Lacunar infarcts
Clinical syndromes, risk factors and diagnostic aspects

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# ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>ADL</td>
<td>Activities of Daily Living</td>
</tr>
<tr>
<td>BP</td>
<td>Blood pressure</td>
</tr>
<tr>
<td>CBF</td>
<td>Cerebral blood flow</td>
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<tr>
<td>CI</td>
<td>Confidence interval</td>
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<tr>
<td>CT</td>
<td>Computed tomography</td>
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<tr>
<td>DWI</td>
<td>Diffusion weighted imaging</td>
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<tr>
<td>ECG</td>
<td>Electrocardiogram</td>
</tr>
<tr>
<td>LACI</td>
<td>Lacunar circulation infarction</td>
</tr>
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<td>LI</td>
<td>Lacunar infarct</td>
</tr>
<tr>
<td>MCA</td>
<td>Middle cerebral artery</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic resonance imaging</td>
</tr>
<tr>
<td>mRS</td>
<td>Modified Rankin Scale</td>
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<tr>
<td>NIHSS</td>
<td>National Institutes of Health Stroke Scale</td>
</tr>
<tr>
<td>NPV</td>
<td>Negative predictive value</td>
</tr>
<tr>
<td>OCSP</td>
<td>Oxfordshire Community Stroke Project</td>
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<td>OR</td>
<td>Odds Ratio</td>
</tr>
<tr>
<td>PACI</td>
<td>Partial anterior circulation infarction</td>
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<tr>
<td>PI</td>
<td>Pulsatility index</td>
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<tr>
<td>POCI</td>
<td>Posterior circulation infarction</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Definition</td>
</tr>
<tr>
<td>--------------</td>
<td>------------------------------------------------</td>
</tr>
<tr>
<td>PPV</td>
<td>Positive predictive value</td>
</tr>
<tr>
<td>SD</td>
<td>Standard deviation</td>
</tr>
<tr>
<td>SVD</td>
<td>Small vessel disease</td>
</tr>
<tr>
<td>TACI</td>
<td>Total anterior circulation infarction</td>
</tr>
<tr>
<td>TCD</td>
<td>Transcranial Doppler ultrasonography</td>
</tr>
<tr>
<td>TIA</td>
<td>Transient ischaemic attack</td>
</tr>
<tr>
<td>TMT</td>
<td>Trail Making Test</td>
</tr>
<tr>
<td>TOAST</td>
<td>Trial of Org 10172 in Acute Stroke Treatment</td>
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<td>WHO</td>
<td>World Health Organisation</td>
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LIST OF PAPERS


1. INTRODUCTION

1.1. Stroke

1.1.1. Definition of cerebral stroke

Stroke is a clinical syndrome, and has been defined by the World Health Organization (WHO) as “rapidly developing clinical signs of focal (at times global) disturbance of cerebral function, lasting more than 24 hours or leading to death with no apparent cause other than that of vascular origin” (1). A stroke is caused by the interruption of the blood supply to the brain, causing damage to the brain tissue. Transient ischaemic attack (TIA) is traditionally defined as “an episode of temporary and focal cerebral dysfunction of vascular origin, rapid in onset, which is variable in duration, commonly lasting from 2 to 15 minutes but occasionally lasting as long as 24 hours. The attack leaves no persistent neurological deficit” (2). The increasing use of diffusion weighted imaging has revealed cerebral infarction in patients with transient symptoms (3), and a new definition of TIA has been suggested (4). The new definition includes the absence of infarction: “a transient episode of neurological dysfunction, caused by focal brain, spinal cord or retinal ischemia, without acute infarction”. As a result of this, an ischaemic stroke is defined as an infarction of central nervous system tissue (4). In this definition, a stroke may be either symptomatic or silent.

Ischaemic stroke accounts for about 80% of all stroke cases, whereas primary intracerebral haemorrhage (about 15%) and subarachnoid haemorrhage explain the rest (5). This thesis will only deal with ischaemic stroke.

Ischaemic stroke is caused by occlusion of an artery, either by an embolus or a thrombus. The reduction of cerebral blood flow leads to an infarct core of irreversibly damaged cells with a surrounding penumbra. In the penumbral zone there is constrained blood supply with intermittently comprised energy metabolism, which leads to dysfunctional neurons (6-8). If reperfusion can be
achieved within a short time, the neurological deficits caused by the penumbra may be reversed.

1.1.2. Epidemiology

Stroke is a common disorder, and one of the leading causes of death worldwide and disability in the western countries (5, 9, 10). The age-standardised stroke incidence rate worldwide in 2010 was 258 per 100,000 person-years, corresponding to 16.9 million people with first stroke (11). In the same study, the stroke incidence rate was 217 per 100,000 person-years in high-income countries.

In a study from 2009 (12), the stroke incidence rates in Europe were 141 per 100,000 in men and 94.6 per 100,000 in women. There were considerable variations between the European regions. In Norway, the estimated number of strokes per year is about 14500 (13).

![Figure 1. Deaths by stroke in Norway (1969-2012)](image)

Adapted from Statistics Norway (14)

The stroke incidence and mortality rate have decreased the last decades in high-income countries, probably due to better stroke risk factor control (11, 15). The
Converse has been shown for low- and middle-income countries. The prevalence of stroke is higher in high-income countries compared to low- and middle-income countries, due to an inverse association between prevalence of stroke and stroke mortality. The incidence rate increases by age, and because of an ageing population, the burden of stroke in high-income countries will increase (15). Even though the incidence of stroke in high-income countries is decreasing, the overall global burden of stroke is increasing (11).

![Figure 2. Stroke incidence in Norway (patients 65 years of age or older)](image)
Adapted from Scenario 2030, Norwegian Board of Health Supervision (June 1999) (16)

### 1.1.3. Stroke diagnosis

Stroke is a clinical diagnosis. It is typically characterised by acute onset of focal symptoms like hemiparesis, sensory loss, facial paresis and dysarthria. The symptoms may vary, and depend on the localisation of the lesion. Cortical lesions may lead to aphasia, apraxia, homonymous hemianopia and neglect, while cerebellar lesions may cause ataxia. The symptoms might be more diffuse like confusion, unsteadiness or loss of balance, which can make diagnosing stroke challenging. Thorough clinical history and neurological examination are required
for diagnosing stroke. The patients should be admitted to a Stroke Unit (SU), and undergo standard examination including blood samples, electrocardiogram (ECG) records and cerebral computed tomography (CT) at admission. Further examination should be performed during the stay to identify the underlying cause of stroke (17-19).

There are several clinical assessments used in monitoring neurological deficits and outcome after stroke, but the reliability of these instruments vary (20). National Institutes of Health Stroke Scale (NIHSS) (21, 22) and the Scandinavian Stroke Scale (SSS) (23) are frequently used in SUs and large clinical trials. NIHSS is useful in monitoring acute status, effect of treatment and outcome (24). Bartel Index (BI) (25) of activities of daily living and modified Rankin Scale (mRS) (26, 27) are functional scales, i.e. refer to the capacity to perform a task.

There is a lack of standardised tools for testing cognitive function after stroke. Cognitive assessments in the acute phase of stroke can be used to detect cognitive deficits and to evaluate the need for rehabilitation or assistance, but not to diagnose dementia. Cognitive tests should be easy to apply and should evaluate different cognitive domains, including language, neglect, memory, executive functions and attention. Mini Mental State Examination (MMSE) (28, 29) is used for global cognitive screening. Trail Making Test (TMT) A and B (30) measure psychomotor speed (A) and executive functioning (B). The Clock Drawing Test (31) primarily measures visuospatial functions in addition to executive functioning.

1.1.4. Ischaemic stroke classification

Ischaemic stroke can be classified into different subgroups, based on e.g. aetiology or topography. The classifications can help us distinguish between the subgroups of ischaemic stroke, and may be helpful in the acute phase when decisions about treatment should be done. They can also tell us about prognosis after stroke. In 1993, the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) (32)
developed a system based on diagnostic criteria to classify the subtypes of ischaemic strokes according to aetiology:

- Large vessel atherosclerosis: Clinical and vessel imaging findings of either >50% stenosis or occlusion of a major brain artery or branch artery, presumably due to atherosclerosis. Clinical findings include those of cortical impairment or brain stem or cerebellar dysfunction. CT or MRI findings of cortical or cerebellar lesions or subcortical or brain stem lesions greater than 1.5 cm in diameter.
- Cardio embolic disease: Arterial occlusions due to an embolus arising in the heart. Clinical and brain imaging findings are similar to those described for large artery atherosclerosis.
- Small artery occlusion: The patient should have clinical lacunar syndromes and no evidence of cerebral cortical dysfunction. Brain imaging is either normal or shows a brain stem or subcortical lesion less than 1.5 cm. Potential cardiac sources or large artery atherosclerosis in the ipsilateral artery should be absent.
- Stroke of unusual aetiology: Patients with rare causes of stroke, such as nonatherosclerotic vasculopathies, hypercoagulable states or hematologic disorders.
- Stroke of undetermined aetiology: No potential cause of stroke is found or more than one potential cause.

This classification system is based on clinical and paraclinical findings including neuroimaging. TOAST is widely used in stroke-related research and clinical studies, and has been found to be valid and reliable (33). However, the criticism against TOAST, is that aetiological diagnoses are based on presumptions instead of pathological findings (34). Jackson and Sudlow (35) referred to the “Classification Bias”, the problem that risk factors are included in the definition of stroke subtype, and will result in a bias when risk factors are compared between
the different subtypes. Emboli from the heart or large vessel stenosis can occasionally occlude small, perforating cerebral vessels. It may be difficult to ascertain whether cardioembolic or large vessel disease is causal or a manifestation of generalised disease. Other classification systems such as Causative Classifications System (CCS) and ASCO (A for atherosclerosis, S for small vessel disease, C for cardiac source, O for other cause) have been introduced to improve the ability to identify the most likely cause where multiple potential mechanisms are found (36-38), but they have not been applied in larger studies.

The Oxfordshire Community Stroke Project (OCSP) classification (39) is based on symptoms and signs, and allocate patients into four defined subgroups according to the topographic location and size:

- **Lacunar circulation infarcts (LACI):** Patients present with a motor, sensory or sensorimotor syndrome or ataxic hemiparesis or dysarthria-clumsy-hand syndrome. The infarcts are confined to the deep perforating arteries.

- **Total anterior circulation infarcts (TACI):** Patients present with symptoms of combined cortical deficit and ipsilateral motor and/or sensory deficit in at least two areas of the face, arm and leg. The infarcts involve both deep and superficial territories of the middle cerebral artery (MCA).

- **Partial anterior circulation infarcts (PACI):** Patients present with only two of the tree components of the TACI syndrome, with cortical deficit alone or sensory and/or motor symptoms in face or one limb. The infarcts are more restricted cortical infarcts due to occlusion of the distal MCA.

- **Posterior circulation infarcts (POCI):** Patients present with any of the following: ipsilateral cranial nerve palsy with contralateral motor and/or sensory deficit; bilateral motor and/or sensory deficit, disorder of the conjugate eye movement; cerebellar dysfunction without ipsilateral long-tract deficit; or isolated homonymous visual field defect. The infarcts are clinically associated with the brainstem, cerebellum or occipital lobes.
The OCSP classification is easy to apply and has a good interobserver reliability (40). However, the accuracy of the OCSP classification has been poor in patients with small infarcts (41). Both TOAST and OCSP are widely used in research studies and bedside in clinical practice.

1.1.5. Brain imaging

Brain imaging is mandatory to distinguish between an intracerebral haemorrhage and ischaemic stroke, and should be performed in the acute phase. Non-contrast cerebral CT is reliable in detecting acute haemorrhage (5), and is most easily accessible. Few acute ischaemic lesions can be seen the first hours, but they become visible over the first 1-7 days as dark hypodense areas. However, in many of ischaemic stroke patients, an infarct never becomes visible on CT (42). The proportion is higher in patients with milder strokes, i.e. lacunar infarcts, and the proportion visible also depends on timing of scanning. CT perfusion (CTP) can be a valuable tool in the diagnosis of ischaemic stroke, even though there are some limitations and pitfalls one should be aware of. CTP can be performed rapidly, and can distinguish the penumbra from the core infarct (43). CT angiography of precerebral and intracranial arteries is used to identify the site of the vessel occlusion.

Magnetic Resonance Imaging (MRI) has similar accuracy as CT in detecting acute haemorrhage in patients presenting with stroke symptoms (44). The most sensitive method for early detection of cerebral ischemia is diffusion-weighted MRI (DWI) (45, 46). DWI measures the net movement of water in tissue due to random molecular motion of water. It shows hyperintense ischaemic tissue changes within minutes to a few hours after arterial occlusion due to a reduction of the apparent diffusion coefficient (ADC) (47). Decreases in the ADC and increased signal on DWI in acute stroke may in many instances represent the ischaemic core. Perfusion-weighted MRI (PWI) reveals the perfusion deficit in the tissue
surrounding the infarct core. The DWI/PWI mismatch estimates the ischaemic penumbra, and can be useful in the selection of patients for reperfusion therapy, especially interventional therapy or unknown onset of symptoms. DWI is not available in the acute phase for all patients, but is superior to CT for the diagnosis of acute ischaemic stroke in patients presenting within 12 hours (47).

1.1.6. Doppler Ultrasonography and further investigations
Carotid Doppler Ultrasonography (CDU) should be performed during hospitalization, to search for the source of an embolus or vessel abnormalities in the precerebral arteries. The carotid bifurcation and the proximal part of the internal carotid artery are predilection sites for atherosclerotic plaques. The sensitivity and specificity of this non-invasive test for detecting a 70-99% stenosis in the carotids are high (48), and it has replaced intra-arterial angiography. CDU also visualizes the Intima Media Thickness (IMT) and may be used to measure different stages of the carotid artery atherosclerotic process.

Transcranial Doppler Ultrasonography (TCD) is frequently used in patients with stroke, and provides information about intracranial hemodynamics and structural changes in the large vessels. It is used to detect intracranial stenosis and occlusion, and to evaluate revascularization after thrombolysis. In addition, continuous TCD monitoring may safely augment thrombolysis-induced arterial recanalization (49). Through the transtemporal window the circle of Willis, middle cerebral artery (MCA), the anterior cerebral artery (ACA) and posterior cerebral artery (PCA) can be visualized. The pulsatility index (PI) is derived from TCD, and was first described by Gosling and King (50). PI characterizes the shape of the spectral waveform and is independent of probe angle to vessel. It is postulated to reflect the vascular resistance in the artery distal of the probe, and has been reported to increase in small vessel disease, diabetes mellitus, ageing and dementia (51-55). Low-resistance vascular beds have high diastolic flow, whereas higher resistance
beds have low diastolic flow, a peaked waveform, and higher PIs. PI can be calculated using the formula $\text{PI} = \frac{\text{peak velocity} - \text{end diastolic velocity}}{\text{mean velocity}}$.

Embolism from the heart is the cause in about 20% of all cerebral infarctions (5). Cardiac monitoring should be conducted routinely after an acute stroke to screen for serious cardiac arrhythmias (17). 24-48 hours Holter monitoring is used to look for atrial fibrillation in patients with suspected arrhythmias. If there is clinical evidence of cardiac disease, it is recommended to perform a transthoracic echocardiography (TTE), but transesophageal echocardiography is superior to TTE in identifying a cardiac embolic source, e.g. thrombus in the left atrial appendage, aortic atheroma and patent foramen ovale (56).

1.1.7. Stroke risk factors
Stroke prevention is about identifying subjects who are at increased risk for stroke, and to modify their risk if possible. Stroke risk factors are often classified as non-modifiable or modifiable. Non-modifiable risk factors are higher age, male gender, ethnicity, heredity and previous stroke or TIA (57). Identification and control of modifiable stroke risk factors can result in marked reductions in stroke morbidity and mortality (58). Well-documented modifiable stroke risk factors are hypertension, diabetes, smoking, atrial fibrillation and certain other cardiac conditions, carotid artery stenosis, hypercholesterolemia, sickle cell disease, postmenopausal hormone therapy, poor diet, physical inactivity and obesity (57). Hypertension, diabetes and smoking are associated with more than half of all ischaemic strokes (57). Identification of risk factors in the individual patient is a part of the routine evaluation in the Stroke Unit, e.g. 24 h blood pressure (BP) measurement to look for hypertension, blood samples to look for coagulation disorders, etc.
1.1.8. Treatment and prognosis
In the treatment of hyperacute ischaemic stroke, there are two strategies to follow. The first is limitation of the ischaemic stroke by early recanalization and reperfusion (thrombolysis or embolectomy). The other is interference with the pathophysiological cascade in the penumbral area, which includes monitoring and treatment of different factors, i.e. BP, hyperglycaemia, hyperthermia and low oxygen saturation. There are guidelines for treatment and rehabilitation of patients with acute ischaemic stroke (17-19) which include detailed recommendations based on current evidence. The time window for treatment of stroke is narrow, and every minute counts. It is important that the management of stroke patients is well organised, both outside and inside the hospital. Suspected stroke victims should be transported without delay to the nearest medical centre with a SU that can provide ultra-early treatment. Treatment in SUs has documented effect on outcome after acute stroke (59) and improves survival and functional outcome in the long term (60). The characteristics of a SU are systematic and standardised programs for diagnosis, monitoring and treatment of stroke by multidisciplinary teams.

Intravenous thrombolysis with recombinant tissue plasminogen activator (rt-PA) within 4.5 hours of stroke onset offers beneficial effect in selected patients with acute ischaemic stroke (61). Patients with occlusion of large intracerebral arteries, who are not eligible for or do not improve after intravenous rt-PA, may be considered for intra-arterial thrombolysis or embolectomy (62). Patients who do not undergo interventional treatment, profit from receiving oral aspirin within 48 hours of stroke onset (15).

Secondary prevention depends on the underlying cause of stroke. Antiplatelet drugs are protective in most types of patients at increased risk of occlusive vascular events (63). For patients with cardioembolic disease, anticoagulant therapy is superior to antiplatelet drugs (64). New oral anticoagulants (NOACs) have documented similar efficacy as warfarin in the prevention of ischaemic stroke, and have a lower risk of intracerebral bleeding (65). If the patient has a
symptomatic carotid stenosis > 70%, carotid endarterectomy should be considered. Further treatment is aimed at the risk factors identified (17), e.g. hypertension and hypercholesterolemia.

1.2. Cerebral small vessel disease
More than a century ago, Otto Binswanger introduced the concept that diffuse white matter lesions could be attributed to small vessel disease (SVD), the narrowing of small penetrating vessels deep in the brain. These end arteries have no collateral supply and their occlusion results in small, discrete regions of infarction. SVD accounts for about 25% of all ischaemic strokes (66). SVD in the brain is characterised on neuroimaging by small subcortical infarcts, white matter hyperintensities, perivascular spaces, microbleeds and lacunes. French neurologists and neuropathologists in the early 19th century introduced the term “lacune” on the small cavities they found in the brain at autopsy. Lacunes are defined as cavities filled with fluid, ranging from approximately 0.3 to 15mm³ in size. These lesions are typically located in the periventricular, deep subcortical white matter and basal ganglia, the same localisation as lacunar infarcts (67). Terminology and definitions for imaging the features of SVD vary widely. Wardlaw and colleagues from the Centres of Excellence in Neurodegeneration (68) have developed definitions and imaging standards for markers and consequences of SVD.

Extensive white matter lesions in the elderly are generally ischaemic in origin and due SVD (69). In the Framington Offspring Study (70), they found that 10.7% of the participants with a mean age of 62±9 years had at least one brain infarct on MRI in the absence of any clinical evidence of stroke. MRI studies in the general population have shown that silent infarcts are present in a quarter or more of those aged >70 years, about five times more common than infarcts presenting with symptoms (71). The incidence increases significantly with age. The silent infarcts have the same risk factor profile as symptomatic infarcts, and are strongly linked
to hypertension and diabetes. They are associated with an increased risk of vascular events, cognitive decline and dementia, and frequently coexist with white matter lesions (71). SVD frequently coexists with neurodegenerative disease, and can worsen cognitive deficits, physical disabilities, and other symptoms of neurodegeneration (68).

A number of studies have shown an association between retinal vasculature, renal dysfunction and cerebrovascular disease. Studies have reported an association between retinopathy and poorer cognitive function (72), and association between retinal vascular abnormalities and silent cerebral infarcts (73, 74). Chronic kidney disease is associated with white matter lesions and age-related macular disease (75-77). Thompson and Hakim (78) hypothesized that SVD is a systemic condition of aging that is exacerbated by vascular risk factors, which results from dysfunction of arteriolar perfusion. Systemic arteriolar dysfunction affects the brain as well as a number of extracranial systems.

1.2.1. Lacunar infarct

Lacunar infarcts (LIs) are small, subcortical infarcts typically located in the basal ganglia, thalamus, internal capsule, corona radiata or brainstem (79, 80). They are defined as <15 mm in diameter in the chronic phase, and are caused by occlusion of a single perforating end artery deep in the brain. Fischer demonstrated that LIs most often are due to lipohyalinosis and microatherosclerosis of the small penetrating vessels, and reported a strong association with SVD. He was of the opinion that SVD was due to hypertension. Hypertension, smoking and diabetes are important, but rather nonspecific risk factors for LI, and do not differ from other stroke subtypes (35, 79). Atrial fibrillation and carotid stenosis, however, are less common in LI (79, 81).

Wardlaw et al.(68) have proposed terms and definitions for neuroimaging features of SVD. They have removed the word lacunar because of new evidence that not all
small subcortical infarcts become lacunes. These are the proposed novel terms for LIs:

- Recent small subcortical infarct: neuroimaging evidence of recent infarction in the territory of one perforating arteriole, with imaging features or clinical symptoms consistent with a lesion occurring in the previous weeks.
- Lacune of presumed vascular origin: a round or ovoid, subcortical, fluid-filled cavity of between 3mm and about 15mm in diameter, consistent with a previous acute small subcortical infarct or haemorrhage in the territory of one perforating arteriole.

In my thesis, I have used the term *acute lacunar infarct*.

Prognosis for patients with LI during the first years is more favourable in terms of survival and disability than for those with other stroke subtypes, probably because of the small lesion size. However, in the long term there is an excess risk for death, recurrent strokes, and development of cognitive dysfunction (66). Asymptomatic progression of SVD is several times more common than new strokes. At 10 years after onset of a LI, a third or less of patients are still alive and free of recurrent stroke (82), although a 15-20% of survivors present cognitive impairment or vascular type dementia.

### 1.2.2. Lacunar syndrome

The clinical symptoms in patients with LIs were described by Fisher more than 30 years ago (80, 83-85). Fisher correlated clinical features with autopsy findings, and described more than 20 different lacunar syndromes following LIs. Face, arm and leg involvement without cortical deficits (aphasia, apraxia, agnosia, neglect phenomena, loss of consciousness, etc.) or homonymous hemianopia are characteristic of the most frequent syndromes. The more restricted a deficit, the
more likely it is to arise from an infarct in the cortex, and not from a LI. The representations of areas are far more spread out in the cortex than in the corticospinal and sensory tracts (80). The most frequent of these clinical syndromes are:

- Pure motor hemiparesis
- Pure sensory stroke
- Sensorimotor stroke
- Dysarthria-clumsy hand syndrome
- Ataxic hemiparesis

The pure motor syndrome is typically caused by an acute LI in the internal capsule or in the brainstem, whereas the pure sensory syndrome in most cases can be explained by an acute infarct in the thalamus. In addition, LIs in the brainstem can result in ataxic hemiparesis or the dysarthria-clumsy-hand syndrome. Ischaemic lacunar strokes often progress and fluctuate during the first 24-38 hours after onset (79), making them the most common cause of “progressing stroke”.

Traditionally it has been thought that LIs do not cause neuropsychological alterations. However, both LIs and SVD are associated with cognitive impairment and dementia (86-88). Studies have documented cognitive impairment in the acute phase (87, 89, 90) as well as in the long term (81, 86, 91). Impaired executive function and working memory have been highlighted as typical cognitive dysfunctions after lacunar stroke, but a systematic review by Edwards et al. documented that these dysfunctions were less characteristic for lacunar stroke than previously thought (92). Cognitive impairment in patients with lacunar stroke may be just as frequent and important as motor and sensory sequelae, but may be overlooked (93).
2. AIMS OF THESIS

With this thesis, we want to elucidate different aspects of the lacunar infarct. In order to tailor the treatment to the individual patient with stroke, we need to know more about the different subtypes of stroke, clinical symptoms and risk factors. The aims of the present thesis are to:

- Evaluate the diagnostic accuracy of the different lacunar syndromes in predicting lacunar infarcts on DWI.
- Investigate risk factors associated with lacunar infarcts.
- Compare blood pressure in patients presenting with clinical lacunar syndromes, but with different radiological subtypes of ischaemic stroke, in order to explore the impact of subtype on blood pressure in the acute phase.
- Assess the association between cognitive impairment and Pulsatility Index in the middle cerebral artery.
3. MATERIAL AND METHODS

3.1. Study design and subjects
We conducted a prospective, observational hospital-based study at the Stroke Unit (SU), Department of Neurology, Akershus University Hospital, from February 2011 to January 2013.

Consecutive patients presenting with an acute lacunar syndrome who were admitted to the SU were recruited. The patients underwent standard examination at our SU including blood samples, electrocardiogram records (ECG), cerebral CT at admission and colour duplex of precerebral and intracranial arteries. All included patients were examined clinically by an experienced stroke neurologist (MA).

The diagnosis of a lacunar syndrome was based upon the patients’ history and neurological examination (findings compatible with a lacunar syndrome). Patients who were treated with intravenous thrombolysis were included, even when their symptoms lasted less than 24 hours. Exclusion criteria were intracerebral haemorrhage and transitory ischaemic attack (TIA, symptoms lasting <24 h and no visible infarct on imaging).

3.2. Assessments
Neurological impairment was assessed by the neurologist on call at admission and on day one and at discharge by MA, using an 11-items version of the NIHSS (Appendix 1). Global function was evaluated using the mRS (Appendix 2) at discharge. Cognitive function was evaluated by MMSE (Appendix 3), Clock Drawing Test (Appendix 4) and TMT A and B (Appendix 5, 6), which are the standardised battery of cognitive assessments at our SU. These were performed between day 2 and day 5 by occupational therapists at the SU. In addition, Barthel
ADL index (Appendix 7) was recorded at discharge. Evaluations and investigations are listed in Table 1.

Table 1. Evaluations and investigations  
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<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>Acute clinical lacunar syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exclusion criteria</td>
<td>Intracerebral Haemorrhage, TIA</td>
</tr>
<tr>
<td>Standard examination</td>
<td>Blood tests</td>
</tr>
<tr>
<td></td>
<td>ECG</td>
</tr>
<tr>
<td></td>
<td>Pre-/intracerebral colour duplex</td>
</tr>
<tr>
<td>Classifications</td>
<td>NIHSS, OCSP, TOAST, mRS,</td>
</tr>
<tr>
<td></td>
<td>Barthel ADL index</td>
</tr>
<tr>
<td>Radiology</td>
<td>CT at admission</td>
</tr>
<tr>
<td></td>
<td>MRI after the acute phase</td>
</tr>
<tr>
<td>Risk factors registration</td>
<td>Hypertension</td>
</tr>
<tr>
<td></td>
<td>Diabetes</td>
</tr>
<tr>
<td></td>
<td>Hypercholesterolemia</td>
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<tr>
<td></td>
<td>Coronary heart disease</td>
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<tr>
<td></td>
<td>Atrial fibrillation</td>
</tr>
<tr>
<td></td>
<td>Previous stroke or TIA</td>
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<tr>
<td></td>
<td>Large vessel disease</td>
</tr>
<tr>
<td></td>
<td>Current smokers</td>
</tr>
</tbody>
</table>

Abbreviations: ADL, Activity of Daily Living; mRS, modified Rankin Scale; NIHSS, National Institutes of Health stroke scale; OCSP, Oxfordshire Community Stroke Project; TOAST, Trial of ORG 10172 in Acute Stroke Treatment

We registered risk factors (hypertension, diabetes, hypercholesterolemia, atrial fibrillation, coronary heart disease (previous myocardial infarction or angina pectoris), mechanical heart valve, smoking and previous stroke/TIA). Prestroke hypertension was defined as on-treatment with antihypertensive drugs, elevated BP as systolic BP>140 mmHg. Hypercholesterolemia was defined as on-treatment with lipid-lowering drugs or total cholesterol >5 mmol/L or low-density lipoprotein cholesterol >3 mmol/L.
BP registrations were performed immediately after admission and bedside in the morning on day three, and were registered prospectively. BP measurements were performed according to standardized protocol, with fully automatic arm BP monitors with the patient in a supine position.

Patients were examined with Doppler ultrasonography of precerebral and intracranial arteries within three days of admission. The examination was performed by one neurologist (M.A.) using GE Vivid 7 Dimension, 4 MHz probe. The middle cerebral arteries (MCAs) were insonated through the transtemporal window at a depth of 50 to 60 mm. The vascular peak systolic velocity, pulsatility index (PI), spectrum shape and direction of blood flow in the proximal MCA (M1) were observed and recorded. The PI value was automatically calculated by the Doppler machine (according to the formula PI= (systolic flow velocity – diastolic flow velocity)/mean flow velocity). A mean MCA PI was calculated by averaging the MCA PI from both hemispheres. If the patient only had good temporal window on one side, unilateral MCA PI was considered as mean PI. Findings of symptomatic carotid or middle cerebral artery stenosis ≥50 % were registered.

Patients underwent magnetic resonance imaging (MRI) with diffusion-weighted images (DWI) within a week after admission to hospital. The brain imaging was done on Philips Achieva 1.5T or 3T MRI scanners employing standard sequences, using T1 weighted sagittal, T2 weighted axial, T2/FLAIR weighted coronal and diffusion weighted (DWI) axial imaging. Due to capacity problems in the MRI scanning, 33 patients underwent only CT scanning. Isolated acute ischaemic lesions on DWI or CT were defined as LIs if <15 mm and located subcortically or in the brainstem (94), whereas all other acute ischaemic lesions were defined as non-lacunar infarcts (NLI).

Figure 3 shows the patient subgroups included in the three papers in the present thesis.
Figure 3. Patient subgroups in Paper I-III

Abbreviations: CT, Computer tomography; DWI, diffusion weighted imaging

\(^1\) Facial paresis or symptoms in only one limb

3.3. Statistics

Data were analysed using SPSS (SPSS Inc., Chicago IL) version 19 (paper I and II) and version 22 (paper III). All significance tests were two-tailed and performed at the 5% level. Continuous variables were presented as means and standard deviations (SD) or medians and the interval between first (Q1) and third (Q3) quartiles. Categorical variables were presented as frequencies and percentages. Normality of continuous variables was assessed by inspecting the histograms. Between-group differences of the characteristics and stroke risk factors were compared using independent samples t-test for normally distributed continuous data, Mann-Whitney test for skewed continuous data, and \(\chi^2\)-test for categorical variables.
The associations between an outcome and candidate variables were assessed by linear regression models for continuous outcomes and logistic regression models for dichotomous outcomes. These results were presented as regression coefficients or ORs with standard errors and corresponding p-values.

In paper I, the sensitivity and specificity of the different lacunar syndromes were assessed using DWI as reference test ("gold standard").

Detailed descriptions of the statistical methods are presented in each paper.

3.4. Ethical considerations
The study was approved by The Regional Committee for Ethics in Medical Research and by the Data Protection Authorities. Oral and written informed consent was obtained from all included patients. There was no benefit for patients participating in the study, neither any disadvantage for those who did not. All patients were managed according to a standard stroke protocol.
4. SUMMARY OF RESULTS

4.1. Paper I
Diagnostic accuracy and risk factors of the different lacunar syndromes
A total of 86 patients were included. 69 patients (80.2%) had an acute ischaemic lesion on DWI, only 6 (8.7%) of these appeared on the initial CT. 56 patients (65.1%) had a lacunar lesion, 13 patients (15.1%) had one or more non-lacunar lesions. 17 patients had no sign of acute infarct. We used DWI as a gold standard for having lacunar infarction, and the positive predictive value (PPV) of the lacunar syndrome was 65.1% (56/86). The PPV of the pure motor syndrome was 75% and of the sensorimotor syndrome was 48%. 41 patients had “biparesis” and 45 had “triparesis” (symptoms in arm and leg + facial paresis). We calculated the sensitivity and PPV for patients presenting with motor syndrome and tripareshis, but this did not change the values.

Table 3. Sensitivity and specificity of the different lacunar syndromes
Adapted from paper I, reprinted with permission from Elsevier. Copyright 2014.

<table>
<thead>
<tr>
<th>Clinical presentation</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Motor syndrome</td>
<td>0.68</td>
<td>0.57</td>
<td>0.75</td>
<td>0.49</td>
</tr>
<tr>
<td>Sensorimotor syndrome</td>
<td>0.23</td>
<td>0.53</td>
<td>0.48</td>
<td>0.27</td>
</tr>
<tr>
<td>Motor syndrome with tripareshis</td>
<td>0.67</td>
<td>0.60</td>
<td>0.77</td>
<td>0.47</td>
</tr>
</tbody>
</table>

Abbreviations: NPV, negative predictive value; PPV, positive predictive value

There were no significant differences between the groups regarding vascular risk factors. In the multivariate logistic regression model, pure motor syndrome [OR
2.66 (1.04-6.80)] and male gender [OR 2.63 (1.01-6.83)] were the only variables with significant associations with LI on DWI.

4.2. Paper II

Blood pressure differences between patients with lacunar and non-lacunar infarcts

In all, 113 patients were included. 85 patients (75.2%) had a LI, 28 patients (24.8%) had one or more NLIs. The LIs were localized in the basal ganglia (44%), the periventricular white matter (21%), the thalamus (14%) and in the brainstem (21%). The NLIs were localized in the cortex or subcortically, but none were due to occlusion of a major vessel. None of the NLIs located subcortically were lesions consistent with occlusion of a single perforant artery.

The mean age was 70.1 years (SD=11.5), and 69% were men. The median NIHSS score was 3 (IQR 2-4) at admission and 1 (IQR 0-3) at discharge, whereas median mRS score was 2 (IQR 1-3) at discharge and median Barthel ADL index (day 2-4) was 20 (IQR 16-20). 75.2% of the patients had systolic BP>140 mmHg at admission and 54.9% had used antihypertensive medication before admission (prestroke hypertension). There were significantly more patients with systolic BP>140 mmHg among patients with LI than NLI at day three (p=0.020). The systolic BP at day three was significantly higher in the LI group than the NLI group (p=0.002).

In the linear regression model, there was a significant association between systolic BP and LI, both at admission (p=0.042) and at day three (p=0.003). Adjusting for covariates (age, gender, smoking, prestroke hypertension, diabetes, hypercholesterolemia, large vessel disease and NIHSS), these associations were still significant (p=0.047 and p=0.006, respectively). There was also a significant association between diastolic BP at day three and LI (unadjusted, p=0.005, adjusted, p=0.036). None of the other covariates were significantly related to the
BP. BP was not associated with mRS or NIHSS at discharge (p=0.777 and p=0.887 respectively).

4.3. Paper III

Pulsatility index in the middle cerebral artery- associated with cognitive impairment in lacunar stroke?

In all, 113 patients were included. The mean MMSE score was 26.1 (SD=3.6), and 43% scored ≤26. The mean TMT A time was 72.6 seconds (SD=43.8) and the mean TMT B time was 195.1 seconds (SD=107.8). 47% had a TMT B age adjusted score ≥2SD (95). 68.1% of the patients had a normal Clock Drawing Test score. Adequate Transtemporal window for Doppler data was achieved in 84% of the patients. The mean PI was 1.46 (SD=0.33). Characteristics and stroke risk factors are presented in Table 2. We found no statistically significant difference in PI between patients with lacunar and non-lacunar infarcts.

There were no statistically significant differences between lacunar and non-lacunar infarct groups with respect to the association between PI and the different outcome variables. PI was significantly (p<0.05) associated with MMSE, TMT A and TMT B in the LI group, even after adjustment for a number of patient characteristics (age, sex, prestroke hypertension, smoking, previous stroke and diabetes). The Clock Drawing Test was not significantly associated with PI (unadjusted p=0.057, adjusted p=0.348).

4.4. Characteristics and vascular risk factors of the population

A total of 147 patients with a lacunar syndrome were recruited to the study. Characteristics and vascular risk factors of the population are presented in Table 2.
Table 2. Characteristics and vascular risk factors

<table>
<thead>
<tr>
<th>Characteristics and vascular risk factors</th>
<th>All patients n=147</th>
<th>Paper I n=86</th>
<th>Paper I+II n=113</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD)</td>
<td>70.3 (11.9)</td>
<td>69.3 (12.1)</td>
<td>70.1 (11.5)</td>
</tr>
<tr>
<td>Males</td>
<td>87 (59)</td>
<td>56 (65)</td>
<td>78 (69)</td>
</tr>
<tr>
<td>Performed only CT</td>
<td>37 (25)</td>
<td>0</td>
<td>18</td>
</tr>
<tr>
<td>Verified infarct</td>
<td>113 (77)</td>
<td>69 (80)</td>
<td>113 (100)</td>
</tr>
<tr>
<td>Verified lacunar infarct</td>
<td>85 (58)</td>
<td>56 (65)</td>
<td>85 (75)</td>
</tr>
<tr>
<td>Monoparesis</td>
<td>28 (19)</td>
<td>0</td>
<td>25 (22)</td>
</tr>
<tr>
<td>Current smokers</td>
<td>50 (34)</td>
<td>32 (37)</td>
<td>39 (35)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>83 (57)</td>
<td>48 (56)</td>
<td>62 (55)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>36 (25)</td>
<td>14 (16)</td>
<td>28 (25)</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>113 (73)</td>
<td>65 (76)</td>
<td>86 (76)</td>
</tr>
<tr>
<td>Coronary disease</td>
<td>27 (18)</td>
<td>19 (22)</td>
<td>21 (19)</td>
</tr>
<tr>
<td>Large vessel disease</td>
<td>19 (13)</td>
<td>15 (17)</td>
<td>17 (15)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>19 (13)</td>
<td>12 (14)</td>
<td>16 (14)</td>
</tr>
<tr>
<td>Previous stroke or TIA</td>
<td>30 (20)</td>
<td>17 (20)</td>
<td>20 (18)</td>
</tr>
<tr>
<td>Blood pressure &gt;140 day 3</td>
<td>92 (63)</td>
<td>50 (58)</td>
<td>85 (75)</td>
</tr>
<tr>
<td>NIHSS at admission, median, (IQR)</td>
<td>3 (2-4)</td>
<td>3 (2-4)</td>
<td>3 (2-4)</td>
</tr>
<tr>
<td>NIHSS at discharge, median, (IQR)</td>
<td>1 (0-3)</td>
<td>1.5 (0-3)</td>
<td>1 (0.5-3)</td>
</tr>
<tr>
<td>Barthel ADL index, median, (IQR)</td>
<td>20 (17-20)</td>
<td>20 (16-20)</td>
<td>20 (16-20)</td>
</tr>
<tr>
<td>mRS at discharge, median, (IQR)</td>
<td>2 (1-3)</td>
<td>2 (1-3)</td>
<td>2 (1-3)</td>
</tr>
<tr>
<td>Treated with iv thrombolysis</td>
<td>15 (10)</td>
<td>9 (11)</td>
<td>10 (9)</td>
</tr>
</tbody>
</table>

Abbreviations: ADL, Activities of Daily Living; iv, intravenous; IQR, Interquartile range; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; SD, Standard deviation.

1 Symptoms only in 1 limb or facial paresis
2 On-treatment with statins or total cholesterol >5 mmol/L and/or LDL cholesterol >3mmol/L
3 Previous myocardial infarction and/or angina pectoris
4 >50% stenosis in the internal carotid artery or middle cerebral artery

Results are n and (%) unless indicated otherwise.
5. GENERAL DISCUSSION

Stroke is a common disorder, and lacunar infarcts account for about 25% of all ischaemic strokes (81, 96). LIs can be symptomatic or asymptomatic, and are a part of the term SVD. In the short term, the clinical course is characterised by a low early mortality and relatively preserved neurological functioning, however, in the long term it is characterised by increased risk of death, stroke recurrence and dementia. Therefore, LIs should be regarded as a potentially severe condition that requires thorough evaluation, management and follow-up.

5.1. Diagnostic accuracy of the lacunar syndromes

Stroke in the acute phase is a clinical diagnosis. The clinical lacunar syndromes are well described, but how well can clinical neurological examination predict a LI? In our study, the lacunar syndrome had an overall low positive predictive value of 65.1% for predicting an acute LI on DWI. This is in accordance with previous DW- MRI studies (41, 46). The PPV was particularly low among patients with a sensorimotor syndrome (48%), which is no better than by chance. Previous reports (97-99), which have shown a high diagnostic accuracy of the lacunar syndrome, used only CT or conventional MRI. In these studies, patients with no verified infarct on CT/MRI were either excluded or classified as LIs (97, 99, 100), which may have resulted in a falsely elevated PPV of the lacunar syndrome. The radiological diagnosis of stroke has been largely improved with early diffusion weighted imaging (DWI), at present the most sensitive imaging in acute ischaemic stroke (46).

Recent studies using DWI have demonstrated that the OCSP classification has a particularly low PPV in predicting infarct location of small infarcts (41, 101). One of these studies found a PPV of LACI as low as 39% (41). These results demonstrate that the OCSP classification does not permit accurate discrimination
between lacunar and small cortical infarcts, which is in accordance with the findings in our study.

In our study, 17 patients had no recent ischaemic lesion on DWI at all. Four of these had been given intravenous thrombolytic treatment, which may explain the absence of an ischaemic lesion. The remaining 13 patients constitute 15.1% of all patients. False-negative DWI cases do occur (47), even though DWI has a high sensitivity for detecting acute ischaemic lesions. This is particularly the case for small ischaemic lesions, especially lacunar infarcts and infarcts located in the brain stem (102). The majority of our patients had minor stroke, and we would expect a higher proportion of false negative DWIs. Some of the 13 patients might have had a non-ischaemic diagnosis (a stroke mimic) such as migraine, functional paresis etc. (103). In clinical practice, these differential diagnoses may be challenging.

We found no significant differences in risk factors between the groups (LI vs. no LI). This has also been described in other studies (97, 104). Hypertension, smoking and diabetes are important but rather nonspecific risk factors for LIs, and do not differ from other stroke subtypes. When we compared the two groups of patients with an acute ischaemic lesion on DWI, lacunar or non-lacunar, the latter were older and had a higher frequency of atrial fibrillation at admission and large vessel stenosis (not statistically significant). We only included patients with lacunar syndrome, and therefore the number of patients with cortical lesions was probably too low to reach significant differences. Others have reported significantly higher proportion of large vessel disease or atrial fibrillation among patients with cortical infarcts (101, 105).

5.2. Blood pressure differences between lacunar and non-lacunar infarcts

Patients with acute LIs had significantly higher BP on day three compared to patients with acute NLIs. This applies to both diastolic and systolic BP. The
difference was significant regardless of prestroke hypertension. We also found a significant association between BP and LI, both at admission and day three. Previous studies comparing BP in patients with different subtypes of stroke have compared groups with different severity of neurological impairments. In patients with major stroke, BP may rise because of large volume effect and high intracranial pressure, as a compensatory mechanism. This was most likely not the case in our study, as none of the NLIs were due to occlusion of a major vessel. Accordingly, there was probably no oedema-effect on the BP in any of the groups.

Previous studies on the association between different subtypes of stroke and different patterns of BP change in acute stroke have shown conflicting results. There are publications reporting highest BP levels in patients with lacunar strokes (106-108), while others found higher BP levels from day one in patients with non-lacunar strokes compared to lacunar strokes (109). Vemmos et al. found no significant difference in BP levels between the different aetiological subtypes of stroke (110). In that study, the spontaneous BP variation in acute stroke differed according to subtypes, with a milder drop in cardio embolic strokes compared to end artery small vessel and large vessel atherosclerotic strokes. BP was proportional to the clinical severity of stroke at presentation, which can be explained by the fact that cerebral ischemia might trigger a physiological response, resulting in higher BP. In the study of Vemmos, there was probably a large oedema effect on the BP in the groups with high clinical severity.

Other studies (106, 107) have reported findings of higher BP in patients with LIs than in NLIs, which corresponds to the findings in our study. Semplicini et al. also found that the outcome of stroke was highly associated with subtype of stroke and initial BP (106), as lacunar stroke and patients with the highest BP on admission had the best prognosis. In our study of patients with lacunar syndromes, the patients had the same severity regardless of subtype of stroke. Both groups had a good clinical outcome with low NIHSS and mRS scores at discharge. There was no association between BP and outcome. Many studies have looked at the
association between admission BP and outcome, and have shown inconsistent results (13, 25-27). Two studies found that high BP is associated with poor outcome (111, 112). They did not look at differences between subtypes of stroke. Kvistad et al. found an inverse association between BP and stroke severity on admission, where elevated BP was associated with mild stroke, and lack of elevated BP was associated with severe stroke (113). They assumed that there might be a protective effect of elevated BP. But maybe the high BP in lacunar stroke is a marker of the underlying cause, and not necessarily a protective mechanism? In previous studies exploring the association between stroke subtype, BP and outcome, the severity differs between the subtypes. As long as studies compare groups with different severity of neurological deficits, we will not get the answer of whether differences in BP are explained by aetiological subtype or severity.

Fifty percent of the patients in our study used antihypertensive treatment at admission, and there were no significant difference regarding prestroke hypertension between the two groups. Still, the BP at day three was significant higher in the LI group (and there was a trend toward higher systolic BP at admission). LIs were independently associated with a higher BP compared to NLIs with the same severity of neurological impairments. The sustained high BP in the LI group may be an indication of untreated (or suboptimally treated) chronic hypertension. Recent data from the SPS3 trial (114) have recommended a lower BP target (systolic BP<130 mmHg) for patients with recent LI. Optimal BP control may reduce white matter hyperintensity progression and cognitive impairment of vascular type (115).
5.3. The association between PI and cognitive impairment in lacunar stroke

The TCD PI values were significantly associated with MMSE, TMT A and TMT B performances in patients with a LI. Our results correspond to the findings in a study of asymptomatic participants between 50-65 years by Lopez-Oloriz et al. (116). In a study of cerebrovascular hemodynamics in patients with Alzheimer’s disease and vascular dementia (117), the authors found that PI was significantly higher in patients with vascular dementia compared to patients with Alzheimer’s disease. Elevated PI may be an indicator of SVD, as it is believed to reflect the resistance in the arteries deep in the brain (52). We found no statistically significant differences between LI and NLI groups with respect to the association between PI and cognitive tests. This may be due to a too small NLI group, and to the fact that the NLI group of the present study is a highly selected group in which all patients presented with a lacunar syndrome, and none had an occlusion of a major vessel. They do not represent a typical NLI group among patients with stroke, and SVD may have been prevalent in this particular NLI group. Well known risk factors for SVD such as hypertension, diabetes and other cerebrovascular risk factors were equally present in both groups.

MMSE is frequently used for global cognitive screening, but may lack sensitivity in patients with stroke (118). Nevertheless, there is a strong association between MMSE and PI values in both groups in our study, even after adjustment for multiple relevant variables. An elevated PI predicts a low score on MMSE. In our models, we adjusted for previous stroke, age, hypertension and diabetes. Prior stroke and age are well recognized predictors of cognitive impairment. TMT A and B are also a part of our standard test battery for patients with stroke. TMT A measures psychomotor speed, while TMT B measures visual attention information processing and executive functioning. Impairment in these functions is often associated with LIs and SVD. The association between PI and TMT A remained significant in both groups after adjustment. The association between PI and TMTB
after adjustment was only present in the LI group. This may suggest a stronger association between PI and TMT B in LIs compared to NLIs, but further studies with larger samples are needed to confirm this finding. In a quantitative systematic review by Edwards and colleagues (92), the authors reported impairment in multiple cognitive domains following LI. In addition to the domains of attention/working memory and executive functioning, the impairment was also reported for memory, language and visuospatial function. The magnitude of impairment was actually largest for global cognition and information processing speed. They found no evidence for change in domain-specific cognitive function over time, and assumed that the longer-term rate of cognitive decline is due to stroke recurrence. The Secondary Prevention of Small Subcortical Strokes (SPS3) clinical trial (119) examined domain-specific cognitive outcomes in patients with symptomatic LIs (93). In this study, they found episodic memory deficits in patients in addition to the typical impairment pattern for SVD. Mild cognitive impairment was present in almost half of their participants, and was more prevalent than physical disability defined by mRS ≥2. This is in accordance with the findings in our study, although we did the testing in the acute phase after stroke. More than 40 % of the patients in the LI group in our study had a MMS score ≤ 26, while 39% had mRS ≥2. Cognitive impairment after lacunar stroke is common, and may have a major impact on the patient’s quality of life.

In the multivariate analyses of the association between PI and MMSE, diabetes was also a strong predictor of low MMSE score. Diabetes is an independent risk factor for ischaemic stroke, including lacunar infarction (81), and has previously been found to be independently associated with a high PI (120). In the SPS3 trial (121), they found that patients with diabetes mellitus had more extensive white matter disease and were almost twice as likely to have a recurrent stroke compared to patients with LI without diabetes. The association between cognitive impairments and diabetes may be a result of SVD. In our study, diabetes was actually more prevalent in the NLI-group (32 vs. 22%). The difference is not
significant, but may support the hypothesis that SVD co-exists in some of the patients in the NLI-group as well.

5.4. Methodological considerations

Akershus University Hospital has a well-defined catchment area, which accounts for about 10% of the Norwegian population. All patients with suspected stroke or TIA are admitted to the SU for further examination, but there will always be some patients who do not seek medical contact. The patients included were diagnosed according to the criteria for a lacunar syndrome, and the median NIHSS was low. The study population should represent a general lacunar stroke population. Strengths of the study are that all patients were included and examined by one person, and all patients consented to the study.

The prospective design of the study including consecutive patients with a lacunar syndrome reflects the real life experience in a SU. The main investigator performed the clinical examination and Doppler ultrasound measurements on all patients, and the data were recorded prospectively. Because the investigator attended various courses as part of the PhD program, there were periods without inclusion. However, these periods were spread throughout the year, and were not on specific months or days. This should therefore not entail any selection bias.

A limitation of our study in comparing lacunar and non-lacunar infarcts was the small sample size in the NLI group, which may entail too little power to discover between-group differences. In the beginning of the study period, the hospital experienced capacity problems in MRI scanning, and many patients underwent only CT scanning. This led to exclusion of many patients in the first study. Another limitation is that we do not have data on the severity of white matter disease in our patients.
In the first paper, we evaluated the diagnostic accuracy of the different lacunar syndromes by calculating the sensitivity, specificity and positive predictive value, see table 4. The sensitivity of a test is the proportion of people with a disease that will be correctly diagnosed by the test. The specificity is the proportion of people without a disease that actually is identified as negative by the test. In a screening situation, high sensitivity is important if a false negative error is serious, while a high specificity is important to avoid false positive errors. The “optimal test” has both high sensitivity and high specificity. In clinical practice, the positive and negative values may be more useful. The positive predictive value (PPV) is a measure of the probability that a patient with a positive test result really has the condition he/she is tested for. The PPV is dependent upon the prevalence of the disease, and if the prevalence is low, the PPV will decline. In our study a positive predictive value for the lacunar syndrome is the probability that the patient who present with a lacunar syndrome actually has a LI on DWI.

**Table 4. Sensitivity, specificity and predictive value of the motor syndrome**

<table>
<thead>
<tr>
<th></th>
<th>Diffusion weighted imaging</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LI</td>
<td>No LI</td>
<td>Total</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Motor syndrome</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>38</td>
<td>13</td>
<td>51</td>
<td>PPV=38/51=75%</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>18</td>
<td>17</td>
<td>35</td>
<td>NPV=17/35=49%</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>56</td>
<td>30</td>
<td>86</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Sensitivity= 38/56=68%  Specificity= 17/30=57%

NPV, negative predictive value; PPV, positive predictive value
We used the DWI as a gold standard. Although DWI has a high sensitivity, false-negative DWI cases do occur (47). Baseline DWI volume is considered useful in predicting final lesion volume in anterior-circulation stroke syndromes, but DWI-positive scans in TIA are also common (47). Studies have shown acute ischaemic DWI lesions in among 40% of the patients with a clinical diagnosis of TIA, a finding that may correlate with symptom duration. Whether a TIA with DWI lesions is to be classified as a cerebral infarct is still under debate (122). In our study, we included only patients with symptoms lasting more than 24 hours, except from the patients who were treated with thrombolysis.

BP registrations in our study were performed immediately after admission and bedside in the morning on day three, and were registered prospectively. BP measurements were performed according to a standardized protocol, with fully automatic arm BP monitors with the patient in a supine position. Unfortunately, we did not have the possibility to use 24 hours BP measurements on our patients. It is known that BP is transiently elevated in patients with acute stroke with a spontaneous decrease within the following days (123-126). We therefore chose two points in time to measure the BP. None of the patients were treated with intravenous antihypertensive drugs in order to reduce BP. The median time interval from onset of symptoms to admission to hospital was 11 hours, and there was no significant difference between the groups according to this. It is known from previous studies (127, 128) that stroke severity is related to prehospital delay. Patients with a higher NIHSS score arrive faster to hospital than patients with a low NIHSS.

In Paper III we measured the pulsatility index in the middle cerebral artery. The PI value was automatically calculated by the Doppler machine using the mean of 5 cycles, and a mean PI was calculated by averaging the PI from both hemispheres. Our mean PI value is higher than in other studies (52). Previous studies have shown an elevation in PIs with increasing age, hypertension and SVD (51-55), which all are factors prevalent in our highly selected population. We included only
patients with lacunar syndromes and verified acute infarcts. The patients were examined in the acute phase, which also may have an effect on the PI values.
6. CONCLUSIONS

- The present study has demonstrated a low diagnostic accuracy of the clinical lacunar syndrome. It is important to be aware of this uncertainty in clinical practice. The clinical diagnosis of patients with lacunar syndromes is inaccurate, especially among patients with non-motor syndromes. DWI is mandatory for obtaining an accurate diagnosis of the lacunar infarct.

- Lacunar infarcts may be independently associated with higher blood pressure compared to non-lacunar infarcts with the same severity of neurological impairments. Blood pressure differences between different subtypes of stroke may not only be related to clinical severity but also to the underlying cause of stroke. Hypertension is strongly linked to lacunar infarcts as a risk factor.

- Pulsatilty index was associated with the cognitive performance in patients with lacunar infarcts. An elevated PI may be related to impairment in several cognitive domains. These findings suggest that TCD may be a useful supplement to other cognitive investigations in clinical practice.
7. FURTHER PERSPECTIVES

We hope that the papers included in this thesis will help draw attention to lacunar infarcts. A correct diagnosis is important because it has implications for further investigations and treatment. Because of the low diagnostic accuracy of the lacunar syndromes, the radiological verification of infarcts in future studies on stroke is essential to differentiate between subtypes of stroke.

Further studies of blood pressure in the different aetiological subtypes of stroke are needed in order to differentiate treatment. It is important to use risk-factor-free classifications of stroke subtypes when comparing risk factor profiles between lacunar and non-lacunar subtypes (35). Better knowledge regarding the impact of the risk factors for different subtypes of stroke may give rise to more specific approaches to therapy.

We need further studies on BP lowering in patients with small vessel disease, to evaluate how they respond to BP treatment. Maybe more aggressive treatment in the long term can stop or even reverse the white matter progression? The SPS3 trial (114) has already suggested a lower BP target (systolic BP<130 mmHg) for patients with recent LI.

The findings of the association between PI and cognitive performances in patients with LIs suggest that TCD may be a useful supplement to other cognitive investigations in clinical practice. Further studies will be required to look at the association between PI and cognitive impairment in different subtypes of stroke.
8. REFERENCES


9. ERRATA
10. APPENDIX

10.1. National Institutes of Health Stroke Scale - Norwegian version

<table>
<thead>
<tr>
<th>NIH Stroke Scale (NIHSS)</th>
<th>Mottak</th>
<th>Start</th>
<th>2 t</th>
<th>24 t</th>
<th>7 dager</th>
</tr>
</thead>
</table>

Total NIHSS-Score

Undersøkerens signatur
Veiledning for NIH stroke scale

Generelt
- Det best skårbare svar/reaksjon er vanligvis det første svaret (bortsett fra ved afasia).
- Man skal ikke forklare/visible pasienten hva hun skal gjøre, men mindre det er spesifisert i instruksjonene.
- Noen punkter skåres kun hvis de med slike skårer er påvirket (for eksempel koordinasjon/ataksi, neglekt).

NIH stroke scale

1a Bevislighetsnivå – "Let stimulering" byr på tilnok på forsiktig berøring.
- "Kraftigere/gjentatt stimulering" byr på forsiktig berøring eller småtestimulering.

- Afasiske/komatose pasienter skåres 2.

1c Respons på kommando – Be pasienten åpen øynene og å løkke øynene; deretter knyte hånden og så å løkke hånden.
- Første kommando brukes for å få øynene/hånd i standardisert testposisjon. Dersom pasienten gjør et entydig forsøk på å følge kommando, skåres dette som utført. Hvis pasienten ikke reagerer på kommando, kan ønsket respons demonstreres av undersøkeren.


5a Kraft i armen – Test hver arm for seg, først den friske armen. Hjelp pasienten til å holde armen utstrakt i 45° vinkel med håndflaten ned, slipp armen og skår bevegelsen. Ved brudd/amputasjon skåres 0.

5b Kraft i benet – Test hvert ben for seg, først det friske benet. Hjelp pasienten til å holde benet utstrakt i 30° vinkel, slipp benet og skår bevegelsen. Ved brudd/ruptur skåres 0.


8a Hudfølelse – Test sensibilitet for stikk (anastikker). Test overarm, kne, lår (men ikke bender og føtter på grunn av mulig polyneuropati).


5b Tal/rafasitrit – Pasienten skal formelt skåres etter standardiserte bilder og (engelske) setjinger. I praksis testes tale gjennom samtlige med pasienten.
- Pasienter som ikke har språk, som ikke kan forstå på en meningstfyllt måte, eller er komatos, skåres 2. Alle andre lettere grader av dysfoni skåres 1.

1a "Neglect"/Ekstinsjon – Se punktene 3 og 5. Hvis pasienten har betydelig synstap (hemianopsi) og sensibiliteten er normal, skåres 0 – normal.
- Hvis pasienten er afasitri, men har oppmerksomhet mot begge sider, skåres 0 – normal. Pasienter som entydig negligerer høydevis av rommet (selv om de ikke har ekstinsjon ved visuell sensorisk testing) skåres 1. Komatose pasienter skåres 2.
## 10.2. Modified Rankin Scale - Norwegian version

**RANKIN SCALE**

<table>
<thead>
<tr>
<th>0. Ingen symptomer i det hele tatt. (No symptoms at all.)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Følger ikke av noen begrensninger eller symptomer.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>1. Ingen betydningsfull funksjonssvikt til tross for symptomer; klarer å utføre alle oppgaver og aktiviteter som før.</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Pas har noen symptomer, enten fysiske eller kognitive, f.eks. affeksjon av språktales, evne til å lese/skrive, fysisk mobilitet, sensibilitet, syn, svelg, humør, men kan fortsatt ta del i alt tidligere arbeid, sosial eller ffådsaktiviteter. Det avgjørende spørsmål for å skille mellom 1 og 2 kan være: Klarer pasienten alle aktiviteter som hun før gjorde mer enn månedlig?</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2. Lett funksjonssvikt; klarer ikke å utføre alle aktiviteter som før, men klarer sine daglige gjøremål.</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Pas klarer ikke lenger gjøre en del av de aktivitetene som hun/han tidligere vanligvis har gjort (f.eks. kjøre bil, danse, lese, arbeide), men klarer fortsatt å ta vare på seg selv uten hjelp fra andre fra dag til dag. Pas kan klare påkleddning, forflytning, matlaging/spisestuevisjon, toalettbesøk, lage enkle måltider, handle og reise i lokalområdet uten å måtte motta hjelp eller tilsyn fra andre. Pas skal kunne være overført til seg selv åleene hjemme i en ukor eller mer uten noen bekymring.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>3. Moderat funksjonssvikt; trenger noe hjelp, men går uten hjelp.</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Pas trenger ikke hjelp til forflytning/gang (selvstendig i forflytning med og uten hjelp/kjøretøy som stokk, trollveg). Klarer påkleddning, toalettbesøk og å spise etc, men trenger hjelp til mer komplekse aktiviteter. Noen andre må handle, lage mat, vaske – og må besøke pasienten oftere enn ukentlig for å sørge for at disse aktivitetene er gjennomført. Assistanse kan være fysisk eller rådgivende, f.eks. pas trenger tilsyn eller motivering for å klare finansialle gjøremål.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>4. Alvorlig funksjonssvikt; klarer ikke å gå uten hjelp og klarer ikke å ivareta sine grunnleggende behov uten hjelp.</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Pasienten må ha hjelp av andre til noen daglige aktiviteter, f.eks gange, påkleddning, toalett, spise. Pas blir besøkt mindre en og vanligvis to eller flere ganger daglig, eller må bo i nærheten av hjelper. For å skille 4 fra grad 5 – ta stilling til om pasienten kan bli fritt alene for moderate perioder i løpet av dagen.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>5. Svært alvorlig funksjonssvikt; sengeliggende og trenger konstant tilsyn og hjelp.</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Noen andre må være tilsigelig på dagtid og noen ganger i løpet av natten – denne trenger ikke være en sykepleier.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>6. Død</th>
<th></th>
</tr>
</thead>
</table>
10.3. Mini Mental State Examination - Norwegian version

NORSK REVIDERT MINI-MENTAL STATE EXAMINATION (MMSE-NR)
Carsten Strobel og Knut Engedal, 2008

Testleder (TL) ___________________________ Dato ___________________________ Tidspunkt ___________________________

Teststed ___________________________ Har MMSE vært administrert samme sted tidligere? Ja ☐ Nei ☐

Hvis ja, når? ___________________________ Når/hvor ble MMSE sist administrert? ___________________________

Oppg. 11 og 12: Angi oppgavesett (ordsett, starttall) administrert i dag: 1. adm ☐ 2. adm ☐ 3. adm ☐ 4. adm ☐ 5. adm ☐

Pasient (PAS) ___________________________

Fødselsdato ___________________________ Nasjonalitet/morsmål ___________________________

Utdanning/antall år ___________________________ /år York ___________________________

Hørse/høreapparat ___________________________ Syn/briller ___________________________ Geriatrisk læsepappe ___________________________

Hevningsgrunn/diagnose ___________________________

Legemidler ___________________________

Instruksjon


Kommentarer/spesielt å bemerke (atferd, stemmingsleie, smerter, afasi, tidsbruk, glemt briller/høreapparat etc.)

__________________________________________________________________________

__________________________________________________________________________

__________________________________________________________________________

OPPMERKSOMHET/BEVISSTHETSNIVÅ

Gradert vurdering av oppmerksomhet/bevissthetstever (Sett kryss passende sted på linjen)

<table>
<thead>
<tr>
<th>Dårlig</th>
<th>Oppmerksom</th>
</tr>
</thead>
</table>

TESTSITUASJON

Gradert vurdering av samarbeidstestinnsats (Sett kryss passende sted på linjen)

<table>
<thead>
<tr>
<th>Dårlig</th>
<th>Ulmerket</th>
</tr>
</thead>
</table>


70
TL starter med følgende spørsmål: Synes du hukommelsen har blitt dårligere? Ja [ ] Nei [ ] Vet ikke [ ]
Jeg skal nå stille deg noen spørsmål, svar så godt du kan. Instruksjon kan gjentas, unntatt på oppg. 12 og 17.

**TIDSORIENTERING**

<table>
<thead>
<tr>
<th>POENG</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Hvilket årsdømt har vi nå? (Kun fult årsdømt med 4 sifre gir poeng)</td>
</tr>
<tr>
<td>2. Hvilken årsid til har vi nå? (Ta hensyn til vær og geografiske forhold)</td>
</tr>
<tr>
<td>3. Hvilken måned har vi nå? (Kun riktig navn på måned gir poeng)</td>
</tr>
<tr>
<td>4. Hvilken ukedag har vi i dag? (Kun riktig navn på dag gir poeng)</td>
</tr>
<tr>
<td>5. Hvilken dato har vi i dag? (Kun dagdelen trenger å være riktig for å få poeng)</td>
</tr>
</tbody>
</table>

**STEDSORIENTERING**

På spørsmål 7 brukes "landsdel" ved testing i Oslo, "Fylke" utenfor Oslo. Slett ring rundt valgt stedsord for spørsmål 8 og 9.

| POENG | 0 |
|-------|
| 6. Hvilket land er vi i nå? | 0 |
| 7. Hvilket fylkelandskal er vi i nå? (Sør-Norge gir også poeng for landsdel) | 0 |
| 8. Hvilken by/kommune er vi i nå? | 0 |
| 9. Hva heter dette stedet/bygningen/lykehuset/legekontoret/hvor er vi nå? | 0 |
| 10. I hvilken etasje er vi nå? (Spørsmål stilles også om man er i 1. etasje) | 0 |

**UMIDDELBAR GJENKALLING/REGISTERING**


Nå kommer ordene:... HUS [pause], KANIN [pause], TOG [pause]. Nå kan du gjenta disse ordene.

Dersom PAS ikke gjentar alle 3 ord ved 1. forsøk, repeteres alle ord intil alle gjengis i samme forsøk, maks. 3 forsøk. Det gir kun poeng for 1. forsøk, rikelige poeng PAS sier ordene er uenig i betydning. Antall forsøk: ___________ stk.

| POENG | 0 |
|-------|
| HUS [Alternativt ord: ____________________________] | 0 |
| KANIN [Alternativt ord: ___________________________] | 0 |
| TOG  [Alternativt ord: _____________________________] | 0 |

Husk disse ordene, for jeg vil be deg gjenta dem senere.

**OPPMERKSOMHET OG HODEREGNING (Vær oppmerksom på eventuell distraksjonsbetingelse*)**


| POENG | 0 |
|-------|
| Starttall: | 80 | 50 | 90 | 40 | 60 |
| Om nødvendig s.i. og så videre... | [73], [43], [83], [33], [53] | 0 |
| Om nødvendig s.i. og så videre... | [66], [36], [76], [26], [46] | 0 |
| Om nødvendig s.i. og så videre... | [59], [29], [69], [19], [39] | 0 |
| Om nødvendig s.i. og så videre... | [52], [22], [62], [12], [32] | 0 |
| Om nødvendig s.i. og så videre... | [45], [15], [55], [5], [25] | 0 |

Etter 5 subtraksjoner s.i: Fint, det holder [Gå til oppg. 13].

*Eventuell distraksjonsbetingelse – OBS, er ikke poenggivende*

Dersom PAS ikke vil utføre eller kan bravere oppg. 12, skal distraksjonsbetingelsen brukes for å sikre kartlegging av langtidshukommelse på oppg. 13. Be da PAS tolle baklangs fra 100 ca. 30 sek. med følgende instruksjon:

(Tell baklangs fra 100 på denne måten: 99, 98, 97..., helt til jeg sier stopp. Vær så godt!)
UTSATT GJENKALLING

13. Hvilke 3 ord var det jeg ba deg om å huske? [Ikke gi hjelp/stikkord]
   HUS [Alternativt ord: ]
   KANIN [Alternativt ord: ]
   TOG [Alternativt ord: ]

Nevn mer enn 3 ord, må PAS velge hvilke 3 ord som skal være svaret. Rokkefølge er uten betydning.
Det gir kun poeng for eksakt gjengivelse, dva. boltghus, hytte, hare, kanindyr, togbane, lokomotiv etc. gir ikke poeng.

BENEVNING


Bruk kun blyant og armbåndsur, gjelder også retesting. Alternative poenggivende svar: Penn, gråblyant, kløkke, ur etc.

REPETISJON


   ALDRI ANNEN OM OG MEN ________________________________________________

FORSTÅELSE

Legg et blant A4-ark på bordet midt foran PAS, kortsidan mot PAS. TL legger egen hånd på arket til all instruksen er gitt.
Gi poeng for hver utført delhandling, også dersom PAS bør ikke arket med én hånd eller legger arket foran TL.
17. Her godt etter, for jeg skal be deg gjøre 3 ting i en bestemt rekkefølge. Er du klar?
Ta arket med én hånd [pause], brett arket på midten én gang med begge hender samtidig [pause], og gi arket til meg. [pause] Vær så god! [Instruksen gir kun én gang]

   TAR ARKET MED KUN EN HÅND ___________________________________________
   BRETTER ARKET PÅ MIDTEN KUN EN GANG __________________________________
   LEGGER ARKET PÅ BORDET FORAN TL, ELLE SVAR ARKET TIL TL ____________

LESING

18. Nå vil jeg at du gjør det som står på arket [Vis PAS teksten]. PAS må lukke øynene for poeng.

   LUKK ØYNEENE DINE ____________________________________________________

SKRIVING/SETNINGSGENERERING

Legg MMSNR skjema side 4 med kortsidan foran PAS og gi vedkommende en blyant.


   Skrives kun imperativsetning med ett ord, f.eks. “Spis”, si: Skriv en lengre setning. Skrives tidligere gitt
   setningstrasse, f.eks. ”Lukk øynene dine”, ”En meningsfull setning”, si: Skriv en setning du lager selv.

Setningen må være forståelig, men trenger ikke innnehold objekt; se eksempler i manual. Det gir poeng ved riktig
utførelse selv etter sponserende instruksen. Ignorerer slave- og grammatikalske feil.

TEGNING/FIGURKOPIERING

Figurar plasseres med figurspis mot PAS over skrevet setning, viskerer ved siden av.

20. Kopler figuren så nøyaktig du kan her [Pek på nedre del av side 4].
Du kan bruke viskere. Ta deg god tid. Si fra når du er ferdig.

Det gir poeng når tegningen består av to 5-kantede figurer som formør en 4-sidet figur der
5-kantene overlapper. Tegnet figur trenger ikke være identisk med modellen, se skikkerseksempler i manual.

TOTAL POENGSUM = ____/30. Presiser hva PAS hadde utført (feil) på:
10.4. Clock drawing test - Norwegian version

Klokketest

Praktisk gjennomsøring:
Metoden med en ferdiglaget sirkel på om lag 10 cm diameter der pasienten setter inn tall er enkel å bruke. Pasienten instrueres om å sette inn tall i sirkelen slik at resultatet blir seende ut som en vanlig klokke.

Man kan utdype og si "alle tall skal være med, skriv tydelig, det skal se ut som en vanlig veggklokke", og så videre. Selvfølgelig skal man ikke vise hvor tallene skal stå. Når pasienten er ferdig med å skrive inn tallene, ber man pasienten om å sette visere på klokken slik at den viser "ti over elleve" (klokkeslettet er viktig!). Dersom klokken er svært mangelfull utelates momentet med visere.

For å få et tall til scoring kan man for eksempel bruke Manos & Wu’s metode som er meget enkel: Man deler inn klokken i 8 like store kakestykker, og gir ett poeng for hvert av tallene 1, 2, 4, 5, 7, 8, 10 og 11 som er plassert i riktig kakestykke og gir til slutt ett poeng for hver korrekt plassert viser, til en maksimal poengsum på 10. Seks poeng eller mindre er klart avvikende, selv om man sjelden ser at friske har under 10 poeng. Spesielt klarer friske alltid å plassere viserne rett!

Som regel har den som tegner en svært dårlig klokke også problem med å lese klokken.
Klokkeslettene "ti over halv" og "ti på halv" er særlig vanskelige.
At man møysommelig må regne og telle seg frem til hvor mye klokken er, er ikke normalt.
# Klokketest

<table>
<thead>
<tr>
<th>Paterens navn</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fodselsdato</td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

Totalprøve
10.5. Trail Making Test A - Norwegian version

**Trial Making Test A**

Dette er en test som opprinnelig kommer fra "Army Individual Test Battery" som ble publisert i 1944.\(^1\) Ettersom den ble utformet av psykologer i US Army er den i offentlig øie og kan reproduceres fritt.\(^2\)

Trial making test tester evnen til kompleks visuell scanning med en samtidig motorisk komponent. Motorisk hastighet og bevegelighet bidrar også sterkt til gode resultater. Som de fleste andre tester som inneholder psykomotorisk hastighet og oppmerksomhet, er den meget følsom for ulike typer av hjerneskade. Alder påvirker også i høy grad resultatet\(^3\).


I følge Lezak er det "unnecessary and unkind" å la personen forsøke i mer enn fire-fem minutter med noen del av testen\(^4\).

For praktisk bruk kan man si at man uansett alder bør klare testen på under 1 minutt.

*Aldersrelaterte normer hentet fra Ivnik et al\(^5\).* SD = standardavvik:

<table>
<thead>
<tr>
<th>Aldersgruppe (år)</th>
<th>Gjennomsnittstid (sek)</th>
<th>minus 1 SD</th>
<th>minus 2 SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>56-62</td>
<td>(30-33)</td>
<td>&gt;40</td>
<td>&gt;58</td>
</tr>
<tr>
<td>63-65</td>
<td>(31-35)</td>
<td>&gt;44</td>
<td>&gt;60</td>
</tr>
<tr>
<td>66-68</td>
<td>(32-36)</td>
<td>&gt;45</td>
<td>&gt;63</td>
</tr>
<tr>
<td>69-71</td>
<td>(34-37)</td>
<td>&gt;46</td>
<td>&gt;75</td>
</tr>
<tr>
<td>72-74</td>
<td>(36-40)</td>
<td>&gt;54</td>
<td>&gt;89</td>
</tr>
<tr>
<td>75-77</td>
<td>(36-41)</td>
<td>&gt;56</td>
<td>&gt;93</td>
</tr>
<tr>
<td>78-80</td>
<td>(40-42)</td>
<td>&gt;58</td>
<td>&gt;93</td>
</tr>
<tr>
<td>81-83</td>
<td>(43-52)</td>
<td>&gt;63</td>
<td>&gt;93</td>
</tr>
<tr>
<td>84-86</td>
<td>(43-52)</td>
<td>&gt;63</td>
<td>&gt;93</td>
</tr>
<tr>
<td>87-89</td>
<td>(43-52)</td>
<td>&gt;63</td>
<td>&gt;93</td>
</tr>
<tr>
<td>90-97</td>
<td>(43-52)</td>
<td>&gt;63</td>
<td>&gt;93</td>
</tr>
</tbody>
</table>

*(Minus 1 SD innebærer at man har et resultat som er dårligere enn det 68% av populasjonen har. Minus 2 SD er et resultat dårligere enn det 95% av populasjonen har.)*

Referanser:
10.6. Trail Making Test B - Norwegian version

**Trail Making Test B**

Dette er en test som opprinnelig kommer fra "Army Individual Test Battery" som ble publisert i 1944. Ettersom den ble utformet av psykologer i US Army er den i offentlig eie og kan reproduceres fritt.

Trail making test tester evnen til kompleks visuell scanning med en samtidig motorisk komponent. Motorisk hastighet og bevegelighet bidrar også sterkt til gode resultater. Som de fleste andre tester som inneholder psykomotorisk hastighet og oppmerksomhet, er den meget følsom for ulike typer av hjerneskade.

Alder påvirker også i høy grad resultatet.

Testen utføres slik: Testpersonen skal her dra streken slik at man alternerer mellom tall og bokstaver (1-A-2-B-3-C etc.). Også her skal personen oppfordres til å jobbe så raskt som mulig og ikke løfte blyanten fra papiret. Dersom personen gjer en feil skal den påpekes slik at han kan korrigerere seg. Eksempler er til for å demonstrere prinsippet og for at man skal kunne forstå seg om at pasienten har forstått. Score = tid i sekunder fra start til slutt.

**Eksempel på pasientinstruksjon:** “I denne del av testen skal annenhver sirkel inneholde et tall og annenhver sirkel en bokstav. Tallene skal være i nummerrekkfølge og bokstavene i alfabetisk rekkefølge. Duh skal aldus gå fra 1 til A til 2 til B. Kan du vise meg her på eksemplene at du har forstått prinsippet?”

I følge Lezak er det "unnecessary and unkind" å la personen forsøke i mer enn fire-fem minutter med noen del av testen2.

For praktisk bruk kan man si at man uansett alder bør klare testen på under 2 minutter dersom man er under 70 år, og ellers under 3 minutter.

### Aldersrelaterte normer hentet fra Ivnik et al. SD = standardavvik:

<table>
<thead>
<tr>
<th>Aldersgruppe (år)</th>
<th>Gjennomsnittstid (sek)</th>
<th>minus 1 SD</th>
<th>minus 2 SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>56-62</td>
<td>(64-77)</td>
<td>&gt;96</td>
<td>&gt;155</td>
</tr>
<tr>
<td>63-65</td>
<td>(73-82)</td>
<td>&gt;103</td>
<td>&gt;188</td>
</tr>
<tr>
<td>66-68</td>
<td>(75-84)</td>
<td>&gt;106</td>
<td>&gt;189</td>
</tr>
<tr>
<td>69-71</td>
<td>(80-90)</td>
<td>&gt;136</td>
<td>&gt;219</td>
</tr>
<tr>
<td>72-74</td>
<td>(84-104)</td>
<td>&gt;156</td>
<td>&gt;234</td>
</tr>
<tr>
<td>75-77</td>
<td>(92-123)</td>
<td>&gt;167</td>
<td>&gt;239</td>
</tr>
<tr>
<td>78-80</td>
<td>(101-134)</td>
<td>&gt;179</td>
<td>&gt;239</td>
</tr>
<tr>
<td>81-83</td>
<td>(115-141)</td>
<td>&gt;182</td>
<td>&gt;239</td>
</tr>
<tr>
<td>84-86</td>
<td>(115-141)</td>
<td>&gt;182</td>
<td>&gt;239</td>
</tr>
<tr>
<td>87-89</td>
<td>(115-141)</td>
<td>&gt;182</td>
<td>&gt;239</td>
</tr>
<tr>
<td>90-97</td>
<td>(115-141)</td>
<td>&gt;182</td>
<td>&gt;239</td>
</tr>
</tbody>
</table>

(Minus 1 SD innebærer at man har et resultat som er dårligere enn det 68% av populasjonen har. Minus 2 SD er et resultat dårligere enn det 95% av populasjonen har.)

**Referanser:**
10.7. Barthel Activities of Daily Living Index - Norwegian version

BARTHEL ADL-INDEKSIDX


Navn: ___________________________ J.nr.: ___________________________
Fødselsår/dato: ___________________________ Dato utfølt: ___________________________
Utftylt av: ___________________________

**GENERELT**
Barthel ADL-indeks er forst og fremst beregnet på å bli brukt av sykepleiere, ergoterapeuter og fysioterapeuter i deres daglige kontakt med pasientene. Det skal registreres hva pasienten faktisk gjør, ikke hva han/ hun vedkommende kan mestre. Skal representere grad av uavhengighet av hjelp fra annen person. Hvis det er nødvendig med tilsyn, er personen ikke uavhengig, men hvis en aktivitet mestres med hjelpemiddel er personen uavhengig i denne aktiviteten. For personer uten vesentlig mental svikt (MMSE > 20) og i et stabilt klinisk situasjon, er egenrapportert Barthel vanligvis pålitelig. For uvis eller man som regel regne med at en skår basert på familie og andre med nøy kjennerfisk til personen også er pålitelig.

1. **Spising**
- 2 Helt sjelfhjulpen. Kan brukke nødvendige hjelpemiddl og spiser innen rimelig tid
- 1 Behov for noe hjelp, f.eks. til å skjære opp maten
- 0 Helt avhengig av hjelp

2. **Bading/dusj**
- 1 Helt sjelfhjulpen
- 0 Trenger hjelp

3. **Personlig hygiene**
- 1 Selvhjulpen. Klarer å vaske ansiktet, kjenner høret, pusse tenner og badere seg
- 0 Trenger hjelp til en eller flere oppgaver

4. **Påkleddning**
- 2 Selvhjulpen i sv- og påkleddning. Klarer selv glideless, knapper og skolets
- 1 Trenger hjelp, men klarer halvparten innen rimelig tid
- 0 Trenger hjelp til mer enn halvparten

5. **Tarmkontroll**
- 2 Kontinent. Klarer selv evtl. å sette stikkpåle/klyx
- 1 Nedsatt kontroll og enkelte "uhell" eller trenger hjelp til evtl. å sette stikkpåler/klyx
- 0 Helt inkontinent eller hyppige "uhell"

6. **Blærekontroll**
- 2 Kontinent. Holder seg evtl. tett ved bruk av urinod eller mester bruk av kateter på egen hånd
- 1 Nedsatt kontroll og enkelte "uhell" eller holder seg tett med urinod eller kateter, men trenger hjelp for å bruke dette
- 0 Helt inkontinent eller trenger permanent kateter

7. **Toalettbesøk**
- 2 Selvhjulpen ved toalettbesøk eller bruk av toalettstol. Ordner klaer, tørker seg, spiller toalettet eller tommes toppen
- 1 Trenger hjelp til forflytning, klær, tørker seg
- 0 Kan ikke bruke toalett

8. **Forflytning mellom seng og stol**
- 3 Selvhjulpen. Klarer også å låse rullestol og bevege fotstøtte
- 2 Klarer forflytningen med litt hjelp eller tilsyn
- 1 Kan sitte, men må ha nytt hjelp ved forflytning
- 0 Kan ikke sitte. Sengeliggende

9. **Mobilitet**
- 3 Klarer å gå 50 meter, kan bruke stokk eller krykker, men ikke anner ganghjelpsemiddl
- 2 Kan gå 50 meter med stolliner og/eller støtte/tilsyn av en person
- 1 Kan ikke gå, men kan kjøre rullestol uten hjelp 50 meter
- 0 Kan ikke kjøre rullestol uten hjelp

10. **Trappegang**
- 2 Selvhjulpen. Kan evtl. ikke brukke ganghjelpsemiddl
- 1 Trenger hjelp/tilsyn av en person
- 0 Kan ikke gå i trappe

Sumskår (maksimal skår 20 poeng)