Cognitive impairment after stroke and TIA

Etiology, diagnosis and prevention

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Faculty of Medicine
University of Oslo
2012

Series of dissertations submitted to the
Faculty of Medicine, University of Oslo
No. 1446

ISBN 978-82-8264-487-7

Cover: Inger Sandved Anfinsen.
Printed in Norway: AIT Oslo AS.

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Vestre Viken Hospital Trust

and

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"There is no comparison between that which is lost by not succeeding and that which is lost by not trying"

Sir Francis Bacon (1561-1626)

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Acknowledgements

This study had not been possible without the positive attitude of the patients who participated in the study. With only a few exceptions, most patients were willing to contribute and devote their time and efforts to complete the intervention and follow-up. An acute stroke is a major life-changing event for the person involved; I have deep respect and gratitude for the generosity of these patients, who participated in this research during a challenging and stressful period of their lives. I am impressed by the ability of these patients to maintain motivation for long-term rehabilitation and by the way they gracefully accept and adjust to their altered life circumstances.

The present work has been carried out in the Department of Geriatric Medicine, Stroke and Rehabilitation, Bærum Hospital, Vestre Viken Hospital Trust. The project was made possible by financial support by Helse SørØst, Vestre Viken Hospital Trust and the Foundation for research in internal medicine and through my position as a consultant geriatrician in the outpatient clinic. As a research fellow in a local hospital, I was dependent on close cooperation with the University of Oslo. I am grateful for all the support.

Working with this thesis has made me a better doctor, a more critical reader of scientific publications, and a person with greater humility and respect for medical research and for the patients' involved. I have learned a lot throughout the whole process: from the idea taking shape and planning the project, applying for grants, collecting the data, motivating patients for lifestyle changes, participating in sub studies, preparing and creating the database, performing the statistical analyses, and writing the manuscripts. I have become more competent in computer science and medical statistics and improved my English! I have become more fascinated by the complexity of the brain and the processes involved in normal and pathological aging. The take-home message is this: Stay physically fit and be intellectually curious!

First, I would like to thank my supervisors for their support throughout the last 6 years. They have all been involved in all phases of the project, from the idea to the manuscripts, and they have given me the greatest support.

My deepest thanks are owed to the following individuals:

Brynjar Fure, for initiating the project, for your concern for patients suffering from stroke and cognitive impairment, for encouraging the multidisciplinary team to do research in order to improve the care and for sharing your knowledge in stroke and research. You have been my mentor and friend, always available and always enthusiastic and encouraging. You have proofread and edited many drafts of articles and lecture presentations. You have also been a listening ear and supported me through the ups and downs of my life, both professionally and personally. You see opportunities and solutions and have a great capacity for work.

Bente Thommessen, for your wisdom, presence, and for having a big heart for both patients and colleagues. You contributed so much scientifically and worked so hard in the consensus group. I have really enjoyed working with you and appreciated the valuable discussions.

Torgeir Bruun Wyller, professor, for your work ethic, your broad knowledge in geriatric medicine and research, for scientific discussions, for constructive criticism and for always being supportive. Your responses to emails are immediate! You have edited the entire manuscript several times. I admire your unique enthusiasm for the complexity of geriatric medicine and research and for your ability to get to the root of the matter.

Knut Engedal, professor, for all your knowledge in dementia and assessment of cognitive function, for communicating a positive attitude toward persons with cognitive impairment, for the ability to find the weak spots, for your help in making me more systematic in the discussion parts of all the manuscripts, and for inspiring me to give presentations and contribute in scientific networks. You have always motivated me and been a pillar of support.

Anne Rita Øksengård, for all your enthusiasm for dementia research, for including me in research groups, encouraging me to join the EAMA, for doing a great job in the consensus group and for introducing us to Kirsti Løken. You are an inspirational person, clinician and researcher.

I also want to express my gratitude towards the following collaborators:

Morten Wang Fargerland, for your indispensible help regarding statistical analyses in two of the articles, for talking statistics in a way that is possible to understand and for taking so much responsibility in the work. You have been very flexible and positive. I hope we can continue to cooperate.

Kirsti Løken, an experienced radiologist, for international cooperation regarding evaluation of the medial temporal lobe, and for doing all the measures of the MTLA.

Vidar Stenset, a neurosurgeon with great knowledge regarding white matter changes in the brain, for evaluating all the MRI scans for vascular changes.

Audhild Tørstad and **Marie Ursin**, physiotherapists, and **Else Graven**, occupational therapists, for doing sub-studies regarding balance and cognition. They have all completed Master's degrees. And thanks to **Nadine Probst** and **Anne Wergeland**, both specially trained nurses in the stroke unit, for their special attention towards the young stroke patients and their involvement in the study recruitment and assessments. You all inspire and improve the work in our unit.

Special thanks to:

***All my co-workers and colleagues** in the stroke unit for their support, for helping to recruit patients and for continually striving to improve the care for stroke patients. A special thanks to **Inger Vandvik** for her involvement in the acute stroke care including thrombolytic therapy.

***All the staff** working in the ward for being so enthusiastic about the project, making all the assessments and taking such good care of the patients. I am proud of the quality of care given to the patients in our unit.

***Kari Wie Skar**, for knowing everything about everybody in the project and helping the patients during their stay in the outpatient clinic, and for being a caring friend. You are indispensable!
***Anne Mette Brenden,** for doing all the tests in a way so that the patients felt secure and well looked after, and for your humour and your positive attitude. We have had such a good time with a lot of laughs.

***Gro Vik Knutsen, Kristin Staib, Mai Bente Myrvold, Knut Erling Moksnes, Gyrid Gjerde, Niels Kristian Thybo and Britt Eidsvoll**, for enthusiastic and encouraging support as my leaders and for positive attitudes towards clinical research. Gyrid, you have been a driving force behind this project. You saw the possibilities! And Gro, you are a great colleague and friend.

***The MRI department**, for taking cranial MRI scans of all patients at follow-up. Excellent service!

***My colleges in the Research Unit** (Loftet), for encouragement to do geriatric research and inspiring lectures. **Anne Garmark**, an extra thanks to you for doing the randomisation and for being helpful and concerning. A special warm thanks to **Siri R Kristjansson**, for being a supportive friend with an interest in running, and to **Anne K Gulsvik,** for being a good friend with a great sense of humor. Both have a curiosity for geriatric medicine and older patients.

***Medical Research Department**, for including me in the last phase of the project. I needed the mental support and the friendships and I have enjoyed being part of the group. I am impressed by the number and quality of ongoing projects and that Bærum Hospital has managed to build up a dedicated research department. **Arnljot Tveit** is a mentor, a gifted teacher, and a source of inspiration. **Steve Enger**, you have helped me so many times with computer problems. And **Mona Olufsen**, I have finally completed the fire safety course online! Thank you for looking after me! **Trygve Berge**, it has been a pleasure to share office space with you! And **Sarah Kaldestad,** thank you so much for all the help with my English! I look forward to continued research collaboration with the department.

*My colleagues at the Department of Internal Medicine, especially **Else Johanne Rønning** and **Jan Svendsen**, my nearest co-workers every day.

***Gitta**, thank you for making me happy.
***Helene, Johan August and Ingeborg,** thank you for your love, support and patience. You make me proud and fill me with joy.

.

Norsk sammendrag

Bakgrunn

Behandling av modifiserbare risikofaktorer gjøres som ledd i primærprofylakse og sekundærprofylakse for å forebygge hjerneslag. Hjerneslag er den tredje hyppigste dødsårsaken i Norge, og den vanligste årsaken til alvorlig funksjonshemning der mange lever med fysiske og mentale endringer som følge av et hjerneslag.

Demens etter hjerneslag er definert som demens som oppstår etter et slag, og inkluderer vaskulær demens, degenerative demens (oftest Alzheimers sykdom) og blandingsdemens (både vaskulære og degenerative forandringer). Vaskulære risikoaktorer bidrar ikke bare til vaskulær demens, men synes å påvirke kaskaden i Alzheimer patologi som utvikles til demens.

Vi ønsket å undersøke om intensiv multifaktoriell karforebyggende behandling kunne forebygge kognitiv svikt etter hjerneslag. Vi ønsket å se på fordelingen av ulike sub-grupper av iskemiske hjerneslag og innbyrdes assosiasjon til vaskulære risikofaktorer. Videre ville vi undersøke insidensen av demens og mild kognitiv svikt etter hjerneslag med mulige etiologiske mekanismer. Vi evaluerte også assosiasjonen mellom kroniske sirkulasjonsforandringer i hjernen (White Matter Lesions=WML) og pasientens prestasjoner på kognitive tester.

Metode

227 pasienter med sitt første hjerneslag eller TIA (drypp) uten kjent kognitiv svikt innlagt i slagenheten, Bærum Sykehus, Vestre Viken HF, ble inkludert. Vaskulære risikofaktorer ble registrert, hjerneslaget klassifisert og nevrologiske og kognitive utfall målt. De primære endepunktene var TMT A og 10-ords-test, som måler henholdsvis tempo og oppmerksomhet og hukommelse. Etter utreise ble pasientene randomisert til å komme til konsultasjoner i vår slagpoliklinikk for intensiv karforebyggende behandling, eller gå til vanlig oppfølging hos fastlegen.

Intervensjonen besto i å forsøke å nå følgende behandlingsmål:

1. Blodtrykk til <140/90
2. Total-kolesterol <5 og LDL <3
3. Røykekutt
4. For diabetikere langtids-blodsukker (HBA1c) <7.0
5. Homocystein < 15
6. Fysisk aktivitet minimum 30 min x3 pr uke
7. BMI < 25
8. Kost inneholdende mer frukt og grønt, mer frukt, mindre mettet fett og karbohydrater
9. Høyt alkoholkonsum (> 2-3 enheter daglig) anbefales ikke

Alle ble innkalt til kontroll 1 år etter hendelsen. Her ble igjen kar risiko registrert og kognisjonen og nevrologiske følgetilstander målt. Alle fikk tilbud om MR av hodet og spinalpunksjon.

Resultater
Vi klarte ikke å vise at intens karforebyggende behandling påvirket utviklingen av hukommelsesvansker etter hjerneslag eller TIA.

Hele 31.4 % av pasientene med iskemiske hjerneslag hadde småkarsykdom som etiologisk diagnose, mens kun 11.4 % hadde slag på bakgrunn av storkarsykdom. Hyperlipidemi (Kolesterol >5 og/eller LDL > 3) og røyking var relatert til småkarsykdom.

57.1 % utviklet hukommelsesforandringer som ledd i demens eller mild kognitiv svikt 1 år etter sitt første hjerneslag. Kun 13.3 utviklet demens på rent vaskulært grunnlag, mens over halvparten utviklet kognitiv svikt grunnet kombinasjonen av vaskulære og degenerative forandringer.

TMT A og 10-ords-test var signifikant assosiert med WML, og de var også signifikant assosiert med atrofi av mediale temporallapp (MTLA).

Konklusjon
Vi klarte ikke å vise at intensiv multifaktoriell karforebyggende behandling forebygget kognitiv svikt etter hjerneslag. Til dette var oppfølgingstiden for kort og variasjonene innad i gruppene for stor.

Vi observerte en endring i fordelingen av etiologiske sub-grupper av iskemiske hjerneslag med hyppigere småkarsykdom og mindre hyppig storkarsykdom. Småkarsykdom var signifikant assosiert med høyt kolesterol og røyking.

Blant første gangs hjerneslag og TIA uten kjent kognitiv svikt utviklet 57 % hukommelsesvansker 1 år etter slaget, og kun en tredjedel på rent vaskulært grunnlag. Sameksistensen av vaskulære og degenerative forandringer var betydelig.

Eksekutiv svikt og hukommelsesproblemer etter hjerneslag er assosiert med kroniske sirkulasjonsforandring. Mekanismene involvert i kognitiv svikt etter hjerneslag skyldes en kombinasjon av degenerative og ulike vaskulære forandringer.

Abbreviations

ACA	Anterior Cerebral Artery
AD	Alzheimer's Disease
ADAS-cog	Alzheimer's Disease Assessment Scale-cognitive subscale
ADL	Activities of Daily Living
AF	Arial Fibrillation
AHA	American Heart Association
Apo E	Apolipoprotein E
BMI	Body Mass Index
BP	Blood pressure
CNS	Central Nervous System
CT	Computer Tomography
DW	Diffusion-Weighted
ECG	Electrocardiography
ESO	European Stroke Organization
GP	General Practitioner
HR	Hazard Ratio
IMT	Intima Media Tickness
IQCODE	Informant Questionnaire on Cognitive Decline in the Elderly
LACI	Lacunar Circulation Infarction
LDL	Low Density Lipoprotein
MCA	Middle Cerebral Artery
MCI	Mild Cognitive Impairment
MMSE	Mini Mental State Examination
MRI	Magnet Resonance Imaging
mRS	Modified Rankin Scale
MTLA	Medial Temporal Lope Atrophy
NIHSS	National Institute of Health Stroke Scale
OCSP	Oxfordshire Community Stroke Project classification
OR	Odds Ratio
PACI	Partial Anterior Circulation Infarction
PCA	Posterior Cerebral Artery
PET	Positron Emission Tomography
POCI	Posterior Circulation Infarction
PW	Perfusion-Weighted
RCT	Randomized Controlled Trial
SPECT	Single Photon Emission Computed Tomography
SU	Stroke Unit
TACI	Total Anterior Circulation Infarction
TEE	Transeosophageal Echocardiography
TTE	Transthoracal Echocardiography
TIA	Transitory Ischemic Attack
TMT A	Trail Making Test A
TMT B	Trail Making Test B
TOAST	The Trial of Org 10172 in Acute Stroke Treatment classification
UAS	Ullevaal Aphasia Screening
VaD	Vascular Dementia
VCI	Vascular Cognitive Impairment
WML	White Matter Lesions
WMH	White Matter Hyperintensities

Publications included in the thesis

I. Ihle-Hansen H, Thommessen B, Wyller TB, Engedal K, Fure B. Risk factors for and incidence of subtypes of ischemic stroke. Functional Neurology 2012; 27(1): 35-40

II. Ihle-Hansen H, Thommessen B, Fagerland M, Øksengård AR, Wyller TB, Engedal K, Fure B. Multifactorial vascular risk factor intervention to prevent cognitive impairment after stroke and TIA: A 12- month randomized controlled trial. Submittet.

III. Ihle-Hansen H, Thommessen B, Wyller TB, Engedal K, Oksengard AR, Stenset V, et al. Incidence and Subtypes of MCI and Dementia 1 Year after First-Ever Stroke in Patients without Pre-Existing Cognitive Impairment. Dement Geriatr Cogn Disord 2011;32(6):401-7.

IV. Ihle-Hansen H, Thommessen B, Fagerland MW, Wyller TB, Engedal K, Oksengard AR, et al. Impact of white matter lesions on cognition in stroke patients free from pre-stroke cognitive impairment: a one-year follow-up study. Dement Geriatr Cogn Dis Extra 2012 Jan;2(1):38-47.

Hippocrates (460-370 BC) credited the brain with intelligence and thought.

Alf Brodal, a 62-year-old professor in anatomy and a pioneer in neurobiological science, suffered a presumed classical launar stroke with left-sided hemiparesis. He describes his own experience in a scientific paper published in Brain, 1973 (1):

"Subjectively, the patient noted that he became much more easily tired than previously from mental work, even from ordinary conversation and reading newspapers. There was a marked reduction in the powers of concentration which made mental tasks far more demanding than before. Reading novels did not cause great problems, but it was often quite difficult and needed much concentration to follow the arguments, for example in a scientific paper. In part, this seemed to be due to a reduced capacity to retain the sense of a sentence long enough to combine it with the meaning of the next sentence. It appeared subjectively as a reduction of short-term memory for abstract symbols. This is supported by the following observation: when trying to remember a series of figures, for example looking reference numbers up in a list, the limits of achievement even with maximal concentration were reduced, compared with previous capacity. These few observations, along with some others of a similar type, suggest that there is some impairment of certain mental functions."

1. General introduction:

Every other second a person suffers a stroke worldwide (2). Because of the aging population, the burden of stroke will increase greatly (3). Stroke is a common disorder in Norway, and around 15.000 people have a stroke each year (4). Stroke is a major cause of disability, and is the third most common cause of death. One year after stroke almost one third of the survivors are functionally dependent (5). The thirty-day mortality in ischemic stroke is reduced to 2.8% in Norway in 2009, compared to 6.1% in 2000 (6).

Cognition, from the Latin term cognoscere, means "to know", "to conceptualize" or "to recognize". Cognition includes attention, remembering, producing and understanding language, solving problems, and making decisions. Cognitive function includes how we use information, think, learn, judge, apply knowledge and change preferences. Dementia is described as an acquired cognitive impairment with affected emotional control and impaired function in daily life (7). Cognitive disturbances are frequent after stroke, but rates regarding post-stroke dementia and cognitive impairments vary from 7.4 to 56.3 % (8).

Acute stroke is an acute illness and a “brain-at-risk” condition, and the patient is in need of acute hospitalisation for the diagnosis, acute treatment and early rehabilitation. Stroke treatment is a rapidly advancing field. Interventions like management of patients with acute stroke in stroke units, intravenous tissue plasminogen activator within 4.5 hours of stroke onset and decompressive surgery for supratentorial malignant hemispheric cerebral infarctions are of benefit. Regarding secondary prevention, we use anticoagulation for patients with atrial fibrillation, perform endarterectomy for symptomatic carotid stenosis and give antiplatelet agents and statin therapy. For stroke prevention, there are two main strategies. The “population” approach aims to reduce stroke by lowering the prevalence with public education and government legislation (9). The “high risk” approach aims to reduce stroke by identifying individuals at high risk of stroke and lowering their risk with optimal medical therapy and lifestyle advices.

In the last decades, there has been a change in the epidemiology regarding life style and risk factors for cognitive impairment. When we compare persons aged 70 years in 2000 with persons aged 70 years in 1970, the first group has better cognitive function, higher educational level and tend to smoke less and be more often obese (10). Likewise, an 85-year-old in 2008 versus 1986 seems to suffer from less dementia but has a higher prevalence of stroke (Skoog I, personal message). Better pre-stroke control of vascular risk factors and better survival and functional outcome as an effect of the stroke unit and thrombolytic therapy for acute ischemic stroke may preserve cognitive functioning after stroke.

Post-stroke dementia is defined as any dementia occurring after stroke, and includes vascular dementia (VaD), degenerative dementia (mostly Alzheimer’s disease, AD) and mixed dementia (coexistence of vascular and degenerative changes). Vascular risk factors contribute not only to vascular dementia, but probably also in the cascade of Alzheimer pathology proceeding to clinical dementia (11).

In addition to a shift in lifestyle-related vascular risk factors, there is a shift in the approach to dementia. Cognitive impairment can be considered as a continuum which affects different cognitive domains, and with different causes. These often include the coexistence of vascular and degenerative changes (12). Further, both AD and cerebrovascular diseases share the same risk factors, most of them treatable. Identification and treatment of vascular risk factors

prevent stroke, and probably, cognitive impairment as well. Prevention of cerebrovascular disease may significantly impact the incidence of cognitive decline and dementia in the elderly.

The present study evaluated different aspects regarding post-stroke cognitive impairments; prevalence, risk factors, etiology, neuroimaging and prevention. For the intervention study, we hypothesized that a multifactorial vascular risk factor intervention would reduce the incidence of cognitive impairment post-stroke.

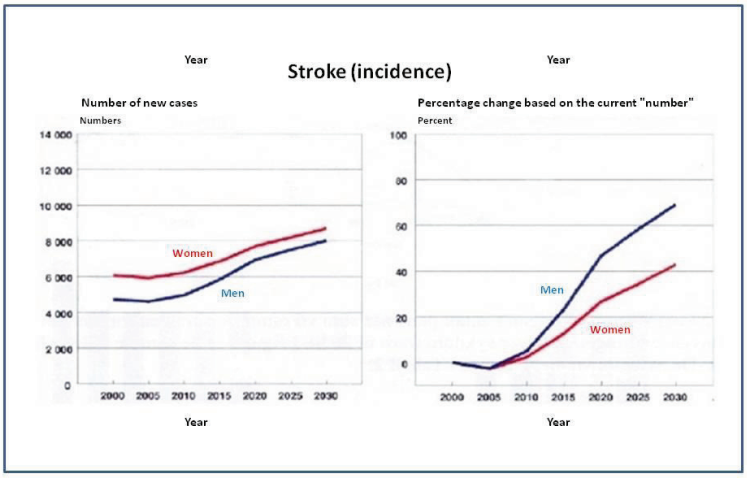
Our findings may have clinical implications regarding vascular risk factor management post-stroke, for prediction of cognitive decline in stroke patients and for the understanding of the coexistence of vascular and degenerative changes in post-stroke cognitive impairment.

2. Background
2.1 Stroke
2.1.1 Definition of stroke
The definition of stroke used by the World Health Organization is a syndrome of rapidly developing clinical signs of focal (or global) disturbance of cerebral function, with symptoms lasting 24 hours or longer or leading to death, with no apparent cause other than of vascular origin (13). Stroke is, per definition, a clinical syndrome. A TIA implies the acute loss of focal cerebral function with symptoms lasting less than 24 hours (14). Due to Magnet Resonance Imaging (MRI) findings in almost 50 % of the TIA patients and permanent tissue damage in at least 25% of them (15), the definition of TIA is under revision, proposing a new definition including symptoms caused by focal brain ischemia without acute infarction (16).

2.1.2 Incidence of stroke
The incidence of stroke is defined as the number of first in a life-time strokes occurring per unit time. In Norway, there is 11.000 first-ever strokes per year (4). At every age, rates for men are higher (17). But due to longer life-expectancy for women, they suffer more strokes in total (18). Almost one in four men and nearly one in five women aged 45 years can expect to have a stroke if they live to their 85th year (5). The converse is true for life-time risk of dying from stroke. About 16% of all women are likely to die of a stroke compared with 8% of the men due to the higher mean age at stroke onset in women and greater life expectancy.

The number of patients suffering from stroke will increase considerably during the next decades (19). Figure 1 shows the expected rise in stroke cases in Norway. In 20 years, there will be an almost 50% increase in stroke. However, if preventive measures are implemented among all Norwegians, these figures will be lower.

Figure 1. Incidence of stroke in Norway

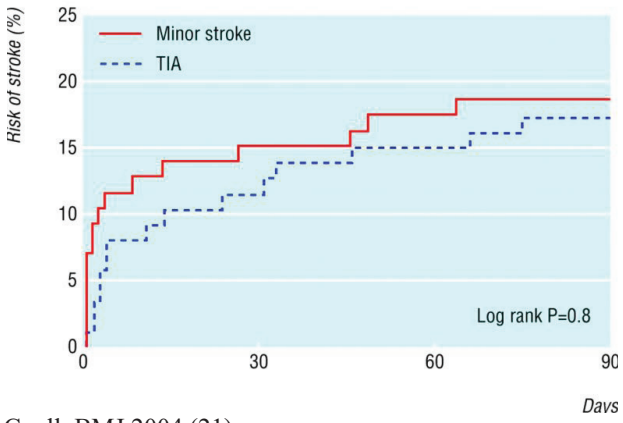


From Scenario 2030, Statens Helsetilsyn (19).

In Norway, 55.000 persons live after stroke today (20).

The risk of a recurrent stroke is 10% within 7 days, and 18% within 3 months (Figure 2) (21).

Figure 2: Cumulative risk of stroke after transient ischemic attack (TIA) or minor stroke



Coull, BMJ 2004 (21).

2.1.3 Diagnosis of stroke

Clinically, stroke is characterized by a rapid onset of focal symptoms such as hemiparesis, sensory loss, facial paresis, dysarthria or diplopia. Stroke affecting cerebellum may lead to e.g ataxia. Affection of the cortex of the left hemisphere may lead to aphasia, apraxia and agnosia, while stroke in the area of right cortex may affect orientation, attention and self awareness.

Early clinical evaluation, including physiological variables and routine blood tests, is recommended (22). Evaluation of neurological deficits (using National Institutes of Health Stroke Scale (NIHSS) score) should be obtained and imaging performed without delay.

A computer tomography (CT scan) of the brain can diagnose a cerebral hemorrhage almost immediately after onset of symptoms (23). Cerebral infarctions, on the other hand, can be visualized on CT scans from a few hours to over 48 hours after onset of symptoms. In almost 50% of the cases, there will be signs on CT scans 6 hours after ictus (24). MRI and CT scans have similar accuracy in detecting intracerebral hemorrhage in the acute phase (25).

Positron Emission Tomography (PET) and MRI techniques including T2 weighted scans as well as diffusion-weighted (DW) and perfusion-weighted (PW) techniques show cerebral infarctions at a very early stage, and may even visualize the ischemic penumbra in the brain before a permanent infarction has developed (26). This penumbra refers to the tissue with preserved neuronal integrity, but due to hypoperfusion, in risk of impairment (27). The larger the penumbra volume and the smaller the ischemic infarct core, the greater the potential benefit with reperfusion therapy (28).

Due to limited resources regarding MRI, most hospitals treat acute stroke patients and offers trombolysis without an MRI in the acute phase. However, most hospitals offer CT angiography for detection of the embolus prior to trombolysis and endovascular re-canalization therapy.

For the detection of the source of an embolus or an internal carotid artery dissection and for optimal secondary prevention, patients undergo a duplex of the precerebral arteries. For stenoses 70-99% this non-invastive test has high sensitivity and specificity (29). In addition to evaluation of a stenosis, color duplex of precerebral arteries visualizes the Intima Media Tickness (IMT) and atherosclerotic plaques (30), especially ruptures of the plaques. The intracranial arteries (the middle cerebral artery (MCA), the anterior cerebral artery (ACA), the posterior cerebral artery (PCA) and the communicants), can be visualized through transcranial, especially transtemporal, color duplex images (31). Transcranial duplex investigations may be technically difficult to perform, as the transtemporal window, in particular in older persons, can be hard to locate (32). Revascularisation of the MCA can be evaluated by repeating transcranial duplex after thrombolysis (33). Transcranial Doppler can also be used for cerebral microemboli detection (34), including artery-to-artery embolisation and cardiac embolisation.

Embolism from the heart results in almost 30% of all cerebral infarctions. All patients should perform a 12-lead electrocardiography (ECG) in the acute phase in order to detect atrial fibrillation (AF) and signs of acute ischemic heart disease. 24-hour Holter ECG monitoring should be performed when arrhythmias are suspected and no other causes of stroke are found (ESO 2008). Transthoracic echocardiography (TTE) in patients with acute stroke is recommended when clinical evidence of cardiac disease by history, physical examination, electrocardiography or chest radiography is present (35). Routine echocardiography is not recommended for patients with clinical cardiac disease who have independent indication for or contraindications to anticoagulant therapy. Transeosophageal echocardiography (TEE) is regarded superior to TTE in identifying a cardiac embolic source (36), in particular the detection of a thrombus in the the left artial appendage, patent foramen ovale and aortic atheroma (37).

Trombophilic conditions including antiphospholipid antibodies and inherited thrombophilias (deficiencies of the natural anticoagulants antithrombin III, protein S and C and mutations in factor V Leiden and factor II) are associated with vascular occlusive events. Routine screening is not recommended, since coagulation disorders is the cause in a minority of ischemic strokes, and may be considered only among young patients with non-cardioembolic stroke (38).

In cerebral haemorrhage, arteriovenous malformations and bleeding in relation to tumours should be excluded.

2.1.4 Treatment of acute stroke

The treatment of acute stroke is evolving. The treatment includes reducing the mortality and morbidity of the acute event and preventing subsequent events.

Patients with spontaneous supratentorial intracerebral hemorrhage show no overall benefit from early surgery when compared with initial conservative treatment (39).

Treatment of acute ischemic stroke has primarily two initial approaches: limitation of the ischemic insult by early reperfusion (the vascular approach) and interference with the pathobiochemical cascade leading to ischemic neuronal damage (the cellular approach) (40). In addition, complication prevention and early rehabilitation are of importance. Treatment in stroke units improves survival and functional state, and the effect lasts for at least 10 years

(41). Reperfusion treatments have been a success, and are associated with improved clinical outcomes, but neuroprotective strategies have failed to show clinical benefit (42).

Patients with acute stroke need both acute care and acute rehabilitation. A stroke unit (SU) is dedicated to both of these elements, and has strong evidence of effectiveness. Stroke units improve outcomes of patients with stroke (41). The SU consists of nurses, doctors and therapists, all specially trained in monitoring patients with stroke and working in coordinated teams. Patients with stroke who receive organized inpatient care in SU are more likely to be alive, independent, and living at home one year after stroke (43). Every hospital receiving patients with stroke should treat them in specialized stroke units. In addition, comprehensive centers are needed for more advanced neuroimaging and intra-arterial treatment.

Antiplatelet therapy with aspirin 300 mg given orally within the first 48 hours reduces the risk of early recurrent ischemic stroke (44). It also increases the chances of being alive and independent with less neurological sequel. The risk of early hemorrhagic complications is low.

Reperfusion induced by thrombolysis has been shown to be effective when initiated within 4.5 hours of onset of symptoms (45). Odds of a favorable 3-months outcome is 2.8 (95 % CI 1.8-4.5) for treatment ≤ 90 min, 1.6 (1.1-2.2) for 91-180 min and 1.4 (1.1-1.9) for 181-270 min (46).

In an acute stroke, the neurons in the infarction core die rapidly due to lack of oxygen (40), and only reperfusion strategies can increase the blood flow in the penumbra zone above the threshold where the nerve cells are irreversibly damaged. The penumbra zone has a therapeutic window extended to several hours. Intra-arterial trombolysis can be effective in treatment of acute stroke (47). Trombolysis is administrated selectively and directly through a catheter. For MCA occlusions, intra-arterial treatment given within 6 hours improved clinical outcome at 90 days (47). It may also be attempted in basilar thrombosis (48). Endovascular recanalization in acute ischemic stroke includes, in addition to intra-arterial thrombolysis, mechanical embolectomy by the use of endovascular devices and intra-arterial stents in order to revascularize occluded intracerebral arteries. Endovascular revascularization in stroke due to large vessel occlusion is described as safe and effective in patients within 8 hours from symptom onset (49-51). Recanalization is the strongest predictor for clinical outcome in patients having a thromectomy (52). Intra-arterial administration of thrombolytic agents and mechanical interventions has been promising, but due to limited data, additional research is need. In the meantime, carefully selected patients may benefit from the reperfusion approach (53).

In patients with signs of malignant oedema, surgical hemicraniectomy must be considered (54).

For optimal blood flow, the systolic blood pressure should be kept under 220 mm Hg and diastolic pressure under 120 mm Hg. Intravenous saline solution during the first 12 hours avoid dehydration and stabilize the blood pressure. Hyperglycemia is associated with poor outcome and should be avoided. Body temperature should be obtained normal (28). Complications should be detected early and properly treated.

Anticoagulation is recommended in patients with AF for secondary prevention after cerebrovascular events (55;56).

Endarterectomy is of some benefit forpatients with 50% to 69% symptomatic carotid stenoses and highly beneficial in 70% to 99% stenoses without near occlusion (57), and should be performed within 14 days from onset of symptoms.

2.1.5 Classification of stroke

Strokes are either ischemic or haemorrhagic. 80-85 % of all strokes are ischemic stroke due to a thrombus or an embolus, 10-15 % are haemorrhagic strokes and <5% suffer from subarachnoid haemorrhage. This first differentiation is often made with CT scan, and is crucial as medical and surgical therapies differ in these groups.

There are a number of classification systems of stroke, none of which are ideal. A classification system describing risk factors associated with the subtypes, which is important for secondary prevention, is missing. Systems for stroke classification have been made due to the needs of clinical trials (The Trial of Org 10172 in Acute Stroke Treatment (TOAST)) and epidemiological studies (the Oxfordshire Community Stroke Project (OSCP) classification).

A useful clinically-based classification developed by Bamford (OSCP) (58) can be helpful when discussing prognostic aspects. This classification relies only on clinical findings. Cerebral infarctions are classified according to the topographic location and size of the cerebrovascular lesions. Total anterior circulation infarcts (TACI) have both cortical and subcortical involvement, partial anterior circulation infarcts (PACI) are more restricted and predominantly cortical infarcts, posterior circulation infarcts (POCI) are associated with the vertebrobasilar arterial territory and lacunar infarcts (LACI) are confined to the deep perforating arteries. LACI, i.e. small vessel disease with small deep infarcts due to occlusion of a penetrating artery, account for up to 25% of all ischemic strokes (59). TACI, traditionally affecting around 20% are associated with more dependency and higher mortality, PACI with higer risk of stroke recurrence earlier than POCI, and both LACI and POCI are associated with better outcome.

The TOAST classification was introduced in 1993 to improve the subclassification of ischemic stroke (60). The TOAST criteria identify the most probable pathophysiological mechanism on the basis of the clinical neurological examination and results of paraclinical findings. Differentiation among etiological subgroups of cerebral infarction has therapeutic implications, and makes it easier to predict prognosis. The TOAST classification divides patients with ischemic stroke into five subgroups according to the presumed etiological mechanism that lead to vessel occlusion: cardio embolic disease, large vessel disease, small vessel disease, unusual causes of stroke and stroke of undetermined etiology. Stroke of unusual etiology is caused by mechanisms such as hypercoagulable conditions or hematologic disorders. Stroke of undetermined etiology has either no probable etiology or more than one potential cause.

Identification of the underlying cause of stroke is important since etiological information may influence both acute treatment and secondary preventive strategies. The TOAST classification is based on clinical and radiological findings as well as supplementary investigations such as colour duplex of precerebral arteries, ECG, echocardiography and blood samples. The TOAST classification has been found to be valid and reliable (61). However, the TOAST classification is under debate (62) since most etiological diagnoses are based on presumptions and not on a pathological confirmation. When MRI techniques are more available, cortical involvement are found in patients with clinical lacunar syndromes and vice versa. In addition, this full assessment for classification requires extensive investigations. Further, the use of

undetermined cause in a clinical setting may be difficult when there is evidence for two possible etiological mechanisms even if one is the most probable. In order to reduce the proportion of patients classified as undetermined cause, other classification systems have been introduced. Causative Classification System (CCS) and ASCO (A for atherosclerosis, S for small vessel disease, C for cardiac source, O for other cause), have shown good agreement with the TOAST classification, but have not been applied in larger stroke studies (63).

Some colleagues differentiate between major and minor stroke. These concepts are related to the degree of dependency, where patients with minor stroke are in no need for assistance in personal activities of daily living (P-ADL), while patients with major stroke are dependent in activities regarding daily living.

2.1.6 Classification of neurological and functional impairments in stroke

Neurological impairments can be assessed using the NIHSS (64). Neurological deficits include assessment of consciousness and orientation, motor deficits, language, impaired coordination, inattention deficits, homonymous hemianopia and sensibility. NIHSS is used by stroke physicians for evaluation of size and topographic location in the acute phase, for decision making regarding acute therapy, for evaluation of the therapy, for predicting prognosis and as a measure of neurological handicap. In our stroke unit, NIHSS is also used by trained nurses to monitor the neurological impairments in the acute phase. NIHSS can be used in clinical trials to predict outcome (65).

Functional disabilities are often measured using the Barthel Activities of Daily Living index (Barthel ADL index) (66). This scale includes impairments involving eating, personal hygiene, bowel-and bladder control, moving and walking. The index may be helpful when plans are made for further rehabilitation and need for care and assistance after discharge from the stroke unit.

The modified Rankin scale (mRs) (66) is regarded as a global stroke scale scoring patients' daily functioning from 0 (no symptoms) to 5 (severe disability, bedridden, in need of constant care) or 6 (death). mRs is widely used to assess global outcome after stroke in various stroke studies (67).

2.1.7 Risk factors for stroke

The term "risk factor" was raised based on results from the Framingham study, initiated in 1949 to seek out a single cause sufficient to produce cardiovascular disease. Age is the most powerful risk factor for stroke (68). The probability of stroke in an individual depends on the presence and level of risk factors (69). The risk associated with each factor varies widely depending on the burden of associated risk factors (68). Further, the increase in risk usually starts from the age 55-64 (70).

The key vascular risk factors for stroke are hypertension, atrial fibrillation and diabetes mellitus, anthropometrical measurements (waist and hip circumference, height and weight), physical activity, diet and alcohol intake, smoking status, and psychosocial factors (stress and depression) (71;72). Persons with a normal BP (<120/80 mm Hg) have approximately half the lifetime risk of stroke compared with those with high BP (≥140/90 mm Hg) (73). For ischemic stroke, 60-80% can be attributed to increased blood pressure, increased blood cholesterol, cigarette smoking, carotid stenosis and diabetes mellitus (atherosclerotic ischemic stroke) and AF and valvular heart disease (cardiogenic ischemic stroke) (72).

Based on the INTERSTROKE study (71), the risk for stroke compared to persons without stroke and the independent contribution of each risk factor to the burden of stroke is listed below (Table 2). Population-attributable risk (PAR) is the risk of stroke in a total population that can be attributed to exposure to a specific risk factor.

Table 2. Risk factors for stroke

Risk factor	OR	CI	PAR %	CI
Hypertension	2.64	2.26-3-08	34.6	30.4-39.1
Current smoking	2.09	1.75-2.51	18.9	15.3-23.1
Waist-to-hip ratio*	1.65	1.36-1.99	26.5	18.8-36.0
Diet*	1.35	1.11-1.64	18.8	11.2-29.7
Physical activity	0.69	0.53-0.90	28.5	14.5-48.5
Diabetes mellitus	1.36	1.10-1.68	5.0	2.6-9.5
Alcohol intake**	1.51	1.18-1.92	3.8	0.9-14.4
Stress	1.30	1.06-1.60	4.6	2.1-9.6
Depression	1.35	1.10-1.66	5.2	2.7-9.8
Cardiac causes	2.38	1.77-3.20	6.7	4.8-9.1
Apolipoproteins B/A1*	1.89	1.49-2.40	24.9	15.7-37.1

*highest vs lowest tertile
**more than 30 drinks per month or binge drinking
OR=Odds Ratio; CI= Confidence interval; PAR=population-attributable risk; Hypertension=self-reported history of hypertension or the composite of self-reported hypertension or blood pressure ≥160/90 mm Hg; Current smoking= any tobacco use the last 12 months; Physical activity=moderate exercise (walking, cycling or gardening) or strenuous exercise (jogging, football and vigorous swimming) for 4 hours or more per week; stress= general stress at home and in the workplace (permanent or several periods of stress vs no or some periods of stress in the past year); Depression= feeling sad, blue or depressed for two or more consecutive weeks during the past 12 months; cardiac causes= atrial fibrillation or flutter, previous myocardial infarction, rheumatic valve disease or prosthetic heart valve

Reynolds et al (74) suggested a J-shaped association of alcohol and all strokes. The diet risk score was based on foods that are associated with an increased or reduced risk of stroke. This score was based on findings in the INTERHEART study. They identified three major dietary patterns: Oriental (high intake of tofu and soya and other sauces), Western (high in fried foods, salty snacks, eggs and meat) and Prudent (high in fruit and vegetables) (75), where higher levels of the prudent pattern were protective against acute myocardial infarction. The dominant components in the Mediterranean diet, associated with a reduction in total mortality and cardiovascular risk, are moderate consumption of ethanol, low consumption of meat and meat products and high consumption of vegetables, fruits and nuts, olive oil and legumes (76;77).

Regarding physical activity, 15 min a day or 90 min a week of moderate-intensity exercise might be of benefit, even for individuals at risk of cardiovascular disease (78). Physical activity is also associated with reduced risk of stroke (79). Cigarette smokers have an excess risk of stroke, RR 1.5 (95% CI 1.4-1.6) (80), and the risk of stroke declines considerably and rapidly after smoking cessation (81). Elevated body mass index (BMI) is a risk factor for

ischemic stroke (82). Abdominal obesity is an independent risk factor for ischemic stroke (83;84), stronger than BMI and with a greater effect among younger persons.

Based on the findings from the INTERSTROKE study, targeted intervention for primary prevention should include reducing blood pressure, hyperlipidaemia and smoking, appropriately treatment of diabetes, promote physical activity, obesity and weight reduction and a healthy diet.

Guidelines regarding primary prevention are listed in Table 4.

2.1.8 Secondary prevention after stroke

Antiplatelet therapy is protective in most types of patients at increased risk of occlusive vascular events (85). Addition of modified-release dipyridamole to aspirin leads to a relative risk reduction of all major vascular events of 22% (86). The combination of aspirin and dipyridamole was recommended as antithrombotic therapy after cerebral ischemia of arterial origin (87). Long-term administration of clopidogrel to patients with atherosclerotic vascular disease was more effective than aspirin in reducing the risk of ischemic stroke, myocardial infarction or vascular death (88). The PRoFESS study (89) showed similar rates of recurrent stroke with aspirin and dipyridamole versus clopidogrel. The combination of aspirin and clopidogrel did not reduce the risk of stroke, MI, vascular death or re-hospitalization, compared to clopidogrel alone, however, life-threatening or major bleeding increased (90). However, the choice of antiplatelet regime is contentious (91), and the recent guidelines (92) no longer specify the antiplatelet regime.

Anticoagulant therapy is superior to antiplatelet therapy for the prevention of stroke in people with non-rheumatic artial fibrillation with or without a history of stroke or TIA (55;56). Warfarin and antiplatelet agents reduce stroke by approximately 60% and 20 % respectively in patients with atrial fibrillation (93). Different risk stratification schemes have been developed. Patients with low risk for developing stroke according to the $CHADS_2$ score (congestive heart failure, hypertension, age, diabetes mellitus and prior stroke or TIA) (94)(Table 3) or who have contraindications against oral anticoagulation with vitamin K antagonists, should be treated with aspirin (95). CHA(2)DS(2)-VASc adds risk factors-age 65-74 years, presence of vascular disease and female sex, and gives two points for age 75 years or older, identifying those with a truly low risk but more with high risk (96). Since both risk of stroke and incidence of AF increase with age, stroke prevention in the elderly is important. Age alone is not regarded as a contraindication for anticoagulation (94).

Table 3. $CHADS_2$ score

Risk factor	Points allocated
Prior stroke or TIA	2
Age >75 years	1
Hypertension	1
Diabetes mellitus	1
Heart failure	1

Weimar, expert reviews 2009 (94).

Dabigatran, an oral reversible direct thrombin inhibitor, reduces stroke in patients with AF and previous cerebrovascular events (97). 150 mg twice daily was superior to warfarin while

110 mg twice daily was non-inferior. Rivaroxaban is an alternative to warfarin for prevention of initial and recurrent stroke in patients with AF (98).

The Framingham study showed that a risk factor seldom occurs alone, and the risk associated with each varies widely depending on the burden of associated risk factors (68). Aggressive control of the individuals' risk factors requires multivariable risk assessment. Further, the Framingham study showed that the average number of risk factors increased with the patients' weight (68). Treatment of high blood pressure (99) is associated with reduced stroke recurrence after stroke or TIA. An absolute target blood pressure level and reduction is uncertain, and should be individualized, but benefit has been associated with an average reduction of almost 10/5 mm Hg, and normal blood pressure levels have been defined as <120/80 mm Hg (92;100). Lifestyle modifications should be included as part of a comprehensive antihypertensive therapy (92). Treatment of hypertension in the acute phase does not affect outcome positively (101).

In the SPARCL (Stroke Prevention by Aggressive Reduction in Cholesterol Levels) trial (102), statin therapy with high dose of atorvastatin reduces stroke recurrence (HR 0.84; 95% CI 0.71-0.99). 96% reached ≥50% decrease in LDL. In the Heart Protection Study (HPS) (103), simvastatin reduced vascular events in patients with prior stroke, and reduced stroke in patients with other vascular disease (RR 0.76). Management of elevated cholesterol includes, in addition to statin agents, lifestyle modifications and dietary guidelines (100). There is good evidence that lowering blood cholesterol with statins reduces stroke risk and carotid atherosclerosis, independently of blood cholesterol, blood pressure and age (104).

Regarding cigarette smoking, diet and overweight, there are no specific data regarding secondary prevention. However, there is evidence for recommending smoking cessation. Further, there is consensus regarding reduction of heavy consumption of alcohol. In the AHA/ASA guidelines, light to moderate levels of no more than two drinks per day for men and one drink per day for non-pregnant women may be considered (92;100). Weight reduction may be considered for all overweight patients with ischemic stroke and TIA to maintain the goal of BMI between 18.5 and 24.9 kg/m^2 and waist circumference of <88 cm in women and <102 cm in men. However, low BMI is an independent risk factor of total mortality in the elderly (105), and a reduction of BMI up to 28 kg/m^2 may not be beneficial in older adults. Clinicians should encourage weight management through an appropriate balance of calorie intake, physical activity and behavioral counseling (100). Regarding diet, the general recommendation from 2006 was to balance calorie intake and physical activity to achieve or maintain a healthy body weight. Further, we should encourage consuming a diet rich in vegetables and fruit, high-fiber foods, oily fish at least twice a week, minimize beverages and foods added with sugar, prepare foods with little or no salt and limit the intake of saturated fat (106).

For patients capable of engaging in physical activity, at least 30 minutes of moderate-intensity physical activity most days is now recommended (100). Earlier recommendations were 30-60 minutes 3-4 days a week (107) and 20-60 minutes 3-7 days a week (108). A supervised therapeutic exercise regime is recommended for individuals with disabilities (100). Rehabilitation programs are designed to optimize functional motor performance in stroke survivors and to improve muscle strength and cardio-respiratory fitness (108). The range of the approach varies from remedial gait retraining in hemiparetic stroke patients to supervised or home-based walking, running or strength training.

Increased homocysteine is associated with increased risk of ischemic stroke (109). In 2006, there was insufficient evidence to confirm that homocysteine was a modifiable risk factor for stroke (110;111), but recommended based on a meta-analysis (112). However, daily administration of folic acid, vitamin B6 and vitamin B12 to patients with recent stroke or TIA was safe but did not reduce the incidence of major vascular events (113). These results did not support the use of B vitamins to prevent recurrent stroke.

Table 4. Risk factor management regarding primary and secondary stroke prevention

Risk factor	Secondary prevention*	Secondary prevention**	Secondary prevention***	Secondary prevention****	Secondary prevention*****	Primary prevention**	Primary prevention****
Hyper-tension	BT <140/90	Blood pressure should be lowered, irrespective of its level	Should be individualized, but benefit has been associated with an average reduction of almost 10/5 mm Hg	Blood pressure lowering is recommended, target BP should be individualized, normal BP is defined as <120/80	BP reduction is recommended, and should be individualized. Benefit is associated with a reduction of approximately 10/5 mm Hg	<140/90 (<135/85 in diabetes)	Aiming normal levels of 120/80 mm Hg (<130/80 in diabetes) Should be lowered to 140/85 mm Hg or below
Current smoking	Cessation	All smokers should stop smoking, especially patients who have had stroke	Advise to quit	Discouraged	Strongly advise the patients to quit	Discouraged	Discouraged
Body mass index	≤120% of ideal body weight for height		Maintain BMI 18.5-24.9	Subjects with an elevated body mass index are recommended to adopt a weight-reducing diet		Subjects with an elevated body mass index should take a weight-reducing diet	Subjects with an elevated body mass index (≥25) should take a weight-reducing diet
Diet				A low salt, low saturated fat, high fruit and vegetable diet rich in fiber is recommended		A low salt, low saturated fat, high fruit and vegetable diet rich in fibre is recommended	A diet low in salt and saturated fat, high in fruit and vegetable and rich in fibre is recommended
Physical activity	30-60 minutes of activity at least 3-4 times/week		At least 30 min of moderat-intensity physical exercise most days	Regular physical activity is recommended	At least 30 min of moderate-intensity physical exercise 1 to 3 times a week	Regular physical activity is recommended	Regular physical activity is recommended 2-5 hour per week
Diabetes mellitus	Glu<6.99		More rigorous control of blood pressure and lipids. Glucose control. HBA1c ≤7		Use existing guidelines for glycemic control and BP targets	Control of glucose level due to benefits of other diabetic complications	Individualized pharmacological therapy. When diabetes: BT below 130/80
Alcohol intake	Moderat consumtion (≤2 drinks/d)		Heavy drinkers should reduce consumption.	Heavy use should be discouraged	Heavy drinkers should eliminate or reduce their consuption	Heavy use should be discouraged	Heavy use should be discouraged
Hyper-lipidaemia	LDL<2.6	Statin therapy should be considered	Target LDL<2,6	Statin therapy is recommended in subjects with non-cardio-embolic stroke	Statin therapy is recommended when evidence of atherosclerosis and LDL >2.5. Target: 50% reduction of LDL or LDL <1.8	Simvastatin in high-risk patients	If LDL >3.9 mmol/l, lifestyle intervention and a statin
Hormone replacement therapy		Not recomended		Not recommended	Not recommended	Should not be used	Not recommended

* Preventing Ischemic Stroke in Patients With Prior Stroke and TIA, AHA, Stroke 1999 (107)
**European Stroke Initiative Recommendations for Stroke Management-Update 2003 (114)
*** Guidelines for Prevention of Stroke in Patients With Ischemic Stroke or Transient Ischemic Attack, AHA/ASA Guidelines 2006 (100)
**** Guidelines for management of Ischaemic Stroke and Transient Ischaemic Attack 2008 (22)
*****Guidelines for the Prevention Of Stroke In Patients With Stroke or Transient Ischemic Attack, AHA/ASA Guidelines 2011 (92)

Hormone replacement therapy, estrogen with or without progestin, was frequently used to treat symptoms of menopause and to prevent osteoporosis and cardiovascular disease. However, use is associated with increased risk of ischemic stroke (115) and not recommended after stroke (92).

Traditionally, there is a gap between recommended secondary prevention and observed practice (116). Secondary prevention treatment declines rapidly during the first two years after stroke (117), and almost one-third of patients with stroke discontinue secondary prevention within the first year of hospital discharge (118). There is lack of effective interventions to improve persistent adherence to treatment post-stroke (117).

2.1.9 Cognitive impairments after stroke

Cognitive impairments after stroke include focal dysfunctions from the stroke lesion and more global dysfunction probably related to hypoperfusion and underlying vascular and degenerative pathology (119).

The most well-known and classical cognitive deficit occurring in acute stroke is aphasia which affects approximately 15-25% of all stroke patients (120;121). Cortical lesions in the dominant hemisphere (left side in most cases) may lead to aphasia (language impairment), apraxia (loss of ability to perform learned tasks) and agnosia (loss of ability to recognize objects), while cortical lesions in the right hemisphere frequently may cause inattention phenomena and neglect (failure to attend or respond to stimuli on the side contralateral to the stroke), visuospatial impairments (the ability to understand visual representations and their spatial relationships) and reduced insight in one's own situation.

Global cognitive deficits post-stroke include impaired memory, impaired concentration, reduced psychomotor speed and attention, reduced executive functioning and general fatigue (122). Executive function involves the ability to sequence, plan, organize, initiate and shift between tasks. The characteristic cognitive profile of subcortical ischemic vascular disease includes early impairment of attention and executive function, with slowing of motor performance and information processing. Additional impairments of global cognition may be associated with worse functional outcomes (123).

Post-stroke dementia is defined as any dementia occurring after stroke, and includes VaD, degenerative dementia (mostly AD) and mixed dementia (coexistence of vascular and degenerative changes). Vascular and degenerative changes seem to interact and coexist in post-stroke dementia, resulting in cumulative brain damage and cognitive decline (12;124). Post-stroke cognitive impairments include the continuum from subjective and mild cognitive impairment to manifest dementia. The prevalence of post-stroke dementia is increasing, probably mainly due to the decline in stroke mortality and the increasing life expectancy in the population. Suffering a stroke doubles the risk of dementia (125). Previous studies have reported different rates of post-stroke dementia; the prevalence estimated one year after stroke varies between 7.4 % in population-based studies of first-ever stroke, when patients with pre-stroke dementia are excluded, to 41.3 % in hospital-based cohorts including recurrent stroke and pre-stroke dementia (126). Rates of post-stroke cognitive impairment differ even more, from 11.6 to 56.3 % (8), depending on the population under study, criteria for cognitive impairment, and the time-interval between stroke and testing.

In 2007, the hypothesis regarding prevention of cognitive symptoms after stroke by intensive vascular risk factor intervention was based mainly on logical assumptions: VaD and AD share

the same vascular risk factors and there is an increased risk of dementia after stroke. In addition, active treatment of blood pressure was related to reduced risk of dementia and cognitive decline associated with recurrent stroke, supporting the recommendation of blood pressure therapy post-stroke (127).

Today, there is still little evidence for effect of vascular risk factor control and prevention of post-stroke cognitive impairment. Few studies include cognitive outcome measures as primary endpoints. However, despite limited evidence, management of vascular risk and lifestyle factors are recommended post-stroke (128). Better pre- and post-stroke control of vascular risk factors and improved stroke care may contribute to preserving cognitive functioning after stroke (129).

Vascular risk factors contribute not only to vascular dementia, but most probably also in the cascade of Alzheimer pathology proceeding to clinical dementia (11). In patients with neuropathological signs of AD, the presence of vascular lesions seems to accelerate the debut of clinical symptoms (130), and the presence of one or two apolipoprotein E (Apo E) 4 alleles is found to be a risk factor for cognitive impairment after stroke (131).

2.1.10 Assessments of cognitive impairments after stroke

Cognitive assessment in the acute phase is complicated due to lack of standardized assessment tools for testing post-stroke and less knowledge regarding pre-stroke cognitive function. In addition, the patients may be influenced by medical factors (ie, previous stroke, aphasia, neglect, fever, medication, delirium). The use of cognitive assessments in the acute phase of stroke cannot be used for the diagnosis of dementia or the diagnosis of Mild Cognitive impairment (MCI), but for detection of cognitive deficits and to evaluate whether there is a need for rehabilitation, assistance to support performance of activities of daily living and for follow-up.

Patients suffering from stroke may have specific cognitive deficits (ie, aphasia or neglect) as well as more global cognitive dysfunction. Cognitive assessments should evaluate different cognitive domains, including testing for language, neglect, praxis and more global cognitive function including memory, motor speed, executive function and attention. Screening tools should be sensitive enough to detect all those with symptoms and specific, in order to identify symptoms only if present. Further, the test should be quick and easy to administer and the patients must be able to tolerate the assessments.

The Mini Mental State Examination (MMSE) (132) is widely used for global cognitive screening, but may not be so useful in detection of cognitive impairments after stroke due to lack of sensitivity (133). The standard cognitive measures tend to underestimate executive dysfunction and effects of cognitive dysfunction on global and daily function. The coexistence with physical deficits may also complicate the assessment.

In the present study we included the following instruments to assess the different domains:.

- The MMSE (standard, 30-point). MMSE is considered as a screening for global cognitive functioning, and evaluates orientation, concentration, language, praxis and memory. The test does not include a measure of executive functioning.
- The Clock Drawing Test (CDT) (134;135). This is primarily a measure for visuospatial functions.

- The Trail Making Test A and B (TMT A and B) (136). The TMT A is a measure of focused visual attention and information processing, while TMT B measures executive functioning in which participants connect a series of alternating numbers and letters. TMT A is a predictor for cognitive ability post-stroke (137).
- The 10 word test (max score 40) including delayed recall from the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) (138). This is a measure of memory impairment. It is a test of verbal episodic memory with immediate and delayed recall scores.
- Figure drawings from Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog) (139). The ADAS-cog was designed to evaluate both cognitive and non-cognitive behavioural dysfunctions in patients with AD. The figure drawings tests visuoconstruction.
- Ullevaal Aphasia Screening (UAS) (140) is used for aphasia screening, a simple test for nurses identifying language disability.

Unfortunately, pre-stroke cognition is impossible to measure post-stroke. Retrospective (post-stroke) assessment of pre-stroke cognition can be done with the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) (141), which was used in the present study. The ICCODE is applied to measure a possible cognitive reduction over the last 10 years preceding the stroke, and is based on an interview with a family member or carer who knows the patient well. The IQCODE is a measure of general cognitive decline, and is relatively unaffected by education and pre morbid intellectual ability (142).

2.1.11 Prognosis after stroke

In 1997 a Norwegian study reported that about 19% of patients with acute stroke died within 30 days, 10,9% due to cerebral infarction (18). Twelve years later, thirty-day mortality by ischemic stroke is reduced to 2.8% in Norway in 2009 (6). Two-thirds of the decreasing mortality in the past decades are attributable to reduced case fatality, and one third to reduced attack rate (143). The first is related to treatment, the latter to prevention (4).

One-year survivors of first-ever stroke continue to die over the next 4 years at a rate of approximately 10% per year (144). The 1-year mortality for patients with TACI is higher (about 60%) than PACI and POCI (about 15-20%), which in turn is higher than patients with LACI (10%) (145). The most common cause of death is cardiovascular disease (145)(same ref). In Norway, the 12-year mortality rate was 86.5% (146), associated with age, male sex, stroke severity, ischemic heart disease, diabetes and hemorrhagic stroke. A significantly higher case-fatality rate was observed among recurrent stroke and with increasing age (143).

In addition to mortality, disability represents the most relevant negative clinical outcome. Stroke is, after AD and other dementia related neurological disorders, the main cause of long-term neurological disability in adults with up to one-third of survivors being left dependent on others for everyday activities (5). The best predictors of stroke recovery at 3 months are the initial neurological deficits and age (147). Other factors influencing the outcome include high blood glucose concentrations, urinary incontinence (148), body temperature, previous stroke and right and left arm weakness together with the mRS score 48 to 72 hours (147). Female gender was found to be a predictor for functional independence, but not mortality. Neurological complications, including recurrent stroke, parenchymal hemorrhage and epileptic seizures were associated with impaired function. Compared to other stroke types, lacunar strokes have better prognosis including almost no acute mortality and a general good

short-time recovery. However, in the long term there is an excess risk of death, recurrent stroke and development of cognitive dysfunctions.

When we consider prognosis, we have to include the risk of developing cognitive impairment, dementia and other behavioral dysfunctions including asymptomatic progression of small-vessel disease. Cognitive impairments after stroke have received growing attention in the past decade. Lacunar infarcts are regarded as a marker of cerebral small vessel disease with increased risk of disability, cognitive impairment and dementia (59).

2.2 Dementia and Mild Cognitive Impairment (MCI)

Dementia is from the Latin term demens, from de- "without" and -mens "mind". Dementia is defined as a chronic condition due to diseases in the brain characterized with cognitive impairment, impairment in activities of daily living and with affection of behavior or personality. Dementia may not be considered as a disease, but as a syndrome. According to International Classification of Diseases (ICD-10) (149) and Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition) (DSM-IV) (150) criteria the syndrome is defined in different ways, but most people with dementia are captured by both definitions (151).

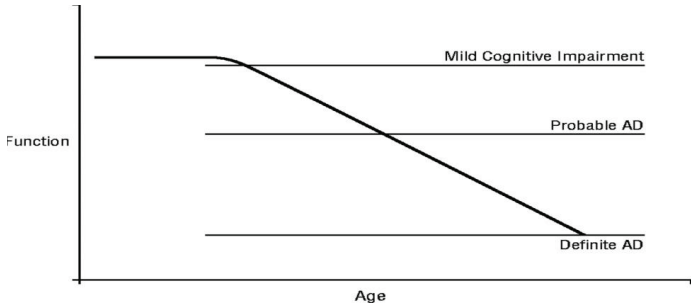
2.2.1 The cognitive impairment in dementia

The cognitive impairment involves memory, attention, language, problem solving, executive functions and the general processing of information. The symptoms influence the patients' performance in the ADL and to some degree the patient's behavior. The symptoms have to be persistent for six months to obtain a confident clinical diagnosis according to the ICD-10 criteria.

2.2.2 Mild Cognitive Impairment (MCI)

MCI is considered a transitional state between the cognitive changes of normal aging and dementia. Many definitions exist, but the one most used is that of the Mayo clinic (152). The degree of cognitive impairment does not influence on the ADL function. When these persons are observed longitudinally, about half of them progress to clinically dementia within five years (153;154). Consequently, this condition has been recognized as suitable for possible therapeutic intervention.

Figure 3. Theoretical progression of a person developing Alzheimer's disease (AD)



Petersen, R. C. (153).

2.2.3 Prevalence of dementia

Dementia affects more than 60.000 persons (probably 70 000) in Norway (7;155). The prevalence increases with increasing age, and affects around 15% at age 75 and higher. Every year, 9000 persons in Norway are diagnosed with dementia, most often of degenerative origin, but also of vascular and mixed etiology. Late-life AD debuts after the age of 65, the early form before.

The prevalence of all-cause dementia almost doubles every 5 years of age (156), and the prevalence of dementia and AD rise linearly with an increase exponentially with age.

2.2.4 Etiology of dementia

In younger patients with dementia, one etiology may dominate. In the elderly, the etiology is often mixed with coexistence of vascular and degenerative components.

Dementia can be due to neurodegenerative disorders like AD (60%) (157;158), fronto-temporal dementia (FTD) (5%), Lewy-Body disease and Parkinson's disease (15%) or cerebrovascular changes (vascular dementia (20%) and dementia in association with traumas, tumors and endocrine, infectious or autoimmune diseases (159-161). In younger persons, 40% suffer from pure AD and 20-30% from FTD. The hallmark lesions of AD are Aβ plaques (amyloid accumulation) and neurofibrillary tangles (marker of neuronal injury) formed by abnormal tau (162).

Cognitive impairments associated with cerebrovascular disease extend beyond the traditional concept of multi-infarct dementia, and refer to cognitive decline due to vascular disease (161).

2.2.5 Diagnosis of dementia

The diagnostic assessments of dementia start with a careful anamnesis from the patient and the spouse or close relative/friend, a clinical examination, cognitive assessments and a physical examination, including blood tests.

Examination of biomarkers in cerebrospinal fluid and advanced brain imaging techniques facilitate a more precise etiological diagnosis (differential diagnosis) of a given type of dementia.

The diagnosis is based on different criteria such as the DSM-IV and the ICD-10. The DSM-IV criteria include changes in personality, whereas the ICD-10 includes changes in behavior.

Table 5. Dementia according to the ICD-10 criteria for research

A. Evidence of each of the following 1. Decline in memory (mainly episodic memory) 2. Decline in other cognitive abilities (at least one)
Deficits in criterion A cause a significant impairment of social functioning
B. Absence or clouding of consciousness
C. Decline in emotional control or motivation or a change in social behavior
D. Symptoms in criterion A have been present ≥6 month

2.2.6 Diagnosis of MCI

Individuals with cognitive impairments but preserved performance in activities of daily living who do not meet the criteria for overt dementia are referred as patients with MCI (152;153). According to the criteria, besides subjective memory impairment, preserved general intellectual function, intact ADL and absence of overt dementia, objective memory impairment must be present to meet the diagnostic criteria for MCI. Another set of criteria is made by Winblads et al (163) that include patients with deficits in different cognitive domains.

Impairment in episodic memory, atrophy on MRI and AD biomarkers in spinal fluid can be used to predict the likelihood of progression to dementia (164), affecting 40-60% of patients with MCI (154). The use of biomarkers for prediction is under debate (165), and clinical

criteria without use of biomarkers persist (166). Some patients with subjective cognitive impairment may also develop AD, but after longer follow-up time (167).

2.2.7 Diagnosis dementia due to Alzheimer's disease

The clinical characteristic for AD is an insidious onset and a gradual decline in cognitive function. For the majority of patients, the initial symptom is impairment in episodic memory, affecting the ability to learn and retain new information. This is followed by impairments in other cognitive domains including executive function, language and spatial ability.

A diagnosis of dementia due to Alzheimer's disease is made in ICD-10 (Table 6).

Table 6. Alzheimer's disease according to the ICD-10 criteria

1. Evidence of dementia according to the ICD-10 criteria
2. Evidence of no other organic brain disorder or drug induces affection

It also differentiates between early onset and late onset AD. Below the age of 65, the start or progression is fast or the cortical deficits are multiple. In AD with debut in older age, the start and progression is slower and the memory impairment is dominating.

A diagnosis of dementia due to Alzheimer's disease based on the DSM-IV criteria is the development of multiple cognitive deficits that include memory impairments and impairment in at least one other cognitive domain that is a decline from the previous level of functioning and is sufficiently severe to cause impairment in function.

A diagnosis of AD can also be made according to the National Institute of Neurological Disorders and Stroke criteria (NINCSDS-ADRDA) (157). These clinical criteria include insidious onset and progressive impairment of memory and other cognitive functions. These criteria were revised in 2011 (158). The core clinical criteria for AD dementia are the cornerstone of the diagnosis in clinical practice.

The most frequently used CSF biomarkers are beta-amyloid peptide, total tau-protien (T-tau) and phosphorylated tau (P-tau) (168). There is an inverse correlation between CSF levels of beta-amyloid and brain amyloid deposition (169). Elevated T-tau and P-tau are probable markers for axonal damage and tangle formation (170). For discrimination of AD from non-AD the sensitivity of all the CSF biomarkers are 80% and the specificity 93% (171).

New research criteria for the AD diagnosis have been proposed by experts (172) and include, in addition to memory impairment, at least one positive biomarker (MRI/PET/CFS markers). Brain images are recommended because they can improve diagnostic accuracy (173). Much work lies ahead for validating the biomarker diagnosis of AD dementia, and the new proposed criteria for use in research.

2.2.8 Diagnosis of vascular dementia

VaD is a heterogeneous clinical condition based on various vascular pathological processes underlying the subtypes of cerebrovascular disease. This includes lacunar infarction, cortical infarction, subcortical infarction, white matter lesions, cardiogenic emboli, hypotensive infarction, intracerebral hemorrhages, lobal hemorrhages and subarachnoid hemorrhage.
The criteria for VaD include the criteria for the dementia syndrome that should be caused by a vascular disorder. The most used criteria are those in ICD-10 (Table 7), DSM-IV and

National Institute of Neurological Disorders and Stroke-Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN), none of which are ideal (174). ICD-10 and NINDS-AIREN require focal neurological signs, ICD-10 and DSM-IV do not include neuroimaging and ICD-10 has a requirement of unequal distribution of higher cognitive functions. In the DSM-V, expected in 2013, the new concept “neurocognitive disorders” will be introduced, dividinginto major and minor depending on whether ADL are affected or not, and includes the underlying cause for the cognitive impairment.

Table 7. Vacular dementia (VaD) according to the ICD-10 criteria

A	Dementia according to theICD-10 criteria
B	Deficits in higher cognitive functions are unequally disturbed
C	Clinical evidence of focal brain damage
D	Evidence from history, examination or tests of a significant cerebrovascular disease (eg. a history of stroke, evidence of cerebral infarction)

2.2.9 Diagnosis of vascular cognitive impairment

The concept of vascular cognitive impairment (VCI) has been introduced to capture the entire spectrum of cognitive disorders associated with cerebrovascular disease (161). VCI refers to the total vascular burden on the brain, and the effect of vascular disease or lesions on cognition. Vascular disease includes both the cerebrovascular event and small vessel disease without stroke (ie, silent lacunar infarcts, ischemic white matter lesions and incomplete ischemic injuries).VCI refers to cognitive impairments due to cerebral vascular disease not fulfilled by traditional criteria for dementia.

2.2.10 Neuroimaging

Cerebral MRI is used to identify a core area of the stroke lesion which is often associated with impairment of a corresponding cognitive function. In addition, imaging can identify subclinical injury including cerebrovascular disease and regional and global atrophy. Since all these factors are thought to act synergistically in the development of cognitive dysfunction after stroke, evaluation of cerebral MRI should be included in post-stroke cognitive assessments.

Measurements of cerebral white matter lesions (WML), white matter hyperintensities (WMH) or white matter changes (WMC) changes from CT and MRI can be done using scores to quantify white matter lesions (175-178), or semi-automated methods (179;180). White matter lesions present as diffuse low-density areas on CT scans and as areas of hyperintensity on T2- and FLAIR-weighted MRI scans. These white matter lesions/hyperintensities/changes, initially described in 1987 and named leuko-araiosis (181), are related to variable degrees of demyelination, axonal loss and gliosis (182).

Cerebral atrophy can be measured according to the method first described by Scheltens et al (183). Based on the height of the hippocampal formation and enlargement of the surrounding cerebrospinal fluid spaces, the medial temporal lobe atrophy (MTLA) is graded from 0 to 4. MTLA grade 0=no atrophy; MTLA 4=highest degree of atrophy. MTLA 0-1 is considered a normal value. Other methods, including volume measures, are available.

2.2.11 Risk factors of dementia

The strongest risk factor for dementia is increasing age (184), followed by having the ApoE ε4 allele (185), midlife hypertension and high cholesterol (186) and head injury (187). Other vascular risk factors, such as high midlife waist-to-hip ratio (188), smoking (189), slow physical performance (184), diabetes (190;191) and elevated homocysteine (192), also represent a risk for late-life dementia. Stroke and vascular risk factors increase the risk of both AD and VaD.

Hypertension is a risk for general atherosclerosis including stroke and cardiovascular disease. There is reported an association between high blood pressure and later development of dementia, both AD (193) and VaD (194). In AD, blood pressure is increased 5-15 years before dementia onset, and then decreases in the years immediately preceding dementia onset (193). Blood pressure continues to decrease during the disease process.

In addition, various genetic and environmental factors, including early-life brain development, body growth, socioeconomic conditions, environmental enrichment and cognitive reserve, are likely to contribute to dementia risk (195). The decreased reserve capacity of the brain include reduced brain size, low educational and occupational attainment, low mental ability in early life and reduced mental and physical activity during late life (162). However, regarding these factors, there is less evidence, compared to the knowledge about the vascular risk factors.

Age, a low educational level and pre-stroke cognitive impairment are known risk factors for post-stroke dementia (126). In addition, diabetes and atrial fibrillation (AF) are significantly associated with post-stroke dementia. Most predictors relate to the stroke per se, i.e. stroke severity, stroke recurrence, left hemispheric lesion, and hemorrhagic etiology. Some of the most common complications of stroke are also described as risk factors, e.g. incontinence, epileptic seizures, hypotension and delirium (126).

Small vessel disease without stroke, including silent lacunar infarcts, ischemic white matter lesions and incomplete ischemic injury, is a marker of poor prognosis with increased risk of stroke, cognitive impairment, steep decline in global cognitive function, dementia and death (59;128;161;196-198).

2.2.12 Prevention and treatment of dementia

There is no clear evidence that any intervention can prevent or delay the onset of dementia.

In spite of this, most clinicians and researchers in the field recommend that vascular risk factors should be treated aggressively, not only to prevent heart disease and stroke, but to decrease the likelihood of cognitive impairment (and dementia) in later life (12;194). Aggressive control of the individual's risk factors requires multivariable risk assessment. Hypertension often clusters with other vascular risk factors, including diabetes mellitus, obesity, homocysteine and hypercholesterolemia, all related to dementia of both degenerative and vascular origin. Midlife control of vascular risk factors are of importance in order to preserve cognitive function, in addition to building a "cognitive reserve" through a healthy lifestyle including physical activity and mental stimulation.

Treatment of hypertension in the elderly shows reduction in stroke and total mortality (199), but does not statistically reduce the incidence of dementia (200), the latter maybe due to short

follow-up. One study has shown an association between antihypertensive treatment and a lower incidence of dementia (201).
The strongest predictor of cognitive decline after an initial stroke is the occurrence of a second stroke (128). The risk rises to approximately 30%. The prevention of VaD is based on stroke prevention which implies risk factor manipulation and use of antithrombotic drugs.

There is still no indication of any significant benefits from cognitive training in early stages of AD and VaD (202), but it is not possible to draw conclusions due to the lack of a- randomized controlled trial (RCT). Regarding diet, the Mediterranean dietary pattern may reduce the rate of cognitive decline with older age (203). Regular physical activity seems to protect against the occurrence of cognitive decline (204).

Prevention and treatment of dementia due to AD includes environmental involvement and medical treatment in order to preserve function. There is no disease modifying treatment in AD. Cholinesterase inhibitors (donepezil, rivastigmin and galantamine) are effective at the symptom level for mild to moderate AD and memantine for moderat to severe AD (173;205). Cholinesterase inhibitors delay the breakdown of acetylcholine released into synaptic clefts, and so enhance cholinergic neurotransmission. There is no evidence of any difference between them with respect to efficacy (205). There is lack of evidence regarding statin, anti-inflammatory drugs, vitamin E and Ginko.

Pharmacological approaches to reduce amyliod and/or tau deposits are in progress. Several clinical trials with monoclonal antibodies against amyloid-β are ongoing (206), but so far no positive results are published.

3. Objectives/aims

The four aims of the thesis were:

The TOAST study: To evaluate the distribution of the different etiological stroke subtypes in a hospital-based sample of first-ever patients with stroke or TIA, and to investigate the association between possible risk factors and stroke subtypes.

The intervention study: To investigate whether more intensive treatment of vascular risk factors in patients with first-ever stroke or TIA can influence post-stroke cognitive functioning in patients free from cognitive decline prior to the stroke.

The MCI/dementia study: To assess the incidence of post-stroke dementia and MCI one year after stroke and TIA in a population free from pre-stroke cognitive decline. Further, we wanted to investigate the different etiological subtypes of post-stroke dementia and MCI, using a new method of sub-classification.

The WML study: To evaluate the associations between WML and patients` performance at one year post-stroke on tests measuring executive functioning, memory and visuospatial function.

4. Methods

4.1 Participants

All patients with a first-ever stroke or TIA admitted to the stroke unit of Asker and Baerum Hospital between February 2007 and July 2008 were invited to participate in the study. Only those patients who survived the acute phase were assessed. The hospital has a policy of admitting all stroke patients directly to the stroke unit, and serves two local municipalities with a total population of approximately 160,000.

We excluded patients with subarachnoid hemorrhage, known cognitive decline as indicated by a score ≥3.7 on the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE), previous stroke or TIA, patients who did not speak Norwegian and patients with a life expectancy less than one year.

After inviting 253 patients, 250 patients accepted to participate in the study. Of these, 23 patients were excluded: 12 did not fill the inclusion criteria (six had an IQCODE score ≥3.7, one did not speak Norwegian, one had an infarct in the spinal cord, one had suffered a previous TIA, two withdrew their consent and one died before signing the consent) and 11 patients were diagnosed with other disease than stroke.

Of the 227 remaining patients, 174 (76.7%) had a cerebral infarction, 36 (15.9%) had suffered a TIA and 17 (7.5%) were diagnosed with a cerebral hemorrhage.

For the TOAST study, only patients with ischemic cerebrovascular disease, i.e. infarction or TIA, were included in statistical analyses regarding the TOAST classification (n=209). After the follow-up, one patient was found to be wrongly classified.

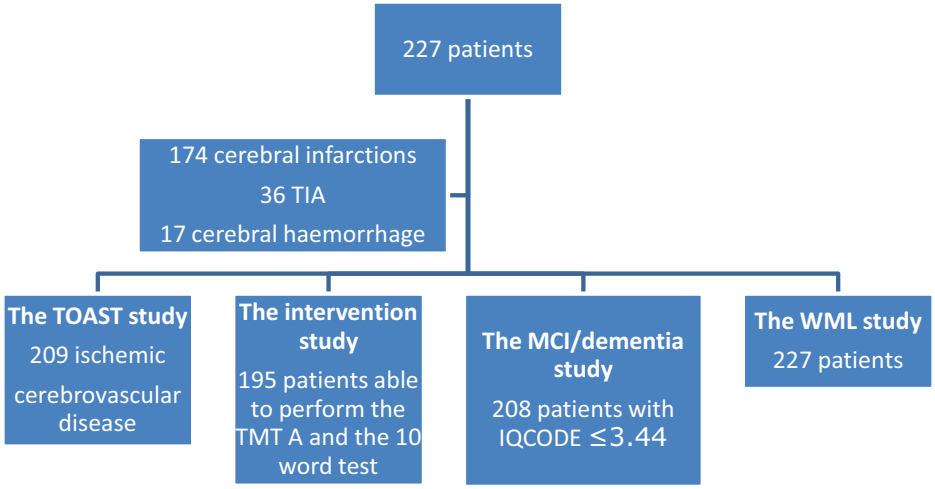
For the intervention study, only patients who were able to perform the TMT A, the 10 word test or both were randomized. After excluding 32 patients (24 not testable, three persons suffered a new stroke before randomization, two did not want randomization, one was diagnosed with a new subdural hematoma, one was diagnosed with advanced cancer and one withdrew his consent after advanced heart surgery), 195 patients were randomized to either the intervention group (n=98) or the control group (n=97).

During the follow-up period of 12 months, eight patients discontinued and five patients died in the intervention group, while four died in the control group. The main reasons for permanent discontinuation were tiredness or unwillingness to be reminded about the stroke. One patient discontinued after having his driver's license withdrawn. None dropped out of the intervention program due to side-effects of drugs. 85 patients in the intervention group and 93 controls completed the follow-up.

In the MCI/dementia study, we used the cut-off 3.44 to minimize the probability of including patients with a pre-stroke MCI, leaving 208 patients.

All 227 patients were included in the WML study.

Figure 4. Flow chart at baseline regarding the four substudies



209 patients were included in the TOAST study. Due to a wrong punching, 210 should have been included.

4.2 Assessments

4.2.1 Assessments at baseline

The primary distinction between ischemic stroke and hemorrhagic stroke was based on neuroimaging with cerebral CT and MRI.

Vascular risk factors recorded at baseline included treated hypertension before hospitalization, hyperlipidemia (total cholesterol >5.0 mmol/l, low density lipoprotein (LDL)-cholesterol >3.0 mmol/l), diabetes mellitus, atrial fibrillation (permanent or paroxysmal), current smoking and daily alcohol intake.

Fasting blood samples were collected and analysed, heart rate and blood pressure examined, and ECG performed. Waist and hip circumferences, weight and height were measured, and waist-to-hip-ratio and BMI calculated. Smoking habits and alcohol use were recorded.

Cognitive instruments included in the study

- The MMSE (standard, 30-point)
- The Clock Drawing Test
- The Trail Making Test A and B (TMT A and B)
- The 10 word test (max score 40) including delayed recall
- Figures from Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog)
- Ullevaal Aphasia Screening (UAS)

The Clock Drawing Test was dichotomized into correct or incorrect answers (5 versus ≤4 according to Schulman (135)). TMT B was interrupted after 5 minutes, but we allowed the patients to continue past 5 minutes if they insisted.

No clear cut-off exists for the IQCODE in post-stroke samples. A cut-off of 3.44 minimizes the probability of including patients with a pre-morbid MCI (142). Information-based instruments can be used to complement the diagnostic process.

The assessments for cognitive functioning were performed on day 3-7 during the hospital stay and at follow-up.

4.2.2 Assessments at 3 and 6 months.
Fasting blood samples were collected and analysed, heart rate and blood pressure examined, and ECG performed. Waist and hip circumferences, weight and height were measured, and waist-to-hip-ratio and BMI calculated. Smoking habits and alcohol use were recorded. We also recorded self-reported physical activity in minutes per week and took a brief diet anamnesis.

4.2.3 Assessments at the 12 month follow-up
Again, fasting blood samples were collected and analysed, heart rate and blood pressure examined, and ECG performed. Waist and hip circumferences, weight and height were measured, and waist-to-hip-ratio and BMI calculated. Smoking habits and alcohol use were recorded. We also recorded self-reported physical activity in minutes per week and took a brief diet anamnesis.

The patients performed a global cognitive screening equivalent to the screening at baseline, extended with figures from ADAS-cog and screening for aphasia using the UAS, and collected a history of memory and behavioural changes. Neurological and functional measurements were performed using NIHSS, mRS and Barthel ADL-index. Supplementary investigations included MRI of the brain, colour duplex of the precerebral arteries and, whenever possible, lumbar puncture for examination of neurodegenerative biomarkers in the cerebrospinal fluid.

4.3. Baseline characteristics
All patients were recruited during their stay in the acute stroke unit.

Classification of stroke subtype was made according to the patients' etiological diagnosis (The TOAST classification) and according to the severity and topographical location of the ischemic lesion (the OSCP classification). The main characteristics of the patients are shown in Table 8.

Table 8. Baseline characteristics, n=227

Variable		**N (%) if not other ways**
Demographics	Male	115 (50.7)
	Mean age, years (SD)	72.7 (12.2)
	Less than nine years of education	55 (24.2)
Cerebrovascular	Cerebral infarction	174 (76.7)
	TIA	36 (15.9)
	Cerebral haemorrhage	17 (7.5)
Risk factors	Hypertension	135 (59.5)
	Hyperlipidaemia	124 (54.6)
	Diabetes	27 (11.9)
	Cigarette smoking (present)	51 (22.5)
	Coronary heart disease	53 (23.3)
	Atrial fibrillation	75 (33.0)
	BMI>25	126 (55.5)
TOAST classification	Large vessel disease	24(11.4)
	Cardioembolic disease	66 (31.4)
	Small vessel disease	66 (31.4)
	Stroke of undetermined etiology	54 (25.7)
Topography	Right hemisphere	85 (37.4)
	Left hemisphere	115 (50.7)
	Cerebellum/brainsteam	27 (11.9)
Assessments	NIHSS day one, median (IQR)	2.0 (1.0-5.0)
	NIHSS at discharge, median (IQR)	1.0 (0-2.0)
	BI, median (IQR)	20.0 (18.0-20.0)
	mRS, median (IQR)	1.0 (0-2.0)
Cognitive function	IQCODE, mean (SD)(n=224)	3.10
	MMSE, mean (SD)(n=214)	25.66
	TMT A, mean (SD)(n=192)	74.5
	TMT B, mean (SD)(n=162)	157.4
	10 word test immediate recall, mean	21.2
	10 word test, delayed recall , mean	4.2

TIA=Transient Ischemic Attack; Hyperlipidemia=total cholesterol >5 mmol/l or LDL-cholesterol >3 mmol/l; LDL=Low Density Lipoprotein; Coronary Heart Disease=previous myocardial infarction or present angina pectoris; BMI=body mass index; TOAST= The Trial of Org 10172 in Acute Stroke Treatment classification; IQR=Interquartile range; BI=Barthel Activities of Daily Living Index; mRs=modified Rankin scale; IQ code=the Informant Questionnaire on Cognitive Decline in the Elderly; MMSE= Mini Mental State Examination; TMT A= the trail making test A; TMT B= the trail making test B

4.4 Methods in the TOAST study, paper 1.
The TOAST study is based on baseline data.

The diagnosis of stroke and classifications according to the TOAST criteria (Table 9) were based on the history of symptoms and their acute presentation, clinical examination and cerebral CT scans. This investigation included repeated ECG, NIHSS and blood samples as well as additional examination with color duplex images of precerebral arteries (in search of large vessel disease) and TTE/TTE (in search of cardio embolic disease). Patients with either no probable etiology or more than one potential cause were classified as stroke of undetermined etiology.

Table 9. Modified TOAST classification.

	Clinical signs	Radiological signs	Supplemetary investigations
Large vessel disease	Signs of affection of the cortex (aphasia, apraxia and visuospatial disturbance, and present no neglect phenomena or visual field defects), subcortex, cerebellum or brainsteam.	Lesion on CT or MRI> 1.5cm in cortex, subcortex, cerebellum or brainstem compatible with the symptoms. No signs on CT or MRI*	Duplex or arteriographic signs of a significant (>50%) stenosis or occlusion of the internal carotid artery or middle cerebral artery on the symptomatic side
Cardio embolic disease	Signs of affection of the cortex (aphasia, apraxia and visuospatial disturbance, and present no neglect phenomena or visual field defects), subcortex, cerebellum or brainsteam.	Lesion on CT or MRI> 1.5cm in cortex, subcortex, cerebellum or brainstem compatible with the symptoms. No signs on CT or MRI*	Paraclinical signs of a source of cardiac embolism, on ECG, TTE or TEE**
Small vessel disease	A lacunar syndrome, either characterized by pure motor stroke, pure sensory stroke, sensomotor stroke, ataxic hemiparesis or the dysarthria-clumsy hand syndrome.	Lesions on CT or MRI should be less than 1.5 cm No signs on CT or MRI*	No large vessel disease or cardio embolic disease identified in color duplex of precerebral arteries or in ECG/TTE/TEE

*Stroke patients with a clinical stroke syndrome without a corresponding lesion on brain imaging were classified according to the clinical presentation and paraclinical findings. A clinical presentation of a lacunar syndrome (see above), with no signs of large vessel disease or cardio embolic disease, was diagnosed as small vessel disease. Stroke syndromes with

signs of cortical affection but without a source of an embolus were classified as stroke of undetermined etiology.
**The most frequent cardio embolic sources are atrial fibrillation, prosthetic heart valves, recent myocardial infarction, dilated cardiomyopathy, intracardiac tumours, rheumatic mitral stenosis and infective endocarditis. A patent foramen ovale (PFO) without any other source of embolism was classified as cardio embolic disease according to Warlow el al (207).

All but one patient were examined with a precerebral colour duplex scan and all patients with an ECG at admittance and on day 1. 92 (44%) had a cerebral MRI and 85 (41%) an echocardiography performed. The routines of our hospital require that a CT scan should be carried out in all patients in the acute setting, and MRI in selected patients. Patients with cortical symptoms and no source of embolism on ECG or echocardiography were monitored with a 24-hour ECG. All paraclinical assessments were performed during the stay or within 14 days if the patients had an early discharge. Patients below 60 years with no findings on routine ECG, echocardiography or precerebral duplex scan, and selected patients with cortical symptoms without a source of an embolus, went through a screening for thrombophilia. The same patients, in total 13, were assessed with a TEE.

4.5 Methods in the intervention study, paper 2

This is a randomized, evaluator-blinded, controlled trial with two parallel groups. The study physician and nurse were blinded to the allocation. The study was registered with Clinicaltrials.gov (NCT00506818).

At discharge from the index stay, the patients were randomized to conventional care in the primary care setting or intensive risk factor intervention in the outpatient clinic. Block randomization (block size of 20) was performed by a study nurse blinded to the patients' clinical data. The stroke physician was blinded to the results of cognitive tests performed before the intervention. The consensus group were blinded to the randomization.

In the intervention study, the patients able to perform the TMT A and the 10 word test were randomized. All survivors were examined after 12 months.

4.5.1 Intervention

Patients in the intervention group were invited to the outpatient clinic for a consultation with the study stroke nurse and physician three and six months post-stroke. Information was given regarding the importance of changing lifestyle in order to preserve brain health. Medical treatment was optimized for the same purpose. Tailored advice was given to the patients regarding risk factor management, and a treatment plan was sent to the general practitioner (GP).

The intervention was mainly based on recommendations regarding secondary prevention after stroke (100;114). Every known risk factor was treated until target: blood pressure ≤140/90, total-cholesterol ≤5.0 mmol/l, LDL-cholesterol ≤3.0 mmol/l, HbA1c≤7.0 %, homocysteine ≤15 µmol/l, and BMI≤25. The patients were offered smoking-cessation courses, and encouraged to perform regular moderate physical activity. Advice regarding diet rich in fruit, vegetables and fish, low-fat dairy products and less sugar was given. In addition, patients were advised not to use alcohol excessively.

The targets are listed in Table 10.

Pharmacological intervention included, in addition to antiplatelet agents or warfarin if indicated, antihypertensives, statins, antidiabetics and vitamin B complex including folic acid. The control patients received treatment as usual by their GPs.

Table 10. Multifactorial risk factor intervention

TARGET	GOAL
Hypertension	<140/90
Lipids	Cholesterol <5 mmol/l, LDL-cholesterol <3 mmol/l
Homocysteine	<15 µmol/l
Smoking	Courses to quit smoking
Diabetes	HbA1c <7,0 %
Physical activity	30 minutes at least 3 times a week
Overweight	BMI <25
Alcohol	Excessive use is not recommended
Diet	Fruits, vegetables, low-fat dairy products, fish

LDL= low density lipoprotein-cholesterol; BMI= body mass index

4.5.2 Outcomes in the intervention study
The primary outcomes were changes in TMT A and the 10 -word test from baseline to one year post-stroke. The secondary outcomes were diagnoses of dementia or MCI one year post-stroke. After the trial, an expert panel consisting of two neurologists (BF and BT) and one geriatrician (ARØ) reviewed the clinical data. A diagnosis of MCI or dementia was based on the results of cognitive assessments and supplementary investigations. MCI was diagnosed according to the Petersen criteria and dementia according to the DSM-IV criteria. The panel was blinded to allocation.

4.6 Methods in the dementia/MCI study, paper 3
4.6.1. Evaluation of cerebral MRI
The MRI scans where examined for possible atrophy of the medial temporal lobe and vascular changes. A consensus group, blinded to the allocation, diagnosed cognitive impairments and dementia and performed the sub-classification.

Cerebral atrophy was measured as MTLA and graded from 0 to 4. MTLA grade 0=no atrophy; MTLA 4=highest degree of atrophy. MTLA 0-1 is considered a normal value. WMH were quantified with a semi-automated method, and results were given in total WMH volume (mL).

4.6.2 Sub-classification of cognitive impairments post-stroke
Sub-classification was made using all available information in a novel method in order to separate persons with a vascular cause of dementia or MCI from those with a neurodegenerative disease.

For both dementia and MCI, we based our sub-classification on i) MRI findings of vascular and degenerative changes in the brain, ii) the results of biomarkers in cerebrospinal fluid (CSF) and iii) the patients' clinical cognitive profile and vascular risk factors. Consequently, radiological findings of WMH without MTLA were classified as vascular disease, while MTLA without WMH was interpreted as being of a degenerative origin. A combination of WMH and MTLA was diagnosed as mixed vascular and degenerative disease. Thus, isolated WMH had a large impact on a diagnosis of vascular dementia and vascular MCI, whereas isolated MTLA had a large impact when a diagnosis of degenerative dementia or degenerative MCI was made. Whenever biomarkers in the CSF were present, pathological values of tau protein, phosphorylated tau protein or beta-amyloid peptide supported a diagnosis of degenerative disease. Predominantly cortical symptoms (memory-impairment, affected visuospatial function, aphasia, apraxia or neglect) were, when not caused by a cerebrovascular lesion, considered to be compatible with degenerative disease, whereas predominantly sub-cortical symptoms (affecting executive functioning) were interpreted as being most likely of vascular origin (123;208). Vascular changes without corresponding subcortical symptoms were interpreted as mixed disease.

This resulted in six sub-groups: degenerative dementia or degenerative MCI, vascular dementia or vascular MCI, and mixed degenerative and vascular dementia or MCI. Thus, the etiological sub-classification was not determined by the use of standardized criteria such as the DSM- IV or ICD-10, but rather by using clinical and paraclinical assessments. This method is based on the presumption that post-stroke MCI must also have a defined cause, since there is a coexistence of vascular lesions and AD pathology in vascular cognitive impairment. Diagnoses were made in consensus meetings by two senior neurologists (BF and BT) and one senior geriatrician (ARØ).

4.7 Methods in the WML study, paper 4

We used the same methods as in the dementia/MCI study for evaluation of WML and MTLA.

The outcome variables were the cognitive test performances on TMT B, 10 word test and clock drawing test. The tests were chosen in order to evaluate different cognitive domains, although single tests may measure more than one specific cognitive function. The 10 word test is a measure of memory impairment. The Clock Drawing Test primarily measures visuospatial functions, while the TMT B measures executive functioning.

5. Statistics
Statistical analyses were performed with the Statistical Package for Social Science (SPSS), version 18.0.

For the TOAST study, statistical analyses were performed using table analyses and bivariate and multiple logistic regression. The vascular risk factors were dichotomized into present or not present according to recommendations from the American Heart Association (100) and the European Stroke Initiative Recommendation from 2003 (114).

For the intervention study, the differences between treatment groups were estimated using linear regression analyses (ANCOVA), with one year measurements as dependent variable and treatment group and baseline measurements as independent variables. We used the Pearson chi-squared test to analyze categorical outcomes. For analyses of primary end points, we used complete-case-analyses that included data for patients having both baseline and 12-month values. All randomized patients were also included in an intention-to-treat analysis by imputing missing values as no change from baseline to follow-up.

In the MCI/dementia study, we used table analyses.

In the WML study, the associations between the cognitive test performances (outcome variables) and WMLs (explanatory variable) were studied using linear regression (TMT B and the 10 word tests) and logistic regression (the Clock Drawing Test).

Table 11 shows the different statistical analyses used in the different sub-studies.

Table 11. Statistical methods used in the sub studies

Sub study	**Statistical methods**
TOAST study	Table analyses and bivariate and multiple logistic regression
The intervention study	Linear regression analyses (ANCOVA), complete-case-analysis
The dementia/MCI study	Table analyses.
The WML study	Linear regression and logistic regression

6. Ethical considerations

The study was approved by the Regional Committee for Ethics in Medical Research and by the Data Protection Authorities. All patients gave their written informed consent before inclusion. First-degree relatives gave consent on behalf of patients with reduced capacity. This procedure was approved by the Ethics Committee.

When the research project was introduced in the stroke unit, the staff became more focused on giving the patients the best medical and personal care including information. This may have led to a better total care, both for patients included in the study and patients hospitalized after the end of the inclusion.

In the present study, we focused on both cognitive symptoms and secondary prevention. We introduced a visit for the stroke patients in the outpatients' clinic three months post-stroke with focus on secondary prevention, cognitive impairments and further rehabilitation. This was a clinical consultation with both a stroke physician and a dedicated stroke nurse, spending longer time with a more holistic profile. Motivation for lifestyle changes included awareness of the patients' preferences. After the study, the three months post-stroke control was incorporated in routine clinical practice at our hospital.

Awareness and knowledge regarding post-stroke cognitive impairments, their mechanisms and possible preventing strategies are of importance, both for the patients involved and for future patients, and these positive effects of the study overweighed the extra effort. We hope that focus on cognition and individualized secondary prevention including information regarding lifestyle changes in stroke patients, will become a part of the daily routine in stroke units.

The most possible harmful or painful procedure introduced in the present study was lumbar puncture. However, only volunteers without oral anticoagulation were asked to take the examination of neurodegenerative biomarkers in the cerebrospinal fluid. Only one suffered headache after the procedure, with spontaneous recovery. In addition, some patients could find the continued encouragement to change lifestyle irritating.

7. Abstracts of papers included in the thesis

Risk factors for and incidence of subtypes of ischemic stroke

Background
The TOAST classification divides patients with ischemic stroke into five subgroups according to the presumed etiological mechanism. The aims of the present study were to evaluate the distribution of the different etiological stroke subtypes in a hospital-based sample of stroke patients, and to investigate the association between important risk factors and stroke subtypes.

Methods
A total of 210 patients with a first-ever ischemic stroke admitted to the stroke unit of Asker and Baerum Hospital in Norway between February 2007 and July 2008 were enrolled in the study. Information on vascular risk factors was collected at admittance, examination of neurological deficits was carried out during their stay, and classification was made according to the TOAST criteria.

Results
According to the TOAST classification, 24 (11.4 %) of the patients suffered from large vessel disease, 66 (31.4%) from cardioembolic disease, 66 (31.4%) from small vessel disease and 54 (25.7%) from a stroke of undetermined etiology. The presence of hyperlipidemia and atrial fibrillation varied significantly between the different subtypes. In multivariate analyses, hyperlipidemia [odds ratio (OR) 2.46, 95% confidence interval (CI) 1.32-4.60] and current smoking (OR 2.06, 95% CI 1.04-4.08) were the only variables that were related to small vessel disease.

Conclusions
Small vessel disease was observed more frequently and large vessel disease less frequently than previously reported. Small vessel disease was significantly associated with hyperlipidemia and current smoking. Our study supports the view that the etiology of lacunar strokes is multifactorial.

Multifactorial vascular risk factor intervention to prevent cognitive impairment after stroke and TIA: A 12- month randomized controlled trial.

Objectives
There is increasing evidence that vascular risk factor control not only prevents stroke, but also reduces the risk of dementia. We aimed to investigate whether better treatment of vascular risk factors, through a multifactorial intervention program, reduces the incidence of cognitive symptoms one year after stroke and TIA in a hospital-based study of first-ever stroke patients without cognitive decline prior to the stroke.

Materials and methods
Patients suffering their first-ever stroke were included in this randomized, evaluator-blinded, controlled trial with two parallel groups. Baseline examination included extensive assessment of exposure to vascular risk factors and cognitive assessments regarding memory, attention and executive function. After discharge, patients were allocated to either intensive vascular risk factor intervention or care as usual. The primary endpoints were changes in TMT A and 10 word test from baseline to 12 months follow-up.

Results
195 patients were randomized. The difference between groups in Trail Making Test A, adjusted for baseline measurements, was 3.8 seconds (95% confidence interval (CI): -4.2 to 11.9; p=0.35) in favour of the intervention group. The difference between groups in the 10 word recall test was 1.1 words (95% CI: -0.5 to 2.7; p=0.17) in favour of the intervention group. We did not observe any differences in the secondary outcomes of incident dementia or mild cognitive impairment (MCI).

Conclusions
We could not demonstrate cognitive effects of an intensive risk factor intervention at one year post-stroke. Longer follow-up and a more heterogeneous study sample might have lead to larger effects. More effective methods for managing the risk of further cognitive decline after stroke are needed.
ClinicalTrials.gov, number NCT00506818.

Incidence and Subtypes of MCI and Dementia 1 Year after First-Ever Stroke in Patients without Pre-Existing Cognitive Impairment

Background
Post-stroke dementia is defined as any dementia occurring after stroke, and includes vascular, degenerative and mixed dementia. The aim of this study was to assess the incidence of dementia and mild cognitive impairment (MCI) one year after stroke in a population free from pre-stroke cognitive decline, and to investigate the different aetiological subtypes of post-stroke dementia and MCI, using a novel method of sub-classification in order to separate vascular causes of MCI or dementia from neurodegenerative disease.

Methods
All patients with a first-ever stroke and TIA admitted to the stroke unit of Asker and Bærum Hospital were invited. After 12 months, dementia and MCI were diagnosed. Sub-classification was made using MRI findings, the results of biomarkers in cerebrospinal fluid and the patients' clinical cognitive profile.

Results
36 (19.6%) patients developed dementia during the first year after stoke and 69 (37.5%) developed MCI. Fourteen (13.3%) were diagnosed as suffering from degenerative cognitive disease, 34 (32.4%) from vascular cognitive disease, and 57 (54.3%) from mixed disease.

Conclusion
Fifty-seven percent suffered from cognitive impairment one year after stroke and only one third from isolated vascular cognitive disease. Post-stroke cognitive impairment is complex with a high coexistence of vascular and degenerative changes.

Impact of White Matter Lesions on Cognition in Stroke Patients Free from Pre-Stroke Cognitive Impairment – A One-Year Follow-Up Study

Background
Post-stroke cognitive impairment and dementia may be caused by pure vascular, pure degenerative or mixed disease. The relation between post-stroke cognitive impairment and the combination of vascular pathology and degenerative changes is less evaluated. We aimed to evaluate the associations between white matter lesions (WMLs) and patient performance 1 year after stroke on tests of executive functioning, memory and visuospatial function, adjusted for the effects of lifestyle and disease-related factors, including medial temporal lobe atrophy (MTLA).

Methods
Patients with a first-ever stroke or transient ischemic attack were invited to participate in the study. The associations between the cognitive test performances and WMLs were studied using linear regression [Trail Makin Test B (TMT B) and 10 word tests] and logistic regression (Clock Drawing Test).

Results
In total, 199 patients completed the follow-up. The TMT B ($p=0.029$) and 10 word test ($p=0.014$) were significantly associated with WMLs; however, the Clock Drawing test ($p=0.19$) was not. The TMT B ($p=0.018$) and the 10 word test ($p\leq0.001$) were both significantly associated with MTLA.

Conclusion
Impaired executive functioning and memory are significantly associated with WMLs and MTLA. The mechanisms explaining post-stroke cognitive impairment are multifactorial, including different types of vascular pathology and coexisting vascular and degenerative changes.

8. General discussion

The present study involves different aspects of cognitive impairment and dementia after stroke and TIA. We wanted to focus on preventive strategies, risk factors and mechanisms involved in post-stroke cognitive impairment. This study is designed with cognitive impairment as the outcome. We have tried to give attention to the importance of assessment of various cognitive symptoms, possible etiological mechanisms and individualized preventive strategies including vascular risk factor management. Prevention of recurrent stroke and vascular diseases will improve the patients' outcome post-stroke. We hypothesized that cognitive impairment could be prevented as well. However, whether optimal management of vascular risk factors will prevent decline or improve cognitive function post-stroke, requires further evaluation in new research projects.

We have shown that cognitive impairment post-stroke are frequent, evaluated 12 months after the cerebrovascular event. Cognitive impairment post-stroke is due to a mixture of degenerative and vascular changes, and these changes seem to overlap and synergize to increase the risk of cognitive impairment. Sub-classification of dementia and MCI after stroke showed that less vascular and more degenerative changes contribute to cognitive impairment one year after the first cerebrovascular event. This may explain why the impact of vascular risk factor management on post-stroke cognition is limited the first year post-stroke.

We recommend the use of neuroimaging and CSF biomarkers in the etiological evaluation of post-stroke cognitive impairment for detection of vascular changes and atrophy of brain. An etiological diagnosis ensures individualized and targeted prevention and treatment. Our findings regarding WML and its association with both memory and executive dysfunction may indicate a vascular contribution to mechanisms involved in trigging cerebral atrophy post-stroke. In addition, pre-stroke asymptomatic degenerative processes may progress to a symptomatic stage after the stroke.

In ischemic stroke, we observed a different distribution between the different stroke sub types. There may be a shift towards more small vessel disease and cardio embolic disease but less large vessel disease. More patients will survive their first stroke, and, therefore, we need to have more focus on cognitive function and rehabilitation of the patients. The original lacunar hypothesis included hypertension and diabetes, but our findings indicate that other vascular risk factors including hyperlipedimia and current smoking may contribute to the risk of small vessel disease. All known risk factors should be treated until target post-stroke in order to prevent recurrent stroke and possibly even further cognitive decline.

8.1 Methodological considerations

8.1.1 Patients

The patients in the present study were included consecutively and prospectively. Admittance to the stoke unit were unselected regarding the clinical condition, as even patients with very severe neurological impairments were admitted to the stroke unit.

By excluding patients with pre-stroke cognitive impairments and including only first-ever stroke patients, the actual brain burden was easier to assess. Only three patients opposed inclusion, indicating a representative sample from the stroke unit.

Due to the intervention, only patients who survived the acute phase and with a life expectancy of more than one year were included. As a result of this, the most severe cases were not included. This may have influenced the distribution regarding the TOAST classification and

further, the proportion of patients with cognitive impairment. In addition, patients suffering from TIA were included, and in this group, cognitive impairment may develop even more slowly.

The participants in this study are highly educated, have excellent access to medical care and have a rather healthy lifestyle. This may have influenced the result of the intervention study and the distribution between TOAST subtypes.

The use of a high IQCODE cut-off may have lead to inclusion of patients with pre-stroke cognitive impairment. In addition, the retrospective assessment with the IQCODE may be biased.

The study was designed as an intervention study, and may therefore not be ideal regarding the other sub studies. However, due to the non-significant result of the intervention, we assumed that the randomization did not influence the other sub studies.

8.1.2 Methods

In the stroke unit, a standardized protocol for diagnosis, observation, acute treatment, including prevention of complications, and early rehabilitation were followed, consistent with national and international standards. A dedicated stroke physician examined all patients, and a CT scan, standard blood samples, NIHSS and ECG registration were carried out in all patients at arrival in the hospital. In this sense, the quality of the diagnostic procedures performed in the stroke unit, was satisfactory.

We used the clinical TIA diagnosis without evidence of focal brain lesions on neuroimaging. MRI scan in the acute setting is continuously more available, and will in the future give a more precise diagnosis of stroke/TIA and a better etiological stroke classification.

In the TOAST study, we failed to establish a clear etiological diagnosis in nearly 25% of the patients, mainly due to the fact that stroke may have more than one etiology. Only 13 patients had a TEE performed, and none of the echocardiography scans detected aortic plaques. The TOAST classification requires a broad detection of etiological mechanisms, and we have used a modified TOAST classification due to the clinical setting with MRI in 47% of the cases. The association between risk factors and etiological sub groups was compared within the stroke group, not with controls free from cerebrovascular disease.

We used cognitive tests available in our stroke unit, based on the assumption that cognitive deficits after stroke affect memory, executive function, attention, language and visuospatial function. There is a lack of standardization of screening tools for cognitive deficits from both vascular and degenerative origin. To screen and grade cognitive status, more reliable tools are needed. In addition, the cognitive assessments are performed rather early in the acute phase, and assessments in a more stable phase may have varied less. Finally, strategic and greater vascular lesions in the acute phase of stroke may cause irreversible injuries, leaving a smaller proportion available for intervention.

The choice of primary endpoints can be debated. TMT A and 10 word test were chosen as the primary outcomes in order to assess different cognitive domains. In addition, we wanted simple and fast tests that are easy to use in clinical practice. Previous studies regarding post-stroke cognitive impairment have included only patients able to complete comprehensive neuropsychological examinations and not patients with aphasia, and as a consequence, by

excluding those with larger strokes, this may have led to an underestimation of cognitive deficits. TMT A was preferred as an outcome due to the number able to complete the test and the association between attention and post-stroke function. Results for TMT B were also included in the analyses since we used affected executive function as part of vascular cognitive impairments. The ideal test for detecting post-stroke cognitive impairment is lacking. However, using the TMT A and 10 word test as the end points may have reduced the ability to discriminate the effect of the intervention.

The use of biomarkers in patients with cognitive impairment can improve diagnostic accuracy, both in the memory clinic and the follow-up of post-stroke patients. In the present study, more patients should have been encouraged to have a lumbar puncture for CSF-markers. Further, the consensus group for dementia/MCI was highly qualified with long clinical practice. The evaluation of MRI scans regarding WML and MTLA was performed by dedicated radiologists and a neurologist, the latter using a software to measure diffusion parameters.

MRI in the acute phase can be used to identify chronic vascular disease and silent brain infarcts, all contributing to sub clinical vascular disease pre-stroke, less brain reserve and more vulnerability for cognitive decline. However, under half of the patients had a MRI scan in this phase.

Although a single test measures more than one specific function, we chose tests that were able to assess the different domains and to indicate vascular or degenerative origins. The screening battery chosen to identify cognitive impairments can be debated and may lead to simplification in a complex field. Still, the diagnoses of dementia and MCI are based on clinical examination and medical history, and cognitive tests in the clinical setting must reflect the clinical symptom expression.

The assessments of neurological, functional and cognitive impairments used in the study, have been included in the daily routine in our stroke unit, and are today part of the standard examination.

8.1.3 The intervention

The intervention program was easy to communicate, well tolerated and is also now a part of the routine in the outpatient clinic. Focus on a healthy lifestyle and motivation to lifestyle changes are included in the stroke unit, in addition to focus on cognitive deficits.

The intervention program was based on available knowledge and recommendations in 2006. Today, the intervention program would have been even stricter. The blood pressure should have been treated to more normal values and the LDL to $\leq$2.0 (209). Physical activity is recommended every day, and even walking 2 hours per week is reported to lower the risk of stroke with 30 % in women compared to those who do not (210). Further, focus should be put on reduction of waist-hip-ratio and prevention of diabetes. There are some evidence for treatment of elevated homocysteine (211), but more studies are needed for recommending therapy with folic acid with or without vitamine B 12 (212).

Despite knowledge, it is hard to get people to increase their cardiovascular fitness. Most healthcare professional have limited experience and experience in guidance in exercise programs for stroke-survivors. The patients will benefit from counseling on participation in physical activity and exercise training. More specific registrations of diet and physical

activities should have been made and we did not evaluate the care given by the patients' GP. Awareness of their risk factors and motivation for lifestyle changes were, in motivated patients, taken care of by the patients' GP. This homogeneity may decrease the difference between the groups in the intervention study.

8.1.4 Statistics

Some negative results may be due to low statistical power and to short follow-up time. Both vascular and degenerative dementias develop over several years, and the observation period in our study might have been too short. In addition, the cognitive assessments may have varied less if performed in a more stable phase, 1-2 month post-stroke. Finally, the effect of the intervention may have been too optimistic.

8.2 The TOAST study

The TOAST classification is a commonly used classification system that is based on the etiology of ischemic stroke.

This classification requires extensive investigations, including colour duplex of precerebral arteries and transcranial duplex, to indentify large vessel disease. Cardio embolic disease can be diagnosed in the acute setting when atrial fibrillation, a mechanical heart valve or an acute myocardial infarction is present. However, other causes of cardio embolic disease and large vessel disease, such as patent foramen ovale or atherosclerotic plaque formation in the ascending aorta, cannot be diagnosed unless TEE is performed.

There is an observed change between different stroke subtypes towards more small vessel disease. Lacunar stroke resulting from small vessel disease has a more favorable outcome than other etiologies, but frequently leads to cognitive impairment. Due to better stroke-survival, the proportion of stroke survivors and patients with cognitive impairments will increase.

The lacunar hypothesis was based on autopsy findings in a very few patients, and has been under discussion for several years (213).

8.3 The intervention study

Modification of multiple risk factors through a combination of comprehensive lifestyle and appropriate pharmacological therapy is recommended for prevention of recurrent stroke in stroke survivors (107). We hypothesized that this should include prevention of cognitive impairments post-stroke as well. However, we were not able to confirm this hypothesis.

A proportion of post-stroke cognitive impairments may be reversible. Large strokes, especially TACI and even PACI and larger cerebral hemorrhages cause irreversible brain damage. Intensive vascular risk factor management may slow the progression of chronic small vessel disease (WML), and prevent silent brain infarctions, preserving cognition over several years. The first year post-stroke, degenerative pathology, more than vascular pathology, may affect cognition and therefore, the timing of evaluation of the prevention strategy was not ideal. Subgroup analyses and longer follow-up can give us answers to these questions.

Intention-to-treat analysis is a strategy for the analysis of RCTs that compares patients in the groups to which they were originally randomly assigned. However, due to missing data, there is a need to impute results from missing data. In different RCTs, however, this approach is often inadequately described and inadequately applied, leading to different methodological

quality. The authors of RCTs should describe the handling of deviations and discuss the potential effect of any missing response (214).

In the intention-to-treat analysis in our study, we imputed data in the manuscript as indicating no change from baseline (Table 12). This is a rather conservative scenario. A significant result was available imputing data in favour of the intervention (scenario 4). No consensus exists about how missing response should be treated in intension-to-treat analyses, indicating that we could have used this scenario. However, patients dropping out of the intervention may behave more like the control group.

Table 12. Intention-to-treat analysis.

	N (contr./int)	Difference (95% CI)	p-value
Complete case			
TMT A	81/80	-3.8 (-11.8 to 4.2)	0.35
10 word test	89/83	1.1 (-0.46 to 2.7)	0.17
Scenario 1			
TMT A	97/98	-7.2 (-15.6 to 1.3)	0.095
10 word test	97/98	0.83 (-0.61 to 2.3)	0.26
Scenario 2			
TMT A	97/98	-7.7 (-15.8 to 0.36)	0.061
10 word test	97/98	0.87 (-0.63 to 2.4)	0.25
Scenario3			
TMT A	97/98	1.5 (-7.3 to 10.3)	0.73
10 word test	97/98	-0.47 (-2.1 to 1.1)	0.56
Scenario 4			
TMT A	97/98	-15.9 (-24.9 to -7.0)	0.001
10 word test	97/98	2.3 (0.77 to 3.8)	< 0.001

Scenario 1: All missing = no change from baseline to 12 months
Scenario 2: All missing = mean change from baseline to 12 months
Scenario 3: Extreme case favoring control
Missing control = 2*mean positive change from baseline
Missing intervention = 2*mean negative change from baseline
Scenario 4: Extreme case favoring intervention
Missing control = 2*mean negative change from baseline
Missing intervention = 2*mean positive change from baseline

Lifestyle changes include smoking cessation, overweight reduction, physical activity, cognitive activity, a healthy diet and mild to moderate alcohol use. Identification of vascular risk factors did not necessarily lead to lifestyle changes. Adherence to lifestyle changes are challenging. More effective methods of managing vascular risks in these patients are needed, including more specific training programs and dietary advice. Further, controls in the hospital's outpatient clinic, with focus on risk factors and compliance, may motivate and commit the patients to the individualized preventive program.

In the present study, the intervention was well tolerated, even among the oldest patients. The intensive vascular risk factor management is easy to communicate to the patient, and adherence to the intervention program can be followed, both in the outpatient clinic and by the GP.

8.4 The dementia/MCI study

The spectrum of ischemic changes in the brain is large, encompassing large cortical strokes, through identifiable lacunes, to white matter changes. The combination of AD and VaD is common in a post-stroke population, making mixed dementia the most common type of dementia. Our findings support a multifactorial model for the process leading to post-stroke cognitive impairments, including different subtypes. Alzheimer type pathology and vascular pathology appear to be common, and may interact in causing cognitive decline, but the impact of cerebrovascular lesions on cognitive impairment and dementia needs to be further elucidated. Stroke may trigger or unmask the neurodegenerative process (215), or the vascular burden may progress and worsen the cognitive status after stroke (216).

The novel method for sub classification was based on the assumption that if dementia post-stroke has a distinct etiology, MCI must have one too. In order to give proper intervention for preventing further decline in cognition, the mechanisms involved must be considered. This sub classification may be used directly in treatment and prevention of cognitive impairment. However, the method is not validated or evaluated. In addition, the information used for classification depended on clinical information and supplementary investigations. The use of biomarkers is, however, under discussion.

The method requires biomarkers including MRI, and most hospitals do not have radiologists specifically competent in evaluating MTLA and WML. However, the methods are available and possible to incorporate when evaluating the MRI. We recommend that patients with cognitive symptoms post-stroke also have their MRI evaluated regarding WML and MTLA for a correct diagnosis and appropriate prevention.

Distinction between MCI and dementia in post-stroke cognitive impairments is of importance, especially for recommendations of prevention, prognosis, treatment and care-level. The impairments are delicate in the sense that they are not automatically uncovered when performing neurological examination or during observation of ADL functions. MCI requires a generally intact ADL function in addition to cognitive impairments that are insufficient to be defined as dementia. Recognizing MCI may contribute to an early diagnosis of dementia, since MCI patients are at increased risk of developing dementia and a more rapid rate of cognitive decline (217).

Post-stroke cognitive impairments are related, in addition to the stroke lesion, to other characteristics that may have been present pre-stroke: WML, MTLA, silent infarcts and pre-stroke cognitive decline (218). Stroke patients seldom have a neuroimaging before the actual stroke, but we did not evaluate WML and MTLA on baseline neuroimaging, only on the follow-up MRI images. Further, we did not differentiate between WML in different locations, only total volume.

8.5 The WML study

An association between WML and cognitive impairment has been reported earlier (219-221). We asked how white matter changes relate to cognition in post-stroke patients, and if WML can explain deficits in test performance from clinical practice. The purpose was to relate the deficits in cognitive performance to possible etiological mechanisms explaining the findings. Results were adjusted for the possible effects of lifestyle and disease-related factors.

Both performances on TMT B and the 10 word test were associated with WML, even after adjusting for other explanatory variables. Cognitive impairment of subcortical vascular origin

has traditionally been strongly associated with impaired executive functioning, while cognitive impairment of cortical, degenerative origin more often affects episodic memory, visuospatial function and praxis. Our findings support this way of distinction, but also indicate an interaction.

Strokes traditionally do not affect structures known to be involved in memory, but rather executive dysfunction and attention. Memory dysfunctions post-stroke may indicate disruption of the cerebral network involved in memory. WML may affect the subcortical – cortical network, leading to cortical disconnection and cognitive decline, again resulting in executive dysfunction and impaired memory. In addition, vascular lesions may trigger and worsen clinical manifestations of AD (222). WML seems to play an important role in the development, not only of vascular, but also of degenerative cognitive impairment and dementia. The association observed in our study supports the assumption that cerebral atrophy post-stroke may be induced by ischemia and therefore reflects the current cerebrovascular lesion. The cerebrovascular event may in addition have an impact on the pre-existing degenerative process, and cause an injury that overwhelms the brains' capacity to compensate. Various pathological processes in different degree may lead to a common final pathway.

8.6 Final comments

In our hospital, a visit three months post-stroke with focus on vascular risk factor intervention, is now a routine follow up after discharge from the stroke unit. This clinical consultation ensures that the patients have an adequate assessment of any cognitive impairment and a rehabilitation plan including how to preserve cognition. Risk factor detection and management should be focused throughout the acute and rehabilitation phases. The adherence to the stroke-prevention program requires both motivated patients and physicians, and ideally, a follow-up with focus on the importance of long-term commitments.

In addition to the main study, we have ongoing studies from the multi-disciplinary team. The physiotherapists evaluate the patients' balance related to different stroke sub types and if balance disturbances can predict cognitive impairment. The occupational therapists evaluate the use of practical assessments for identifying patients with cognitive impairments in the acute phase. Two specialized stroke nurses investigate if the etiology is different in young adults suffering a stroke.

Stroke and dementia share similar risk factors and the lifetime risk of developing one or both is one in three (73). Delaying the onset of dementia, both post-stroke and in general, by modifying risks or lifestyle, can decrease the prevalence and the public health burden of dementia. Although no definitive interventions have been found that could prevent and slow the progression of cognitive impairment in vascular dementia, degenerative dementia or post-stroke dementia, findings from the literature point to the fact that the treatment of vascular risk factors could be favorable. Clinically, stroke and chronic small vessel disease are both causes and contributors to cognitive impairment. Vascular risk factor management should start early midlife and early in the underlying disease process in order to prevent or delay the onset of cognitive impairment. Many stroke survivors are long-term disabled, leading to a sedentary lifestyle that limits performance of activities of daily living, increases the risk for falls and may contribute to a heightened risk for recurrent stroke and cardiovascular disease. The most simple, natural and cheapest ways of preventing a stroke is to exercise regularly. In order to preserve cognitive functioning and enhancing quality of life, intellectual activity, social engagement, physical activity and treatment of vascular and other diseases are

recommended (223;224). Early detection of cognitive deficits and individualized preventive strategies may delay onset and progression of cognitive impairment.

8.7 Suggestions for further research

Better knowledge regarding the impact of the individual risk factor profile may give rise to more specific approaches to prevention and therapy after a cerebrovascular event. Additional research needs to be conducted in this area.

-We would recommend a longer follow-up period than one year, MRI scans in the acute phase, even lower targets for blood pressure and lipids and stronger commitments to programs regarding regular physical activity and diet.

-In addition, focus on coping and brain reserve may help both regarding compliance to the intervention program, to better understand the discrepancy between brain pathology and the clinical presentation and the outcome of the rehabilitation.

-A follow-up study of the same study population, after 6-10 years.

9. Conclusions

-The present study indicates that there may be a change in the distribution of the different etiological subtypes of ischemic stroke with less large vessel disease and more small vessel disease. Further, hyperlipidemia and current smoking seem to be stronger associated with small vessel diseases than the other subtypes.

-We were not able to show that intensive multifactorial vascular risk factor intervention preserves cognition one year post-stroke.

-Cognitive impairment post-stroke is frequent and should receive more attention. Further, cognitive impairment after stroke is complex and due to heterogenous causative factors. There is a coexistence of vascular and degenerative changes in post-stroke cognitive deficits.

-Both executive dysfunction and affected memory are related to WML post-stroke.

Brain injury from stroke and cerebral vascular disease produce cognitive decline and dementia. Further, vascular changes in the brain may worsen the degenerative processes in the brain. Identification and treatment of vascular risk factors are of importance to prevent stroke and further vascular brain damage. Cognitive reserves built through a healthy lifestyle may increase the brain's capacity to compensate for progressive disease. Each individual can prepare for aging through increased awareness of risk factors, regular physical activity and intellectual activity. Optimal care in dementia and MCI is multifactorial, and includes early diagnosis and multidisciplinary care with educational and non-pharmacological interventions. Health research is the best way to bring knowledge regarding vascular contribution to cognitive impairment, prevention and treatment.

"Knowing is not enough; we must apply. Willing is not enough; we must do".
Johann Wolfgang von Goethe.

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II

Multifactorial vascular risk factor intervention to prevent cognitive impairment after stroke and TIA: A 12- month randomized controlled trial.

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Words count: 4561

Key words: Cognitive impairment, dementia after stroke, risk factor management, secondary prevention, stroke

Abstract

Objectives

There is increasing evidence that vascular risk factor control not only prevents stroke, but also reduces the risk of dementia. We aimed to investigate whether better treatment of vascular risk factors, through a multifactorial intervention program, reduces the incidence of cognitive symptoms one year after stroke and TIA in a hospital-based study of first-ever stroke patients without cognitive decline prior to the stroke.

Materials and methods

Patients suffering their first-ever stroke were included in this randomized, evaluator-blinded, controlled trial with two parallel groups. Baseline examination included extensive assessment of exposure to vascular risk factors and cognitive assessments regarding memory, attention and executive function. After discharge, patients were allocated to either intensive vascular risk factor intervention or care as usual. The primary endpoints were changes in TMT A and 10 word test from baseline to 12 months follow-up.

Results

195 patients were randomized. The difference between groups in Trail Making Test A, adjusted for baseline measurements, was 3.8 seconds (95% confidence interval (CI): -4.2 to 11.9; p=0.35) in favour of the intervention group. The difference between groups in the 10 word recall test was 1.1 words (95% CI: -0.5 to 2.7; p=0.17) in favour of the intervention group. We did not observe any differences in the secondary outcomes of incident dementia or mild cognitive impairment (MCI).

Conclusions

We could not demonstrate cognitive effects of an intensive risk factor intervention at one year post-stroke. Longer follow-up and a more heterogeneous study sample might have lead to larger effects. More effective methods for managing the risk of further cognitive decline after stroke are needed.

ClinicalTrials.gov, number NCT00506818.

Introduction

Prevention of cerebrovascular disease may significantly impact the incidence of cognitive decline and dementia in the elderly (1;2), and common risk factors are identified for cerebrovascular disease and Alzheimer's disease (AD) (3-5). Vascular cognitive impairment refers to the total vascular burden on the brain and the effect of vascular disease or lesions on cognition (6). Small vessel disease without stroke, including silent lacunar infarcts, ischemic white matter lesions and incomplete ischemic injury (6), is a marker of poor prognosis with increased risk of stroke, cognitive impairment, dementia and death (7). However, post-stroke dementia and cognitive impairment are probably due to cumulative effects, especially of vascular and degenerative changes in the brain (8;9). Strategies for prevention of post-stroke cognitive impairment are of importance in order to reduce the consequences of stroke for the patients, their relatives and society.

Previous studies have found different rates of post-stroke dementia; the prevalence estimated one year after stroke varies between 7.4 % in population-based studies of first-ever stroke when patients with pre-stroke dementia are excluded, to 41.3 % in hospital-based cohorts including recurrent stroke and pre-stroke dementia (10). Rates regarding post-stroke cognitive impairment differ even more, from 11.6 to 56.3 % (11), depending on the study population, criteria for cognitive impairment and the time-interval after stroke for testing. Age, level of education, depression, neurological deficits, stroke subtype, and arterial territory correlate with cognitive functioning post-stroke (12). Pre-stroke cognitive impairment, progression of small vessel disease, stroke severity and recurrence are known risk factors for post-stroke dementia, whereas the influence of various vascular risk factors is under debate. The actual stroke lesion seems to be the most important factor in determining the cognitive impairments post-stroke (10), where vascular risk factors may enhance the brain`s vulnerability to the stroke lesion. Vascular risk factors seem to have a greater impact on delayed post-stroke dementia developing more than one year after the cerebrovascular event (13) than on dementia that develops earlier (14). However, the mechanisms involved in cognitive impairments after stroke are complex, and a previous publication suggests that degenerative mechanisms may be more involved in delayed cognitive impairment after stroke than vascular pathology (15).

As much as 90% of the risk of stroke is found to be attributable to vascular risk factors such as hypertension, hyperlipidemia, current smoking, waist-to-hip ratio, diet, physical inactivity, diabetes mellitus, alcohol intake, psychosocial stress, depression, cardiac conditions and apolipoprotein B/A1 ratio (16). In secondary prevention after stroke, the aim is to prevent stroke recurrence as well as to slow the progression of brain changes that lead to cognitive impairment and dementia. Evidence-based methods for the latter are lacking since most studies after stroke have failed to evaluate cognition as an end point.

Aggressive control of risk factors requires a multifactorial risk factor assessment and treatment (17). The motivation to adopt a healthier lifestyle can result from the stroke event itself, but requires an individualised intervention including motivation and goal setting(18). Traditionally, there is a gap between recommended secondary prevention and observed practice (19). The aim of the present study was to investigate whether more intensive treatment of vascular risk factors in patients with first-ever

stroke or transient ischemic attack (TIA) can influence post-stroke cognitive functioning in patients free from cognitive decline prior to the stroke.

Methods

Trial design and randomization

This is a randomized, evaluator-blinded, controlled trial with two parallel groups. The study physician and nurse were blinded to the allocation. The study was registered with Clinicaltrials.gov (NCT00506818).

At discharge from the index stay, the patients were randomized into conventional care in the primary care setting or intensive risk factor intervention in the outpatient clinic. Block randomization (block size of 20) was performed by a study nurse blinded to the patients' clinical data. The stroke physician was blinded to the results of cognitive tests performed before the intervention.

Participants

All patients with a first-ever stroke or TIA admitted to the stroke unit of Asker and Baerum Hospital between February 2007 and July 2008 were invited to participate in the study. Only those patients who survived the acute phase (day 7-10) were included. The hospital has a policy of admitting all stroke patients directly to the stroke unit, and serves two local municipalities with a total population of 160,000.

We excluded patients with subarachnoid haemorrhage, known cognitive decline as indicated by a score ≥3.7 on the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) (20), previous stroke or TIA, patients who did not speak Norwegian and patients with a life expectancy less than one year.

Only patients who were able to perform the Trail Making Test A (TMT A) (21), the 10 word test from the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) (22) or both were randomized.

Assessments

The primary distinction between ischemic stroke and haemorrhagic stroke was based on neuroimaging with cerebral CT and MRI. Vascular risk factors recorded at baseline included treated hypertension before hospitalisation, hyperlipidemia (total cholesterol >5.0 mmol/l, low density lipoprotein (LDL)-cholesterol >3.0 mmol/l), diabetes mellitus, atrial fibrillation (permanent or paroxysmal), current smoking and daily alcohol intake.

At baseline as well as after 12 months, fasting blood samples were collected and analysed, heart rate and blood pressure examined, and electrocardiography (ECG) performed. Waist and hip circumferences,

weight and height were measured, and waist-to-hip-ratio and body mass index (BMI) calculated. Smoking habits and alcohol use were recorded.

Cognitive function was measured with the Mini Mental State Examination (MMSE) (23), clock drawing test (24), TMT A and B and the 10 word test. TMT involves multiple cognitive processes. TMT A is a measure of focused visual attention and information processing, and is rated in seconds. TMT B is a measure of executive functioning. TMT A is a predictor for cognitive ability post-stroke (25). The 10 word test is a measure of verbal memory (minimum score zero and maximum 40). These assessments were performed on day 3-7 during the hospital stay and at follow-up. Patients with limited neurological impairments were assessed on day 3, whereas patients with large strokes were assessed on day 7.

At the 12-month follow-up, we also recorded self-reported physical activity, performed a global cognitive screening and collected a history of memory and behavioural changes. The cognitive screening battery contained the MMSE, the clock drawing test, the TMT A and B, figures from Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog) (26). In addition, all patients were screened for aphasia using the Ullevaal Aphasia Screening (UAS) (27), a simple test for nurses identifying language disability. Supplementary investigations included MRI of the brain, colour duplex of the precerebral arteries and, whenever possible, lumbar puncture for examination of neurodegenerative biomarkers in the cerebrospinal fluid.

Intervention

Patients in the intervention group were invited to the outpatient clinic for a consultation with the study stroke nurse and physician three and six months post-stroke. Information was given regarding the importance of changing lifestyle in order to preserve brain health. Medical treatment was optimalised for the same purpose. Tailored advice was given to the patients regarding risk factor management, and a treatment plan was sent to the general practitioner (GP).

The intervention was based on recommendations regarding secondary prevention after stroke (28;29). Every known risk factor was treated until target: blood pressure ≤140/90, total-cholesterol ≤5.0 mmol/l, LDL-cholesterol ≤3.0 mmol/l, HbA1c≤7.0 %, homocysteine ≤15 µmol/l, and BMI≤25. The patients were offered smoking-cessation courses and encouraged to perform regular moderate physical activity. Advice regarding diet rich in fruit, vegetables and fish, low-fat dairy products and less sugar was given. In addition, patients were advised not to use alcohol excessively. The targets are listed in Table 1. Pharmacological intervention included, in addition to antiplatelet agents or warfarin if indicated, antihypertensives, statins, antidiabetics and vitamin B complex including folic acid. The control patients received treatment as usual by their GPs.

Outcomes

The primary outcomes were changes in TMT-A and the 10 -word test from baseline to one year post-stroke. The choice of primary endpoints was based on three assumptions: different cognitive domains are involved in post-stroke cognitive impairment (memory, executive dysfunction and attention), simple and fast tests used in a clinical acute setting may lead to inclusion of more patients and complex

neuropsychological tests would have excluded several more patients including those with aphasia. TMT A was preferred as an outcome due to the number able to complete the test. However, TMT B was also included in the analyses. The secondary outcomes were diagnoses of dementia or mild cognitive impairment (MCI) one year post-stroke. After the trial, an expert panel consisting of two neurologists (BF and BT) and one geriatrician (ARØ) reviewed the clinical data. A diagnosis of MCI or dementia was based on the results of cognitive assessments and supplementary investigations. MCI was diagnosed according to the Petersen criteria (30) and dementia according to the ICD 10 criteria (31) with support from the DSM-IV TR criteria (32). Dementia was diagnosed when there were impairments in cognitive functioning, impairment in activities of daily living and changes in behavior or personality. In MCI, the degree of cognitive impairment did not influence on ADL functioning. Both dementia and MCI diagnoses were based on the patients' history and cognitive performances adjusted for age (TMT A and B, local norms). The panel was blinded to allocation.

Statistics

Statistical analyses were performed with the Statistical Package for Social Science (SPSS), version 18.0. The differences between treatment groups were estimated using linear regression analyses (ANCOVA), with one year measurements as dependent variable and treatment group and baseline measurements as independent variables. We used the Pearson chi-squared test to analyze categorical outcomes.

For analyses of primary end points, we used complete-case-analysis that included data for patients having both baseline and 12-month values. All patients randomized were also included in an intention-to-treat analysis by imputing missing values as no change from baseline to follow-up.

Statistical comparisons of vascular risk factor management utilized the chi-square test.

Power

We expected a difference between treatment groups of 10 seconds in the primary outcome of TMT A changes from baseline to one year. With an expected standard deviation of 15 seconds for the changes (corresponding to a standardized effect size of 0.5), we needed to include 86 patients in each treatment arm in order to have 90% power given a 5% significance level. Since the effect estimate was uncertain, we aimed for 100 patients in each arm.

Ethics

The study was approved by the Regional Committee for Ethics in Medical Research and by the Data Protection Authorities. All patients gave their written informed consent before inclusion. First degree relatives gave consent on behalf of patients with reduced capacity.

Results

Baseline characteristics

After inviting 253 patients, 250 agreed to participate in the study. Of these, 23 were excluded for the following reasons: 12 did not fill the inclusion criteria; six had an IQCODE score ≥3.7, one did not speak

Norwegian, one had an infarct in the spinal cord, one had suffered a previous TIA, two withdrew their consent and one died before signing the consent. The other 11 patients were diagnosed with other diseases than stroke. Of the 227 remaining patients, 174 (77%) had a cerebral infarction, 36 (16%) had suffered a TIA and 17 (8%) were diagnosed with a cerebral haemorrhage.

After excluding 32 patients (24 not testable, three persons suffered a new stroke before randomization, two did not want randomization, one was diagnosed with a new subdural haematoma, one was diagnosed with advanced cancer and one withdrew his consent after advanced heart surgery), 195 patients were randomized to either the intervention group (n=98) or the control group (n=97). Figure 1 shows the flow chart. Baseline characteristics are shown in Table 2.

Adherence to randomization

During the follow-up period of 12 months, eight patients discontinued and five patients died in the intervention group, while four died in the control group. The main reasons for permanent discontinuation were tiredness or unwillingness to be reminded about the stroke. One patient discontinued after having his driver's license withdrawn. None dropped out of the intervention program due to side-effects of drugs. 85 patients in the intervention group and 93 controls completed the follow-up.

Outcomes one year post-stroke (complete-case analysis)

Results are shown in Tables 3 and 4.

After one year, the mean TMT A was reduced by 8.1 seconds (95% CI: 0.7 to 15.5) in the control group (n=81) and by 17.4 seconds (95% CI: 6.8 to 28.1) in the intervention group (n=80). The difference between treatment groups, adjusted for baseline measurements, was 3.8 seconds (95% CI: -4.2 to 11.9; p=0.35) in favour of the intervention group.

The mean increase in 10 word test score was 2.7 words (95% CI: 1.6 to 3.9) in the control group (n=89), and 3.9 words (95% CI: 2.8 to 5.1) in the intervention group (n=83). The difference between groups was 1.1 (95% CI: -0.5 to 2.7; p=0.17) in favour of the intervention group.

For TMT B, the mean was reduced by 20.5 seconds (95% CI: 0.72 to 40.3) in the control group, (n=68) and by 18.5 seconds (95% CI: 3.46-33.6) in the intervention group (n=67). The difference between the treatment groups was 5.29 seconds (95% CI: -14.0 to 24.6; p=0.59). TMT B was not a primary outcome, but as a measure of executive function it was studied in a post hoc analysis.

One year post-stroke, 11 (13%) patients in the intervention group and 17 (19%) in the control group had developed dementia (p=0.30), while 35 (41%) in the intervention group and 33 (36%) in the control group had developed MCI (p=0.50). Combining these two results, 46 (54%) in the intervention group and 50 (55%) in the control group had developed MCI or dementia (p=0.91). None suffered a recurrent stroke during follow-up, but four in the intervention group and one in the control group suffered a TIA.

Outcomes one year post-stroke (intention-to-treat analysis)

For this analysis, missing data were imputed so that the additional observations indicated no change from baseline. The results are shown in Table 3. The only noticeable change compared with the complete-case analyses was a slight increase in between group difference in mean TMT A, although the difference remained statistically insignificant (p=0.099). Neither for TMT B did any significant difference appear (p=0.97).

When comparing the groups regarding vascular risk factor management, significantly more patients in the intervention group than in the control group reached the target for the intervention regarding systolic blood pressure ≤140 (59/85 in the intervention group and 50/92 in the control group, p=0.04), LDL-cholesterol ≤3.0 (81/85 in the intervention group and 75/93 in the control group, p=0.006) and homocysteine≤15 (68/82 in the intervention group and 59/91 in the control group, p=0.004). The results were nearly significant for total-cholesterol ≤5.0 (76/85 in the intervention group and 74/93 in the control group, p=0.073) and smoking cessation (10/18 in the intervention group and 6/24 in the control group, p=0.061). Non-pharmacological interventions such as reducing BMI to ≤25 and increasing physical exercise to over 90 minutes per week were not significantly different between the groups. Physical activity in the intervention group was performed 225 minutes/week (SD 224) and 192 minutes/week (SD 201) in the control group.

In many stroke patients, cognitive impairments resolve over the first 1-2 months post-stroke, and the ideal time for evaluation of stable cognitive outcome would have been at this time. In order to evaluate whether this aspect influenced the results, we did a crude 12 months comparison. These analyses showed no significant differences between the intervention and control groups, neither in the complete case nor in the intention-to-treat analyses.

Discussion

We hypothesized that a multifactorial vascular risk factor intervention would reduce the incidence of cognitive symptoms one year after stroke. We were not able to confirm this hypothesis. There was an observed difference, though not statistically significant, in favour of the intervention group. The negative result may be due to insufficient statistical power or selective drop-outs, but this remains speculative and should be the focus of further studies. In addition, the possible expected effect of treatment may have been too optimistic. In the intension-to-treat analysis, the power was improved, but imputed data for missing values were set to no change, leading to a conservative estimate.

Both vascular and degenerative dementias develop over several years, and the observation period in our study might have been too short. Further, patients suffering from TIA were included, and in this group cognitive impairment may develop even more slowly. Strategic lesions and greater vascular lesions in the acute phase of stroke may cause irreversible injuries, leaving a smaller proportion available for intervention. In addition, degenerative mechanisms, and not vascular pathology, may have greater impact on cognition in the first year post-stroke (15). Finally, the baseline assessments were performed rather early after the stroke event. If the cognitive assessments had been performed in a more stable phase, the results probably would have varied less (33;34).

At discharge, all patients were given optimal secondary treatment, including antithrombotic and antihypertensive therapies as well as statins. Patients in our well-educated sample have good access to health care and are aware of their risks. Care for the control group may have been so good that further improvements in the intervention group became marginal. Further, persons of lower socio-economic status are more likely to have a poor diet, to be overweight, to smoke, and to be sedentary; all these factors contribute to higher burdens of vascular risk. Both the risks of stroke and late-life AD are associated with a low socio-economic status and a lower educational level (35). The high educational level in our sample may thus contribute to a healthier lifestyle including regular physical activity, and hence protect against cognitive decline.

Despite the general knowledge in Western societies regarding vascular risk factors, lifestyle changes are challenging. Johnson et al (36) showed that the identification of vascular risk factors did not necessarily lead to lifestyle changes. More effective methods of managing vascular risks in these patients are needed, including more specific training programs and dietary advice. Maybe the stroke event per se makes people more ready to change behaviour, rather than the intervention.

There are some additional limitations. Only persons able to perform the cognitive tests in the acute phase were randomized. Consequently, patients with large cortical strokes were not included in the randomization. Patients who died during the follow-up period more often suffered large strokes. Since patients with pre-stroke cognitive impairments and previous cerebrovascular events were not included, the risk of post-stroke cognitive decline was lower than in the general stroke population. The primary outcomes were based on the assumption that vascular cognitive impairment affects attention and executive functioning, while AD patients suffer more memory impairments. The tests may not, however, be sensitive enough to show a difference, especially due to the high educational level and relatively short follow-up time. Further, TMT A is a quite rough test, and there might have been a possible effect of the intervention not detected by this test. Even for TMT B, however, there was no significant difference between the groups. The imbalance between the groups regarding sex, age and stroke subtype may have influenced the risk for cognitive impairment. The variance in TMT-A within the patient group was larger and the difference between the groups smaller than estimated in the power-calculation. A single-center study cannot automatically be generalized to all stroke populations. The drop-out from the intervention group may have influenced the results negatively since persons less motivated for structured intervention may have dropped out. The high cut-off for the IQ CODE may have resulted in inclusion of patients with pre-stroke cognitive decline, both due to degenerative and vascular disease. Finally, taking part in the study may have altered behavior regardless of group allocation (Hawthorne effect).

This is one of the first studies specifically designed for the prevention of cognitive impairments, and even if we did not observe more than a small, non-significant effect, the study is still of importance. The relative contribution of coexisting vascular and neurogenerative pathologies to cognitive decline needs to be better defined in order to implement more targeted and specific preventive strategies. This includes structured care, combining lifestyle and pharmacological interventions. Further studies should also be performed over a longer period of time and use baseline assessments from a stable phase. Vascular risk factors and unhealthy behavior present in midlife have a deleterious effect on late-life

cognition and dementia (37), implying that early vascular risk factor detection and treatment is recommended(38). At present, there are no effective guidelines for prevention of cognitive impairments in this patient group.

Acknowledgments

South-Eastern Norway Health Authority and Vestre Viken Hospital Trust sponsored this study. Thanks to the patients participating in the study. Thanks to colleague, physiotherapists, occupational therapists, the secretaries and study nurses in Vestre Viken Hospital Trust and at the University of Oslo and to Sarah Kristine Kaldestad for English proofreading.

Conflict of interests

None for this work

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Figure 1. Flow diagram

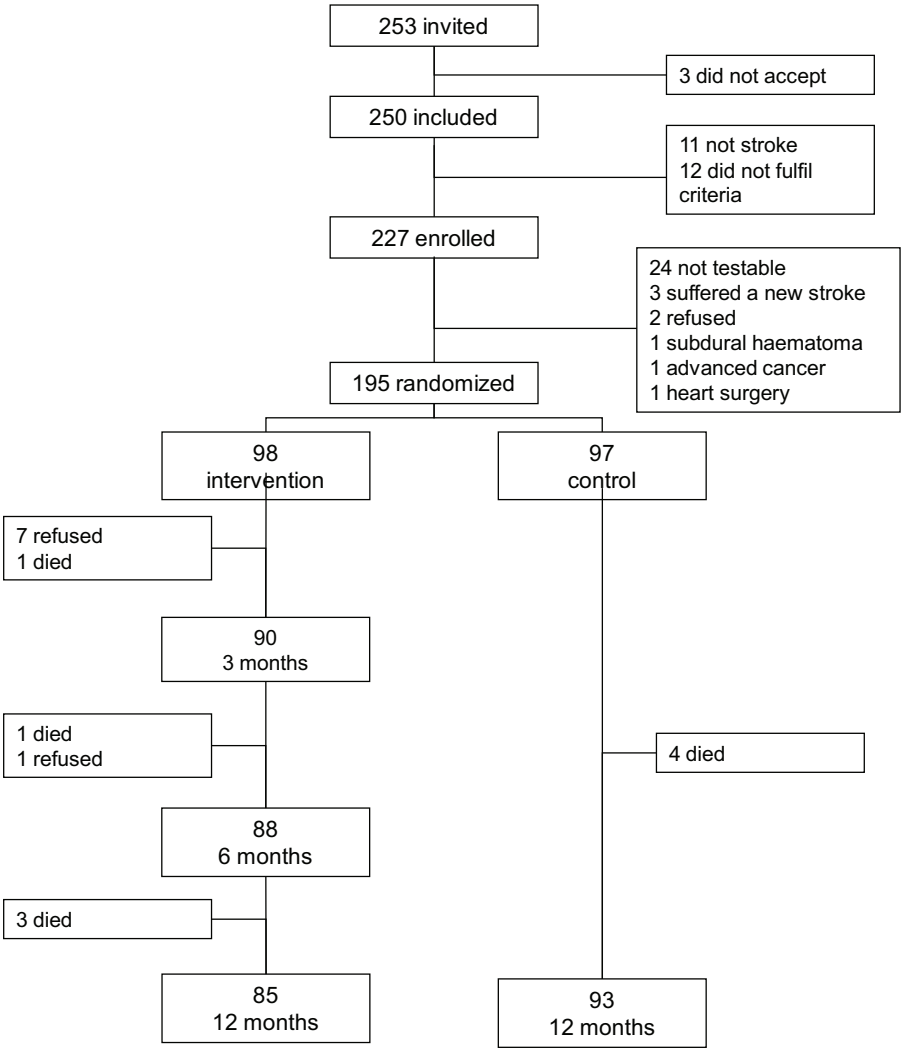

Table 1. Multifactorial risk factor intervention

TARGET	**GOAL**
Hypertension	<140/90
Lipids	Cholesterol <5 mmol/l, LDL-cholesterol <3 mmol/l
Homocysteine	<15 µmol/l
Smoking	Courses to quit smoking
Diabetes	HbA1c <7,0 %
Physical activity	30 minutes at least 3 times a week
Overweight	BMI <25
Alcohol	Excessive use is not recommended
Diet	Fruits, vegetables, low-fat dairy products, fish

LDL= low density lipoprotein-cholesterol; BMI= body mass index

Table 2. Baseline characteristics of patients (n=195). Figures are n (%) unless specified otherwise

Assessment	Intervention	Control
Demographics		
Male	45 (46)	59 (61)
Mean age, years (SD)	72.6 (11.2)	70.6 (13.6)
Less than nine year of education	19 (19)	25 (26)
Stroke subtype		
Cerebral infarction	69 (70)	75 (77)
TIA	23 (24)	12 (12)
Cerebral haemorrhage	6 (6.1)	10 (10)
Risk factors		
Hypertension	60 (61)	54 (56)
Hyperlipidemia	56 (57)	53 (55)
Diabetes	8 (8.2)	13 (13)
Cigarette smoking (present)	18 (18)	24 (25)
Coronary heart disease	21 (21)	26 (27)
Atrial fibrillation	34 (35)	24 (25)
Daily alcohol use	21 (21)	17 (18)
BMI>25	60 (61)	53 (55)
OCSP classification		
TACI	3 (3.1)	7 (7.2)
PACI	50 (51)	47 (49)
LACI	32 (33)	29 (30)
POCI	13 (13)	14 (14)
Topography		
Right hemisphere	36 (37)	38 (39)
Left hemisphere	46 (47)	49 (51)
Cerebellum/brainsteam	16 (16)	10 (10)
Assessments		
NIHSS day one, mean (IQR)	2.0 (0-3)	3.0 (0-3.5)
NIHSS at discharge, mean (IQR)	1.0 (0-2)	1.6 (0-2)
BI at discharge, mean (IQR)	19 (20-20)	18 (19.25-20)
mRS at discharge, mean (IQR)	1.0 (0-1)	1.3 (0-2)

Hyperlipidemia=total cholesterol >5 mmol/l or LDL-cholesterol >3 mmol/l; LDL= Low Density Lipoprotein; Coronary Heart Disease=previous myocardial infarction or present angina pectoris; BMI=body mass index; OCSP=Oxfordshire Community Stroke Project classification; TACI=Total Anterior Circulation Infarction; PACI=Partial Anterior Circulation Infarction; LACI=Lacunar Circulation Infarction; POCI=Posterior Circulation Infarction; NIHSS=National Institute of Health Stroke Scale; BI=Barthel Activities of Daily Living Index; mRs=modified Rankin scale; TIA=Transient Ischemic Attack; IQR=Interquartile range

Table 3. Results

	Intervention group				Control group				Between-group difference (intervention – control)
	N	Baseline Mean (SD)	12 months Mean (SD)	Change Mean (95% CI)	N	Baseline Mean (SD)	12 months Mean (SD)	Change Mean (95% CI)	**Mean (95% CI)***
Complete case**									
TMT A	80	73.4(68.3)	55.0 (38.3)	-17.4 (-28.1 to -6.8)	81	63.0 (36.0)	55.0 (28.9)	-8.1 (-15.5 to -0.7)	-3.8 (-11.9 to 4.2), p=0.35
10 word test	83	21.3 (6.9)	25.3 (7.4)	3.9 (2.8 to 5.1)	89	21.7 (7.1)	24.5 (7.4)	2.7 (1.6 to 3.9)	1.1 (-0.5 to 2.7), p=0.17
Intention to treat***									
TMT A	98	75.1 (65.4)	60.9 (42.4)	-14.2 (-23.0 to 5.5)	97	74.3 (53.4)	67.5 (51.3)	-6.7 (-12.9 to -0.6)	-7.1 (-15.6 to 1.3), p=0.099
10 word test	98	21.2 (6.7)	24.5 (7.4)	3.3 (2.3 to 4.4)	97	21.1 (7.8)	23.6 (8.3)	2.5 (1.4 to 3.6)	0.8 (-0.6 to 2.3), p=0.26

*Adjusted for baseline measurements, using ANCOVA.

**Includes patients with both baseline and 12 months measurements only.

*** Missing data imputed as no change from baseline to 12 months.

Table 4. Results, secondary outcomes

Secundary outcome **N (%)**	**Intervention** **N=85**	**Control** **N=91**	**P value**
Dementia	11 (13%)	17 (19%)	0.30
MCI	35 (41%)	33 (36%)	0.50
Dementia or MCI	46 (54%)	50 (55%)	0.91

III

IV

EXTRA Dementia and Geriatric Cognitive Disorders

Dement Geriatr Cogn Disord Extra 2012;2:38–47
DOI: 10.1159/000336817
Published online: March 28, 2012

Original Research Article

Impact of White Matter Lesions on Cognition in Stroke Patients Free from Pre-Stroke Cognitive Impairment: A One-Year Follow-Up Study

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Key Words
Stroke · Cognitive impairment · Cerebrovascular diseases · Degenerative diseases · White matter lesions

Abstract
Background/Aim: Post-stroke cognitive impairment and dementia may be caused by pure vascular, pure degenerative or mixed disease. The relation between post-stroke cognitive impairment and the combination of vascular pathology and degenerative changes is less evaluated. We aimed to evaluate the associations between white matter lesions (WMLs) and patient performance 1 year after stroke on tests of executive functioning, memory and visuospatial function, adjusted for the effects of lifestyle and disease-related factors, including medial temporal lobe atrophy (MTLA). ***Methods:*** Patients with a first-ever stroke or transient ischemic attack were invited to participate in the study. The associations between the cognitive test performances and WMLs were studied using linear regression [Trail Making Test B (TMT B) and 10-word test] and logistic regression (Clock Drawing Test). ***Results:*** In total, 199 patients completed the follow-up. The TMT B ($p = 0.029$) and the 10-word test ($p = 0.014$) were significantly associated with WMLs; however, the Clock Drawing Test ($p = 0.19$) was not. The TMT B ($p = 0.018$) and

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EXTRA Dementia and Geriatric Cognitive Disorders

Dement Geriatr Cogn Disord Extra 2012;2:38–47

DOI: 10.1159/000336817
Published online: March 28, 2012

the 10-word test ($p \leq 0.001$) were both significantly associated with MTLA. ***Conclusion:*** Impaired executive functioning and memory are significantly associated with WMLs and MTLA. The mechanisms explaining post-stroke cognitive impairment are multifactorial, including different types of vascular pathology and coexisting vascular and degenerative changes.

Introduction

Stroke is associated with an increased risk of cognitive impairment and dementia [1, 2] and contributes to cognitive decline in various neurodegenerative dementia disorders [3]. Post-stroke cognitive impairment and dementia may be caused by pure vascular disease, pure degenerative disease or the coexistence of vascular and degenerative diseases [4]. In addition to evident stroke lesions, post-stroke vascular changes include subcortical white matter lesions (WMLs), silent lacunar infarctions and cerebral microhemorrhages [5]. WMLs, initially described in 1987 [6] and named leukoaraiosis [7], are defined as areas of high signal intensity on T_2-weighted magnetic resonance imaging (MRI) and are related to variable degrees of demyelination, axonal loss and gliosis [8].

WMLs are associated with vascular risk factors, especially hypertension and higher age [9]. Further, WMLs are associated with the development of vascular and mixed dementia in patients with mild cognitive impairment [10]. Elderly patients with severe WMLs are at risk of becoming more dependent in activities of daily living [11]. Severe post-stroke WMLs predict cognitive decline [12] and indicate a higher risk of recurrent stroke [13]. WMLs are present in 11–21% of adults aged around 64 years [14], in up to 44% of patients with stroke or transient ischemic attack (TIA) and in 50–75% of patients with vascular dementia [15].

Executive and visuospatial dysfunctions are associated with severe WMLs, whereas memory and language dysfunctions are only weakly associated with WMLs [16, 17]. However, the correlation between specific clinical symptoms and the topographical location of WMLs is under debate [18, 19]. The relation between post-stroke cognitive impairment and the combination of vascular pathology and degenerative changes has not been fully examined.

Accordingly, we aimed to evaluate the associations between WMLs and patient performance 1 year after stroke on tests measuring executive functioning, memory and visuospatial function. Results were adjusted for the possible effects of lifestyle and disease-related factors, including medial temporal lobe atrophy (MTLA) as an indicator of possible neurodegenerative disease mechanisms.

Methods

Participants

All patients with a first-ever stroke or TIA admitted to the Stroke Unit of Bærum Hospital, Vestre Viken Hospital Trust between February 2007 and July 2008 were invited to participate in the study. Only those patients who survived the acute phase the first week were assessed. The hospital has a policy of admitting all stroke patients directly to the Stroke Unit. It serves two counties with a total population of approximately 160,000 inhabitants.

We excluded patients with subarachnoid hemorrhage, dementia or mild cognitive impairment diagnosed before stroke onset, a history of cognitive decline or cognitive decline as indicated by a score of ≥3.7 on the Informant Questionnaire on Cognitive Decline in the

Dement Geriatr Cogn Disord Extra 2012;2:38–47
DOI: 10.1159/000336817
Published online: March 28, 2012

Elderly (IQ-CODE) [20], previous stroke or TIA, patients who did not speak Norwegian and patients with a remaining life expectancy of less than 1 year as estimated by the treating physician. The IQ-CODE was filled in by the patient's spouse, a first-degree relative or a close friend. The cut off 3.7 was chosen based on the results of a previous study that reported pre-stroke cognitive decline with an IQ-CODE score of ≥4.0 [21] and modified to ensure exclusion of pre-stroke dementia.

Assessments

The primary distinction between ischemic stroke and hemorrhagic stroke was based on neuroimaging with cerebral computer tomography (CT). We used the WHO definition of stroke and the clinical diagnosis of TIA based on the acute loss of focal cerebral function with symptoms lasting less than 24 h [22]. TIA patients were included since cognitive impairments in TIA patients may persist beyond the resolution of focal symptoms [23].

Cognitive functioning was measured at baseline and after 12 months using the Mini-Mental State Examination (MMSE) [24], the Clock Drawing Test [25], the Trail Making Test A and B (TMT A and B) [26] and the 10-word test including delayed recall from the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) (maximal score 40) [27]. The Clock Drawing Test was dichotomized into correct or incorrect answers (5 vs. ≤4 according to Shulman [25]). The TMT B was interrupted after 5 min, but we allowed the patients to continue afterwards if they insisted. All patients tried to perform all tests, including the TMT A and TMT B, in the acute phase, but results are only reported from those who were able to complete the tests.

The cognitive assessments were chosen in order to evaluate different cognitive domains. The 10-word test is a measure of memory impairment. The Clock Drawing Test primarily measures visuospatial functions, while the TMT B measures executive functioning. Cognitive impairment of subcortical vascular origin has traditionally been strongly associated with impaired executive functioning, while cognitive impairment of cortical, degenerative origin more often affects episodic memory, visuospatial function and praxis. Although single tests may measure more than one specific cognitive function, we chose a test battery that could assess different cognitive domains.

Neurological impairment was assessed using the National Institutes of Health Stroke Scale (NIHSS) [28]. The neurological examinations were performed on the first day after admittance by an experienced stroke physician. The NIHSS was repeated at discharge and at the 12-month follow-up. We screened for pre-stroke cognitive impairment using the 26-question version of the IQ-CODE [20], repeated after 12 months. Activities of daily living were assessed by the Barthel ADL index [29], and global functioning was evaluated by the modified Rankin Scale [29]. Patients with ischemic stroke were classified according to The Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification [30] by a stroke physician.

Patients underwent an MRI of the brain at the 12-month follow-up. Cerebral atrophy was measured according to the method first described by Scheltens et al. [31]. Based on the height of the hippocampal formation and the enlargement of the surrounding cerebrospinal fluid spaces, the MTLA is graded from 0 to 4 (MTLA grade 0 = no atrophy; MTLA 4 = highest degree of atrophy; MTLA 0–1 are considered normal values).

WMLs were quantified with a semi-automated method in the Nordic lCE Basis Module as described earlier [32]. The manual placement of regions of interest in known white matter fiber tracks is a common method to measure diffusion parameters. This software is preferred for this purpose, but other programs for diffusion tensor imaging are available [33]. In the fluid-attenuated inversion recovery images, pixel values in the white matter higher than 2 SD above the mean pixel value of the respective slices were defined as WMLs. The total WML areas in all slices were added together and multiplied with the slice thickness to obtain the

Dement Geriatr Cogn Disord Extra 2012;2:38–47
DOI: 10.1159/000336817
Published online: March 28, 2012

total WML volume (ml). In this sample, patients with pencil line lesions along the ventricles and non-confluent small subcortical lesions did not have a total WML volume exceeding 1.5 ml. Moderate and severe lesions may represent subcortical ischemic small vessel disease [16].

Statistics

The associations between the cognitive test performances (outcome variables) and WMLs (explanatory variable) were studied using linear regression (TMT B and 10-word test) and logistic regression (Clock Drawing Test). First, univariate analyses were performed. Second, 19 candidate variables were analyzed as possible confounding variables, i.e. age, sex, Apo E alleles, MTLA, education, vascular risk factors, etiological subtypes of ischemic stroke, neurological deficits as measured by NIHSS and stroke in the left hemisphere (table 2). Only predictors assessed at baseline, except for physical activity which was assessed at the follow-up, were included in the analyses in order to evaluate the effect on cognitive outcomes, WMLs and MTLA 12 month after stroke. All explanatory variables with a p value <0.20 in unadjusted analyses were included in the multivariate regression models. All variables (except for WMLs) with a p value >0.05 were thereafter removed from the models, one at a time, until the final adjusted models were reached. We assessed the interaction between WMLs and MTLA for each outcome using regression models that included WMLs, MTLA and their product as explanatory variables. We used all data available for each analysis, which ranged from n = 148 in multivariable analyses to n = 197 in univariable analyses.

Statistical analyses were performed with STATA 11. All significance tests were two-tailed and performed at the 5% level.

Ethics

The study was approved by the Regional Committee for Ethics in Medical Research and by the Data Protection Authorities. All patients gave their written informed consent before inclusion. First-degree relatives gave consent on behalf of patients with reduced capacity. This procedure was approved by the Ethics Committee.

Results

Baseline Characteristics

After inviting 253 patients, 250 agreed to participate in the study. Of these, 23 were excluded; 12 did not fulfill the inclusion criteria (6 had an IQ-CODE score ≥ 3.7, 1 did not speak Norwegian, 1 had an infarction in the spinal cord, 1 had suffered a previous TIA, 2 withdrew their consent and 1 patient died before signing the consent) and 11 patients were diagnosed with other disease than stroke.

Of the 227 remaining patients, 174 (76.7%) had a cerebral infarction, 36 (15.8%) had suffered a TIA and 17 (7.5%) were diagnosed with cerebral hemorrhage. Baseline characteristics are listed in table 1.

In total, 199 patients completed the follow-up. Of the 28 patients missing, 19 died and 9 refused to complete the follow-up period. Further, 182 had an MRI for analysis of WMLs and MTLA.

The estimated associations between WMLs and the tests for different cognitive domains, including the potentially confounding variables, are displayed in table 2. The cognitive tests for executive functioning, memory and visuospatial function after 1 year of follow-up were all significantly associated with the degree of WMLs. After fitting multivariable regression models including patients' characteristics, vascular risk factors and stroke characteristics, the associations remained statistically significant between the severity of WMLs and the

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DOI: 10.1159/000336817
Published online: March 28, 2012

Table 1. Patients characteristics at baseline and 12 months

Variable	Baseline (n = 227)	12 months (n = 199)
Demographics		
Male gender	115 (50.7)	
Age, years	72.7 ± 12.2	
Education <9 years	55 (24.2)	
Stroke subtype		
Cerebral infarction	174 (76.7)	
TIA	36 (15.9)	
Cerebral hemorrhage	17 (7.5)	
Risk factors		
Hypertension	135 (59.5)	
Hyperlipidemia	124 (54.6)	
Diabetes	27 (11.9)	
Cigarette smoking (present)	51 (22.5)	
Coronary heart disease	53 (23.3)	
Atrial fibrillation	75 (33.0)	
BMI >25	126 (55.5)	
TOAST classification		
Large vessel disease	24 (11.4)	
Cardioembolic disease	66 (31.4)	
Small vessel disease	66 (31.4)	
Stroke of undetermined etiology	54 (25.7)	
Topography		
Right hemisphere	85 (37.4)	
Left hemisphere	115 (50.7)	
Cerebellum/brain stem	27 (11.9)	
Assessments		
NIHSS score on day 1	4.1 (1.0–5.0)	
NIHSS score at discharge	2.4 (0–2.0)	1.8 (0–1.0)
BI score	20.0 (18.0–20.0)	18.6 (19.0–20.0)
mRS score	1.0 (0–2.0)	1.3 (1.0–2.0)
Cognitive assessments (n)		
IQ-CODE	3.10 ± 0.23 (224)	3.31 ± 0.41 (188)
MMSE	25.66 ± 4.78 (214)	25.86 ± 5.8 (194)
TMT A	74.5 ± 65.0 (192)	63.3 ± 48.9 (185)
TMT B	157.4 ± 94.5 (162)	142.4 ± 86.7 (160)
10 word-test, immediate recall	21.2 ± 7.1 (203)	23.6 ± 8.5 (195)
10 word-test, delayed recall	4.2 ± 2.5 (201)*	5.0 ± 3.1 (195)

Values denote n (%), median (IQR) or mean ± SD.

Hyperlipidemia = Total cholesterol >5 mmol/l or low-density lipoprotein cholesterol >3 mmol/l; Coronary heart disease = previous myocardial infarction or present angina pectoris; BMI = body mass index; IQR = interquartile range; BI = Barthel activities of daily living index; mRS = modified Rankin Scale.

* 15 patients did not complete the delayed recall. This test was introduced a little later in the study.

Table 2. Results of unadjusted and adjusted regression models for all proposed explanatory variables and the three outcomes

Variable	10-word test				TMT B				Clock Drawing Test			
	unadjusted		adjusted (final model)		unadjusted		adjusted (final model)		unadjusted		adjusted (final model)	
	regression coefficients (95% CI)	p value	regression coefficients (95% CI)	p value	regression coefficients (95% CI)	p value	regression coefficients (95% CI)	p value	OR estimate (95% CI)	p value	OR estimate (95% CI)	p value
WMLs	−0.30 (−0.44, −0.17)	<0.001	−0.16 (−0.28, −0.03)	0.014	3.50 (1.83, 5.18)	<0.001	1.75 (0.18, 3.33)	0.029	1.06 (1.02, 1.10)	0.003	1.03 (0.99, 1.07)	0.19
Age	−0.24 (−0.33, −0.14)	<0.001			2.82 (1.80, 3.84)	<0.001	2.09 (0.94, 3.23)	<0.001	1.06 (1.03, 1.09)	<0.001	1.06 (1.02, 1.10)	0.001
Sex (male = 0)	−1.17 (−3.59, 1.25)	0.34			6.12 (−21.5, 33.7)	0.66			3.59 (1.97, 6.55)	<0.001	3.26 (1.62, 6.55)	0.001
Number of Apo E 4 alleles present	overall: p = 0.72				overall: p = 0.10				overall: p = 0.62			
1 vs. 0	−0.85 (−3.80, 2.11)	0.57			−36.7 (−71.3, −2.10)	0.038			0.01 (−0.16, 0.18)	0.89		
2 vs. 0	2.05 (−5.49, 9.60)	0.59			−27.3 (−114, 59.1)	0.53			0.22 (−0.22, 0.66)	0.33		
MTLA (2–4 vs. 0–1)	−6.26 (−8.50, −4.02)	<0.001	−4.51 (−6.67, −2.35)	<0.001	70.9 (44.3, 97.5)	<0.001	33.0 (5.86, 60.1)	0.018	3.76 (1.96, 7.22)	<0.001		
Education (≤9 years = 0)	6.55 (3.73, 9.37)	<0.001	4.83 (2.32, 7.34)	<0.001	−22.3 (−57.5, 12.8)	0.21			0.58 (0.29, 1.16)	0.12		
Homocysteine (μmol/l)	−0.25 (−0.50, −0.009)	0.042			2.45 (−0.41, 5.32)	0.093			1.01 (0.95, 1.07)	0.82		
Hypertension (treated)	−3.07 (−5.51, −0.63)	0.014			30.7 (3.52, 57.9)	0.027			1.65 (0.91, 2.99)	0.10		
Hyperlipidemia	4.57 (2.22, 6.92)	<0.001	2.72 (0.59, 4.85)	0.013	−38.3 (−65.5, −11.2)	0.006			0.82 (0.46, 1.45)	0.49		
Diabetes	−3.84 (−7.63, −0.06)	0.047			63.7 (14.9, 112)	0.011	60.4 (17.2, 104)	0.006	1.61 (0.66, 3.92)	0.29		
Atrial fibrillation (at present)	−1.11 (−3.80, 1.57)	0.41			17.1 (−13.0, 47.2)	0.26			1.00 (0.54, 1.88)	0.99		
Coronary heart disease	−2.23 (−5.06, 0.61)	0.12			45.5 (13.7, 77.3)	0.005			0.86 (0.44, 1.71)	0.68		
Cigarette smoking (at present)	−0.14 (−3.54, 3.26)	0.94			−5.65 (−45.1, 33.8)	0.78			0.83 (0.36, 1.90)	0.65		
BMI	0.20 (−0.11, 0.51)	0.21			−1.47 (−5.22, 2.29)	0.44			0.91 (0.84, 0.98)	0.018		
Physical activity (min/week)	0.007 (0.001, 0.01)	0.017			−0.035 (−0.10, 0.03)	0.27			0.997 (0.995, 0.999)	0.007		
Diagnosis	overall: p = 0.010				overall: p = 0.53				overall: p = 0.13			
TIA vs. infarction	3.63 (0.36, 6.90)	0.030			−20.7 (−57.3, 15.9)	0.27			0.40 (0.16, 0.98)	0.046		
Hemorrhage vs. infarction	−3.93 (−8.17, 0.31)	0.069			0.78 (−53.4, 54.9)	0.98			0.71 (0.25, 2.03)	0.53		
TOAST (small vessel disease = 0)	−2.05 (−4.67, 0.56)	0.12			30.7 (2.20, 59.2)	0.035	32.9 (7.69, 58.0)	0.011	1.15 (0.61, 2.15)	0.67		
NIHSS (score on day 1)	−0.62 (−0.85, −0.38)	<0.001	−0.28 (−0.53, −0.04)	0.017	5.33 (0.54, 10.1)	0.029	5.63 (1.02, 10.2)	0.017	1.15 (1.07, 1.23)	<0.001	1.12 (1.04, 1.22)	0.005
Topographic location (left = 0)	3.06 (0.68, 5.44)	0.012	2.59 (0.58, 4.59)	0.009	−9.21 (−36.4, 18.0)	0.50			1.00 (0.56, 1.77)	1.00		

Apo E = Apolipoprotein E; Hyperlipidemia = total cholesterol >5 mmol/l or low-density lipoprotein cholesterol >3 mmol/l; Coronary heart disease = previous myocardial infarction or present angina pectoris; BMI = body mass index. The values are the regression coefficients for the 10-word test and TMT B (linear regression) and the odds ratio for the Clock Drawing Test (logistic regression).

performances on TMT B (p = 0.029) and the 10-word list with immediate recall (p = 0.014), but not between WMLs and the Clock Drawing Test (p = 0.19) (table 2).

In addition, age ($p < 0.001$), MTLA (p = 0.018), diabetes (p = 0.006), NIHSS score on day 1 (p = 0.017) and small vessel disease as cause of the stroke (p = 0.011) were significantly and independently associated with the TMT B, whereas low education ($p < 0.001$), MTLA ($p < 0.001$), hyperlipidemia (p = 0.011), NIHSS score on day 1 (p = 0.023) and left hemisphere

Dement Geriatr Cogn Disord Extra 2012;2:38–47
DOI: 10.1159/000336817
Published online: March 28, 2012

stroke (p = 0.012) were significantly and independently associated with the 10-word test. Failure on the Clock Drawing Test was significantly associated with increasing age (p = 0.001), NIHSS score on day 1 (p = 0.005) and female sex (p = 0.001).

No interaction between WMLs and MTLA was observed for any of the three outcomes (all p ≥ 0.34), indicating that different processes are involved in atrophy and chronic vascular changes.

Discussion

We found that the cognitive tests for both executive functioning (TMT B) and impaired memory (10-word test) were significantly associated with WMLs. However, the bivariate association between the Clock Drawing Test and WMLs was not statistically significant after adjusting for the influence of increasing age, NIHSS score on day 1 and gender.

The association between deficits in executive functioning and WMLs in stroke patients has been reported earlier [16, 17] and may be due to chronic cerebral small vessel disease with endothelial dysfunction, hypoperfusion and affected blood-brain barrier leading to subsequent cell injury [34, 35]. Furthermore, our results also indicate an association between impaired memory and WMLs after stroke. This contrasts the traditional belief that memory disturbances are less severe in vascular dementia than in Alzheimer's disease [36]. Previous findings regarding non-memory-related cognitive deficits in association with WMLs diverge even more [19], and in stroke patients, impaired memory has been related to reduced temporal lobe functioning [37]. However, vascular changes in the brain can be associated with executive functioning as well as with impaired memory [14, 38], ostensibly due to subcortical damage and a disruption of the pathways between gray and white matter. WMLs are related to more rapid global functional decline [39] and, in the post-stroke situation, may contribute to cognitive decline and progression of cognitive dysfunction. In addition, we observed an association between reduced performance on the 10-word test and stroke in the left hemisphere, indicating cortical damage affecting language and understanding.

Both reduced executive functioning and impaired memory were significantly associated with MTLA, supporting the theory that a degenerative component plays a central role in some patients with post-stroke cognitive impairments [3]. Vascular lesions may amplify the effect of existing degenerative pathology or affect beta-amyloid deposits. Further, MTLA, in addition to subcortical vascular changes, seems strongly related to post-stroke executive dysfunction. Our findings support the assumption that white matter changes, vascular lesions of the brain and Alzheimer's disease pathology coexist and give rise to an increased risk of post-stroke cognitive impairment [13, 40].

We observed an association between some vascular risk factors and cognitive impairment; hyperlipidemia was associated with the 10-word test and diabetes with the TMT B. Midlife high cholesterol increases the risk of Alzheimer's disease later in life [41], represents a well-known risk for vascular disease [42] and may indicate a risk for post-stroke cognitive impairments of both degenerative and vascular origin, whereas diabetes is one of the traditional risks for lacunar infarcts [43].

Surprisingly, hypertension was not associated with any of the cognitive tests. Midlife hypertension is a risk factor for dementia [41] as well as for WMLs [9]. One explanation for our finding may be that we only identified treated hypertension, and the hypertension in our patients was mostly well controlled before the stroke. Treatment of vascular risk factors in patients with cerebrovascular disease may slow the progression of WMLs [44] and, therefore, intensive secondary prevention may contribute to preserve cognitive functioning.

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DOI: 10.1159/000336817
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Our study has some limitations. We included patients with TIA, and both the incidence of cognitive impairment and the WML load are lower in these patients. Limitations also include the absence of a measure of silent infarcts, microbleeds and global cortical atrophy. In addition, WMLs were measured only in volume. A more precise topographical description of the lesions could have been even more helpful in understanding the relationship between WMLs and cognitive functioning.

We found that the cognitive tests for both executive functioning (TMT B) and impaired memory (10-word test) were significantly associated with WMLs. There was also a significant association between impaired executive functioning and memory with MTLA. Our findings support the assumption that the mechanisms explaining post-stroke cognitive impairment are multifactorial, including different types of vascular pathology and coexistence of vascular and degenerative changes. The relationship between WMLs and MTLA was not significant.

Clinically, it is of importance to determine which patients are at risk of dementia among those who survive a stroke. The onset of cognitive impairment may be linked to the initial severity of WMLs as well as the pre-stroke degenerative process. This aspect has clinical implications in choosing the most appropriate therapeutic strategy and to start prevention earlier in order to preserve cognition. Treatment requires control of all modifiable risk factors.

Acknowledgments

The authors' work has been supported by Helse Sør-Øst RHF and Vestre Viken Hospital Trust. We want to thank the patients participating in the study as well as colleagues, physiotherapists and occupational therapists at our hospital. We are indebted to the clinical research nurses Nadine Prost, Anne Wergeland and Anne-Mette Brenden and our secretary Kari Wie Skar for excellent assistance. Thanks to Sarah Kristine Kaldestad for English proofreading.

Disclosure Statement

The authors have no conflict of interest.

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