom. The index TIA was defined as the most recent TIA leading the patient to seek medical help. Dual TIA was defined as the occurrence of at least one other TIA during the 7 days before the index event. The blood pressure measurement used for the ABCD2 and ABCD3-I assignment was the first ever recorded after the onset of the TIA.

The TIA diagnosis was based on the World Health Organization criteria [9], which defines a TIA as an acute loss of focal cerebral or ocular function lasting less than 24 hours, without an apparent nonvascular cause. The WHO criteria were also used for stroke [10].

2.2. Statistical Analysis. The area (AUC) under the receiver operating characteristic (ROC) for the two scores was estimated using Roger Newson's program—somersd (available in Stata). Somers' D computes the Harrell's C, an equivalent to the AUC, referred to as the AUC here [11]. Perfect prediction produces an AUC of 1.0, whereas prediction that is no better than chance produces an AUC of 0.5. We performed Cox proportional hazards regression analyses to calculate hazard ratios (HRs), using the low-risk ABCD3-I group as the reference category. Cox regression analyses with the covariates positive DWI, dual TIA, and carotid stenosis one at a time were also performed to identify to what degree these additional features in the ABCD3-I score contributed to the predictive value of the score.

Descriptive statistics for continuous variables are given as means with standard deviations (SD) and for categorical variables as frequencies and percentages. Statistical analyses were performed using SPSS Statistics 25 and Stata 15.

3. Results

Of the 577 patients included in the original study, 305 patients had complete data for secondary analysis of both the ABCD3-I and ABCD2 scores (see Figure 1). The main reason for exclusion was that MRI investigation had not been performed.

Table 2 summarizes the clinical characteristics of the patients included and excluded from the analysis. The mean (SD) age of the included patients was 68.0 years (10.9), of whom 60% were men. Hypertension was the most frequent

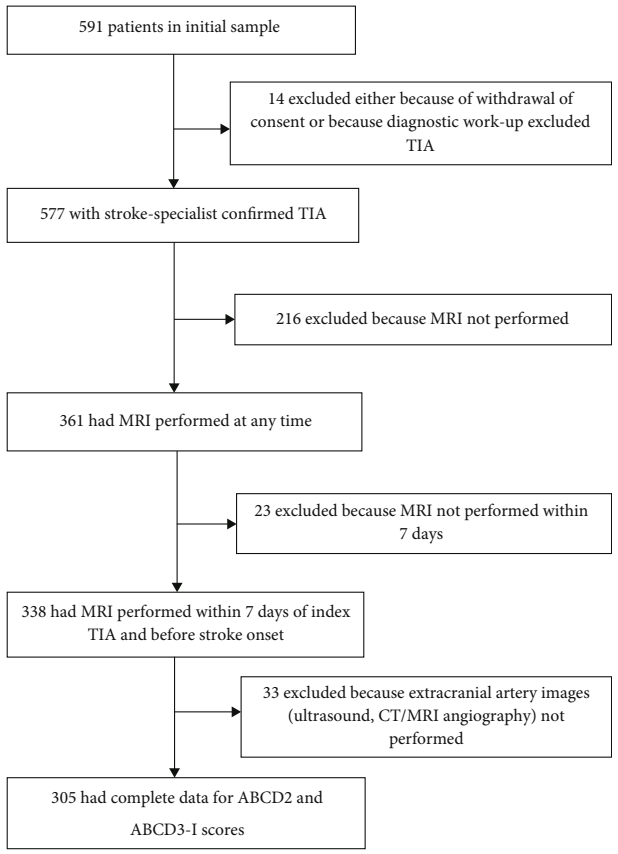

Figure 1: Flow chart of study profile.

vascular risk factor. In total, 35 patients (11.5%) had dual TIAs. Ultrasonography was the preferred investigational method of carotid arteries in most cases and was performed in 92% ($n = 279$) of the patients, while CT or MR angiography was performed in 25% ($n = 75$). Twenty-six patients (8.5%) had >50% stenosis of ipsilateral internal carotid artery. Of these, 17 patients (65.4%) underwent carotid surgery (carotid endarterectomy). There were no periprocedural strokes. Acute ischemic lesions on DWI were identified in 89 patients (29.2%). Two hundred and fifty-eight patients (84.6%) were admitted to hospital in less than 24 hours after symptom onset. Eighty-nine (29.2%) had their DWI performed within 24 hours after the index TIA, 63% ($n = 192$) within 48 hours, and 81% ($n = 247$) within 72 hours. Aphasia and dysarthria (46.2%) and arm paresis (34.1%) were the most common symptoms. The number of patients on antiplatelet therapy increased from 37% before TIA to 90.5% ($n = 276$) at the time of discharge from the hospital. Among these, 95% ($n = 261$) were treated with aspirin, either in monotherapy or in combination with dipyridamole ($n = 133$) or clopidogrel ($n = 20$). The patients excluded from the analysis were older and had a higher burden of vascular risk factors, but except for age, former TIA, hypertension, and atrial fibrillation, there were no other significant differences in baseline characteristics between the groups.

Cumulative incidence of stroke was 1.0% (3 patients), 3.3% (10 patients), and 5.2% (16 patients) within 1 week, 3 months, and 1 year after onset of TIA, respectively. Comparing low- and medium- to high-risk ABCD3-I categories, the rate of stroke increased from 0% to 2.5% within 1 week, 0% to 7.5% within 3 months, and 2.1% to 10.0% within 1 year. When comparing low- to high-risk ABCD2 categories, the rate of stroke increased from 0.9% to 1.0% within 1 week, 1.9% to 4.1% within 3 months, and 2.8% to 6.6% and within 1 year (see Table 3).

A Cox regression analysis comparing medium (4–7) and high (8–13) ABCD3-I score with low (reference) score (0-3) showed hazard ratios of 3.84 (95% CI, 0.49 to 30.0; $p = 0.20$) and 9.38 (95% CI, 1.10 to 80.3; $p = 0.041$), respectively.

The AUC values of ABCD3-I were higher than those of ABCD2 at each time point (see Figure 2), but the difference only reached statistical significance for stroke recurrence at

Table 2: Clinical characteristics in included patients with complete data for analysis of the ABCD2 and ABCD3-I scores and excluded patients, *n* (%) or mean ± SD.

Patient characteristics	Included ($n = 305$)	Excluded ($n = 272$)
Demographics		
Age in years, mean (±SD)	68 (10.9)	73.4 (10.5)
Male	183 (60.0)	144 (52.9)
Age in years, mean ± SD	68.0 ± 10.9	73.4 ± 10.5*
Medical history, *n* (%)		
Former TIA	44 (14.4)	57 (21)
Former ischemic stroke	38 (12.5)	49 (18.0)
Former TIA	44 (14.4)	57 (21.0)*
Former myocardial infarction	33 (10.8)	34 (12.5)
Diabetes mellitus	33 (10.8)	33 (12.1)
Hypertension	140 (45.9)	171 (62.9)†*
Hypercholesterolemia	104 (34.1)	112 (41.2)‡
Atrial fibrillation	29 (9.5)	50 (18.4)*
Current smoker	55 (18.0)	39 (14.3)
Former smoker	115 (37.7)	107 (39.3)
Modified Rankin score value 0 to1	259 (84.9)	218 (80.1)
ABCD2 score range		
0	4 (1.3)	3 (1.1)
1	5 (1.6)	10 (3.7)
2	29 (9.5)	33 (12.1)
3	70 (23.0)	52 (19.1)
4	97 (31.8)	80 (29.4)
5	51 (16.7)	56 (20.6)
6	37 (12.1)	31 (11.4)
7	12 (3.9)	7 (2.6)
Medication		
At baseline		
Any antiplatelet treatment	113 (37.0)	120 (44.1)
Any anticoagulation	24 (7.9)	32 (11.8)
Blood pressure-lowering agent	140 (45.9)	171 (62.9)*
Lipid-lowering agent	104 (34.1)	112 (41.2)
At discharge		
Any antiplatelet treatment	276 (90.5)	224 (82.4)*
Any anticoagulation	37 (12.1)	54 (19.9)*
Blood pressure-lowering agent	168 (55.1)	188 (69.1)*
Lipid-lowering agent	264 (86.6)	219 (80.5)*
No. of strokes		
<1 week	3 (1.0)	2 (0.7)
<3 months	10 (3.3)	9 (3.3)
<1 year	16 (5.2)	15 (5.5)

†Using blood pressure-lowering medication. ‡Using lipid-lowering medication. *Significant difference between the groups ($p < 0.05$).

1 week. AUCs for the ABCD2 score were 0.55 (95% CI, 0.24 to 0.86) within 1 week, 0.55 (95% CI, 0.42 to 0.68) within 3 months, and 0.63 (95% CI, 0.50 to 0.76) within 1 year. AUCs for the ABCD3-I score within the same time points were 0.72 (95% CI, 0.54 to 0.89) (compared with the ABCD2 score, $p = 0.019$), 0.66 (95% CI, 0.53 to 0.80) ($p = 0.11$), and 0.68 (0.95% CI, 0.56 to 0.79) ($p = 0.39$), respectively (see Table 3).

A Cox regression analysis to evaluate the risk of stroke in the presence of positive DWI, dual TIA, and carotid stenosis of the ABCD3-I score compared to none of these

Table 3: The 1-week, 3-month, and 1-year risks of stroke according to cutoff values of the ABCD2 and ABCD3-I scores with corresponding AUC levels.

	Patients, *n* (%)	Stroke events (% of patients)		
		<1 week	<3 months	<1 year
ABCD2 score				
0-3	108 (35.4)	1 (0.9)	2 (1.9)	3 (2.8)
4-7	197 (64.6)	2 (1.0)	8 (4.1)	13 (6.6)
AUC (95% CI)		0.55 (0.24-0.86)	0.55 (0.42-0.68)	0.63 (0.50-0.76)
ABCD3-I score				
0-3	72 (23.6)	0	0	1 (2.1)
4-7	193 (63.3)	2 (1.0)	7 (3.6)	11 (5.7)
8-13	40 (13.1)	1 (2.5)	3 (7.5)	4 (10.0)
AUC (95% CI)		0.72 (0.54-0.89)	0.66 (0.53-0.80)	0.68 (0.56-0.79)
Total no. of strokes	305 (100)	3 (1.0)	10 (3.3)	16 (5.2)

characteristics showed hazard ratios of 2.53 (95% CI, 0.95 to 6.73; $p = 0.064$), 1.11 (95% CI, 0.25 to 4.90; $p = 0.89$), and 0.71 (95% CI, 0.09 to 5.39; $p = 0.74$), respectively, for the entire follow-up period of 1 year.

4. Discussion

This secondary analysis of the data from the MIDNOR TIA study validated the usefulness of the ABCD3-I score to predict the 1-week, 3-month, and 1-year risk of stroke after TIA. We found an association between the higher ABCD3-I scores and increased stroke risk one week, three months, and one year after TIA both with the use of the AUC values for ABCD3-I and Cox proportional hazards regression analyses comparing the medium- and high-risk with low-risk ABCD3-I score. This is consistent with several previous TIA risk studies that have shown an increase in stroke risk with increasing ABCD3-I score points [12–16]. However, there were few strokes registered and the AUC statistics showed very wide confidence intervals with the lower limit reaching close to 0.5 at every time point in the follow-up period. There were also wide confidence intervals for the hazard ratios reported.

The ABCD2 score was not able to predict stroke after TIA in this cohort with AUC values of 0.55 to 0.63 and the lower limit of the confidence intervals as low as 0.24 within 1 week. Compared to this, the AUC values for the ABCD3-I score were higher, but only significantly for stroke recurrence at 1 week, suggesting that the overall predictive value of the ABCD3-I score is low. We found a very low risk of stroke, and this probably affected the predictive value of the clinical scores in our study. These results are, however, in line with the risks described in our own prospective TIA cohort [7]. Other recent studies reporting the effect of rapid evaluation and treatment initiation of TIA patients have found similar low stroke risks [3, 4, 17, 18]. As described earlier [7], this trend towards a lower stroke recurrence during the recent years may be explained by more rapid evaluation by stroke specialists, better implementation of secondary stroke prevention strategies, and changing risk factors in the population, for instance, through a decline in cigarette smoking rates. The first days to a week after TIA is generally regarded as the time window with the highest stroke risk [19]. In our study, within the first week, only 3 out of 233 patients (1.3%) with an ABCD3 – I score ≥ 4 (moderate to high risk) experienced a stroke. The corresponding numbers for the entire follow-up period of 1 year for the same group were also low—15 out of 233 patients (6.4%). In the low-risk group (score 0-3), there were no registered strokes within 1 week and 3 months, and only 1 stroke within 1 year.

The ABCD3-I score was developed to improve risk scoring accuracy in a specialist setting. It was not intended to be used in the prehospital settings, as DWI (and carotid artery imaging) is generally not available to community-based clinicians who make referrals. Though many studies have pointed out the increased discrimination ability of the ABCD3-I score (compared to the ABCD2 score), there is little evidence on how this score could be implemented in a clinical setting and used in practice. Truly, the clinical context in which a risk score is applied determines its usefulness, and not its predictive power alone. It has been argued that some higher-risk patients could benefit from hospital admission, where they can have immediate access to early acute treatment (thrombolysis and thrombectomy) in case of recurrent strokes [12]. A recent study on the use of the ABCD3-I score in the emergency department reported significantly decreased hospital admissions and cost with similar 90-day neurological outcomes after the initiation of an ABCD3-I-based pathway for TIA evaluation [20]. This was however a small study with statistical methodological limitations, a small sample size, and a short follow-up. It was also based on an emergency department which could perform MRI DWI quickly. The use of DWI is recommended in the investigation of TIA [21, 22]. It is also proposed as the basis for the tissue-based definition of TIA as opposed to the traditional time-based definition, which we used in our study [23]. Our Cox proportional hazards regression on the additional components in the ABCD3-I score supports the relation between positive DWI after TIA and the risk of future strokes, and we agree that such investigation should be done, if available. But the

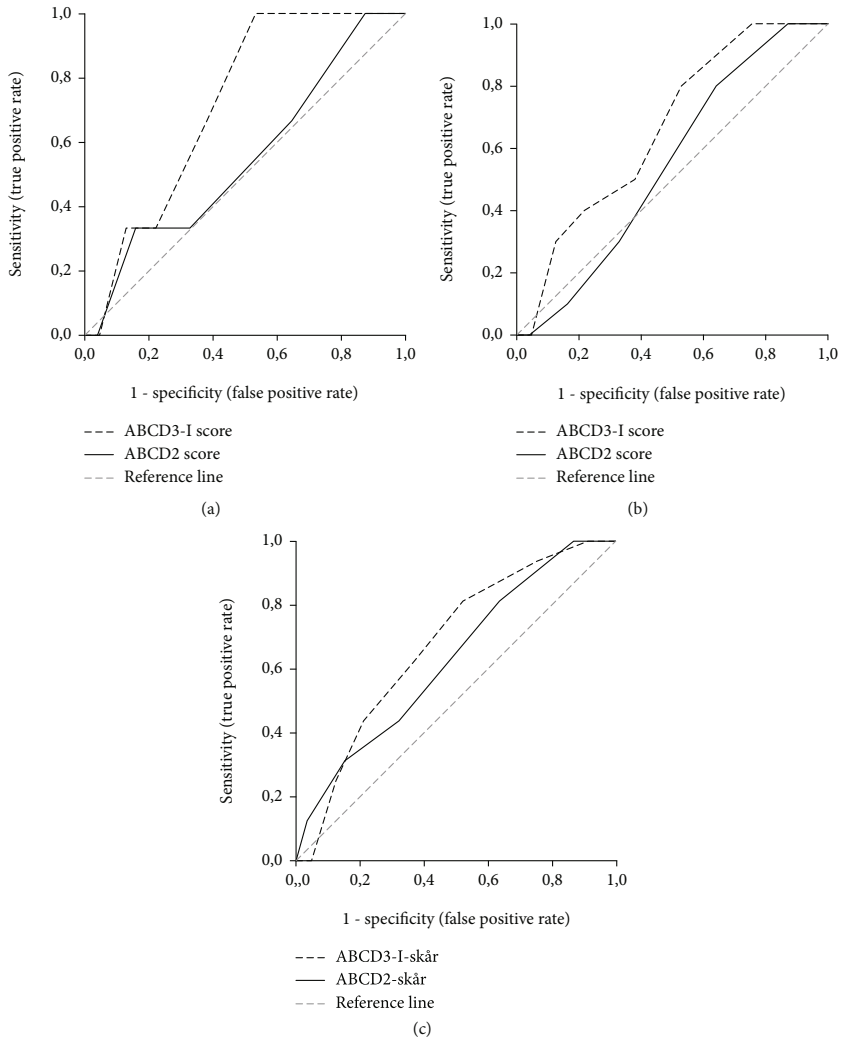

Figure 2: ROC curves of the ABCD3-I score and ABCD2 score at 1 week (a), 3 months (b), and 1 year (c).

availability of MRI DWI varies greatly between hospitals, regions, and countries, so also in rural districts with small hospitals in a high-income country like Norway.

Interpreting our data, we noticed that patients with a low ABCD2 score and a low ABCD3-I score even more so had an extremely low risk of stroke after TIA. However, due to the generally very low post-TIA stroke risk in our study and in similar contemporary studies [17, 24], both for patients with low and high score, there were no significant differences between the groups. In areas where TIA clinics are not available, one can argue that these scores could be used to identify those low-risk patients who can have assessment beyond the recommended 24-48 hours after TIA [21, 22]. There is strong evidence that early administration of aspirin is a key intervention to prevent stroke after TIA [25]. However, as reasoned for in our primary analysis of the ABCD2 score in our TIA cohort [7], patients with a low score also can have severe underlying pathology; hence, rapid evaluation in a specialized stroke center, either in an outpatient or inpatient setting, seems to be the essential factor for optimizing the outcome in all TIA patients. In our TIA population, almost all patients were admitted immediately to the hospital, underwent rapid TIA assessment (including MRI DWI and extracranial artery investigations), and were medically treated according to guidelines. Consequently, further progression in investigations or treatment did probably not differ greatly between the low- and high-risk groups. This may reduce the usefulness of the ABCD2 and ABCD3-I scores

and contribute in explaining why the scores do not discriminate better between the low- and high-risk groups. Atrial fibrillation is a known risk factor for cerebrovascular ischemic events. However, validation studies of post-TIA risk scores have not found an increased predictive stroke risk accuracy by taking atrial fibrillation into account [26, 27]. In our study, when comparing proportions of atrial fibrillation between low- and medium- to high-risk patients, we did not find significant differences. Therefore, adding this to the risk score probably would not have changed our results.

The main strength of our study lies in the prospective methodology collecting a cohort in close collaboration between the local hospitals and the primary health care system. Recruited patients were given early and comprehensive stroke unit care based on current guidelines. This makes it a "real-life" clinical scenario. Additionally, the diagnosis of included patients was made by stroke specialists making inclusion of TIA mimics less likely. We acknowledge that our study has some important limitations. The main limitation is the lack of statistical power due to the low rates of stroke. However, the power calculation in the original study was based on current knowledge of stroke risk after TIA, and the patients included in this analysis had similar stroke rates as the original cohort. Second, the patients that were excluded from the analysis because DWI was not performed or performed too late, or because extracranial imaging was not performed, were older and had generally higher load of vascular risk factors. At the same time, there were several similarities: there were no significant differences in subsequent stroke rates between included and excluded patients. Also, excluded patients had proportions of dual TIAs similar to the included patients (22/272), and patients in this group that did undergo carotid artery imaging had similar rates of carotid stenosis (22/215) as the included patients. Therefore, it is not highly likely that excluding a part of the cohort on the grounds of lack of availability of investigational data would constitute a relevant selection bias. Also important, the baseline clinical characteristics of the included patients were similar to those of comparable TIA stroke prediction studies [12]. Third, the ABCD3-I scores were calculated retrospectively, which could have increased the risk of errors in registration of data. Likewise, the fact that there were few strokes in the follow-up time makes results vulnerable to errors being done in the registration process. In our study, the prevalence of dual TIA was low. The reported prevalence of dual TIA, however, varies widely among different populations in previous studies [6, 14, 16]. As a fact, several of the components of the ABCD2 and ABCD3-I scores are based on patients' own memory, and therefore susceptible to recall bias.

5. Conclusions

The ABCD3-I score had limited value in a short-term prediction of subsequent stroke after TIA, and the ability to predict stroke deteriorated further during a long-term follow-up. The ABCD2 score did not predict subsequent stroke accurately at any time point. Due to the low numbers of stroke, the study did not have enough power to detect significant differences in stroke risk between patients with high- and low-risk scores, and our results therefore must be interpreted with caution. They still give an indication that these clinical TIA risk scores are less beneficial to discriminate between the high- and low-stroke-risk groups in populations with a general low risk of stroke after TIA. This is also supported by recent publications and guidelines [21, 28]. We believe that the best approach to TIA patients is to carefully consider each of the components of the investigated scores through rapid assessment and initiation of treatment, rather than using dichotomized scores.

Data Availability

Deposition of patient level data in a public repository was not specified in the study protocol, which was approved by the ethics committee before the study began. Provided that the Regional Ethics Committee gives approval, patient-level data will be available on request.

Additional Points

Statement. An earlier version of our manuscript was (March 5th, 2020) presented as a preprint (preliminary report) in Research Square.

Disclosure

The funders had no role in the design of the study or the collection, analysis, interpretation of data, or in the writing of this manuscript.

Conflicts of Interest

The authors report no conflicts of interest.

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Paper III

TITLE: FIVE-YEAR RISK OF CARDIOVASCULAR EVENTS AFTER TRANSIENT ISCHEMIC ATTACK - RESULTS FROM A PROSPECTIVE COHORT

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Acknowledgements

Not applicable.

Appendices

Henvisning av TIA-pasienter i Midt-Norge

Pasient med TIA (uten symptomer ved henvendelse)

AMK
» Henvendelse til fastlege/legevakt

Fastlege / Legevakt
» Undersøk samme dag

Annet helse-personell
» Henvendelse til fastlegelegevakt

Sannsynlig TIA
» ABCD2-skår
» Acetylsalicylsyre 160-300 mg
» Ring AMK som kontakter vakthavende lege ved aktuelle sykehus

Sannsynlig ikke TIA
» Ingen videre henvisning og utredning av TIA
» Ingen ABCD2-skår
» Videre tiltak ut ifra medisinske tilstand

Sannsynlig TIA
» Vakthavende lege gir direkte beskjed om videre utredning med dato og tid innen 72 timer

Sannsynlig ikke TIA
» Avtale om pasienten skal innlegges av annen grunn eller henvises skriftlig til vurdering senere

Innleggelse ø-hjelp
» ABCD2 = 4-7
» Repeterende TIA
» Ingen poliklinisk kapasitet

Poliklinisk tilbud
» ABCD2 = 0-3
» Mulighet for utredning innen 72 timer

Dagpasient
» ABCD2 = 0-3
» Mulighet for utredning innen 72 timer

» Lege i akuttmottak rekvirerer bildediagnostikk av hjerne, gir ASA hvis ikke gitt prehospitalt

Mest typiske TIA-symptomer

FAST

Halvsidig parese i Fjes, Arm (+ ben), Språkvansker, Taleproblemer

Halvsidig sensibilitetsutfall

Synsfeltsutfall, evt. diplopi

Synstap (oftest på ett øye)

Mindre typiske TIA-symptomer

Balanseproblemer/koordinasjons-problemer

Isolerte sensoriske symptomer

Sannsynlig ikke TIA:

Isolert svimmelhet

Synkope/bevissthetsendring

Desorientering

Transitorisk global amnesi

Hørselstap

"Vandrende" symptomer

Inklusjon i MIDNOR TIA

- ☐ Sannsynlig TIA? (på bakgrunn av anamnese, klinisk undersøkelse, bildediagnostikk og øvrige undersøkelser)
- ☐ Bosatt i Midt-Norge?
- ☐ Mellom 18 og 90 år?
- ☐ Henvist til utredning innen 2 uker fra symptomdebut?
- ☐ Modified Rankin Scale ≤ 3 og bor hjemme
- ☐ Informert samtykke til deltagelse?

- ☐ **Aktuell for inklusjon i MIDNOR TIA?** Hvis du kan svare ja på alle spørsmålene over

ABCD2-skår

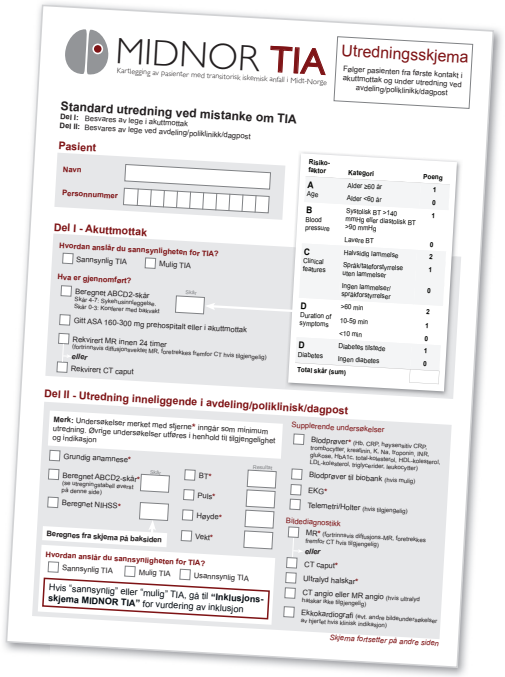
Risiko-faktor	Kategori	Poeng
A Age	Alder ≥ 60 år	1
	Alder < 60 år	0
B Blood pressure	Systolisk BT >140 mmHg eller diastolisk BT >90 mmHg	1
	Lavere BT	0
C Clinical features	Halvsidig lammelse	2
	Språk/taleforstyrrelse uten lammelser	1
	Ingen lammelser/ språkforstyrrelser	0
D Dur. of symptoms	>60 min	2
	10-59 min	1
	<10 min	0
D Diabetes	Diabetes tilstede	1
	Ingen diabetes	0
Total skår (sum)		

MIDNOR TIA

Et prosjekt for kartlegging av pasienter med transitorisk iskemisk anfall (TIA) i Midt-Norge

Har du en pasient hvor du mistenker gjennomgått TIA?

Bruk *Utredningsskjema - Standard utredning ved mistanke om TIA*


MIDNOR TIA
Kartlegging av pasienter med transitorisk iskemisk anfall i Midt-Norge

Utredningsskjema
Følger pasienten fra første kontakt i akuttmottak og under utredning ved avdeling/poliklinikk/dagpost

Standard utredning ved mistanke om TIA
Del I: Besvares av lege i akuttmottak
Del II: Besvares av lege ved avdeling/poliklinikk/dagpost

Pasient
Navn
Personnummer

Del I - Akuttmottak
Hvordan anslår du sannsynligheten for TIA?
Sannsynlig TIA
Mulig TIA
Hva er gjennomført?
Beregnet ABCD2-skår
Skår 4-7: Sykehusinnleggelse.
Skår 0-3: Kontakter med fastlege
Gitt ASA 160-300 mg prehospitalt eller i akuttmottak
Rekvirert MR innen 24 timer
(fortrinnsvis diffusjonsvektet MR, foretrekkes fremfor CT hvis tilgjengelig)
eller
Rekvirert CT caput

Risiko-faktor	Kategori	Poeng
A Age	Alder ≥60 år	1
	Alder <60 år	0
B Blood pressure	Systolisk BT >140 mmHg eller diastolisk BT >90 mmHg	1
	Lavere BT	0
C Clinical features	Halvsidig lammelse	2
	Språk/taleforstyrrelse uten lammelser	1
	Ingen lammelser/ språkforstyrrelser	0
D Duration of symptoms	>60 min	2
	10-59 min	1
	<10 min	0
D Diabetes	Diabetes tilstede	1
	Ingen diabetes	0
Totalt skår (sum)		

Del II - Utredning innleggende i avdeling/poliklinisk/dagpost
Merk: Undersøkelser merket med stjerne* inngår som minimum utredning. Øvrige undersøkelser utføres i henhold til tilgjengelighet og indikasjon
Grundig anamnese*
Beregnet ABCD2-skår*
(se utregningsgrunnlaget øverst på denne side)
Beregnet NIHSS*
Skår
BT*
Puls*
Høyde*
Vekt*
Resultat
Beregnes fra skjema på baksiden
Hvordan anslår du sannsynligheten for TIA?
Sannsynlig TIA
Mulig TIA
Usannsynlig TIA
Hvis "sannsynlig" eller "mulig" TIA, gå til "Inklusjons-skjema MIDNOR TIA" for vurdering av inklusjon
Supplerende undersøkelser
Blodprøver* (Hb, CRP, høyverdig CRP, trombocytter, kreatinin, K, Na, Troponin, INR, glukose, HbA1c, total-kolesterol, HDL-kolesterol, LDL-kolesterol, triglyserider, leukocytter)
Blodprøver til biobank (hvis mulig)
EKG*
Telemetri/Holter (hvis tilgjengelig)
Bildediagnostikk
MR* (fortrinnsvis diffusjons-MR, foretrekkes fremfor CT hvis tilgjengelig)
eller
CT caput*
Ultralyd halskar*
CT angio eller MR angio (hvis ultralyd hinder ikke tilgjengelig)
Ekkokardiografi (hvt. andre bildeundersøkelser av hjertet hvis klinisk indikasjon)
Skjema fortsetter på andre siden

Hvis pasienten er aktuell for deltagelse i **MIDNOR TIA** etter gjennomføring av skjemaets *Del II*, ta straks kontakt med TIA-sykepleier

www.ntnu.no/inm/midnor-tia

ABCD2-skår

Risiko-faktor	Kategori	Poeng
A Age	Alder ≥60 år	**1**
	Alder <60 år	**0**
B Blood pressure	Systolisk BT >140 mmHg eller diastolisk BT >90 mmHg	**1**
	Lavere BT	**0**
C Clinical features	Halvsidig lammelse	**2**
	Språk/taleforstyrrelse uten lammelser	**1**
	Ingen lammelser/ språkforstyrrelser	**0**
D Duration of symptoms	>60 min	**2**
	10-59 min	**1**
	<10 min	**0**
D Diabetes	Diabetes tilstede	**1**
	Ingen diabetes	**0**
Total skår (sum)		

Vi ber om at alle TIA-pasienter vurderes med ABCD2-skår av henvisende lege

Om bruk av retningslinjene ved TIA

Helsedirektoratet har utgitt retningslinjer for utredning og behandling av TIA som er innlemmet i "Nasjonal retningslinje for behandling og rehabilitering ved hjerneslag" (utgitt april 2010)

Informasjonen i denne brosjyren er grunnlagt på disse retningslinjene, og gjennomføring av prosjekt MIDNOR TIA baserer seg på at disse retningslinjene følges i hele behandlingskjeden

Alle fastleger, legevakter, sykehus og AMK-sentraler oppfordres til å benytte denne informasjonsbrosjyren i kontakt med pasienter med sannsynlig gjennomgått TIA.

Kontaktinformasjon ved spørsmål vedrørende MIDNOR TIA:

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MIDNOR TIA

Et prosjekt for kartlegging av pasienter med transitorisk iskemisk anfall (TIA) i Midt-Norge

For kommunehelsetjenesten, fastleger, legevakt og AMK-sentraler

Innhold

MIDNOR TIA starter formelt i september/ oktober 2012 etter at vi har fått godkjenning fra Forskningsetisk komité. Prosedyrene kan imidlertid med fordel tas i bruk tidligere, da de er basert på nasjonale retningslinjer.

Studien er finansiert av Samarbeidsorganet mellom Helse Midt-Norge og NTNU og Kontaktutvalget mellom St.Olavs hospital og Det medisinske fakultet, NTNU

Informasjon om prosjekt MIDNOR TIA

MIDNOR TIA er et samarbeidsprosjekt for kartlegging av pasienter med TIA (transitorisk iskemisk anfall) i de tre midt-norske fylkene. Vi ønsker å undersøke risiko for hjerneslag hos TIA-pasienter i vår region, og om ABCD2-skåren er et godt verktøy for risikovurdering. Verdien av bildediagnostikk, ulike biologiske markører og farmasøytisk rådgivning vil også bli undersøkt. Studiens formål er å undersøke om dagens utredning og behandling av TIA-pasienter er adekvat, og om de gjeldende retningslinjer er tilfredsstillende eller bør endres.

Hva er TIA?

Defineres som akutte, iskemisk betingede, fokalnevrologiske utfall som går helt tilbake innen 24 timer og i de fleste tilfeller innen 60 minutter.

I praksis skal pasienter som har fokalnevrologiske utfall ved henvendelse oppfattes som akutt hjerneslag og innlegges som ø-hjelp. For pasienter med TIA (symptomene har gått helt tilbake ved henvendelse), se tiltak i flytskjema.

Symptomer på TIA

Denne inndelingen er ment som en veiledning for identifisering av pasienter med TIA.

Mest typiske symptomer på TIA:

- **FAST**
  Halvsidig parese i **F**jes, **A**rm (+ ben), **S**pråkvansker, **T**aleproblemer
- Halvsidig sensibilitetsutfall
- Synsfeltsutfall, evt. diplopi
- Synstap (oftest på ett øye)

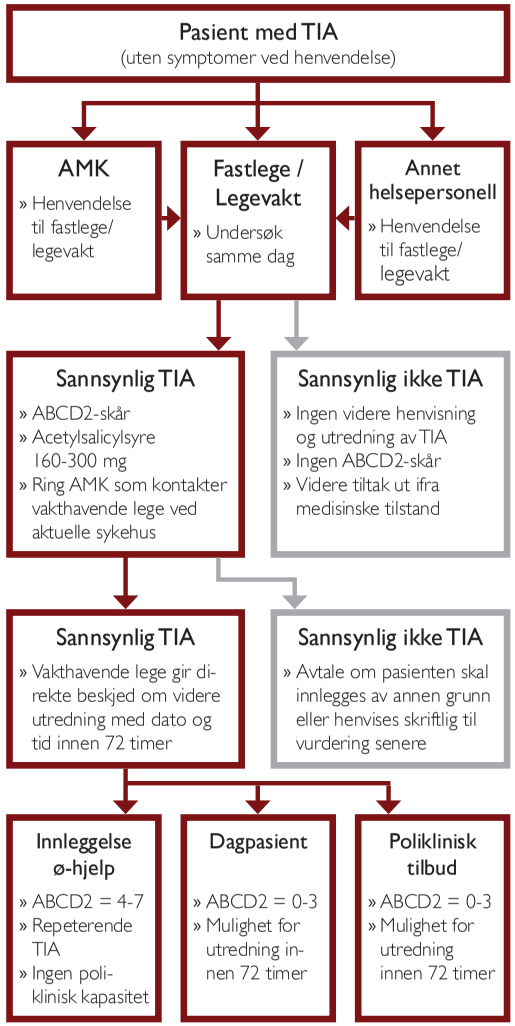
Mindre typiske symptomer på TIA:

- Balanseproblemer/koordinasjonsproblemer
- Isolerte sensoriske symptomer

Sannsynlig ikke TIA:

- Isolert svimmelhet
- Synkope/bevissthetsendring
- Desorientering
- Transitorisk global amnesi
- Hørselstap
- ”Vandrende” symptomer

Henvisning av TIA-pasienter i Midt-Norge



MIDNOR TIA

Trondheim, mai 2012

Til hjemmetjenesten i midt-norske kommuner

INFORMASJON OM PROSJEKT "MIDNOR TIA" OG TRANSITORISK ISKEMISK ANFALL (TIA)

MIDNOR TIA er et samarbeidsprosjekt for kartlegging av pasienter med TIA i de tre midt-norske fylkene. Vi har som mål å undersøke om dagens utredning og behandling av TIA-pasienter er adekvat. Vi ønsker i den anledning å gi en påminnelse til hjemmetjenesten om hva TIA innebærer og hvordan slike pasienter skal henvises.

TIA defineres som en akutt sirkulasjonsforstyrrelse i hjernen hvor symptomene går over innen 24 timer og i de fleste tilfeller innen 1 time.

Det hender at brukere forteller til hjemmetjenesten at de for eksempel "i går" eller "for noen dager siden" hadde en hendelse, og hvor symptomene nå har gått helt tilbake. Dette *kan* dreie seg om TIA.

De mest karakteristiske symptomer ved TIA er **FAST**-symptomer (lammelse i **F**jes, **A**rm (+ ben), **S**pråkvansker eller **T**aleproblem). Andre symptomer er akutt oppstått halvsidig følelsestap, akutt utfall i synsfelt, akutt dobbeltsyn og akutt synstap.

Hvis brukere forteller om slike forbigående symptomer, bes det om at hjemmetjenesten henviser dem videre til fastlege eller legevakt for undersøkelse samme dag.

Hvis pasientens symptomer fremdeles er til stede ved kontakt med hjemmetjenesten, fastlege eller legevakt skal dette betraktes som et mulig hjerneslag og pasienten skal innlegges akutt i sykehus.

De ovenstående påminnelsene er basert på nasjonale retningslinjer for utredning og behandling av TIA og hjerneslag.

Med vennlig hilsen,

Bent Indredavik (prosjektleder) og Fredrik Ildstad (stipendiat)
(på vegne av prosjektgruppen i MIDNOR TIA)

Forespørsel om deltakelse i forskningsprosjektet

MIDNOR TIA

Kartlegging av pasienter med «transitorisk iskemisk anfall» i Midt-Norge

Bakgrunn og hensikt
Dette er et spørsmål til deg om å delta i et forskningsprosjekt hvor formålet er å skaffe mer kunnskap om transitorisk iskemisk anfall (TIA eller «hjernedrypp»), det vil si en forbigående sirkulasjonsforstyrrelse til et lite område i hjernen. Grunnen til at du blir forespurt om å delta i dette prosjektet er at vi tror at du har gjennomgått TIA.

Tidligere studier har vist at det er økt risiko for hjerneslag etter TIA, men vi mangler fortsatt mye kunnskap om hvem som får TIA og hvor stor risiko dette representerer, og derfor gjennomføres nå dette forskningsprosjektet. Det finnes forskjellige måter å bedømme risiko for slag etter TIA, men det er fortsatt usikkerhet knyttet til disse metodene. Vi ønsker derfor å finne fram til bedre metoder for risikovurdering som kan gi grunnlag for bedre behandlingsopplegg i framtida. Hos enkelte pasienter vil vi også undersøke verdien av legemiddelrådgivning ved farmasøyt og du vil eventuelt bli forespurt om deltagelse i denne tilleggsstudien.

Hva innebærer studien?
Alle pasienter vil gå gjennom den utredning som Helsedirektoratets nasjonale retningslinjer for TIA anbefaler. Det betyr at det vil bli foretatt legeundersøkelse, tatt blodprøver, og bildeundersøkelser av hjernen og blodåresystemet, og resultatene av dette vil bli registrert. I tillegg vil vi be deg svare på noen spørsmål omkring risikofaktorer for TIA, hjerneslag og hjertekarsykdom. Vi vil også registrere opplysninger om legemidler som du eventuelt bruker. Etter 1 uke og 3 måneder, og sannsynligvis etter 1 år, vil du bli kontaktet per telefon for å svare på spørsmål om du har hatt noen nye sykdomsepisoder, hvordan oppfølgingen har vært og hvordan du har opplevd din helse og livskvalitet etter TIA. Det kan også bli aktuelt å kontakte deg senere for å få informasjon om din helsetilstand.

Mulige fordeler og ulemper
Alle undersøkelser som foretas og behandling som gis vil følge de nasjonale retningslinjer for TIA. Ved deltagelse vil du gå gjennom en systematisk utredning med sikte på å finne fram til årsaken til ditt TIA, og for å finne fram til et best mulig behandlingsopplegg. Sykehuset har lang erfaring med de aktuelle undersøkelsene og disse er ikke forbundet med spesiell risiko eller ubehag. De legemidlene som eventuelt oppstartes er også legemidler som er godt utprøvd både etter TIA og ved andre tilstander. Behandlende lege vil som alltid ta hensyn til eventuelle forhold som gjør at man må vise forsiktighet, enten det gjelder bruk av legemidler eller gjennomføring av undersøkelser.

Du vil som nevnt bli kontaktet av en forskningssykepleier per telefon etter 1 uke, 3 måneder og ett år, og det vil ta deg 5-10 minutter å svare på spørsmålene som blir stilt.

Hva skjer med prøvene og informasjonen om deg?
Prøvene tatt av deg og informasjonen som registreres om deg skal kun brukes slik som beskrevet i hensikten med studien. Alle prosjektmedarbeidere har taushetsplikt, og alle personopplysninger vil bli behandlet konfidensielt. Alle undersøkelsesresultater og navnelister vil bli oppbevart forskriftsmessig.

Det kan være nødvendig å supplere med opplysninger fra sykehusets pasientjournal for å sikre studiens kvalitet. Kun opplysninger relevant for dette prosjektet vil bli innhentet. Det vil også kunne være

aktuelt å innhente opplysninger fra Norsk hjerneslagregister, Norsk hjerteinfarktregister, Norsk karkirurgisk register, Nasjonalt register over hjerte- og karlidelser og Norsk pasientregister for å få informasjon om eventuelle sykdomshendelser. Ved å si ja til deltagelse gir du også samtykke til innhenting av informasjon fra disse registrene. Den informasjonen som vil kunne bli innhentet er i hovedsak om det har vært gjennomgått hjerneslag, hjerteinfarkt, inngrep på hjerte/kar, og opplysninger rundt eventuelle nye sykehusinnleggelser og eventuelt årsak ved død.

Noen instanser har rett til innsyn i relevante deler av journalen, dette gjelder for eksempel forskningsansvarlige, Uredelighetsutvalget for forskning og Helsetilsynet. Formålet med eventuelt innsyn er å kontrollere at studieopplysningene stemmer overens med tilsvarende opplysninger i din journal. Av den grunn vil opplysningene bli lagret i 5 år etter publisering. Alle som får innsyn har taushetsplikt. Det vil ikke være mulig å identifisere deg i resultatene av studien når disse publiseres.

Frivillig deltakelse
Det er frivillig å delta i studien. Du kan når som helst og uten å oppgi noen grunn trekke ditt samtykke til å delta i studien. Dette vil ikke få konsekvenser for din videre behandling. Dersom du ønsker å delta, undertegner du samtykkeerklæringen på siste side. Om du nå sier ja til å delta, kan du senere trekke tilbake ditt samtykke uten at det påvirker din øvrige behandling. Dersom du senere ønsker å trekke deg eller har spørsmål til studien, kan du kontakte *prosjektleder Bent Indredavik på telefon 72 57 54 91 (arbeid)/90 92 54 98(mobil).*

Biobank
En del av blodprøvene som blir tatt vil bli lagret i en forskningsbiobank ved «Regional forskningsbiobank Midt-Norge». Hvis du sier ja til å delta i studien, gir du også samtykke til at det biologiske materialet og analyseresultater inngår i biobanken. Faglig leder Jostein Halgunset er ansvarshavende for forskningsbiobanken. Regional komité for medisinsk og helsefaglig forskningsetikk (REK) har gitt tillatelse til lagring og bruk av dette biologiske materialet i studien.

Utlevering av materiale og opplysninger til andre
Det kan bli aktuelt å analysere noen av prøvene ved andre laboratorier. Hvis du sier ja til å delta i studien, gir du også ditt samtykke til at prøver og avidentifiserte opplysninger utleveres til samarbeidende forskningsgrupper.

Rett til innsyn og sletting av opplysninger om deg og sletting av prøver
Hvis du sier ja til å delta i studien, har du rett til å få innsyn i hvilke opplysninger som er registrert om deg. Du har videre rett til å få korrigert eventuelle feil i de opplysningene vi har registrert. Dersom du trekker deg fra studien, kan du kreve å få slettet innsamlede prøver og opplysninger, med mindre opplysningene allerede er inngått i analyser eller brukt i vitenskapelige publikasjoner.

Økonomi
Studien er finansiert gjennom forskningsmidler fra Samarbeidsorganet mellom Helse Midt-Norge og NTNU, og Kontaktutvalget mellom St.Olavs hospital og Det medisinske fakultet ved NTNU.

Forsikring
Ordningen for pasientskadeerstatning gjelder ved deltagelse i studien.

Etisk og faglig vurdering
Studien er godkjent av Regional komité for medisinsk og helsefaglig forskningsetikk (REK).

Informasjon om utfallet av studien
Resultatene fra studien vil bli publisert i internasjonalt anerkjente tidsskrift. Du vil også få informasjon om utfallet av studien dersom du henvender deg direkte til oss i ettertid.

Med vennlig hilsen

Fredrik Ildstad (lege/stipendiat)
Avdeling for hjerneslag, St.Olavs Hospital/NTNU

Bent Indredavik (avdelingsoverlege/professor)
Avdeling for hjerneslag, St.Olavs Hospital/NTNU

Samtykke til deltakelse i studien

Jeg er villig til å delta i studien

(Signert av prosjektdeltaker, dato)

Jeg bekrefter å ha gitt informasjon om studien

(Signert, rolle i studien, dato)

MIDNOR TIA

Kartlegging av pasienter med transitorisk iskemisk anfall i Midt-Norge

Inklusjonsskjema

Inklusjon skjer ved utredende avdeling/poliklinikk/dagpost

Pasient

Navn

Person-nummer

Utredning

Ansvarlig lege

Dato for utredning Dag Måned År

Avdeling

☐ Innlagt ☐ Poliklinisk ☐ Dagpost

Inklusjon

	Ja	Nei
1. Sannsynlig/mulig TIA? (på bakgrunn av anamnese, klinisk undersøkelse, bildediagnostikk og øvrige undersøkelser)	☐	☐
2. Bosatt i Midt-Norge?	☐	☐
3. Mellom 18 og 90 år?	☐	☐
4. Henvist til utredning innen 2 uker fra symptomdebut?	☐	☐
5. Modified Rankin Scale ≤ 3 og bor hjemme? (se nederst)	☐	☐
6. Informert samtykke til deltagelse?	☐	☐

Konklusjon

Inkluderes pasienten? (kryss i alle hvite ruter pkt. 1-6)

Ja	Nei
☐	☐

Kontakt TIA-sykepleier omgående for innhenting av samtykke og dataregistrering

Modified Rankin Scale

0 = Ingen symptomer
1 = Noe symptomer, men i stand til å utføre alle vanlige aktiviteter
2 = Noe begrensninger i livsstilen, men kan ta vare på seg selv uten hjelp
3 = Har behov for noe hjelp, men kan gå uten hjelp
4 = Kan ikke gå uten hjelp og trenger hjelp i daglige aktiviteter
5 = Sengeliggende, inkontinent, med behov for kontinuerlig hjelp
6 = Død

MIDNOR TIA

Kartlegging av pasienter med transitorisk iskemisk anfall i Midt-Norge

Utredningsskjema

Følger pasienten fra første kontakt i akuttmottak og under utredning ved avdeling/poliklinikk/dagpost

Standard utredning ved mistanke om TIA

Del I: Besvares av lege i akuttmottak
Del II: Besvares av lege ved avdeling/poliklinikk/dagpost

Pasient

Navn

Personnummer

Del I - Akuttmottak

Hvordan anslår du sannsynligheten for TIA?

☐ Sannsynlig TIA ☐ Mulig TIA

Hva er gjennomført?

☐ Beregnet ABCD2-skår
Skår 4-7: Sykehusinnleggelse.
Skår 0-3: Konferer med bakvakt
Skår

☐ Gitt ASA 160-300 mg prehospitalt eller i akuttmottak

☐ Rekvirert MR innen 24 timer
(fortrinnsvis diffusjonsvektet MR, foretrekkes fremfor CT hvis tilgjengelig)

eller

☐ Rekvirert CT caput

Risiko-faktor	Kategori	Poeng
A Age	Alder ≥60 år	**1**
	Alder <60 år	**0**
B Blood pressure	Systolisk BT >140 mmHg eller diastolisk BT >90 mmHg	**1**
	Lavere BT	**0**
C Clinical features	Halvsidig lammelse	**2**
	Språk/taleforstyrrelse uten lammelser	**1**
	Ingen lammelser/ språkforstyrrelser	**0**
D Duration of symptoms	>60 min	**2**
	10-59 min	**1**
	<10 min	**0**
D Diabetes	Diabetes tilstede	**1**
	Ingen diabetes	**0**
Total skår (sum)		

Del II - Utredning inneliggende i avdeling/poliklinisk/dagpost

Merk: Undersøkelser merket med stjerne* inngår som minimum utredning. Øvrige undersøkelser utføres i henhold til tilgjengelighet og indikasjon

☐ Grundig anamnese*

☐ Beregnet ABCD2-skår* (se utregningstabell øverst på denne side) Skår

☐ Beregnet NIHSS* Skår

Beregnes fra skjema på baksiden

	Resultat
☐ BT*	
☐ Puls*	
☐ Høyde*	
☐ Vekt*	

Hvordan anslår du sannsynligheten for TIA?

☐ Sannsynlig TIA ☐ Mulig TIA ☐ Usannsynlig TIA

Hvis "sannsynlig" eller "mulig" TIA, gå til **"Inklusjons-skjema MIDNOR TIA"** for vurdering av inklusjon

Supplerende undersøkelser

☐ Blodprøver* (Hb, CRP, høysensitiv CRP, trombocytter, kreatinin, K, Na, troponin, INR, glukose, HbA1c, total-kolesterol, HDL-kolesterol, LDL-kolesterol, triglycerider, leukocytter)

☐ Blodprøver til biobank (hvis mulig)

☐ EKG*

☐ Telemetri/Holter (hvis tilgjengelig)

Bildediagnostikk

☐ MR* (fortrinnsvis diffusjons-MR, foretrekkes fremfor CT hvis tilgjengelig)

eller

☐ CT caput*

☐ Ultralyd halskar*

☐ CT angio eller MR angio (hvis ultralyd halskar ikke tilgjengelig)

☐ Ekkokardiografi (evt. andre bildeundersøkelser av hjertet hvis klinisk indikasjon)

Skjema fortsetter på andre siden

NIHSS-skår

- Det best skårbare svar/reaksjon er vanligvis det første svaret (bortsett fra ved afasi)
- Man skal ikke forklare/vise pasienten hva han skal gjøre, med mindre det er spesifisert
- Noen punkter skåres kun hvis de med sikkerhet er påvisbare (for eksempel neglekt)
- Noter hva pasienten gjør, ikke hva du tror pasienten kan gjøre, selv om resultater er motstridende
- Scoring skal inkludere sekvele etter tidligere sykdom, bortsett fra hudfølelse

1a. Bevissthetsnivå Skår

0 = Våken

1 = Døsig, reagerer adekvat ved lett stimulering

2 = Døsig, reagerer ved kraftigere/gjentatt stimulering

3 = Reagerer ikke, eller med ikke målrettet bevegelse

1b. Orientering (spør om måned + alder) Skår

0 = Svarer riktig på to spørsmål

1 = Svarer riktig på ett spørsmål (eller ved alvorlig dysartri)

2 = Svarer ikke riktig på noe spørsmål/koma

1c. Respons på kommando (lukke øyne + knytte hånd) Skår

0 = Utfører begge kommandoer korrekt

1 = Utfører én kommando korrekt

2 = Utfører ingen korrekt

2. Blikkbevegelse (horisontal bevegelse til begge sider) Skår

0 = Normal

1 = Delvis blikkparese (eller ved øyemuskelparese)

2 = Fiksert blikkdreining til siden eller total blikkparese

3. Synsfelt (bevege fingre/ fingertelling i laterale synsfelt) Skår

0 = Normalt

1 = Delvis hemianopsi

2 = Total hemianopsi

3 = Bilateral hemianopsi/ blind

4. Ansikt (vise tenner, knipe igjen øynene, løfte øyenbryn) Skår

0 = Normal

1 = Utvisket nasolabialfure, asymmetri ved smil

2 = Betydelig lammelse i nedre ansiktshalvdel

3 = Total lammelse i halve ansiktet (eller ved koma)

5. Kraft i armen (holde armen utstrakt 45 grader i 10 sek) Skår

0 = Normal (også ved "ikke testbar")

1 = Drifter til lavere posisjon

2 = Noe bevegelse mot tyngdekraften

3 = Kun små muskelbevegelser, faller til sengen

4 = Ingen bevegelse

6. Kraft i benet (holde benet utstrakt 30 grader 'i 5 sek) Skår

0 = Normal (også ved "ikke testbar")

1 = Drifter til lavere posisjon

2 = Noe bevegelse mot tyngdekraften

3 = Ingen bevegelse mot tyngdekraften, faller til sengen

4 = Ingen bevegelse

7. Koordinasjon/ ataxi (finger-nese-prøve/ kne-hæl prøve) Skår

0 = Normal (også ved "ikke-testbar" eller ved koma)

1 = Ataksi i arm eller ben

2 = Ataksi i arm og ben

8. Hudfølelse (sensibilitet for stikk) Skår

0 = Normal

1 = Lettere sensibilitetsnedsettelse

2 = Markert sensibilitetstap (også ved koma, tetraparese)

9. Språk/ afasi (spontan tale, tale-forståelse, leseforståelse, benevning) Skår

0 = Normal

1 = Moderat afasi, samtale mulig

2 = Markert afasi, samtale svært vanskelig eller umulig

3 = Ikke språk (også ved koma)

10. Tale/ dysartri (spontan tale) Skår

0 = Normal

1 = Mild – moderat dysartri

2 = Nær uforståelig tale eller anartri (også ved koma)

11. "Neglekt" (bilat. simultan stimulering av syn og hudsensibilitet) Skår

0 = Normal (også ved hemianopsi med normal sensibilitet)

1 = Neglekt i én sansemodalitet

2 = Neglekt i begge sansemodaliteter

Total NIHSS-skår
(Settes inn i NIHSS-felt på fremsiden)

MIDNOR TIA

Kartlegging av pasienter med transitorisk iskemisk anfall i Midt-Norge

Registrerings-skjema
Anvendes ved inklusjon

Pasient

Kjønn ☐ Mann ☐ Kvinne

Person-nummer | | | | | | | | | | | |

Navn

Telefon

Telefon, pårørende

Behandlingskjede

Rapporterende sykehus

Avdeling

Utfylt av

Kommune ved symptomdebut

Var pasienten alene ved symptomdebut?
☐ Ja
☐ Nei

Tidspunkt for symptomdebut
Dato | Måned | År
Ca. Time | Minutt

Tidspunkt for når pasienten er kommet til utredning
Dato | Måned | År
Ca. Time | Minutt

Hvor er pasienten blitt utredet/behandlet?
☐ Inneliggende
☐ Poliklinisk
☐ Dagpasient

Evt. utskrivningsdag
Dato | Måned | År

Anamnese ved aktuelle TIA

Fokale utfall
☐ Facialisparese
☐ Armparese
☐ Beinparese
☐ Språk- eller taleproblemer

Andre fokale symptomer?
☐ Ja
☐ Nei

Hvilke fokale symptomer?
☐ Halvsidig sensibilitetsutfall
☐ Dobbeltsyn
☐ Synsfeltsutfall
☐ Akutt synstap
☐ Andre symptomer

Sidelokalisasjon
☐ Høyre ☐ Bilateralt
☐ Venstre ☐ Ukjent

Varighet (timer, minutter, sekunder)
Timer | Minutter | Sekunder

Skjema fortsetter på andre siden

Klinisk status ved aktuelle TIA

NIHSS (Totalscore) ☐

Tempo

	Overekstremiteter (f.eks. alternerende bevegelser eller klapp på brystkassen)	Underekstremiteter (f.eks. rask takttramp)
	☐ Sidelikt	☐ Sidelikt
	☐ Redusert høyre	☐ Redusert høyre
	☐ Redusert venstre	☐ Redusert venstre

Blodtrykk ☐ / ☐ **Puls** ☐ **Høyde** ☐ **Vekt** ☐ **BMI** ☐

Supplerende utredning gjennomført

Blodprøver

HB ☐	CRP ☐	Kreatinin ☐	Troponin T (Fortrinnsvis) ☐	HDL-kolesterol ☐	Glukose ☐
Leukocytter ☐	Høysensitiv CRP (Hvis tilgjengelig) ☐	K ☐	Troponin I (Hvis TnT ikke tilgjengelig) ☐	LDL-kolesterol ☐	HbA1c ☐
Trombocytter ☐	INR ☐	Na ☐	Total-kolesterol ☐	Triglycerider ☐	

Blodprøver til biobank tatt

- ☐ Ja
- ☐ Nei
- ☐ Ikke relevant

Registrering av hjerterytme

EKG utført?

☐ Ja ☐ Nei ☐ Ukjent

- ☐ Sinusrytme
- ☐ Atrieflimmer/atrieflutter
- ☐ Iskemi
- ☐ Annet

Telemetri/Holter utført?

☐ Ja ☐ Nei ☐ Ukjent

- ☐ Sinusrytme
- ☐ Atrieflimmer/atrieflutter
- ☐ Iskemi
- ☐ Annet

Bildediagnostikk av hjerne

MR utført?

☐ Ja ☐ Nei ☐ Ukjent

- ☐ Ferskt infarkt
- ☐ Gamle forandringer
- ☐ Kronisk iskemi
- ☐ Blødning
- ☐ Tumor
- ☐ Negativt
- ☐ Annet

Diffusjonsvektet?

☐ Ja ☐ Nei ☐ Ukjent

CT utført?

☐ Ja ☐ Nei ☐ Ukjent

- ☐ Ferskt infarkt
- ☐ Gamle forandringer
- ☐ Blødning
- ☐ Tumor
- ☐ Negativt
- ☐ Annet

Bildediagn. av ekstrakranielle kar

Ultralyd utført?

☐ Ja ☐ Nei ☐ Ukjent

- ☐ Totalokklusjon ☐ Plakk
- ☐ Stenose > 70% ☐ U.a.
- ☐ Stenose 50 - 70%
- ☐ Stenose 30 < 50%
- ☐ Stenose < 30% / plakk
- ☐ Disseksjon

Bildediagn. av intrakranielle kar

CT/MR angio utført?

☐ Ja ☐ Nei ☐ Ukjent

- ☐ Stenose/okklusjon ☐ %
- ☐ U.a.

Bildediagnostikk av hjerte

Tegn til kardial emboli? ☐ Ja ☐ Nei

- ☐ Ingen
- ☐ Transthorakal ekkokardiografi
- ☐ Transøsofageal ekkokardiografi
- ☐ MR
- ☐ Annen
- ☐ Ukjent

Tilstand før aktuelle TIA

Boligforhold

- ☐ Egen bolig uten hjemmesykepleie/hjemmehjelp
- ☐ Egen bolig med hjemmesykepleie/hjemmehjelp
- ☐ Ukjent

Bosituasjon

- ☐ Pasienten bodde alene
- ☐ Pasienten bodde sammen med noen (f.eks. ektefelle/samboer, søsken, barn)
- ☐ Ukjent

Sivilstatus

- ☐ Gift/samboende
- ☐ Enke/enkemann
- ☐ Enslig
- ☐ Ukjent

Hvordan håndteres legemidler?

- ☐ Selvhjulpen
- ☐ Ved hjelp fra pårørende
- ☐ Ved hjelp fra hjemmesykepleien

Bruker pasienten multidose?

- ☐ Ja
- ☐ Nei
- ☐ Ukjent

Funksjonsstatus

Modified Rankin Scale (Se egen veiledning) ☐ 0-6

Risikofaktorer

Tidligere hjerneslag?

- ☐ Ja
- ☐ Nei
- ☐ Ukjent

Hvilken type?

- ☐ Infarkt
- ☐ Blødning
- ☐ Uspesifisert
- ☐ Ukjent

Tidligere fått diagnosen TIA?

☐ Ja ☐ Nei ☐ Ukjent

Har det vært andre episoder med symptomer forenlig med TIA i løpet av de siste 2 ukene (i tillegg til aktuelle TIA)?

☐ Ja ☐ Nei ☐ Ukjent

Antall episoder ☐

Når? Fyll inn dato(er)

Tidligere hjerteinfarkt?

☐ Ja ☐ Nei ☐ Ukjent

Gjennomgått kardiologisk intervensjon?

☐ Ja ☐ Nei ☐ Ukjent

Når?

- ☐ Innen siste uke
- ☐ 1-4 uker før aktuelle TIA
- ☐ 4-12 uker før aktuelle TIA
- ☐ Over 12 uker før aktuelle TIA

Gjennomgått karkirurgisk intervensjon?

☐ Ja ☐ Nei ☐ Ukjent

Når?

- ☐ Innen siste uke
- ☐ 1-4 uker før aktuelle TIA
- ☐ 4-12 uker før aktuelle TIA
- ☐ Over 12 uker før aktuelle TIA

Atrieflimmer bekreftet med EKG tidligere eller i løpet av utredningen? (Gjelder også paroksystisk atrieflimmer/atrieflutter)

☐ Ja ☐ Nei ☐ Ukjent

Diabetes, tidligere diagnostisert eller nyoppdaget?

☐ Ja ☐ Nei ☐ Ukjent

Medikamentell behandling for høyt BT ved debut?

☐ Ja ☐ Nei ☐ Ukjent

Medikamentell behandling for lipidsenking ved debut?

☐ Ja ☐ Nei ☐ Ukjent

Røykestatus

- ☐ Aldri
- ☐ Røyker
- ☐ Eks-røyker (røykfri > 1 mnd)
- ☐ Ukjent

Mosjon/fysisk aktivitet (går tur, går på ski, svømmer eller driver trening/idrett)

- ☐ Aldri
- ☐ Sjeldnere enn en gang i uka
- ☐ En gang per uke
- ☐ 2-3 ganger i uka
- ☐ Omtrent hver dag

Spørsmål for identifisering av alkoholproblemer (CAGE)

	Ja	Nei
Drikker du alkohol?	☐	☐

Hvis ja:

	Ja	Nei
Har du tenkt på å redusere alkoholforbruket ditt?	☐	☐
Hender det at andre kritiserer ditt drikkemønster?	☐	☐
Har du noen gang skyldfølelse på grunn av alkoholbruken din?	☐	☐
Tar du noen gang en drink for å komme i gang om morgenen etter at du har drukket?	☐	☐

Hadde du drukket alkohol de siste 24 timene før aktuelle TIA?

☐ Ja ☐ Nei ☐ Usikker

Antall enheter ☐

ABCD2-skår

Se utredningsskjema/lommekort/plakat Skår ☐

Medikamentell behandling før debut og etter utredning

Medikament (Eksempler)	Før debut av TIA: Ja 1	Nei 2	Ukjent 9	Etter utredning: Ja 1	Nei 2	Ukjent 9
Platehemmende behandling med ASA (Albyl E, Aspirin, Dispril, Globoid, Magnyl-E, Novid)	☐	☐	☐	☐	☐	☐
Klopidogrel (ADP-reseptor-blokker) (Clopidogrel, Plavix, Ticlid)	☐	☐	☐	☐	☐	☐
ASA + Dipyridamol (Asasantin Retard (kombinasjonspreparat med både ASA og Dipyridamol/Persantin Retard) eller Albyl E + Persantin Retard)	☐	☐	☐	☐	☐	☐
Dipyridamol (Persantin)	☐	☐	☐	☐	☐	☐
Antikoagulasjon med Warfarin (Marevan)	☐	☐	☐	☐	☐	☐
Andre perorale antikoagulasjonsmidler enn Warfarin (Angiox, Arixtra, Novastan, Pradaxa, Refludan, Xarelto)	☐	☐	☐	☐	☐	☐
Diuretika (Aldactone, Atacand Plus, Burinex, CoAprovel, Cozaar Comp, Centyl, Diovan Comp, Diural, Enalapril Comp, Esidrex, Furix, Furosemid, Inspra, Lasix Retard, Lisinopril/hydroklortiazid, Lodoz, Moduretic mite, Normorix mite, Renitec Comp, Samsca, Spirix, Zestoretic mite)	☐	☐	☐	☐	☐	☐
ACE-hemmer (Captopril, Enalapril, Enalapril Comp, Gopten, Lisinopril, Lisinopril/Hydroklortiazid, Ramipril, Renitec, Renitec Comp, Triatec, Zanipress, Zestoretic, Zestoretic mite, Zestril.)	☐	☐	☐	☐	☐	☐
A2-antagonist (Amias, Aprovel, Atacand, Atacand Plus, CoAprovel, Cozaar, Cozaar Comp, Diovan, Diovan Comp, Irbesartan, Losartan, Micardis, MicardisPlus, Olmetec, Olmetec Comp, Teveten, Teveten Comp, Valsartan)	☐	☐	☐	☐	☐	☐
Betablokker (Atenolol, Bisoprolol, Brevibloc, Carvedilol, Emconcor, Inderal Retard, Lodoz, Metoprolol, Pranolol, Seloken, Selo-zok, Sotalol, Tenormin, Trandate, Uniloc)	☐	☐	☐	☐	☐	☐
Kalsiumantagonist (Adalat, Amlodipin, Cardizem, Felodipin, Isoptin, Lerkandipin, Lomir, Nimotop, Norvasc, Plendil, Verakard, Zanidip)	☐	☐	☐	☐	☐	☐
Statin - Lipidsenkende (Cholestagel, Crestor, Ezetrol, Inegy, Lescol, Lestid, Lipitor, Lovastatin, Mevacor, Niaspan, Omacor, Pravachol, Pravastatin, Questran, Simvastatin, Tredaptive, Sortis, Zocor)	☐	☐	☐	☐	☐	☐

Medisinliste er innhentet av

- ☐ TIA-sykepleier
- ☐ Farmasøyt

Hovedårsak til at warfarin eller andre perorale antikoagulantia ikke er innsatt ved utskrivning ved TIA-diagnose og samtidig atrieflimmer?

- ☐ Planlagt innsatt etter utskrivning
- ☐ Kontraindisert
- ☐ Interaksjoner
- ☐ Falltendens
- ☐ Kognitiv svikt/demens
- ☐ Pasienten avstår fra behandling
- ☐ Annen årsak
- ☐ Ukjent
- ☐ Ikke relevant

Informasjon og oppfølging

Informasjon gitt om røykestopp til de som røyker ved symptom-debut?

☐ Ja ☐ Nei ☐ Ukjent

Informasjon gitt om kosthold/ mosjon?

☐ Ja ☐ Nei ☐ Ukjent

Informasjon gitt om bilkjøring?

☐ Ja ☐ Ukjent

☐ Nei ☐ Ikke relevant

Kontroll avtalt ved sykehus for det aktuelle TIA?

☐ Ja ☐ Nei

☐ Avtale om kontroll hos fastlege

Sendt epikrise til den lege som skal følge opp?

☐ Ja ☐ Nei

Henvist til carotiskirurgi?

☐ Ja ☐ Nei ☐ Ikke relevant

Fått info om FAST-symptomer?

☐ Ja ☐ Nei ☐ Ukjent

MIDNOR TIA

Kartlegging av pasienter med transitorisk iskemisk anfall i Midt-Norge

Oppfølgings-skjema

Anvendes **1 uke** etter inklusjon

Pasient

Kjønn ☐ Mann ☐ Kvinne

Person-nummer | | | | | | | | | | | |

Telefon

Navn

Telefon, pårørende

Pasientstatus

Er oppfølging utført

☐ Ja

☐ Nei

Årsak

☐ Får ikke tak i pasienten

☐ Pasienten ønsker ikke å svare

☐ Død

☐ Annet (spesifiser)

Oppfølgingsdato

Dato | Måned | År

Boligforhold

☐ Fortsatt innlagt i sykehus

☐ Egen bolig uten hjemmesyke-pleie/hjemmehjelp

☐ Egen bolig med hjemmesyke-pleie/hjemmehjelp

☐ Omsorgsbolig med døgnkon-tinuerlige tjenester og person-ale

☐ Sykehjem

☐ Ukjent

Sivilstatus

☐ Gift/samboende

☐ Enke/enkemann

☐ Enslig

☐ Ukjent

Bosituasjon

☐ Fortsatt innlagt i sykehus

☐ Pasienten bor alene

☐ Pasienten bor sammen med noen (f.eks. ektefelle/samboer, søsken, barn)

☐ Pasienten bor i institusjon/ sykehjem

☐ Ukjent

Har du hatt nye hendelser etter inklusjon?

☐ Nei

☐ Ja, men ikke reinnlagt i sykehus

☐ Reinnlagt/poliklinisk vurdert for nytt TIA

☐ Reinnlagt/fortsatt innlagt for slag

☐ Reinnlagt for hjerteinfarkt

☐ Utført kardiologisk intervensjon

☐ Utført karkirurgisk intervensjon

☐ Reinnlagt av annen årsak

Spesifiser

Er du operert i halspulsåre?

☐ Ja

☐ Nei

☐ Ukjent

Har du gjennomgått noen form for rehabilitering (på hvilken som helst indikasjon)?

☐ Ja

☐ Nei

☐ Ukjent

Spesifiser

Vurdert av lege?

☐ Ja ☐ Nei

Spesifiser

☐ Infarkt

☐ Blødning

☐ Ukjent

Skjema fortsetter på andre siden

Beskrivelse av helsetilstand og livskvalitet

Har du kommet deg helt i forhold til hvordan du var før aktuelle TIA?

- ☐ Ja
- ☐ Nei
- ☐ Vet ikke

Hvordan er helsa di nå?

- ☐ Dårlig
- ☐ Ikke helt god
- ☐ God
- ☐ Svært god

Har du merket endring med hensyn til det følgende etter TIA?

Gange

- ☐ Uendret
- ☐ Forverret
- ☐ Usikker

Utføre vanlige gjøremål: (f.eks. arbeid, studier, husarbeid, familie- eller fritidsaktiviteter)

- ☐ Uendret
- ☐ Forverret
- ☐ Usikker

Smerte og ubehag

- ☐ Uendret
- ☐ Forverret
- ☐ Usikker

Angst og depresjon

- ☐ Uendret
- ☐ Forverret
- ☐ Usikker

Yrkesaktivitet før TIA

- ☐ Yrkesaktiv
- ☐ Pensjonist
- ☐ Uføretrygdet
- ☐ Annet

Hvis yrkesaktiv, er du yrkesaktiv nå?

- ☐ Ja
- ☐ Ja, etter avsluttet sykmelding
- ☐ Nei, aktuelt sykmeldt
- ☐ Annet

Hvis aktuelt sykmeldt eller avsluttet sykmelding, spesifiser lengde/gradering

Kjørte du bil før TIA?

- ☐ Ja
- ☐ Nei

Hvis ja, kjører du bil nå?

- ☐ Ja
- ☐ Nei, kjørekarens
- ☐ Nei, annen årsak

Spesifiser

Funksjonsstatus

Modified Rankin Scale
(Se egen veiledning)

0-6

Oppfølging

Har du hentet ut/fått utlevert medisiner som ble startet etter aktuelle TIA?

- ☐ Ja
- ☐ Nei
- ☐ Ukjent

Har du vært til legekontroll etter TIA?

- ☐ Ja
- ☐ Nei
- ☐ Ukjent

Røykestatus før aktuelle TIA

- ☐ Aldri
- ☐ Røyker
- ☐ Eks-røyker (røykfri > 1 mnd)
- ☐ Ukjent

Røyker du nå?

- ☐ Ja
- ☐ Nei

Hvor godt fornøyd er du med den utredning, behandling og oppfølging du har fått fra helsevesenet i forbindelse med aktuelle TIA?

- ☐ Svært godt fornøyd
- ☐ Godt fornøyd
- ☐ Ganske fornøyd
- ☐ Misfornøyd
- ☐ Ikke besvart

Kan du spesifisere hva som eventuelt kunne vært bedre?

Hvem har gitt opplysningene?

- ☐ Pasient
- ☐ Familie
- ☐ Helsepersonell
- ☐ Andre

Spesifiser

MIDNOR TIA

Kartlegging av pasienter med transitorisk iskemisk anfall i Midt-Norge

Oppfølgings-skjema

Anvendes **1 år** etter inklusjon

Pasient

Kjønn ☐ Mann ☐ Kvinne

Person-nummer | | | | | | | | | | | |

Telefon

Navn

Telefon, pårørende

Pasientstatus

Er oppfølging utført

☐ Ja

☐ Nei

Årsak

☐ Får ikke tak i pasienten

☐ Pasienten ønsker ikke å svare

☐ Død

☐ Annet (spesifiser)

Oppfølgingsdato

Dato | Måned | År

Boligforhold

☐ Innlagt i sykehus

☐ Egen bolig uten hjemmesyke-pleie/hjemmehjelp

☐ Egen bolig med hjemmesyke-pleie/hjemmehjelp

☐ Omsorgsbolig med døgnkon-tinuerlige tjenester og person-ale

☐ Sykehjem

☐ Ukjent

Sivilstatus

☐ Gift/samboende

☐ Enke/enkemann

☐ Enslig

☐ Ukjent

Bosituasjon

☐ Innlagt i sykehus

☐ Pasienten bor alene

☐ Pasienten bor sammen med noen (f.eks. ektefelle/samboer, søsken, barn)

☐ Pasienten bor i institusjon/ sykehjem

☐ Ukjent

Har du hatt nye hendelser etter 3-måneders oppfølging?

☐ Nei

☐ Ja, men ikke reinnlagt i sykehus

☐ Reinnlagt/poliklinisk vurdert for nytt TIA

☐ Reinnlagt/fortsatt innlagt for slag

☐ Reinnlagt for hjerteinfarkt

☐ Utført kardiologisk intervensjon

☐ Utført karkirurgisk intervensjon

☐ Reinnlagt av annen årsak

Spesifiser

Vurdert av lege?

☐ Ja ☐ Nei

Spesifiser

☐ Infarkt

☐ Blødning

☐ Ukjent

Er du operert i halspulsåre?

☐ Ja

☐ Nei

☐ Ukjent

Har du gjennomgått noen form for rehabilitering (på hvilken som helst indikasjon)?

☐ Ja

☐ Nei

☐ Ukjent

Spesifiser

Skjema fortsetter på andre siden

Beskrivelse av helsetilstand og livskvalitet

Har du kommet deg helt i forhold til hvordan du var før aktuelle TIA?

- ☐ Ja
- ☐ Nei
- ☐ Vet ikke

Hvordan er helsa di nå?

- ☐ Dårlig
- ☐ Ikke helt god
- ☐ God
- ☐ Svært god

Får du hjelp til daglige gjøremål (ADL)? (Flere alternativer mulig)

- ☐ Ingen
- ☐ Familie
- ☐ Hjemmehjelp
- ☐ Hjemmesykepleie
- ☐ Institusjon
- ☐ Andre

Trenger du hjelp til forflytning?

- ☐ Jeg kan forflytte meg alene / uten tilsyn både ute og inne
- ☐ Jeg kan forflytte meg alene / uten tilsyn inne, men ikke ute
- ☐ Jeg trenger hjelp av en annen person
- ☐ Vet ikke / ukjent

Trenger du hjelp til toalettbesøk?

- ☐ Jeg klarer toalettbesøk selv
- ☐ Jeg klarer ikke toalettbesøk alene. Trenger hjelp til bruk av bekken eller bleie, eller trenger hjelp under toalettbesøk
- ☐ Vet ikke / ukjent

Trenger du hjelp til av-/påkledning?

- ☐ Jeg klarer av-/påkledning selv, også ytterklær, sko og strømper
- ☐ Jeg trenger hjelp med av-/påkledning
- ☐ Vet ikke / ukjent

Er du yrkesaktiv nå?

- ☐ Ja
- ☐ Ja, etter avsluttet sykmelding
- ☐ Nei, aktuelt sykmeldt
- ☐ Annet

Hvis aktuelt sykmeldt eller avsluttet sykmelding, spesifiser lengde/gradering

Kjører du bil?

- ☐ Ja
- ☐ Nei, kjørekarens
- ☐ Nei, kjørte ikke bil før TIA
- ☐ Nei, annen årsak

Spesifiser

Funksjonsstatus

Modified Rankin Scale (Se egen veiledning)

0-6

Kan du spesifisere hva som eventuelt kunne vært bedre?

Spesifiser

Oppfølging

Tar du medisin mot høyt blodtrykk?

- ☐ Ja
- ☐ Nei
- ☐ Vet ikke/ukjent

Tar du blodfortynnende medisin mot blodtpropp?

- ☐ Ja
- ☐ Nei
- ☐ Vet ikke/ukjent

Tar du medisin mot høyt kolesterol?

- ☐ Ja
- ☐ Nei
- ☐ Vet ikke/ukjent

Har du vært til legekontroll etter 3-måneders oppfølging?

- ☐ Ja
- ☐ Nei
- ☐ Ukjent

Røyker du nå?

- ☐ Ja
- ☐ Nei

Hvor godt fornøyd er du med den utredning, behandling og oppfølging du har fått fra helsevesenet i forbindelse med aktuelle TIA?

- ☐ Svært godt fornøyd
- ☐ Godt fornøyd
- ☐ Ganske fornøyd
- ☐ Misfornøyd
- ☐ Ikke besvart

Hvem har gitt opplysningene?

- ☐ Pasient
- ☐ Familie
- ☐ Helsepersonell
- ☐ Andre

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