Lacunar infarcts

Clinical syndromes, risk factors and diagnostic aspects

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Marianne Altmann

ABBREVIATIONS

ADL	Activities of Daily Living
BP	Blood pressure
CBF	Cerebral blood flow
CI	Confidence interval
CT	Computed tomography
DWI	Diffusion weighted imaging
ECG	Electrocardiogram
LACI	Lacunar circulation infarction
LI	Lacunar infarct
MCA	Middle cerebral artery
MRI	Magnetic resonance imaging
mRS	Modified Rankin Scale
NIHSS	National Institutes of Health Stroke Scale
NPV	Negative predictive value
OCSP	Oxfordshire Community Stroke Project
OR	Odds Ratio
PACI	Partial anterior circulation infarction
PI	Pulsatility index
POCI	Posterior circulation infarction

PPV	Positive predictive value
SD	Standard deviation
SVD	Small vessel disease
TACI	Total anterior circulation infarction
TCD	Transcranial Doppler ultrasonography
TIA	Transient ischaemic attack
TMT	Trail Making Test
TOAST	Trial of Org 10172 in Acute Stroke Treatment
WHO	World Health Organisation

LIST OF PAPERS

I. Altmann M, Thommessen B, Rønning OM, Reichenbach AS, Fure B. Diagnostic accuracy and risk factors of the different lacunar syndromes. J Stroke Cerebrovasc Dis 2014; 23:2085-2090.

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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).

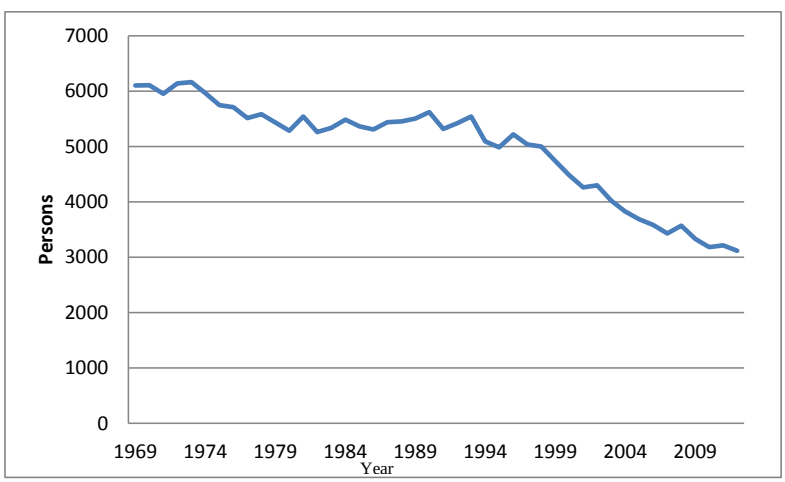

Figure 1. Deaths by stroke in Norway (1969-2012)
Adapted from Statistics Norway (14)

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).

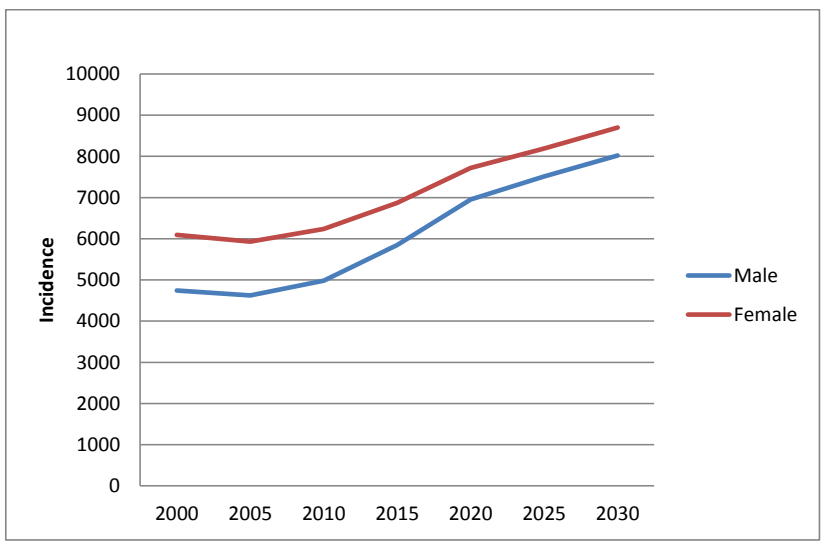

Figure 2. Stroke incidence in Norway (patients 65 years of age or older)
Adapted from Scenario 2030, Norwegian Board of Health Supervision (June 1999) (16)

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 PI = (peak velocity - end diastolic velocity)/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 endartherectomy 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 19^{th} 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 $15mm^3$ 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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Inclusion criteria	Acute clinical lacunar syndrome
Exclusion criteria	Intracerebral Haemorrhage, TIA
Standard examination	Blood tests
	ECG
	Pre-/intracerebral colour duplex
Classifications	NIHSS, OCSP, TOAST, mRS, Barthel ADL index
Radiology	CT at admission
	MRI after the acute phase
Risk factors registration	Hypertension
	Diabetes
	Hypercholesterolemia
	Coronary heart disease
	Atrial fibrillation
	Previous stroke or TIA
	Large vessel disease
	Current smokers

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 $\geq$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.

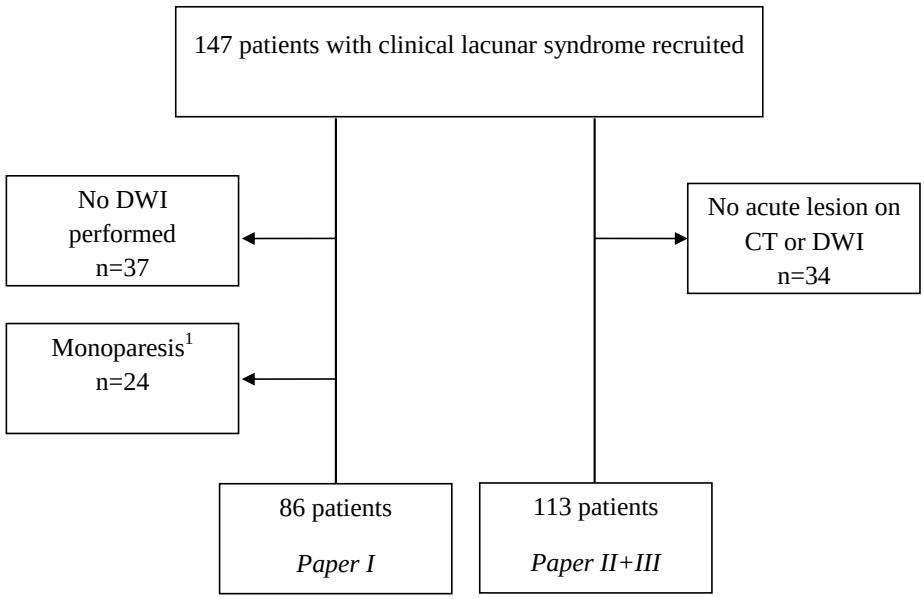


Figure 3. Patient subgroups in Paper I-III

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 χ^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 triparesis, 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.

Clinical presentation	Sensitivity	Specificity	PPV	NPV
Motor syndrome	0.68	0.57	0.75	0.49
Sensorimotor syndrome	0.23	0.53	0.48	0.27
Motor syndrome with triparesis	0.67	0.60	0.77	0.47

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

Characteristics and vascular risk factors	All patients n=147	Paper I n=86	Paper I+II n=113
Age, mean (SD)	70.3 (11.9)	69.3 (12.1)	70.1 (11.5)
Males	87 (59)	56 (65)	78 (69)
Performed only CT	37 (25)	0	18
Verified infarct	113 (77)	69 (80)	113 (100)
Verified lacunar infarct	85 (58)	56 (65)	85 (75)
Monoparesis[1]	28 (19)	0	25 (22)
Current smokers	50 (34)	32 (37)	39 (35)
Hypertension	83 (57)	48 (56)	62 (55)
Diabetes	36 (25)	14 (16)	28 (25)
Hypercholesterolemia[2]	113 (73)	65 (76)	86 (76)
Coronary disease[3]	27 (18)	19 (22)	21(19)
Large vessel disease[4]	19 (13)	15 (17)	17(15)
Atrial fibrillation	19 (13)	12 (14)	16 (14)
Previous stroke or TIA	30 (20)	17 (20)	20 (18)
Blood pressure >140 day 3	92 (63)	50 (58)	85 (75)
NIHSS at admission, median, (IQR)	3 (2-4)	3 (2-4)	3 (2-4)
NIHSS at discharge, median, (IQR)	1 (0-3)	1,5 (0-3)	1 (0,5-3)
Barthel ADL index , median, (IQR)	20 (17-20)	20 (16-20)	20 (16-20)
mRS at discharge, median, (IQR)	2 (1-3)	2 (1-3)	2 (1-3)
Treated with iv thrombolysis	15 (10)	9 (11)	10 (9)

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

		Diffusion weighted imaging			
		LI	No LI	Total	
Motor syndrome	Yes	38	13	51	PPV=38/51=75%
	No	18	17	35	NPV=17/35=49%
	Total	56	30	86	
		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.

- Pulsatility 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

1. Aho K, Harmsen P, Hatano S, Marquardsen J, Smirnov VE, Strasser T. Cerebrovascular disease in the community: results of a WHO collaborative study. Bulletin of the World Health Organization. 1980;58(1):113-30.

2. A classification and outline of cerebrovascular diseases. II. Stroke 1975;6(5):564-616.

3. Kidwell CS, Alger JR, Di Salle F, Starkman S, Villablanca P, Bentson J, et al. Diffusion MRI in patients with transient ischemic attacks. Stroke 1999;30(6):1174-80.

4. Easton JD, Saver JL, Albers GW, Alberts MJ, Chaturvedi S, Feldmann E, et al. Definition and evaluation of transient ischemic attack: a scientific statement for healthcare professionals from the American Heart Association/American Stroke Association Stroke Council; Council on Cardiovascular Surgery and Anesthesia; Council on Cardiovascular Radiology and Intervention; Council on Cardiovascular Nursing; and the Interdisciplinary Council on Peripheral Vascular Disease. The American Academy of Neurology affirms the value of this statement as an educational tool for neurologists. Stroke 2009;40(6):2276-93.

5. Warlow C, Sudlow C, Dennis M, Wardlaw J, Sandercock P. Stroke. Lancet 2003;362(9391):1211-24.

6. Fisher M, Bastan B. Identifying and utilizing the ischemic penumbra. Neurology 2012;79(13 Suppl 1):S79-85.

7. Ginsberg MD, Pulsinelli WA. The ischemic penumbra, injury thresholds, and the therapeutic window for acute stroke. Ann Neurol 1994;36(4):553-4.

8. Hossmann KA. Viability thresholds and the penumbra of focal ischemia. Ann Neurol 1994;36(4):557-65.

9. Lozano R, Naghavi M, Foreman K, Lim S, Shibuya K, Aboyans V, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet 2012;380(9859):2095-128.

10. Truelsen T, Begg, S., Colin, M. The global burden of cerebrovascular disease. World Health Organization web side. http://www.who.int/healthinfo/statistics/bod_cerebrovasculardiseasestroke.pdf?ua=1. Accessed June 2, 2015

11. Feigin VL, Forouzanfar MH, Krishnamurthi R, Mensah GA, Connor M, Bennett DA, et al. Global and regional burden of stroke during 1990-2010: findings from the Global Burden of Disease Study 2010. Lancet 2014;383(9913):245-54.

12. European Registers of Stroke I, Heuschmann PU, Di Carlo A, Bejot Y, Rastenyte D, Ryglewicz D, et al. Incidence of stroke in Europe at the beginning of the 21st century. Stroke 2009;40(5):1557-63.

13. Ellekjaer H, Selmer R. Stroke -similar incidence, better prognosis. Tidsskr Nor Laegeforen 2007;127(6):740-3.

14. Statistics Norway. 2015.Web side. https://www.ssb.no/statistikkbanken. Accessed June 2, 2015

15. Donnan GA, Fisher M, Macleod M, Davis SM. Stroke. Lancet 2008;371(9624):1612-23.

16. Norwegian Board of Health Supervision. Scenario 2030. Sykdomsutviklingen for eldre fram til 2030. Oslo, 1999. Available from: https://www.helsetilsynet.no/upload/Publikasjoner/utredningsserien/2030_sykdomsutvikling_eldre_ik-2696.pdf. Accessed June 2, 2015.

17. Guidelines for management of ischaemic stroke and transient ischaemic attack 2008. Cerebrovasc Dis 2008;25(5):457-507.

18. Jauch EC, Saver JL, Adams HP, Jr., Bruno A, Connors JJ, Demaerschalk BM, et al. Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2013;44(3):870-947.

19. The Norwegian Directorate of Health. Nasjonal retningslinje for behandling og rehabilitering av hjerneslag 2010. Available from: http://www.helsedirektoratet.no/publikasjoner/nasjonal-retningslinje-for-behandling-og-rehabilitering-ved-hjerneslag-fullversjon/Sider/default.aspx. Accessed June 2, 2015.

20. D'Olhaberriague L, Litvan I, Mitsias P, Mansbach HH. A reappraisal of reliability and validity studies in stroke. Stroke 1996;27(12):2331-6.

21. Goldstein LB, Samsa GP. Reliability of the National Institutes of Health Stroke Scale. Extension to non-neurologists in the context of a clinical trial. Stroke 1997;28(2):307-10.

22. Brott T, Adams HP, Jr., Olinger CP, Marler JR, Barsan WG, Biller J, et al. Measurements of acute cerebral infarction: a clinical examination scale. Stroke 1989;20(7):864-70.

23. Multicenter trial of hemodilution in ischemic stroke--background and study protocol. Scandinavian Stroke Study Group. Stroke 1985;16(5):885-90.

24. Muir KW, Weir CJ, Murray GD, Povey C, Lees KR. Comparison of neurological scales and scoring systems for acute stroke prognosis. Stroke 1996;27(10):1817-20.

25. Mahoney FI, Barthel DW. Functional Evaluation: The Barthel Index. Md State Med J 1965;14:61-5.

26. Rankin J. Cerebral vascular accidents in patients over the age of 60. III. Diagnosis and treatment. Scott Med J 1957;2(6):254-68.

27. van Swieten JC, Koudstaal PJ, Visser MC, Schouten HJ, van Gijn J. Interobserver agreement for the assessment of handicap in stroke patients. Stroke 1988;19(5):604-7.

28. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12(3):189-98.

29. Molloy DW, Standish TI. A guide to the standardized Mini-Mental State Examination. Int Psychogeriatr 1997;9 Suppl 1:87-94; discussion 143-50.

30. Reitan RM. The relation of the trail making test to organic brain damage. J Consult Psychol 1955;19(5):393-4.

31. Shulman KI. Clock-drawing: is it the ideal cognitive screening test? Int J Geriatr Psychiatry 2000;15(6):548-61.

32. Adams HP, Jr., Bendixen BH, Kappelle LJ, Biller J, Love BB, Gordon DL, et al. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. Stroke 1993;24(1):35-41.

33. Fure B, Wyller TB, Thommessen B. TOAST criteria applied in acute ischemic stroke. Acta Neurol Scand 2005;112(4):254-8.

34. Landau WM, Nassief A. Editorial comment -time to burn the TOAST. Stroke 2005;36(4):902-4.

35. Jackson C, Sudlow C. Are lacunar strokes really different? A systematic review of differences in risk factor profiles between lacunar and nonlacunar infarcts. Stroke 2005;36(4):891-901.

36. Amarenco P, Bogousslavsky J, Caplan LR, Donnan GA, Hennerici MG. New approach to stroke subtyping: the A-S-C-O (phenotypic) classification of stroke. Cerebrovasc Dis 2009;27(5):502-8.

37. Ay H, Benner T, Arsava EM, Furie KL, Singhal AB, Jensen MB, et al. A computerized algorithm for etiologic classification of ischemic stroke: the Causative Classification of Stroke System. Stroke 2007;38(11):2979-84.

38. Marnane M, Duggan CA, Sheehan OC, Merwick A, Hannon N, Curtin D, et al. Stroke subtype classification to mechanism-specific and undetermined categories by TOAST, A-S-C-O, and causative classification system: direct comparison in the North Dublin population stroke study. Stroke 2010;41(8):1579-86.

39. Bamford J, Sandercock P, Dennis M, Burn J, Warlow C. Classification and natural history of clinically identifiable subtypes of cerebral infarction. Lancet 1991;337(8756):1521-6.

40. Lindley RI, Warlow CP, Wardlaw JM, Dennis MS, Slattery J, Sandercock PA. Interobserver reliability of a clinical classification of acute cerebral infarction. Stroke 1993;24(12):1801-4.

41. Asdaghi N, Jeerakathil T, Hameed B, Saini M, McCombe JA, Shuaib A, et al. Oxfordshire community stroke project classification poorly differentiates small cortical and subcortical infarcts. Stroke 2011;42(8):2143-8.

42. Wardlaw JM, Lewis SC, Dennis MS, Counsell C, McDowall M. Is visible infarction on computed tomography associated with an adverse prognosis in acute ischemic stroke? Stroke 1998;29(7):1315-9.

43. Allmendinger AM, Tang ER, Lui YW, Spektor V. Imaging of stroke: Part 1, Perfusion CT -overview of imaging technique, interpretation pearls, and common pitfalls. AJR Am J Roentgenol 2012;198(1):52-62.

44. Kidwell CS, Chalela JA, Saver JL, Starkman S, Hill MD, Demchuk AM, et al. Comparison of MRI and CT for detection of acute intracerebral hemorrhage. JAMA 2004;292(15):1823-30.

45. Brazzelli M, Sandercock PA, Chappell FM, Celani MG, Righetti E, Arestis N, et al. Magnetic resonance imaging versus computed tomography for detection of acute vascular lesions in patients presenting with stroke symptoms. Cochrane Database Syst Rev 2009(4):Cd007424.

46. Lee LJ, Kidwell CS, Alger J, Starkman S, Saver JL. Impact on stroke subtype diagnosis of early diffusion-weighted magnetic resonance imaging and magnetic resonance angiography. Stroke 2000;31(5):1081-9.

47. Schellinger PD, Bryan RN, Caplan LR, Detre JA, Edelman RR, Jaigobin C, et al. Evidence-based guideline: The role of diffusion and perfusion MRI for the diagnosis of acute ischemic stroke: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology 2010;75(2):177-85.

48. Wardlaw JM, Chappell FM, Best JJ, Wartolowska K, Berry E, Research NHS, et al. Non-invasive imaging compared with intra-arterial angiography in the diagnosis of symptomatic carotid stenosis: a meta-analysis. Lancet 2006;367(9521):1503-12.

49. Saqqur M, Tsivgoulis G, Nicoli F, Skoloudik D, Sharma VK, Larrue V, et al. The role of sonolysis and sonothrombolysis in acute ischemic stroke: a systematic review and meta-analysis of randomized controlled trials and case-control studies. J Neuroimaging 2014;24(3):209-20.

50. Gosling RG, King DH. Arterial assessment by Doppler-shift ultrasound. Proc R Soc Med 1974;67(6 Pt 1):447-9.

51. Foerstl H, Biedert S, Hewer W. Multiinfarct and Alzheimer-type dementia investigated by transcranial Doppler sonography. Biol Psychiatry 1989;26(6):590-4.

52. Kidwell CS, el-Saden S, Livshits Z, Martin NA, Glenn TC, Saver JL. Transcranial Doppler pulsatility indices as a measure of diffuse small-vessel disease. J Neuroimaging 2001;11(3):229-35.

53. Lee KY, Sohn YH, Baik JS, Kim GW, Kim JS. Arterial pulsatility as an index of cerebral microangiopathy in diabetes. Stroke 2000;31(5):1111-5.

54. Mok V, Ding D, Fu J, Xiong Y, Chu WW, Wang D, et al. Transcranial Doppler ultrasound for screening cerebral small vessel disease: a community study. Stroke 2012;43(10):2791-3.

55. Tegeler CH, Crutchfield K, Katsnelson M, Kim J, Tang R, Passmore Griffin L, et al. Transcranial Doppler velocities in a large, healthy population. J Neuroimaging 2013;23(3):466-72.

56. de Bruijn SF, Agema WR, Lammers GJ, van der Wall EE, Wolterbeek R, Holman ER, et al. Transesophageal echocardiography is superior to transthoracic echocardiography in management of patients of any age with transient ischemic attack or stroke. Stroke 2006;37(10):2531-4.

57. Goldstein LB, Adams R, Alberts MJ, Appel LJ, Brass LM, Bushnell CD, et al. Primary prevention of ischemic stroke: a guideline from the American Heart Association/American Stroke Association Stroke Council: cosponsored by the Atherosclerotic Peripheral Vascular Disease Interdisciplinary Working Group; Cardiovascular Nursing Council; Clinical Cardiology Council; Nutrition, Physical Activity, and Metabolism Council; and the Quality of Care and Outcomes Research Interdisciplinary Working Group. Circulation 2006;113(24):e873-923.

58. Sacco RL. Risk factors, outcomes, and stroke subtypes for ischemic stroke. Neurology 1997;49(5 Suppl 4):S39-44.

59. Organised inpatient (stroke unit) care for stroke. Cochrane Database Syst 2013;9:Cd000197.

60. Indredavik B, Bakke F, Slordahl SA, Rokseth R, Haheim LL. Stroke unit treatment. 10-year follow-up. Stroke 1999;30(8):1524-7.

61. Wardlaw JM, Murray V, Berge E, del Zoppo G, Sandercock P, Lindley RL, et al. Recombinant tissue plasminogen activator for acute ischaemic stroke: an updated systematic review and meta-analysis. Lancet 2012;379(9834):2364-72.

62. Berkhemer OA, Fransen PS, Beumer D, van den Berg LA, Lingsma HF, Yoo AJ, et al. A randomized trial of intraarterial treatment for acute ischemic stroke. N Engl J Med 2015;372(1):11-20.

63. Antithrombotic Trialists C. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. BMJ 2002;324(7329):71-86.

64. Saxena R, Koudstaal P. Anticoagulants versus antiplatelet therapy for preventing stroke in patients with nonrheumatic atrial fibrillation and a history of stroke or transient ischemic attack. Cochrane Database Syst Rev 2004(4):Cd000187.

65. Gomez-Outes A, Terleira-Fernandez AI, Calvo-Rojas G, Suarez-Gea ML, Vargas-Castrillon E. Dabigatran, Rivaroxaban, or Apixaban versus Warfarin in Patients with Nonvalvular Atrial Fibrillation: A Systematic Review and Meta-Analysis of Subgroups. Thrombosis 2013;2013:640723.

66. Norrving B. Long-term prognosis after lacunar infarction. Lancet neurology 2003;2(4):238-45.

67. Mohr JP. Lacunes. Stroke 1982;13(1):3-11.

68. Wardlaw JM, Smith EE, Biessels GJ, Cordonnier C, Fazekas F, Frayne R, et al. Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration. Lancet Neurol 2013;12(8):822-38.

69. Pantoni L, Garcia JH. Pathogenesis of leukoaraiosis: a review. Stroke 1997;28(3):652-9.

70. Das RR, Seshadri S, Beiser AS, Kelly-Hayes M, Au R, Himali JJ, et al. Prevalence and correlates of silent cerebral infarcts in the Framingham offspring study. Stroke 2008;39(11):2929-35.

71. Vermeer SE, Longstreth WT, Jr., Koudstaal PJ. Silent brain infarcts: a systematic review. Lancet Neurol 2007;6(7):611-9.

72. Wong TY, Klein R, Sharrett AR, Nieto FJ, Boland LL, Couper DJ, et al. Retinal microvascular abnormalities and cognitive impairment in middle-aged persons: the Atherosclerosis Risk in Communities Study. Stroke 2002;33(6):1487-92.

73. Patton N, Pattie A, MacGillivray T, Aslam T, Dhillon B, Gow A, et al. The association between retinal vascular network geometry and cognitive ability in an elderly population. Invest Ophthalmol Vis Sci 2007;48(5):1995-2000.

74. Cooper LS, Wong TY, Klein R, Sharrett AR, Bryan RN, Hubbard LD, et al. Retinal microvascular abnormalities and MRI-defined subclinical cerebral infarction: the Atherosclerosis Risk in Communities Study. Stroke 2006;37(1):82-6.

75. Martinez-Vea A, Salvado E, Bardaji A, Gutierrez C, Ramos A, Garcia C, et al. Silent cerebral white matter lesions and their relationship with vascular risk factors in middle-aged predialysis patients with CKD. Am J Kidney Dis 2006;47(2):241-50.

76. Liew G, Mitchell P, Wong TY, Iyengar SK, Wang JJ. CKD increases the risk of age-related macular degeneration. J Am Soc Nephrol 2008;19(4):806-11.

77. Khatri M, Wright CB, Nickolas TL, Yoshita M, Paik MC, Kranwinkel G, et al. Chronic kidney disease is associated with white matter hyperintensity volume: the Northern Manhattan Study (NOMAS). Stroke 2007;38(12):3121-6.

78. Thompson CS, Hakim AM. Living beyond our physiological means: small vessel disease of the brain is an expression of a systemic failure in arteriolar function: a unifying hypothesis. Stroke 2009;40(5):e322-30.

79. Norrving B. Lacunar infarcts: no black holes in the brain are benign. Pract Neurol 2008;8(4):222-8.

80. Fisher CM. Lacunar strokes and infarcts: a review. Neurology 1982;32(8):871-6.

81. Arboix A, Marti-Vilalta JL. Lacunar stroke. Expert Rev Neurother 2009;9(2):179-96.

82. Staaf G, Lindgren A, Norrving B. Pure motor stroke from presumed lacunar infarct: long-term prognosis for survival and risk of recurrent stroke. Stroke 2001;32(11):2592-6.

83. Fisher CM. Lacunes: Small, Deep Cerebral Infarcts. Neurology 1965;15:774-84.

84. Fisher CM. A lacunar stroke. The dysarthria-clumsy hand syndrome. Neurology 1967;17(6):614-7.

85. Fisher CM. Thalamic pure sensory stroke: a pathologic study. Neurology 1978;28(11):1141-4.

86. Aharon-Peretz J, Daskovski E, Mashiach T, Tomer R. Natural history of dementia associated with lacunar infarctions. J Neurol Sci 2002;203-204:53-5.

87. Fure B, Bruun Wyller T, Engedal K, Thommessen B. Cognitive impairments in acute lacunar stroke. Acta Neurol Scand 2006;114(1):17-22.

88. Vermeer SE, Prins ND, den Heijer T, Hofman A, Koudstaal PJ, Breteler MM. Silent brain infarcts and the risk of dementia and cognitive decline. N Engl J Med 2003;348(13):1215-22.

89. Grau-Olivares M, Arboix A, Bartres-Faz D, Junque C. Neuropsychological abnormalities associated with lacunar infarction. J Neurol Sci 2007;257(1-2):160-5.

90. Blanco-Rojas L, Arboix A, Canovas D, Grau-Olivares M, Oliva Morera JC, Parra O. Cognitive profile in patients with a first-ever lacunar infarct with and without silent lacunes: a comparative study. BMC neurol 2013;13:203.

91. Yamamoto Y, Akiguchi I, Oiwa K, Hayashi M, Kasai T, Ozasa K. Twenty-four-hour blood pressure and MRI as predictive factors for different outcomes in patients with lacunar infarct. Stroke 2002;33(1):297-305.

92. Edwards JD, Jacova C, Sepehry AA, Pratt B, Benavente OR. A quantitative systematic review of domain-specific cognitive impairment in lacunar stroke. Neurology 2013;80(3):315-22.

93. Jacova C, Pearce LA, Costello R, McClure LA, Holliday SL, Hart RG, et al. Cognitive impairment in lacunar strokes: the SPS3 trial. Ann Neurol 2012;72(3):351-62.

94. Wessels T, Wessels C, Ellsiepen A, Reuter I, Trittmacher S, Stolz E, et al. Contribution of diffusion-weighted imaging in determination of stroke etiology. AJNR Am J Neuroradiol 2006;27(1):35-9.

95. Ivnik RJ. Neuropsychological tests' norms above age 55: COWAT, BNT, MAE token, WRAT-R reading, AMNART, STROOP, TMT, and JLO. Clinical Neuropsychol 1996; 10(3):262-78

96. Arboix A, Blanco-Rojas L, Marti-Vilalta JL. Advancements in understanding the mechanisms of symptomatic lacunar ischemic stroke: translation of knowledge to prevention strategies. Expert Rev Neurother 2014;14(3):261-76.

97. Boiten J, Lodder J. Lacunar infarcts. Pathogenesis and validity of the clinical syndromes. Stroke 1991;22(11):1374-8.

98. Melo TP, Bogousslavsky J, van Melle G, Regli F. Pure motor stroke: a reappraisal. Neurology 1992;42(4):789-95.

99. Gan R, Sacco RL, Kargman DE, Roberts JK, Boden-Albala B, Gu Q. Testing the validity of the lacunar hypothesis: the Northern Manhattan Stroke Study experience. Neurology 1997;48(5):1204-11.

100. Phillips SJ, Dai D, Mitnitski A, Gubitz GJ, Johnston KC, Koroshetz WJ, et al. Clinical diagnosis of lacunar stroke in the first 6 hours after symptom onset: analysis of data from the glycine antagonist in neuroprotection (GAIN) Americas trial. Stroke 2007;38(10):2706-11.

101. Naess H, Brogger JC, Jr., Idicula T, Waje-Andreassen U, Moen G, Thomassen L. Clinical presentation and diffusion weighted MRI of acute cerebral infarction. The Bergen Stroke Study. BMC Neurol 2009;9:44.

102. Sylaja PN, Coutts SB, Krol A, Hill MD, Demchuk AM. When to expect negative diffusion-weighted images in stroke and transient ischemic attack. Stroke 2008;39(6):1898-900.

103. Fernandes PM, Whiteley WN, Hart SR, Al-Shahi Salman R. Strokes: mimics and chameleons. Pract Neurol 2013;13(1):21-8.

104. Seifert T, Enzinger C, Storch MK, Pichler G, Niederkorn K, Fazekas F. Acute small subcortical infarctions on diffusion weighted MRI: clinical presentation and aetiology. J Neurol Neurosurg Psychiatry 2005;76(11):1520-4.

105. Mead GE, Lewis SC, Wardlaw JM, Dennis MS, Warlow CP. Should computed tomography appearance of lacunar stroke influence patient management? J Neurol Neurosurg Psychiatry 1999;67(5):682-4.

106. Semplicini A, Maresca A, Boscolo G, Sartori M, Rocchi R, Giantin V, et al. Hypertension in acute ischemic stroke: a compensatory mechanism or an additional damaging factor? Arch Intern Med 2003;163(2):211-6.

107. Toyoda K, Okada Y, Fujimoto S, Hagiwara N, Nakachi K, Kitazono T, et al. Blood pressure changes during the initial week after different subtypes of ischemic stroke. Stroke 2006;37(10):2637-9.

108. Meurer WJ, Sanchez BN, Smith MA, Lisabeth LD, Majersik JJ, Brown DL, et al. Predicting ischaemic stroke subtype from presenting systolic blood pressure: the BASIC Project. J Intern Med 2009;265(3):388-96.

109. Rodriguez-Garcia JL, Botia E, de La Sierra A, Villanueva MA, Gonzalez-Spinola J. Significance of elevated blood pressure and its management on the short-term outcome of patients with acute ischemic stroke. Am J Hypertens 2005;18(3):379-84.

110. Vemmos KN, Tsivgoulis G, Spengos K, Synetos A, Manios E, Vassilopoulou S, et al. Blood pressure course in acute ischaemic stroke in relation to stroke subtype. Blood Press Monit 2004;9(3):107-14.

111. Ishitsuka K, Kamouchi M, Hata J, Fukuda K, Matsuo R, Kuroda J, et al. High blood pressure after acute ischemic stroke is associated with poor clinical outcomes: Fukuoka Stroke Registry. Hypertension 2014;63(1):54-60.

112. Willmot M, Leonardi-Bee J, Bath PM. High blood pressure in acute stroke and subsequent outcome: a systematic review. Hypertension 2004;43(1):18-24.

113. Kvistad CE, Logallo N, Oygarden H, Thomassen L, Waje-Andreassen U, Naess H. Elevated Admission Blood Pressure and Stroke Severity in Acute Ischemic Stroke: The Bergen NORSTROKE Study. Cerebrovasc Dis 2013;36(5-6):351-4.

114. Pearce LA, McClure LA, Anderson DC, Jacova C, Sharma M, Hart RG, et al. Effects of long-term blood pressure lowering and dual antiplatelet treatment on cognitive function in patients with recent lacunar stroke: a secondary analysis from the SPS3 randomised trial. Lancet Neurol 2014;13(12):1177-85.

115. Soros P, Whitehead S, Spence JD, Hachinski V. Antihypertensive treatment can prevent stroke and cognitive decline. Nat Rev Neurol 2013;9(3):174-8.

116. Lopez-Oloriz J, Lopez-Cancio E, Arenillas JF, Hernandez M, Dorado L, Dacosta-Aguayo R, et al. Diffusion tensor imaging, intracranial vascular resistance and cognition in middle-aged asymptomatic subjects. Cerebrovasc Dis 2014;38(1):24-30.

117. Sabayan B, Jansen S, Oleksik AM, van Osch MJ, van Buchem MA, van Vliet P, et al. Cerebrovascular hemodynamics in Alzheimer's disease and vascular dementia: a meta-analysis of transcranial Doppler studies. Ageing Res Rev 2012;11(2):271-7.

118. Blake H, McKinney M, Treece K, Lee E, Lincoln NB. An evaluation of screening measures for cognitive impairment after stroke. Age Ageing 2002;31(6):451-6.

119. Benavente OR, White CL, Pearce L, Pergola P, Roldan A, Benavente MF, et al. The Secondary Prevention of Small Subcortical Strokes (SPS3) study. Int J Stroke 2011;6(2):164-75.

120. Park JS, Cho MH, Lee KY, Kim CS, Kim HJ, Nam JS, et al. Cerebral arterial pulsatility and insulin resistance in type 2 diabetic patients. Diabetes Res Clin Pract 2008;79(2):237-42.

121. Palacio S, McClure LA, Benavente OR, Bazan C, 3rd, Pergola P, Hart RG. Lacunar strokes in patients with diabetes mellitus: risk factors, infarct location, and prognosis: the secondary prevention of small subcortical strokes study. Stroke 2014;45(9):2689-94.

122. Brazzelli M, Chappell FM, Miranda H, Shuler K, Dennis M, Sandercock PA, et al. Diffusion-weighted imaging and diagnosis of transient ischemic attack. Ann Neurol 2014;75(1):67-76.

123. Britton M, Carlsson A, de Faire U. Blood pressure course in patients with acute stroke and matched controls. Stroke 1986;17(5):861-4.

124. Carlberg B, Asplund K, Hagg E. Factors influencing admission blood pressure levels in patients with acute stroke. Stroke 1991;22(4):527-30.

125. Harper G, Castleden CM, Potter JF. Factors affecting changes in blood pressure after acute stroke. Stroke 1994;25(9):1726-9.

126. Wallace JD, Levy LL. Blood pressure after stroke. JAMA 1981;246(19):2177-80.

127. Faiz KW, Sundseth A, Thommessen B, Ronning OM. Prehospital delay in acute stroke and TIA. Emerg Med J 2013;30(8):669-74.

128. Agyeman O, Nedeltchev K, Arnold M, Fischer U, Remonda L, Isenegger J, et al. Time to admission in acute ischemic stroke and transient ischemic attack. Stroke 2006;37(4):963-6.

9. ERRATA

10. APPENDIX

10.1. National Institutes of Health Stroke Scale - Norwegian version

NIH Stroke Scale (NIHSS)

		Mottak	Start	2 t						24 t	7 dager
	Tas ved dato										
	• *innkomst, 2 timer, neste morgen og 24 timer*										
	• *mistenkt forverrelse*										
	• *7 dager eller utreise hvis før 7d*										
	• *tilkall lege ved klinisk forverring ≥4 poeng* kl.										
1a	**Bevissthetsnivå** 0 = Våken 1 = Døsig, reagerer adekvat ved lett stimulering 2 = Døsig, reagerer først ved kraftigere/gjentatt stimulering 3 = Reagerer ikke, eller bare med ikke-målrettet bevegelse										
1b	**Orientering** (spør om måned + alder) 0 = Svarer riktig på to spørsmål 1 = Svarer riktig på ett spørsmål (eller ved alvorlig dysartri) 2 = Svarer ikke riktig på noe spørsmål										
1c	**Respons på kommando** (lukke øyne + knyte hånd) 0 = Utfører begge kommandoer korrekt 1 = Utfører en kommando korrekt 2 = Utfører ingen korrekt										
2	**Blikkbevegelse** (horisontal bevegelse til begge sider) 0 = Normal 1 = Delvis blikkparese (eller ved øyenmuskelparese) 2 = Fiksert blikkdreining til siden eller total blikkparese										
3	**Synsfelt** (bevege fingre/fingertelling i laterale synsfelt) 0 = Normalt 1 = Delvis hemianopsi 2 = Total hemianopsi 3 = Bilateral hemianopsi / blind										
4	**Ansikt** (vise tenner, knipe igjen øynene, løfte øyenbryn) 0 = Normal 1 = Utvisket nasolabialfure, asymmetri ved smil 2 = Betydelig lammelse i nedre ansiktshavdel 3 = Total lammelse i halve ansiktet (eller ved coma)										
5	**Kraft i armen** (holde armen utstrakt 45° i 10 sekunder) ve 0 = Normal (også ved "ikke testbar") 1 = Drifter til lavere posisjon 2 = Noe bevegelse mot tyngdekraften, drifter til sengen hø 3 = Kun små muskelbevegelser, faller til sengen 4 = Ingen bevegelse										
6	**Kraft i benet** (holde benet utstrakt 30° i 5 sekunder) ve 0 = Normal (også ved "ikke testbar") 1 = Drifter til lavere posisjon 2 = Noe bevegelse mot tyngdekraften, drifter til sengen hø 3 = Ingen bevegelse mot tyngdekraften, faller til sengen 4 = Ingen bevegelse										
7	**Koordinasjon / ataxi** (finger-nese-prøve / hæl-kne-prøve) 0 = Normal (også ved "ikke testbar" eller ved coma) 1 = Ataksi i arm eller ben 2 = Ataksi i arm og ben										
8	**Hudfølelse** (sensibilitet for stikk) 0 = Normal 1 = Lettere sensibilitetsnedsettelse 2 = Markert sensibilitetstap (også ved coma, tertraparese)										
9	**Språk /afasi** (spontan tale, taleforståelse) 0 = Normal 1 = Moderat afasi, samtale mulig 2 = Markert afasi, samtale svært vanskelig eller umulig 3 = Ikke språk (også ved coma)										
10	**Tale / dysartri** (spontan tale) 0 = Normal 1 = Mild - moderat dysartri 2 = Nær uforståelig tale eller anartri (også ved coma)										
11	**"Neglect"** (bilateral simultan stimulering av syn og hudsensibilitet) 0 = Normal (også ved hemianopsi med normal sensibilitet) 1 = Neglect i en sansemodalitet 2 = Neglect i begge sansemodaliteter										
	Total NIHSS-Score										
	Undersøkerens signatur										

Veiledning for NIH stroke scale

Generelt

- Det best skårbare svar/reaksjon er vanligvis det første svaret (bortsett fra ved afasi).
- Man skal ikke forklare/vise pasienten hva han skal gjøre, men mindre det er spesifisert i instruksjonene.
- Noen punkter skåret kun hvis de med sikkerhet er påvisbare (for eksempel koordinasjon/ataksi, neglect)
- 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 for hudfølelse. Scoring skal inkludere sekvele etter tidligere sykdom, bortsett fra for hudfølelse.

NIH stroke scale

1a **Bevissthetsnivå** – "Lett stimulering" betyr tilsnakk eller forsiktig berøring.
"Kraftigere/gjentatt stimulering" betyr kraftig berøring eller smertestimulering.

1b **Orientering** – Spør om måneden og alder. Bruk det første svaret. Svaret må være helt korrekt. Pasienter med alvorlig dysartri skårer 1. Afatiske/komatøse pasienter skårer 2.

1c **Respons på kommando** – Be pasienten åpne øynene og så lukke øynene; deretter knyte hånden og så åpne hånden. Første kommando brukes for å få øyne/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.

2a **Blikkbevegelse** – Test horisontale øyebevegelser, voluntært eller reflektorisk (oculocephal refleks). Unormale funn i ett (isolert øyemuskelparese) eller begge øyne skårer 1. En fiksert blikkdreining til siden (som ikke kan overvinnes ved oculocephal manøver) skårer 2. Kalorisk testing utføres ikke.

3a **Synsfelt** – Test øvre og nedre laterale synsfelt ved hjelp av fingerbevegelse, fingertelling eller plutselige (truende) bevegelser inn fra siden i synsfeltet. Hvis pasienten ser mot den siden hvor fingrene beveges, skåret dette som 0 = normal. En entydig asymmetri i funnene skårer 1. Blindhet skårer 3. Test bilateralt simultan stimulering av syn – hvis pasinten har "neglect", skåres 1 og resultatet benyttes også til å besvare punkt 11.

4a **Ansikt** Instruer eller demonstrer å vise tenner, løfte øyenbrynene og lukke øynene. Hos stuporøse pasienter eller pasienter som ikke forstår instruksjonene, benyttes reaksjon/grimasering på smertestimuli som grunnlag for scoring. Komatøse pasienter skårer 3.

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.

6a **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/amputasjon skåres 0.

7a **Koordinasjon/ataksi** – Test finger – nese prøve og hæl – kne prøve på begge sider. Ataksi skåres kun dersom den er entydig til stede og mer uttalt enn den usikkerheten som følger av pasientens pareser. Ved paralyse eller hos pasienter som ikke k larer å følge instruksjonen, skåres 0 = normal.

8a **Hudfølelse** – Test sensibilitet for stikk (tannstikker). Test overarmer, kropp, lår (men ikke hender og føtter på grunn av mulig polynevropati). Markert sensibilitetstap skåres kun når det er entydig til stede. Stuporøse og afatiske pasienter skåres vanligvis 0 eller 1. Pasienter med hjernestammeinfarkt og bilateralt sensibilitetstap, eller komatøse pasienter skåres 2.

9a **Språk/ afasi** – Pasienten skal formelt skåres etter standardiserte bilder og (engelske) setninger. I praksis testes språket ved å vurdere spontan tale og taleforståelse. Leseforståelse testes ved å skrive med store bokstaver "lukk øynene" på et papir og be pasienten gjøre hva som står på lappen. . Benevning testes ved at pasienten sier navnet på forskjellige kjente gjenstander. Samlet språkvurdering går på om samtale er "mulig" eller "svært vanskelig eller umulig". Komatøse pasienter skårer 3

5

10a **Tale/dysartri** – Pasienten skal formelt skåres etter standardiserte bilder og (engelske) setninger. I praksis testes tale gjennom samtale med pasienten. Pasienter som ikke har språk, som ikke kan forstås på en meningsfylt måte, eller er komatøs, skårer 2. Alle andre lettere grader av dysartri skårer 1.

11a **"Neglect"/Ekstinksjon** – Se punktene 3 og 8. Hvis pasienten har betydelig synstap (hemianopsi) og sensibiliteten er normal, skåres 0 = normal. Hvis pasienten er afatisk, men har oppmerksomhet mot begge sider, skåres 0 = normal. Pasienter som entydig neglisjerer halvdelen av rommet (selv om de ikke har ekstinksjon ved visuell/ sensorisk testing) skåres 1. Komatøse pasienter skåres 2.

10.2. Modified Rankin Scale - Norwegian version

RANKIN SCALE

0. Ingen symptomer i det hele tatt. *Pasienten skal ikke ha noen begrensinger eller symptomer.*				
1. Ingen betydningsfull funksjonssvikt til tross for symptomer; klarer å utføre alle oppgaver og aktiviteter som før. *Pas har noen symptomer, enten fysiske eller kognitive, f.eks affeksjon av språk/tale, evne til å lese/skrive, fysisk mobilitet, sensibilitet, syn, svelg, humør, men kan fortsatt ta del i alt tidligere arbeid, sosial eller fritidsaktiviteter. Det avgjørende spørsmål for å skille mellom 1 og 2 kan være: Klarer pasienten alle aktiveter som han før gjorde mer enn månedlig?*				
2. Lett funksjonssvikt; klarer ikke å utføre alle aktiviteter som før, men klarer sine daglige gjøremål. *Pas klarer ikke lengre 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 påkledning, forflytning, matlaging/spisesituasjonen, toalettbesøk, lage enkle måltider, handle og reise i lokalmiljøet uten å måtte motta hjelp eller tilsyn fra andre. Pas skal kunne være overlatt til seg selv alene hjemme i en uke eller mer uten noen bekymring.*				
3. Moderat funksjonssvikt: trenger noe hjelp, men går uten hjelp. *Pas trenger ikke hjelp til forflytning/gang (selvstendig i forflytning med og uten hjelpemidler som stokk, rullator). Klarer påkledning, 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. Assistansen kan være fysisk eller rådgivende, f.eks pas trenger tilsyn eller motivering for å klare finansielle gjøremål.*				
4. Alvorlig funksjonssvikt; klarer ikke å gå uten hjelp og klarer ikke å ivareta sine grunnleggelnde behov uten hjelp. *Pasienten må ha hjelp av andre til noen daglige aktiviteter, f.eks gange, påkledning, toalett, spise. Pas blir besøkt minst 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 latt alene for moderate perioder i løpet av dagen.*				
5. Svært alvorlig funksjonssvikt; sengeliggende og trenger konstant tilsyn og hjelp. *Noen andre må være tilgjengelig på dagitd og noen ganger i løpet av natten – denne trenger ikke være en sykepleier.*				
6. Død				

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 Yrke _____

Hørsel/høreapparat _____ Syn/briller _____ Geriatrisk leseprøve _____

Henvisningsgrunn/diagnose _____

Legemidler _____

Instruksjon

Testing skal finne sted i enerom, fortrinnsvis på morsmål til PAS. Unngå at PAS ser skåringsark/skåring. Fet skrift (**bold**) leses høyt, tydelig og langsomt. Pause (markert [*pause*]) skal vare i 1 sek. Noter ordrett PAS-svar på hvert spørsmål. Vær nøye med å følge eksakt standardisert instruksjon (se utfyllende retningslinjer for administrasjon, oppfølgende spørsmål og skåring i manual). Ved retest benyttes oppgavesett som angitt for å redusere øvelseseffekt. Det gis kun hele poeng eller 0, aldri halve poeng. Sett ring rundt 0 dersom svaret er feil og rundt 1 ved riktig svar. Dersom PAS ikke er testbar på en oppgave, angi hvorfor og sett ring rundt 0. Er du usikker på hvordan et svar skal skåres, etter å ha sjekket manual, rådfør deg med en erfaren kollega. MMSE-NR er ikke en demenstest, kun en grov kognitiv screen, og kun et supplement ved utredning. Vær oppmerksom på at alder og utdanning påvirker resultat; lavere alder og høyere utdanning gir ofte bedre skåre. Totalskåre sier lite om spesifikke utfall. Noter PAS-spesifikke utfall.

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

_____

_____

_____

_____

_____

OPPMERKSOMHET/BEVISSTHETSNIVÅ

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

Døsig — Oppmerksom

TESTSITUASJON

Gradert vurdering av samarbeid/testinnsats
(Sett kryss passende sted på linjen)

Dårlig — Utmerket

Basert på; Folstein, M.F., Folstein, S.E., & McHugh, P.R. (1975). "Mini-Mental State": A practical method for grading the cognitive state of patients for the clinician. Journal of Psychiatric Research, 12, 189-198.
Engedal, K., Haugen, P.K., Gilje, K., & Laake, P. (1988). Efficacy of short mental tests in the detection of mental impairment in old age. Compr Gerontol A, 2, 87-93.

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 **POENG**

1. **Hvilket årstall har vi nå?** (kun fullt årstall med 4 sifre gir poeng) _____ 0 1
2. **Hvilken årstid har vi nå?** (ta hensyn til vær og geografiske forhold) _____ 0 1
3. **Hvilken måned har vi nå?** (kun riktig navn på måned gir poeng) _____ 0 1
4. **Hvilken ukedag har vi i dag?** (kun riktig navn på dag gir poeng) _____ 0 1
5. **Hvilken dato har vi i dag?** (kun dagsledd trenger å være riktig for å få poeng) _____ 0 1

STEDSORIENTERING

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

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

UMIDDELBAR GJENKALLING/REGISTRERING

Ved retesting: 2. adm: STOL-BANAN-MYNT, 3. adm: BIL-LAMPE-SAFT, 4. adm: KATT-AVIS-LØK, 5. adm: BÅT-EPLE-SKO

11. **Hør godt etter. Jeg vil si 3 ord som du skal gjenta etter at jeg har sagt dem, og som du skal prøve å huske, for jeg kommer også til å spørre deg om dem senere. Klar? 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 inntil alle gjengis i samme forsøk, maks. 3 forsøk.
Det gis kun poeng for 1. forsøk, rekkefølge PAS sier ordene er uten betydning. Antall forsøk: ____ stk.

HUS	[Alternativt ord: .....] _____	0	1
KANIN	[Alternativt ord: .....] _____	0	1
TOG	[Alternativt ord: .....] _____	0	1

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

OPPMERKSOMHET OG HODEREGNING (Vær oppmerksom på eventuell distraksjonsbetingelse*)

Bruk følgende starttall ved retesting: 2. adm: 50, 3. adm: 90, 4. adm: 40, 5. adm: 60. Sett ring rundt starttall, skriv ned tallsvar. Poeng gis når svar er akkurat 7 fra forrige tall, uavhengig av om forrige tall var riktig.

12. **Kan du trekke 7 fra 80?** [*Dersom PAS ikke gir et tallsvar, si:* **Hva er 80 minus 7?**] [*Rett etter tallsvar, gis videre instruksjon*]: **Og så fortsetter du å trekke 7 fra tallet du kommer til, helt til jeg sier stopp** [*Instruksjon gis kun én gang*]. Dersom PAS heller ikke nå gir et tallsvar, gå videre til distraksjonsbetingelsen.

Starttall:	**80**	**50**	**90**	**40**	**60**		
Om nødvendig si: **og så videre...**	[73],	[43],	[83],	[33],	[53]	_____	0 1
Om nødvendig si: **og så videre...**	[66],	[36],	[76],	[26],	[46]	_____	0 1
Om nødvendig si: **og så videre...**	[59],	[29],	[69],	[19],	[39]	_____	0 1
Om nødvendig si: **og så videre...**	[52],	[22],	[62],	[12],	[32]	_____	0 1
Om nødvendig si: **og så videre...**	[45],	[15],	[55],	[5],	[25]	_____	0 1

Etter 5 subtraksjoner si: **Fint, det holder** [Gå til oppg. 13].

***Eventuell distraksjonsbetingelse – OBS, er ikke poenggivende!**
Dersom PAS ikke vil utføre eller kan besvare oppg. 12, skal distraksjonsbetingelsen brukes for å sikre kartlegging av langtidshukommelse på oppg. 13. Be da PAS telle baklengs fra 100 ca. 30 sek. med følgende instruksjon:
(Tell baklengs fra 100 på denne måten: 99, 98, 97..., helt til jeg sier stopp. Vær så god!)

UTSATT GJENKALLING

13. **Hvilke 3 ord var det jeg ba deg om å huske?** [*Ikke gi hjelp/stikkord*]

HUS [Alternativt ord: .....] _____ 0 1
KANIN [Alternativt ord: .....] _____ 0 1
TOG [Alternativt ord: .....] _____ 0 1

Nevnes mer enn 3 ord, må PAS velge hvilke 3 ord som skal være svaret. Rekkefølge er uten betydning.
Det gis kun poeng for eksakt gjengivelse, dvs. bolighus, hytte, hare, kanindyr, togbane, lokomotiv etc. gir ikke poeng.

BENEVNING

14. **Hva heter dette?** [*Pek på en blyant*] _____ 0 1
15. **Hva heter dette?** [*Pek på et armbåndsur*] _____ 0 1

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

REPETISJON

16. **Gjenta *ordrett* det jeg sier. Er du klar?** [*Si tydelig*]: **"ALDRI ANNET ENN OM OG MEN".**

Frasen kan repeteres, maks. 3 forsøk. Det gis kun poeng for 1. forsøk. Dialektvarianter godtas. Antall forsøk: _____ stk.

ALDRI ANNET ENN OM OG MEN _____ 0 1

FORSTÅELSE

Legg et blankt A4-ark på bordet midt foran PAS, kortsiden mot PAS. TL legger egen hånd på arket til all instruksjon er gitt. Gi poeng for hver utført delhandling, også dersom PAS bretter arket med én hånd eller legger arket foran TL.

17. **Hør 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!** [*Instruksjon gis kun én gang*]

TAR ARKET MED KUN *EN* HÅND _____ 0 1
BRETTER ARKET PÅ MIDTEN KUN *EN* GANG _____ 0 1
LEGGER ARKET PÅ BORDET FORAN TL eller GIR ARKET TIL TL _____ 0 1

LESING

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

LUKK ØYNENE DINE _____ 0 1

SKRIVING/SETNINGSGENERERING

Legg MMSE-NR skjema side 4 med kortsiden foran PAS og gi vedkommende en blyant.

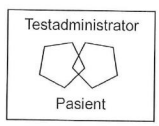
19. **Skriv en meningsfull setning her** [*Pek på øvre del av side 4*]. Skriver ikke PAS noe, si: **Skriv om været.** 0 1
Skrives kun imperativsetning med ett ord, f.eks. "Spis", si: **Skriv en lengre setning.** Skrives tidligere gitt setning/frase, f.eks."Lukk øynene dine", "En meningsfull setning", si: **Skriv en setning du lager selv**.

Setningen må være forståelig, men trenger ikke inneholde objekt; se eksempler i manual. Det gis poeng ved riktig utførelse selv etter supplerende instruksjon. Ignorer stave- og grammatikalske feil.

TEGNING/FIGURKOPIERING

Figurark plasseres med figurspiss mot PAS over skrevet setning, viskelær ved siden av.

20. **Kopier figuren så nøyaktig du kan her** [*Pek på nedre del av side 4*]. 0 1
Du kan bruke viskelær. Ta deg god tid. Si fra når du er ferdig.



Det gis poeng når tegningen består av to 5-kantede figurer som former en 4-sidet figur der 5-kantene overlapper. Tegnet figur trenger ikke være identisk med modellen; se skåringseksempler i manual.

TOTAL POENGSUM = _____ /30. Presiser hva PAS hadde utfall (feilsvar) på:

10.4. Clock drawing test - Norwegian version

Klokketest

Praktisk gjennomføring:
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!

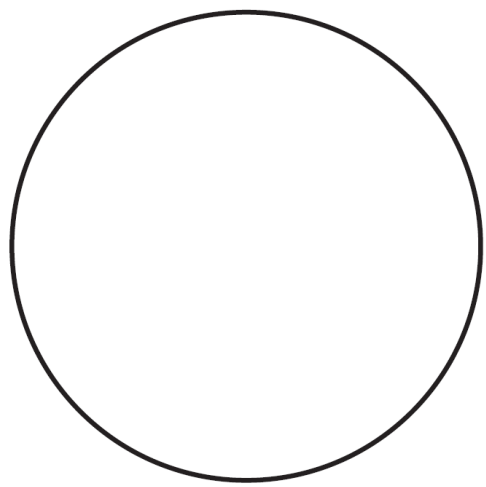
Som regel har den som tegner en svært dårlig klokke også problem med å lese klokken.
Klokkeslettene "ti over halv" og "ti på halv" er særlig vanskelige.
At man møysommelig må regne og telle seg frem til hvor mye klokken er, er ikke normalt.

Klokketest

Totalpoeng

Pasientens navn	
Fødselsdato	Dato utfylt

Diagnose
Utfylt av



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 eie og kan reproduseres 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[2,3].

Testen utføres slik: Testpersonen skal så raskt som mulig dra en strek med en blyant fra tall til tall.
Blyanten skal ikke løftes fra papiret. Dersom personen gjør en feil skal den påpekes slik at han kan korrigere seg.
Eksempelet er til for å demonstrere prinsippet og for at man skal kunne forsikre seg om at pasienten har forstått.
Score = tid i sekunder fra start til slutt.

I følge Lezak er det "unnecessary and unkind" å la personen forsøke i mer enn fire-fem minutter med noen del av testen[2].
For praktisk bruk kan man si at man uansett alder bør klare testen på under 1 minutt.

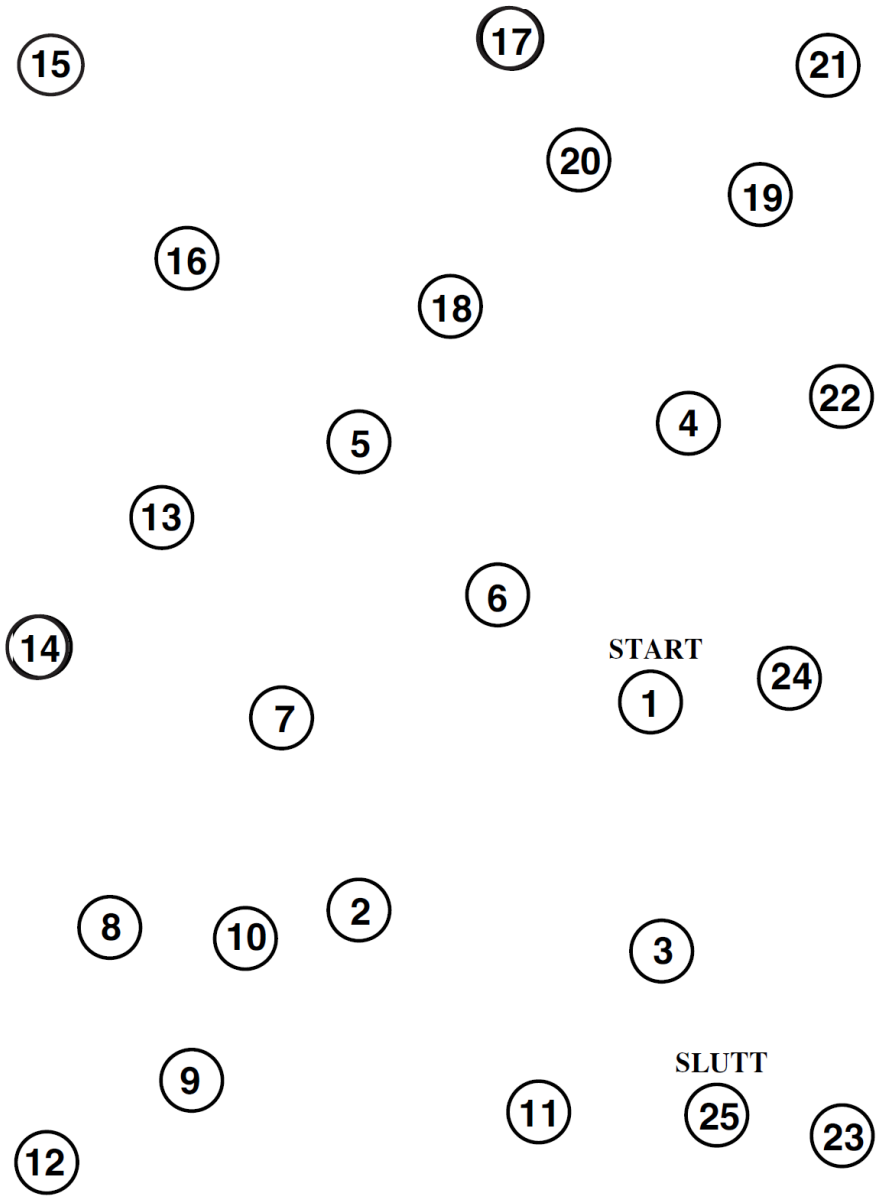
Aldersrelaterte normer hentet fra Ivnik et al[4]. SD = standardavvik:

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

(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:

1. Army Individual Test Battery. Manual of directions and scoring. War Department, Adjutant General's Office, Washington DC, 1944.
2. Lezak M. Neuropsychological assessment, 3rd ed. Oxford University Press, New York 1995.
3. Mitrushina MN, et al. Handbook of normative data for neuropsychological assessment. Oxford University Press, New York 1999.
4. Ivnik RJ, et al. Neuropsychological tests' norms above age 55. Clin Neuropsychol 1996:10(3);262-278.

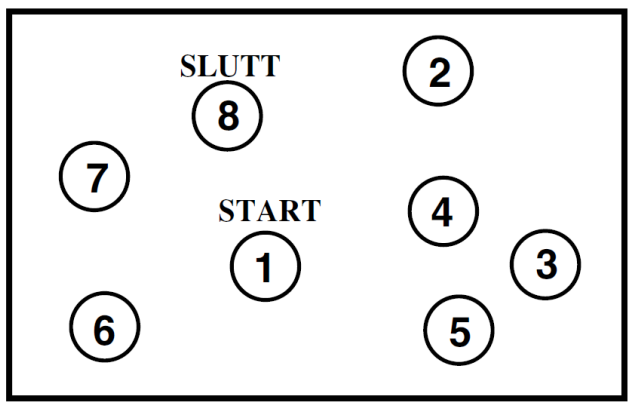

15
17
21
20
19
16
18
22
4
5
13
6
14
START
24
1
7
8
10
2
3
9
SLUTT
11
25
23
12

Resultat:

Pasientens navn	
Fødselsdato	Dato utfylt

Diagnose
Utfylt av

EKSEMPEL



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[1].
Ettersom den ble utformet av psykologer i US Army er den i offentlig eie og kan reproduseres fritt[2].
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[2,3].

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 gjør en feil skal den påpekes slik at han kan korrigere seg. Eksempelet er til for å demonstrere prinsippet og for at man skal kunne forsikre seg om at pasienten har forstått. Score = tid i sekunder fra start til slutt[1,2,3]
Eksempel på pasientinstruksjon: *"I denne del av testen skal annenhver sirkel inneholde et tall og annenhver sirkel en bokstav. Tallene skal være i nummerrekkefølge og bokstavene i alfabetisk rekkefølge. Du skal altså gå fra 1 til A til 2 til B. Kan du vise meg her på eksempelet 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.

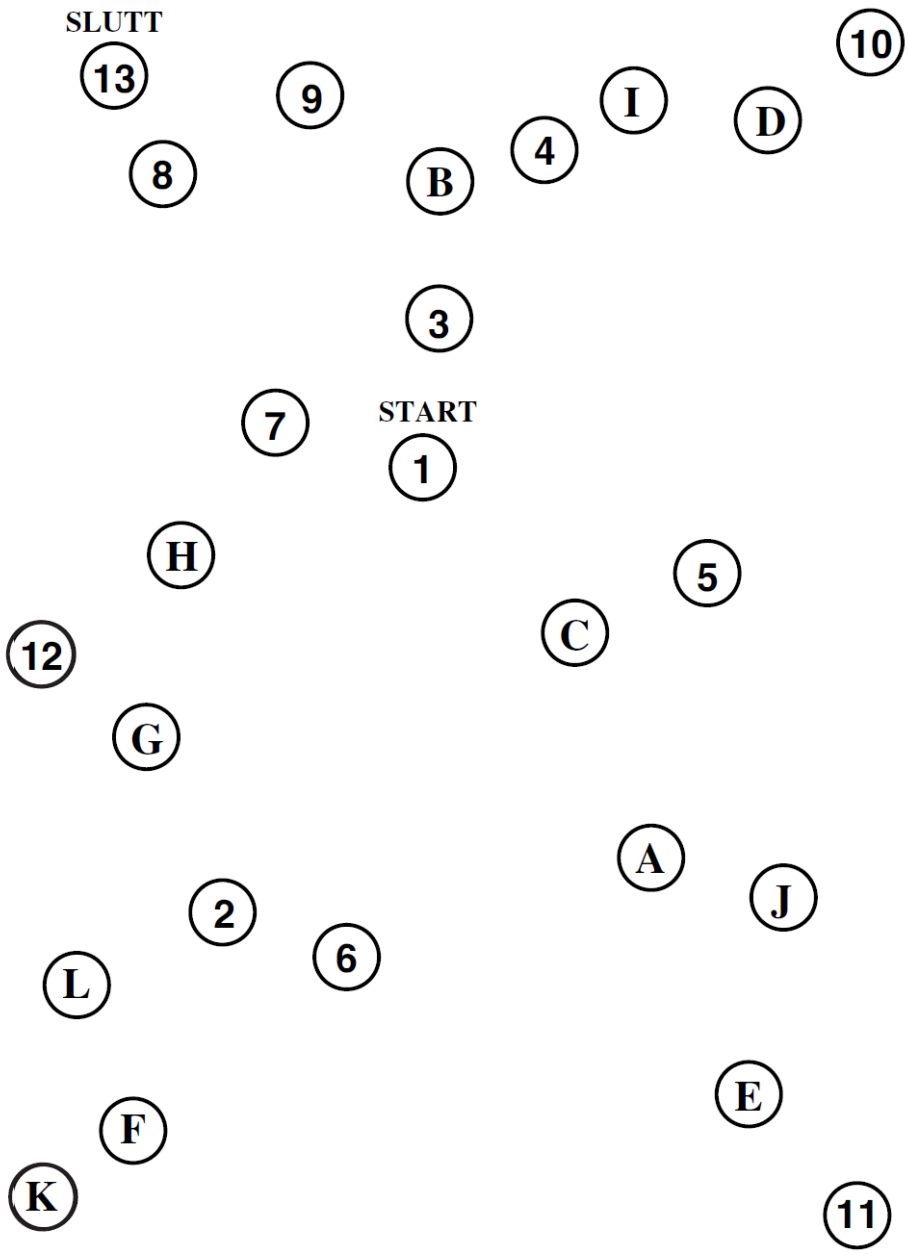
Aldersrelaterte normer hentet fra Ivnik et al4. SD = standardavvik:

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

(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:

1. Army Individual Test Battery. Manual of directions and scoring. War Department, Adjutant General's Office, Washington DC, 1944.
2. Lezak M. Neuropsychological assessment, 3rd ed. Oxford University Press, New York 1995.
3. Mitrushina MN, et al. Handbook of normative data for neuropsychological assessment. Oxford University Press, New York 1999.
4. Ivnik RJ, et al. Neuropsychological tests' norms above age 55. Clin Neuropsychol 1996:10(3);262-278.

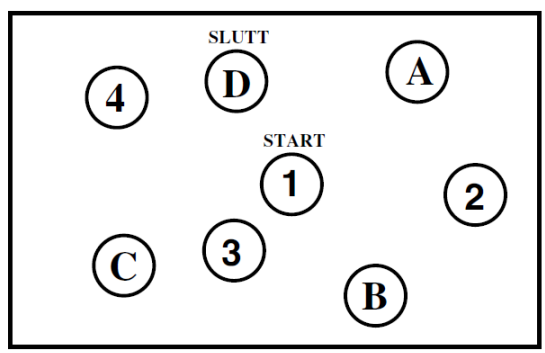

SLUTT
13
9
10
I
D
4
8
B
3
7
START
1
H
5
C
12
G
A
J
2
6
L
E
F
K
11

Resultat:

Pasientens navn	
Fødselsdato	Dato utfylt

Diagnose
Utfylt av

EKSEMPEL



10.7. Barthel Activities of Daily Living Index - Norwegian version

BARTHEL ADL-INDEKS

Mahoney FI, Barthel DW. Maryland State Med J 1965;14:61-65.
Denne norske versjonen er redigert i 2008 av Ingvild Saltvedt, Jorunn L. Helbostad, Unni Sveen, Pernille Thingstad, Olav Sletvold og Torgeir Bruun Wyller på grunnlag av flere tidligere norske oversettelser og med hovedvekt på originalpublikasjonen fra 1965.

Navn: _____ J.nr.: _____

Fødselsår/dato: _____ Dato utfylt: _____

Utfylt av: _____

GENERELT

Barthel ADL-indeks er først 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 man tror vedkommende kan mestre. Skår representerer grad av uavhengighet av hjelp fra annen person. Hvis det er nødvendig med tilsyn, er personen **ikke** uavhengig, men hvis en aktivitet mestres med hjelpemidler **er** personen uavhengig i denne aktiviteten. For personer uten vesentlig mental svikt (MMSE > 20) og i en stabil klinisk situasjon, er egenrapportert Barthel vanligvis pålitelig. For øvrig kan man som regel regne med at en skår basert på familie og andre med nær kjennskap til personen også er pålitelig.

1. Spising

- ☐ 2 Helt selvhjulpen. Kan bruke nødvendige hjelpemidler 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 selvhjulpen
- ☐ 0 Trenger hjelp

3. Personlig hygiene

- ☐ 1 Selvhjulpen. Klarer å vaske ansiktet, kjemme håret, pusse tenner og barbere seg
- ☐ 0 Trenger hjelp til en eller flere oppgaver

4. Påkledning

- ☐ 2 Selvhjulpen i av- og påkledning. Klarer selv glidelås, knapper og skolisser
- ☐ 1 Trenger hjelp, men klarer halvparten innen rimelig tid
- ☐ 0 Trenger hjelp til mer enn halvparten

5. Tarmkontroll

- ☐ 2 Kontinent. Klarer selv evt. å sette stikkpille/klyx
- ☐ 1 Nedsatt kontroll og enkelte "uhell" eller trenger hjelp til evt. å sette stikkpiller/klyx
- ☐ 0 Helt inkontinent eller hyppige "uhell"

6. Blærekontroll

- ☐ 2 Kontinent. Holder seg evt. tørr ved bruk av uridom eller mestrer bruk av kateter på egen hånd
- ☐ 1 Nedsatt kontroll og enkelte "uhell" eller holder seg tørr med uridom 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 klær, tørker seg, spyler toalettet eller tømmer bekken
- ☐ 1 Trenger hjelp til forflytning, klær, tørke 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 mye hjelp ved forflytning
- ☐ 0 Kan ikke sitte. Sengeliggende

9. Mobilitet

- ☐ 3 Klarer å gå 50 meter, kan bruke stokk eller krykker, men ikke annet ganghjelpemiddel
- ☐ 2 Kan gå 50 meter med rullator 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 evt. bruke ganghjelpemidler
- ☐ 1 Trenger hjelp/tilsyn av en person
- ☐ 0 Kan ikke gå i trapp

	Sumskår (maksimal skår 20 poeng)