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The Norwegian Stroke in the Young Studies

NOR-SYS I and II

Risk factors, staging of arteries, "invisible problems" and rehabilitation after ischemic stroke at a young age (<50 years)

A Norwegian Stroke Research Co-operation Program

Trial protocol by

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1 Title

The Norwegian Stroke in the Young Studies-Risk factors, staging of arteries, invisible problems and consequences after ischemic stroke at a young age

2 Background

Cardiovascular diseases are among the 10 leading diagnoses of disease burden in the world and are the main causes of disability and death in the western world [1, 2]. Stroke is the second leading cause of death in the world, and despite of decreasing mortality, increasing incidence rates, also for young patients, are concerning [3-5]. After cerebral infarction, costs for hospitalization and treatment are high [6]. Young stroke was once considered a disease with fairly good outcomes. It is not. The Hordaland study of patients <50 years suffering their index-stroke between 1988-97, showed after 12 years a 10-fold increased mortality rate compared with controls, long-term survivors had a 5-fold increased vascular morbidity rate and an 8-fold increased rate of memory problems compared with controls [7]. High rates of mortality and arterial morbidity [8] demand better and standardised diagnostics. Knowledge from these previous clinical research and similar results from other European studies led to the design of The Norwegian Stroke in the Young Study (NOR-SYS I) [9], performed from 2010 to 2015. Stroke at a young age encompasses vastly different social and economic challenges than stroke in elderly stroke patients does. For young stroke survivors, stroke hits in a vulnerable period of life when education, building a career, establishing a family or caring for offspring, and achieving a sustainable economic security are factors most decisive for the future. Close to 90% of young stroke survivors regain functional independence. In many of these patients with seemingly full remission of their stroke the stroke-related brain damage nevertheless leads to deranged cognition and communication, psychic instability and fatigue. These “hidden” disturbances have a substantial negative impact on the patient’s quality of life. They may become apparent when the patient starts working again, “hits the wall” and does not manage to stay in job. An economic and social decline with loss of social networks is an imminent danger after stroke at a young age. For the society, Young stroke generates therefore exceptionally high health care and socioeconomic costs [10].

Diagnosis and treatment is challenging in young stroke with a high percentage of unknown cause. Despite a high-tech work-up, 30-50% of patients have a stroke of unknown cause. Long-term follow-up is often inadequate concerning secondary prevention, risk factor control and cognitive/communicative rehabilitation. A stringent diagnostic protocol is required to define aetiology. Further, it is of utmost importance to tailor personalised prophylactic treatment of modifiable risk factors in order to prevent recurrent stroke, even subclinical ones, and thus prevent cognitive decline, loss of job and of social position. Knowledge from NOR-SYS I with close clinical follow-ups after one week, three months, one year and since 2015 the 5 year follow-up, led to design of NOR-SYS II that started inclusion in March 2016 in Bergen.

2.1 Benefit for patients and family members

2.1.1 The Norwegian Stroke in the Young Study (NOR-SYS) I

Apart from generally increased knowledge, such as improved diagnostics with magnetic resonance imaging and duplex-sonography, introduced during the late 90-ies, patients in the NOR-SYS studies benefit from detailed, standardised diagnostics of the arteries and individually tailored medical treatment according to the results and the risk factor profile. Oral, written and visual (ultrasound pictures) information should make it easier (one of the aims of the PhD-project to prove this) to accept and continue treatment in order to reach the treatment goals, such as smoking cessation, increased physical activity, consciousness concerning nutrition and alcohol and normal blood pressure. NOR-SYS included from 2010 to 2015 386 admitted young and middle-aged ischemic

stroke patients at age 15-60 years with parents, partners and adult offspring [9]. Patients were followed after 1 week, 3 months, 1 year, and since 2015 the 5-year follow-up phase has started for patients, partners and offspring. NOR-SYS has shown that even young patients have many risk factors, a high degree of subclinical arterial disease, and early vascular aging [11, 12] and many "invisible problems" that lead to "fatigue" and depression, very probably possible to influence by the NOR-SYS II study.

2.1.2 The Norwegian Stroke in the Young Study (NOR-SYS) II

NOR-SYS II is a third step research effort, acknowledging the complexity of acute brain disease in young persons. The NOR-SYS II continues the diagnostic work-up from NOR-SYS I. But in addition standardised testing of balance, communication, cognition, vision and hearing are performed to help those patients later when they discover these problems by starting working again. Apart from continuation of the well-established co-working with the dep. of Cardiology, we also collaborate now with the departments of Ophthalmology, Ear-Nose-Throat, with physiotherapists, occupational therapists, speech therapists for standardised testing and offering a second-line rehabilitation for any included patient in NOR-SYS II that has a potential to return to work. Doctors and patients have to learn more about these invisible problems that inhibit patients to return to work or force them to reduce working. Not every problem will be possible to quit by more and focused training, but the confusion then patient´s depression and loss of social functions may get lower by training to deal with the persisting, invisible problems.

3 Aims

Primary aims

1. To assess risk factors for cardiovascular disease and to perform staging of the arteries by standardized neurovascular, peripheral and cardiac ultrasound examinations.
2. To implement a stringent follow-up of all risk factors in close co-operation with the patient in order to achieve predefined treatment targets
3. To assess the presence of cognitive and communicative dysfunctions (speech, vision, hearing), psychic instability and fatigue, through first-line standardized evaluations, and to establish a focused second-line rehabilitation for these "hidden" deficits in order to reduce the rates of anxiety and depression and to contribute to higher "back to work" rates for those who had a job before the stroke and with good prognosis to contribute to working tasks.

Secondary aims

4. NOR-SYS bio-bank building for future translational research on lipid -, inflammatory - and genetic mediators of arterial vessel disease.

4 Methods

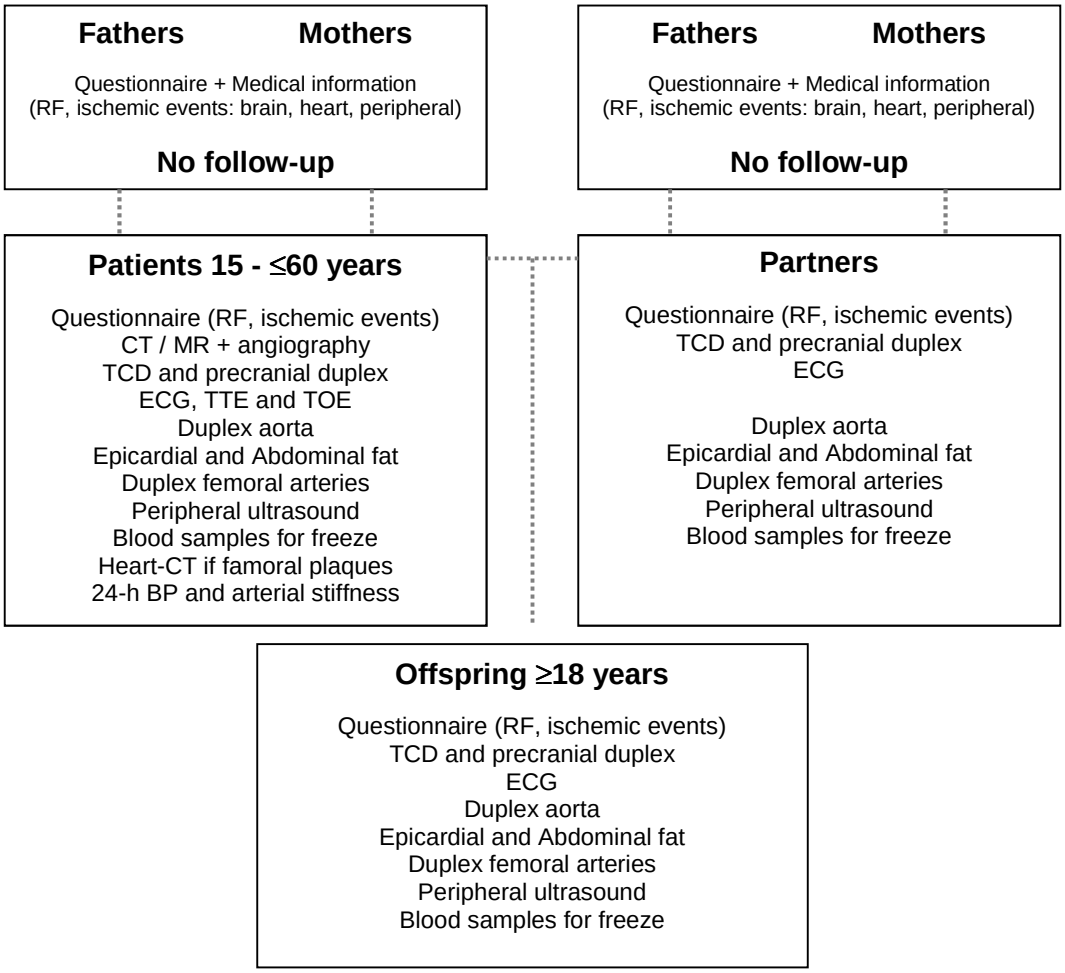
Inclusion criteria: The NOR-SYS studies are prospective with documented acute ischemic stroke at age 15 to 60 years (NOR-SYS I, inclusion period 2010-2015) and 15 to 49 years (NOR-SYS II, started inclusion in March 2016). Patients must speak Norwegian fluently and have a permanent address in the catchment area of the hospital.
Exclusion criteria: Post-traumatic stroke; stroke caused by sinus venous thrombosis, sepsis or endocarditis; serious co-morbidity (advanced cancer, multiple sclerosis); mental retardation and/or otherwise limited co-operation (severe psychiatric disease).

The methods in NOR-SYS II reflect standard operating procedures (SOP) that should be applied for every young stroke patient after achieved knowledge from earlier research.
Please see Figure 1 and Figure 2 as SOP and overviews methods for the studies.

4.1 Design, choice of standard operating procedures

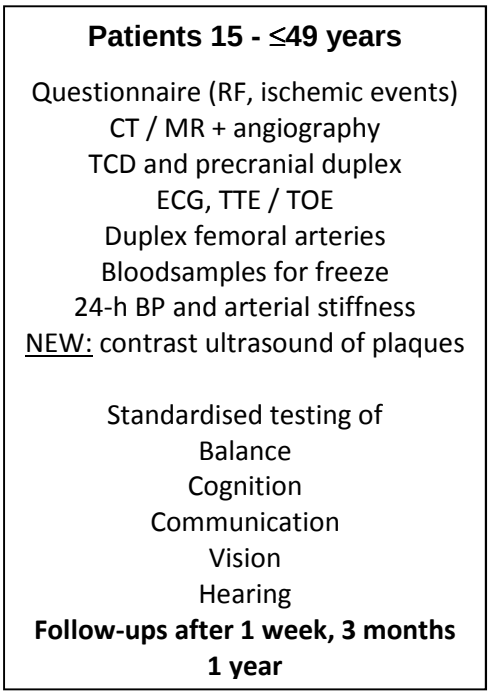
Methods in NOR-SYS II are not new, but the complex use of standardised diagnostics is new. If several centres participate, the study is pragmatic and allows use of different equipment and test methods (as used at the different centres). The diagnostic methods have then to be described in brief in the study registry of NOR-SYS II. This is a pragmatic solution in order to keep costs as low as possible. All time and efforts are spent on standardised diagnostics of patients.

Figure 1: The Norwegian Stroke in the Young Study I.
Inclusion of three generations completed from 2010 to 2015



RF = risk factors; CT = computed tomography; MR = magnetic resonance imaging;
TCD = transcranial duplex sonography; ECG = electrocardiogram; TTE = transthoracal echocardiography, TOE = transoesophageal echocardiography, 24-h BP= 24 hours blood pressure measurement.

Figure 2: Norwegian Stroke in the Young Study II.
Start of inclusion in March 2016



RF = risk factors; CT = computed tomography; MR = magnetic resonance imaging;
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Functional outcome and biometrics Neurological deficits are documented with National Institutes of Health Stroke Scale (NIHSS), function with modified Rankin Scale (mRS) and social dependency with Barthel Index (BI), at predefined time points. Anthropometric variables as height, weight, waist- and hip circumference are measured.

Cerebral CT and MRI

Cerebral CT (or preferably MRI) is performed at admission for evaluation of early ischemic lesions [13]. MRI is done within 36 hours for volume measurements of the infracted areas.

Cerebral CT-angiography (CTA) and MR-angiography (MRA)

Cerebral CTA (or preferably MRA) is performed at admission for evaluation of arterial occlusions [13]. Cerebral MRA is done within 36 hours for assessment of recanalization. Artery stenosis is graded as minor (≤50 %), moderate (51–70 %), severe (>70 %) or occlusion (100 %).

Transcranial colour-coded sonography

TCCS is performed according to SOP in the department of Neurology. An artery stenosis is assessed and graded based on maximum flow velocities, using the continuity principle [14].

Carotid artery ultrasonography

Measurements are performed in accordance with the NOR-SYS ultrasound protocol, including assessment of vessel wall alterations, stenosis, hemodynamics and ultrasound contrast for instability testing (Annette Fromm, NOR-PLAQ. Other protocols or methods may be used in other centres.

Femoral artery ultrasonography

Femoral IMT measurments are performed in 10 mm wide artery segments representing the distal common femoral artery and the proximal superficial femoral artery. Other methods may be used in other centres.

Cardiac imaging and investigation
Transthoracic echocardiography (TTE) and/or transoesophageal echocardiography (TEE) are applied in most patients according to SOP at the dept. of cardiology.

Coronary Computed Tomography Angiography and CT of the thoracic aorta
CT is done for patients with embolic cerebral infarction where no embolic source is discovered by routine neuro/cardiovascular examinations. Calcium scoring of the coronary arteries is performed, and alterations of lumen and wall of coronary arteries and thoracic aorta are evaluated after intravenous contrast administration.

Arterial stiffness measured by aplanation tonometry
Carotid-femoral pulse wave velocity is assessed following a standardized program with inborn quality control assessment. From the carotid pulse wave, central (aortic) blood pressure is estimated.

Ambulatory blood pressure monitoring
Twenty-four hour ambulatory blood pressure monitoring is performed within 3 months after discharge.

Blood tests
NOR-SYS II routine blood samples include parameters covering traditional risk factors, coagulation and pro-thrombotic tests and are measured at admission and day 1.

Biomarkers and genetic analyses
Further blood samples are stored in approved general bio-banks (REK: 2010/1025 f NOR-SYS I and 2015/2338, NOR-SYS II) for future analysis, including pro-inflammatory, anti-inflammatory and genetic markers for neurovascular diseases, and genotype analyses for different causes of acute ischemic stroke. Methods will be defined as appropriate for specific analysis and hypothesis.

Clinical classification of the infarction
Results of clinical, neuro-radiological, neuro-sonographic and cardiologic data are used for classification of causes of ischemic stroke according to the TOAST criteria [15, 16] and ASCOD criteria [17].

Balance, cognition and communication
Standardized testing of balance, cognition and communication (swallowing) should be performed during the first hospital stay. In case of pathological findings, tests should be repeated after 3 months and 1 year. Different centres are allowed to continue with their standard procedures.

Vision, hearing and neuropsychological function
Standardized testing of vision (dept. of ophthalmology) and hearing (ENT-department) should be performed within the first 3 months after ischemic stroke. Testing of neuropsychological function should be done approximately at 6 months, and not later than one year after the stroke.

Follow-up
One week after discharge, patients are contacted by telephone by a trained stroke study nurse asking whether the given information about the disease and risk factors was understandable, to what extent the patient expects to manage changes of modifiable risk factors, if he/ she feels comfortable with the medication, and if any changes have been made concerning the medication.
Three months after the stroke, patients return for an outpatient clinical consultation with focus on new cerebral or other arterial events, cognitive function, anxiety, depression, sleep problems, work and leisure activities, and, if applicable, change of lifestyle. If testing of vision, hearing, cognition, communication and physical function revealed pathological findings, tests are repeated. Blood pressure, pulse, height, weight, waist-hip ratio and ECG are registered.
One year after the stroke, patients return for a second outpatient clinical consultation with the same assessment protocol as used at 3 months.

Statistical power
The NOR-SYS studies are observation studies over 5 years of inclusion. Frequency and degree of artery disease are in focus of both NOR-SYS programs. Frequency and degree of "invisible problems" among seemingly well-functioning persons are in the focus of NOR-SYS II.

4.2 Organisation and collaboration

Annette Fromm and UWA, both internationally certified for the NOR-SYS ultrasound protocol, are at present the including study doctors for NOR-SYS II. Collaboration at own department will continue with Annette Fromm, leader of the NOR-PLAQ study concerning plaque instability detection by emboli-monitoring and contrast enhanced ultrasound. Further, during hospital stay after acute ischemic stroke, patients in NOR-SYS II are examined by standardized diagnostics, including ultrasound of the heart, testing of balance, cognition and speech in close collaboration with the Dep. of Cardiology, Haukeland University Hospital (Prof. Eva Gerdts; Sahrai Saeed MD, PhD; Prof. Terje H. Larsen; Karel Kuiper MD, PhD), and leading clinical expertise on the field of Physiotherapy (Elisabeth Kvile), Speech therapy (Mari Myklebust) and Occupational therapy (Silje Nødtvedt). Within 3 months after discharge, 24- hour blood pressure and arterial stiffness are measured at the outpatient clinic of Cardiology, vision at the Dep. of Ophthalmology (PhD Alexander Stanley Thrane), and hearing at the Dep. of ENT diseases (Jeanette Hess-Erga, MD, senior consultant). Each department is responsible for storing of own data, and decides about how to use them. If several centres join NOR-SYS II, a study collaboration group will be established to plan and decide about publications. Other collaboration partners are listed at the electronic first page.

4.3 Budget

Main expenses will appear by securing contributions (administration and telephone contacts with patients) and plotting of data by study nurses of contributing centres. Competence of a neuro-radiologist is mandatory for standardised evaluation of cerebral tissue due to new and old cerebral infarction, other cerebral tissue pathology, such as the extent of cerebral micro-bleedings, and evaluation of the cerebral arteries, done by CT-, MR- or conventional angiographies.

4.4 Plan for progression and publishing

Both NOR-SYS studies are actively ongoing studies in Bergen. Other sites are interested to contribute, but this is dependent on contributions by study nurses to make the studies run. Ten to 20% financing of study nurses, depending of the size of the study site, is calculated with 60.000 to 120000 NKr / year, and is specified in the electronically given budget.

The following work will be done in a 3-year period of funding from 2017-2019:
Three main papers after conclusion of the inclusion phase of NOR-SYS I about results of "How sick are the arteries" (Staging of the arteries):

1. Staging of the arteries results among patients and partners – related to risk factors: Annette Fromm
2. Staging of the arteries results among patients and partners - related to cerebral, coronary, aorta and peripheral arterial events among parents (heredity): Ulrike Waje-Andreassen, UWA
3. Staging of the arteries results among offspring - related to staging of the arteries among patients and partners, their parents: UWA

After publishing of these 3 articles with "core-information" about the degree of arterial disease, UWA will search for national and international laboratories concerning start of analysis of bio-bank material, contributing to increased knowledge of genetics and biomarkers.

The phd-candidate will answer questions concerning incidence, frequencies about new risk factors, such as use of snuff and severe obesity, and previous cardiovascular events before the index stroke.

Further, she will analyse mortality and new cardiovascular clinical events, such as recurrent stroke, coronary and peripheral artery disease during the short-time follow-up of one year. Finally, functional outcome, medication and change of habits are evaluated after discharge and during the first short-time follow-up of NOR-SYS I patients. Apart from publications, she will contribute to active work of patient inclusion into NOR-SYS II, contributing to progression of this recently started study.
Further, the phd-candidate will publish results and experiences from NOR-SYS II on posters at national and international conferences, as done previously (see last part of the publication list of UWA). Research results of general public interest will be presented in public settings, public media and for patient organisations.

4.5 Plan for implementation

All new knowledge we gained by continuous clinical research from the 90-ies is implemented and focused on in the NOR-SYS studies. The NOR-SYS studies will create by the 3-generation set-up valuable information for future translational research. The 3-generation set-up has not been dropped in NOR-SYS II program, but family information about cardiovascular events is just compressed to the patient´s or the family´s "homework" during hospital stay. NOR-SYS I face-to face interviews with patients were done, not giving the chance to contact other family members by mobile phone. In the NOR-SYS II program, patients still have face-to-face interviews but can now discuss cardiovascular events among family members to create best "family history information".
The completely new implementation of a second-line rehabilitation for patients in Bergen that are not able to come back to the previous working situation, starts now by the LHL-clinics, Bergen. Reduced function of young brains costs society millions and causes a lot of individual suffering. The final plan is to implement the work now done by NOR-SYS II into future routine clinical work. Patients and their families gain much more support than ever before. Doctors and scientists gain much more knowledge on heredity and development of arterial disease than ever before, a perfect win-win situation for patients and science.

5 Support by patients to improve research

Patients who impressed the leader, UWA of the NOR-SYS I study by their tough struggling and dealing with "invisible problems" support the new focus of NOR-SYS II. Their letter is attached to the CV and publication list of UWA. From the start of NOR-SYS I since 2010, we have had close contact to patients and families. The idea to include partners and offspring came from earlier experience, especially partners that nearly panicked with acute anxiety for own health, especially in case of dissection or unknown cause of stroke. This immediate threat appeared especially when being the main caring person for young children (no research data, only working experience). Planning NOR-SYS I, we did not expect much participation of offspring at age 18 to 25 years old, but were overwhelmed of big participation numbers of these youngest adults. In addition we had to reject questions and telephone calls from parents, siblings, cousins and younger offspring < 18 years about the wish of active participation with ultrasound and other cardiovascular preventive examinations.

6 Ethics

Both NOR-SYS research programs are approved by the Regional Ethics Committee, REK 2010/74 and 2015/1769, and have approved general research bio-banks, REK: 2010/1025 and 2015/2338). They have the ClinicalTrials.gov identifiers NCT01597453 (I) and NCT02762396 (II).
All participants or legal representatives gave and give written consent before inclusion, and included patients or their legal representatives (for patients < 18 years and for patients not able to speak or to sign as consequence of the stroke) have to speak Norwegian fluently.
The NOR-SYS studies are strictly academic research programs with preliminary internal financing in Bergen at present of a 20% stroke study nurse to register results.

7 References

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