RESEARCH PROTOCOL

COACH-pilot study

COgnition After intraCerebral Hemorrhage

Full title:
Assessing cognitive function and related small vessel disease markers after intracerebral hemorrhage;
a pilot study.

COACH-pilot study
COgnition After intra-
Cerebral Hemorrhage

Onderzoeksprotocol

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PROTOCOL TITLE

Assessing cognitive function and related small vessel disease markers after intracerebral hemorrhage; a pilot study.

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Coordinating investigator/project leader	Prof. Dr. M.J.H. Wermer Department of Neurology LUMC
Principal investigator(s) (in Dutch: hoofdonderzoeker/ uitvoerder)	Drs. E.S. van Etten; Department of Neurology LUMC Prof. Dr. Ir. M.J.P. van Osch; Department of Radiology LUMC Dr. G.M. Terwindt; Department of Neurology LUMC
Sponsor (in Dutch: verrichter/opdrachtgever)	Leiden University Medical Center Albinusdreef 2 2333 ZA Leiden
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Independent expert	Dr. E.H. Niks; Department of Neurology LUMC

PROTOCOL SIGNATURE SHEET

Name	Signature	Date
Head of Neurology Department Prof. Dr. J.J.G.M. Verschuuren		
Coordinating Investigator Prof dr. M.J.H. Wermer		

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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

Aβ Amyloid beta

CAA Cerebral amyloid angiopathy

cSAH Cortical subarachnoid hemorrhage

CSF Cerebrospinal fluid

DTI Diffusion tensor imaging

HA Hypertensive arteriopathy

ICH Intracerebral hemorrhage

IQCODE Informant Questionnaire on Cognitive Decline in the Elderly

MB microbleeds

METC Medical research ethics committee (MREC); in Dutch: medisch-ethische toetsingscommissie (METC)

MRI Magnetic Resonance Imaging

mRS Modified Rankin Scale

NIHSS National Institutes of Health Stroke Scale

ePVS Enlarged Perivascular spaces

sCAA Sporadic cerebral amyloid angiopathy

cSS Superficial Siderosis

SVD Small vessel disease

WMH White matter hyperintensities

1. SUMMARY

Rationale: Dementia is a major contributor of dependence and disability in the ageing population and is mainly caused by neurodegenerative and cerebrovascular disease. Vascular cognitive impairment (VCI) occurs in at least 10% of patients who recover from an intracerebral hemorrhage (ICH) and has a major impact on post ICH recovery. In the acute phase of ICH, cognitive impairment may be caused directly by the hemorrhage damaging the brain parenchyma. In the chronic phase, however, further cognitive decline is also prevalent.

Cognitive decline after ICH might be caused by the underlying etiology of the ICH. The most frequent underlying small vessel diseases (SVD) that cause ICH are cerebral amyloid angiopathy (CAA) and hypertensive arteriopathy (HA). CAA and HA have their own radiological signatures of SVD markers which allow for in vivo tracking of disease progression using MRI. Although the initial clinical presentation these two types of SVD differs – CAA classically presents with a lobar ICH, whereas HA causes deep ICH – both groups of patients are at risk of developing dementia. However, it has recently been shown that patients with lobar ICH develop new onset dementia twice as often as patients with deep ICH. Whether underlying CAA pathology causes this increase, remains unclear. In addition, whether ICH accelerates the process of vascular damage and if cognitive decline can be predicted by certain disease markers is uncertain. Understanding the underlying mechanisms for cognitive decline after ICH helps to improve knowledge of prognosis and clinical management of patients who are recovering from ICH.

Objectives: The overall aim of this pilot study is to investigate the development of MRI and CSF markers after CAA-related and HA-related ICH in relation to cognitive decline. The results from this pilot trial will be used to design a larger cohort study to investigate underlying mechanisms of cognitive decline after ICH.

Study design: The study design is a prospective cohort study.

Study population: The study population consists of 32 patients; 16 patients with CAA-related ICH and 16 patients with HA-related ICH who are 55 years or older.

Methods: Data will be collected at four measuring points: at baseline (during hospital admission for the ICH or at the outpatients clinic within one month of presentation with an acute ICH), after three months, after six months and after 12 months. Premorbid cognitive functioning will be assessed with the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) to select participants without pre-existing cognitive impairment.

At baseline, the premorbid functional status will be assessed with the modified Rankin Scale (mRS) and Barthell index. A 3Tesla MRI will be performed to assess the most likely underlying cause of the ICH (patients with either CAA or HA-related ICH will be included). Stroke severity will be assessed with the National Institutes of Health Stroke Scale (NIHSS) and a neurologic exam will be performed. Participants will undergo an extensive interview on life-style, vascular risk factors and medication, and

will undergo a blood withdrawal. Neuropsychological testing will be performed and questionnaires will be used for screening for depression, anxiety and psychopathology. In addition, participants will be asked to undergo a lumbar puncture to collect cerebrospinal fluid (CSF).

After three months, neurological examination, and neuropsychological testing will be repeated.

After six and 12 moths, the neurological examination, the 3 Tesla MRI and neuropsychological testing will be repeated. Additionally, participants will be asked for a lumbar puncture at these two time points.

Main study parameters/endpoints: The main parameters are cognitive decline (according to the neuropsychological assessment) at 12 months. Secondary outcomes are burden of SVD markers on MRI and CSF markers at baseline, at six months and 12 months.

Nature and extent of the burden and risk associated with participation, benefit and group relatedness: The risks of MRI are minimal (risk of everyday life), because there are no consequences to the health of the participant. Contra-indications will be carefully investigated per subject, burden will be kept at a minimum by using short protocols. There is no direct benefit for the patients except for more insight into the underlying pathophysiology of the hemorrhages related to their disease.

Blood withdrawal and lumbar puncture are routine procedures at the Department of Neurology. Lumbar puncture will be performed by experienced physicians. We will use atraumatic spinal needles to reduce the risk of post-lumbar puncture headache.

Patients will be informed extensively about the potential risks of these procedures, after which written informed consent will be obtained.

2. INTRODUCTION AND RATIONALE

Cognitive impairment after intracerebral hemorrhage

Dementia is a serious public health problem in the ageing population and cerebrovascular disease is a major cause of cognitive decline. After a first stroke, at least 10% of patients without previous cognitive impairment will develop dementia.[1] In a large observational cohort study, even one in three patients develop new onset dementia within five years after stroke.[2] Even though intracerebral hemorrhage (ICH) and ischemic stroke can both cause vascular cognitive impairment (VCI), ICH has received far less scientific attention than ischemic stroke. Nevertheless, ICH is more strongly associated with new post-stroke dementia than other stroke subtypes.[2]

Predicting outcome after ICH is challenging. Cognitive decline is believed to cause the greatest impact on quality of life after ICH.[3] A certain degree of cognitive deficit in the acute phase of ICH is

likely a direct result of the hemorrhage damaging the brain parenchyma, although it also depends on co-existing neurodegenerative pathology, the hemorrhage volume, and the location of the hemorrhage. Even though these cognitive deficits might partly resolve as the hemorrhage resorbs over time, some of the ICH survivors will have progressive cognitive decline and therefore a poor long-term outcome.[3] The ICH might trigger or boost underlying small vessel disease underlying this cognitive decline.

Post-ICH cognitive decline might be caused by the underlying causes of ICH. The most important cause of primary ICH is small vessel disease (SVD).[1] The two most common subtypes of SVD are hypertensive arteriopathy (HA) and sporadic cerebral amyloid angiopathy (CAA). HA results from hypertension-related damage predominantly affecting small perforating end-arteries in the basal ganglia, brain stem, deep white matter, and cerebellum. CAA is caused by β-amyloid deposition within the wall of cortical and leptomeningeal arteries causing pathology in the lobar regions of the brain.[4] Therefore, when HA leads to an ICH it is most likely located in the deep brain structures, whereas CAA typically causes lobar ICH.[5]

The incidence of new-onset dementia after stroke has been addressed in a cohort of 218 ICH patients. In these ICH survivors without dementia at baseline, new-onset dementia occurred with an incidence of 14.2% at 1 year and 28.3% at 4 years of follow up. Interestingly, this incidence was twice as high in patients with lobar ICH (23.4% at one year follow-up) than for patients with non-lobar ICH (9.2% at one year follow-up). This finding is in line with previous studies linking CAA to cognitive impairment.[6]

MRI markers and cognitive impairment

Underlying SVD-related pathology can be identified using MRI. Even though MRI does not show the entire spectrum of the underlying SVD pathology, it has improved our understanding of SVD pathology extensively in the recent years.[7] MRI markers associated with CAA often are different or have a different distribution compared with MRI markers associated with HA.[8] Deep cerebral microbleeds (MB's), white matter hyperintensity (WMH), and MRI visible enlarged perivascular spaces (ePVS) located in the area of the basal ganglia are associated with HA.[9] Markers associated with CAA include lobar MB's, WMH, ePVS in the subcortical white matter, cortical subarachnoid hemorrhage (cSAH), intragyral hemorrhages, microinfarcts, cortical thinning, and cortical superficial siderosis (cSS).[4]

Severe WMH, lacunar infarcts, microinfarcts, have been associated with vascular cognitive impairment.[10] The association between cognitive impairment and MB's has also been well established,[11] and recent studies have shown that cSS plays an important role in predicting progression of CAA.[12, 13] Additionally, altered white matter integrity measured with diffusion tensor imaging (DTI) has been found in patients with mild cognitive impairment[14] and CAA[15] and might be a marker of cognitive decline in post-ICH patients.

As both HA and CAA are likely to progress over time, and therefore continue to damage the brain, it can be assumed that these two forms of SVD cause further cognitive deterioration after ICH and that this can be demonstrated by progression of the burden of MRI markers.

Biomarkers in cerebrospinal fluid

Although the implications of MRI markers in CAA and HA patients become increasingly clear, it is unknown in what way disease progression and changes in cerebrospinal fluid (CSF) show a correlation. In the hereditary form of CAA, decreasing CSF levels of Aβ occur before patients develop an ICH, implicating vascular deposition of Aβ species as early steps in CAA pathogenesis.[16] Whether they have a predictive value, however, for cognitive decline after ICH remains unclear.

Potential risk factors that might affect cognitive decline after ICH

Factors like hyperglycemia, obesity, insulin resistance, and hypertension cause microvascular disfunction and are therefore associated with cognitive impairment.[17] In order to investigate the effect of SVD on cognition it is important to assess these risk factors, as well as medication use.

Implications on clinical practice

Currently no therapies to prevent or slow down cognitive impairment after stroke exist. However, understanding the underlying cause and the natural disease course might help physicians to inform patients and screen for cognitive decline in patients who are at risk. Furthermore, identifying markers that correlate with cognitive decline might be important for future therapeutic trials. The results of this pilot study will be used to power a larger cohort study to investigate underlying mechanisms of cognitive decline after ICH and the differences between non-CAA and CAA related pathology. We will learn about the prevalence of cognitive decline, the differences between markers and their association with cognitive decline and the optimal time points for MRI (6 or 12 months) to assess the potential of creating a prediction model of the SVD markers and cognitive decline.

Overall aim: The overall aim is to study cognitive decline in patients who recover from ICH and the relation with SVD markers. The results will be used to design a larger cohort study.

3. OBJECTIVES

1. To investigate the proportion of patients with new-onset dementia after HA-related ICH and CAA-related ICH by performing serial follow-up with neuropsychological testing.
2. To investigate MRI markers for SVD disease at baseline and their progression during follow-up and study if and how these markers correlate with cognitive decline after HA-related ICH versus CAA-related ICH.
3. To assess CSF markers at baseline and progression during follow-up and study if and how CSF markers correlate with cognitive decline after HA-related ICH versus CAA-related ICH.
4. To store blood and CSF of CAA and HA patients for biobanking purposes and future research.

The results from this pilot study will be used to design a larger cohort study to investigate underlying mechanisms of cognitive decline after ICH.

The cognitive decline and influencing factors ICH patients will be (whenever appropriate and dependent on the particular research question) compared with data from other research projects in the LUMC like the hereditary form of CAA (HCHWA-D, n=75), sporadic CAA (n=50), Alzheimer's disease, and Huntington's disease or available data on healthy controls.

4. STUDY DESIGN

The study design for this pilot study is a prospective cohort study.

5. STUDY POPULATION

5.1 Population

The study population are patients with ICH that have no family history of hereditary forms of ICH such as hereditary CAA (HCHWA-D) and no cognitive impairment before the ICH. Patients will be aged ≥ 55y, since the radiological Boston criteria for CAA-related ICH only include patients ≥ 55y.[18]

5.2 Inclusion criteria

ICH patients:

1. Age ≥ 55y
2. Ability and willingness to provide written informed consent.
3. Supratentorial ICH with CAA[a] or HA[b] as the most likely cause.

[a] CAA-related ICH is defined as an ICH that meets the criteria for definite or probable CAA according to the Modified Boston Criteria (appendix A)

[b] HA-related ICH is defined as ICH located in the basal ganglia, thalamus, or the deep white matter and the presence of hypertension defined as: on treatment for hypertension, or known with high blood pressure (two measurements SBP >140 or DBP >90 mmHg) but not treated for hypertension.

5.3 Exclusion criteria

1. Age < 55y
2. Unable to provide informed consent.
3. Pre-existing cognitive impairment assessed with the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE); scores between 53 - 63 reflect pre-existing cognitive mpairment.[19]

4. Contra indications, such as:

Contra-indications for 3T MRI. Examples of possible contra-indications are:

- Claustrophobia
- Pacemakers and defibrillators
- Nerve stimulators
- Intracranial clips
- Intra-orbital or intraocular metallic fragments
- Cochlear implants
- Ferromagnetic implants
- Hydrocephalus pump
- Intra-uterine device
- Permanent make-up
- Tattoos above the shoulders
- Reduced kidney function (estimated GFR < 30 ml/min/1,73m2; or nephrogenic systemic fibrosis / nephrogenic fibrosing nephropathy (NSF/NFD))
- Known prior allergic reaction to gadolinium contrast or one of the constituents of its solution for administration

Contraindications for lumbar puncture:

- Intracranial tumor
- Compressio medullae
- Signs and symptoms of increased intracranial pressure
- Local infections of the skin
- A coagulopathy including use of anti-coagulant drugs (INR ≥ 1.8) or thrombocytopenia (<40)

Use of acetylsalicylic acid, NSAIDs, COX2 inhibitors or prophylactic low-molecular-weight heparin are no contraindications for lumbar puncture,

5.4 Sample size calculations

For this pilot study, we require 32 participants (16 CAA-related ICH and 16 HT-related ICH). This sample size is considered to be sufficient to study the feasibility of the study procedures. Furthermore, the results of a pilot study with this sample size should provide sufficient data that are needed to determine a sample size of a future, larger cohort study.

6. METHODS

6.1 Study parameters/endpoints

Cognitive functioning

The neuropsychological assessment will consist of a battery of tests that measure different cognitive domains. Premorbid cognitive functioning will be assessed with the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE). Cognitive functioning will be tested using a Mini-Mental State Examination (MMSE), a Montreal Cognitive Assessment (MOCA), a Frontal Assessment Battery (FAB), Digit Span Test (DST), RAVLT-15 words test, Stroop test, Trail making test, the Hospital Anxiety and Depression Scale (HADS), the Center for Epidemiologic Studies Depression Scale (CES-D), the Neuropsychiatric Inventory Questionnaire (NPI-Q), the Starkstein Apathy Scale (SAS) and the Prikkelbaarheidsschaal (PS). Cognitive impairment was defined as a score ≤ 1.5 standard deviation below the general population mean in one or more cognitive domains.

MRI markers

The presence and number of MBs, cSS, WMH, cSAH, ePVS, microinfarcts, intragyral hemorrhages, cortical atrophy and other new and known small vessel biomarkers will be assessed on 3T and scored according to the STRIVE criteria.[20] White matter integrity will be assessed using quantitative MR measurements and perfusion will be assessed.

Biomarkers in blood and CSF

Blood samples will be analyzed for coagulation profiles, cholesterol levels, APOE status, inflammation profile and hormone levels. In addition, extra blood will be stored in the LUMC Biobank sCAA Neurological Diseases for future biomarker studies. Concentrations of Aβ40, Aβ42, t-tau, and p-tau181 will be measured in CSF and other biomarkers that may be identified in the future.

Other study parameters

Further parameters of this study will include demographic data, current medical conditions, vascular risk factors (including smoking, alcohol use, drugs, physical exercise, sleep, hypertension, hypercholesterolemia, diabetes mellitus, family history and medication; in women also information on female medical history such as number of pregnancies, menstruation cycle and menopause will be retrieved), neurologic history (including previous ischemic or hemorrhagic stroke), BMI, and blood pressure.

6.2 Study procedures

Data will be collected at four measuring points: at baseline, after three months, after six months and after 12 months:

- **Baseline (during admission or at the outpatient clinic < 1 month after ICH onset)**
  Intake, baseline characteristics and neurological examination will be performed, as well as neuropsychological testing, blood sample collection, and a 3Tesla MRI scan. Additionally participants will be asked to undergo a lumbar puncture.
- **Three months (regular follow-up visit)**
  At three months during the routine outpatient clinic visit a neurological examination will be performed, as well as neuropsychological testing.
- **Six and twelve months (two additional study visits)**
  At six and twelve months, neurological examination will be performed, as well as neuropsychological testing, and a 3Tesla MRI scan. Additionally, participants will be asked to undergo a lumbar puncture.

• Intake, baseline characteristics and neurological examination

During the baseline assessment the following demographic and base line characteristics will be recorded: date of birth, gender, current medical conditions, daily intake alcohol/drugs/caffeine, sleep, physical activity, smoking, medication, cardiovascular risk factors and neurologic history (including previous ischemic or hemorrhagic stroke and history of migraine). In women information about menstruation cycle, pregnancies and menopause will be recorded. BMI will be recorded. Contra-indications for MRI will be checked. A standard neurological examination will be performed.

• Neuropsychological testing

As mentioned in 6.1, cognitive function will be tested using a Mini-Mental State Examination (MMSE), a Montreal Cognitive Assessment (MOCA), a Frontal Assessment Battery (FAB), Digit Span Test (DST), RAVLT-15 words test, Stroop test, Trail making test, the Hospital Anxiety and Depression Scale (HADS), the Center for Epidemiologic Studies Depression Scale (CES-D), the Neuropsychiatric Inventory Questionnaire (NPI-Q), the Starkstein Apathy Scale (SAS) and the Prikkelbaarheidsschaal (PS).

• 3Tesla MRI

MRI is a non-invasive method, which is able to detect abnormalities in the brain with a high resolution. MRI will be performed on a 3Tesla MR system. MR scanning is harmless to the health of the participant, for the scans in this protocol no contrast agents will be used. Scans are made by a certified MRI operator, who will accompany the participant and will check any MR contraindication. Scanning time will be kept to a maximum of 60 minutes for the complete protocol.

The following 3Tesla scan protocol will be used:

• Anatomical T1-weighted imaging
• T2-weighted imaging
• Fluid Attenuation Inversion Recovery (FLAIR)
• A Susceptibility Weighted Imaging (SWI)
• Diffusion-weighted imaging (DWI)
• Diffusion tensor Imaging (DTI)
• Arterial Spin Labeling (ASL)
• Post-gadolinium 3DT1 and 3DFLAIR

The 3T MRIs will be performed at inclusion and will be repeated at 6 months and after 1 year. The MRIs will be used to search for SVD markers (paragraph 6.1).

3T MRI's performed in the clinical setting can be used for study purposes with the participants permission. When a 3T is performed for research purposes only, participants generally will not receive the MRI results unless they want to know their personal outcome. In this case the results will be discussed with them by one of the neurologists/neurology residents.

• Blood sample collection
Blood samples (50 ml) will be analyzed for laboratory tests such as APOE status, cholesterol levels, inflammation and coagulation profile and hormone levels.

If participants give permission for LUMC Biobank sCAA (part of the LUMC Biobank Neurological Diseases), an additional 50 ml blood will be drawn. These blood samples will be stored for future (yet unknown) biomarker analysis after approval of the participants. These blood samples will be handled confidentially and coded and will be stored in the LUMC Biobank sCAA Neurological Diseases. The regulations of the LUMC Biobank Neurological Diseases will be applicable to the LUMC Biobank sCAA under Neurological Diseases

• CSF sample collection
The earlier mentioned contraindications (see paragraph 5.3) to lumbar puncture will be checked. CSF will be sampled by lumbar puncture under standardized conditions by experienced physicians. The lumbar puncture will be performed in the interspaces between the lumbar vertebrae, at the L3-S1 level, below the level where the spinal cord typically ends (L1) in adults. The lumbar puncture will be performed with sterile materials. The duration of the lumbar puncture is about 10 minutes. Atraumatic spinal needles will be used to minimize chances of post lumbar puncture headache. If a lumbar puncture fails with an atraumatic needle, a traumatic needle may be used.

In total approximately 20 ml CSF will be collected. For routine parameters, cell count, protein and glucose, a maximum of 8ml will be collected. CSF for the proposed biomarker assays (paragraph 6.1) will be collected in polypropylene tubes, centrifuged, divided into 0.5 ml aliquots, and stored at -80^{o}C until analysis.

If participants give permission, additional CSF (12 ml) will be stored for future (yet unknown) biomarkers. By giving permission for CSF withdrawal and the LUMC Biobank sCAA Neurological Diseases, the subject gives permission for withdrawal and storing the CSF and coded medical information into the LUMC Biobank sCAA Neurological Diseases, which can be used for other scientific studies on biomarkers related to CAA without being notified. The regulations of the LUMC Biobank Neurological Diseases will be applicable to the LUMC Biobank sCAA Neurological Diseases.

Three days after the visit, subjects will be contacted to check whether the lumbar puncture has resulted in any persistent complaints. Subject will not receive the CSF results because the lumbar puncture will be performed for research purposes only.

6.3 Withdrawal of individual subjects

Subjects can leave the study at any time for any reason if they wish to do so without any consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons. Decision to leave the study will not influence the diagnostic trajectory or treatment of patients in any way. In case a participant becomes mentally incompetent during the study period, the participant continues with the study unless he/she desires to end the participation or shows (verbal or non-verbal) resistance to the study procedures.

6.4 Replacement of individual subjects after withdrawal

Individual subjects who withdraw from the study or die before the end of the study will be replaced. The reason of withdrawal will be asked, but participants are also ensured that they don't need to give a reason for ending their participation. Replaced individuals will not be excluded from the analysis.

7. SAFETY REPORTING

7.1 Section 10 WMO event

In accordance to section 10, subsection 1, of the WMO, the investigator will inform the subjects and the reviewing accredited METC if anything occurs, on the basis of which it appears that the disadvantages of participation may be significantly greater than was foreseen in the research proposal. The study will be suspended pending further review by the accredited METC, except insofar as suspension would jeopardize the subjects' health. The investigator will take care that all subjects are kept informed.

7.2 AEs, SAEs, and SUSARs

Adverse Events Adverse events are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to the study procedures. All adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded.

- Serious Adverse Events A serious adverse event is any untoward medical occurrence or effect that
- results in death;

- is life threatening (at the time of the event);
- requires hospitalisation or prolongation of existing in patients' hospitalisation;
- results in persistent or significant disability or incapacity;
- any other important medical event that did not result in any of the outcomes listed above due to medical or surgical intervention but could have been based upon appropriate judgement by the investigator.

An elective hospital admission will not be considered as a serious adverse event. AEs and SAEs will be reported by the treating physician in the electronic medical patient file. The investigator will report all SAEs to the sponsor without undue delay after obtaining knowledge of the events.
The sponsor will report the SAEs through the web portal ToetsingOnline to the accredited METC that approved the protocol, within 7 days of first knowledge for SAEs that result in death or are life threatening followed by a period of maximum of 8 days to complete the initial preliminary report. All other SAEs will be reported within a period of maximum 15 days after the sponsor has first knowledge of the serious adverse events.

- Suspected Unexpected Serious Adverse Reactions Adverse reactions are all untoward and unintended responses to an investigational product related to any dose administered.

Unexpected adverse reactions are SUSARs if the following three conditions are met:
1. the event must be serious;
2. there must be a certain degree of probability that the event is a harmful and an undesirable reaction to the study procedure
3. the adverse reaction must be unexpected, that is to say, the nature and severity of the adverse reaction are not in agreement with the product information as recorded in:
- Summary of Product Characteristics (SPC) for an authorised medicinal product;

7.3 Unexpected findings

In case of an unexpected findings, the participant will be informed. In the informed consent the participant is also asked for permission to share any unsuspected findings with his/her general practitioner.

8. STATISTICAL ANALYSIS

Descriptive statistics will be performed. New onset cognitive impairment and dementia will be determined (according to the MMSE scale) and compared between CAA-related and HA-related ICH. Prevalence of different biomarkers in CSF and MRI and their evolution over time will be assessed. Linear regression analysis will be used to examine associations of MRI and CSF markers primarily with the MMSE and secondarily with the other cognitive scores. Some MRI markers, such as MB's count will be transferred logarithmically. Based on our power calculation (see references paragraph 5.4) we expect that the number of participants will be sufficient for analyses of difference in cognitive decline between CAA-related ICH and HA-related ICH. This pilot study is, however, not powered to detect significant associations between cognitive decline, MRI markers and CSF markers. The

evolution of MRI and CSF markers will, however, give enough insight to power a larger trial to investigate the underlying mechanisms of cognitive decline after ICH. In addition, we will assess whether levels of MRI and CSF markers change between 6 and 12 months after the ICH to decide which timepoint is most relevant for a larger study as in the subsequent study we aim to have one follow-up time point for a MRI and lumbar puncture.

9. ETHICAL CONSIDERATIONS

9.1 Regulation statement

The study will be conducted according to the principles of the "Declaration of Helsinki" (as amended in Fortaleza, Brazil, October 2013) and in accordance with the Guideline for Good Clinical Practice (CPMP/ICH/135/95 - 17th July 1996).

9.2 Recruitment and consent

The protocol of this study will be submitted to the Medical Ethics Committee of the Leiden University Medical Center and the study will not commence before formal approval has been granted.

Participants will be selected from our LUMC ICH population. This population consists of patients referred to our emergency department for ICH and are admitted to our clinic. Patients will be contacted by one of the neurologists, neurologic residents or research physicians. In addition, neurologists from other hospitals can send their patients who want to participate in our studyif they are < 1 month after ICH onset. The purpose of the study will be explained and the eligible participants will receive a letter with information about the study. The purpose and method of the study will be described in the information letter (see attachment ‘proefpersoneninformatie’). Participants who are not able to give informed consent will not be included in the study. All participants are free to discontinue the study at any time. Participation in this study will have no negative financial consequences for the patient, travel expenses will be compensated for.

Written informed consent will be obtained for the (repeated) 3T MRI, venous puncture and lumbar puncture. Subjects will be asked for a written informed consent for future projects with blood and CSF stored for biobanking purposes.

Investigations at the different time points can take place on a single day at each time point, depending on the preference of the patient.

9.3 Benefits and risks assessment, group relatedness

To learn more about the pathophysiology, progression and prognosis of cognitive decline after ICH, we need to investigate ICH patients over a long period of time. By investigating MRI markers, CSF markers and cognitive functioning we will obtain more insight on individuals at risk. Moreover, this study hopefully eventually leads to new targets for therapy and will give insight in the sample size needed for a larger study to investigate mechanisms behind cognitive decline after ICH. Patients will

be informed extensively about the potential risks of the study procedures, after which written informed consent will be obtained.

The potential risks of this study are limited. The risks of gadolinium enhanced 3Tesla MRI are minimal. Gadolinium enhanced 3T MRI is performed in patients with ICH in routine clinical practice as part of the workup to find an underlying cause such as a tumor or a macrovascular cause according to the guidelines of the American Heart Association (2015) and the European Stroke Organisation (2019). Deposits of gadolinium can remain in the brains of some patients who have undergone 4 or more MRI scans with gadolinium for a prolonged time after the last administration. Deposits of gadolinium have also been reported in skin and bone. The European Medicines Agency has concluded that here is no evidence that gadolinium deposition in the brain has caused any harm to patients. A nephrogenic systemic fibrosis (NSF) has also been reported after gadolinium-based contrast agent administration. The most important risk factor for NSF is a severely reduced kidney function (eGFR < 30 ml/min/1.73m^2). The type of gadolinium-based contrast agent is also determinant for the risk of NSF. Allergic reactions to gadolinium-based contrast agents have also been reported. Other potential risks include movement of ferromagnetic objects in the body. Some participants may feel claustrophobic in the restricted space of the MR scanner.
The potential risks related to MRI will be minimized in the following manner:
• Claustrophobia
Claustrophobia from the MRI scan will be reduced by explaining the nature of the scanner in detail before enrolment. At all times, the subjects will be able to communicate with the researcher, so if claustrophobia becomes a problem the subject can request to be removed from the scanner.
• Movement of ferromagnetic objects in the body
A list of questions concerning risk factors of MRI must be filled in by the subject. Based on the answers the subject is or is not allowed to go into the scanner.
• Gadolinium will be administered once, the administered dose of gadolinium will be kept as low as possible, and a macrocyclic gadolinium-based contrast agent (Gadoteraat (Dotarem 0,5 mmol/ml, Guerbet) will be used to maximize safety. After administering gadolinium participants will be under observation for at least 30 minutes to check on signs of an allergic reaction. Participants will be advised to avoid repeated gadolinium administering in the next 24hours and creatinine clearance will be checked for reduces kidney function.

Blood withdrawal via venous puncture in the elbow has a very low rate of adverse events. The needle puncture may cause bruising and in very rare cases an infection of the skin or blood vessel may occur at the puncture site.

A lumbar puncture is a minimal burdening to patients if the patient is in the right position and if the patient has a normal anatomy of the vertebrae. Usually, the lumbar puncture itself takes about 10 minutes and patients stay in the hospital afterwards for about half an hour. The most frequently occurring complication of lumbar puncture is post-lumbar puncture headache. This complication is much rarer when atraumatic spinal needles are used. If post-lumbar puncture headache occurs, subjects should take bed rest, drink ample water, and may use paracetamol if required. If the post-

lumbar puncture headache persists for more than a week, a blood patch may be considered which is usually effective in treating the headache.[21, 22] Very rarely, infection such as meningitis or spinal abscess may occur. Patients will be contacted by phone three days after lumbar puncture to check whether the lumbar puncture has resulted in any persistent complaints. If there are complaints following the puncture, one of the neurologists will contact the patient to make sure adequate measures (e.g. a blood patch) are taken.

The potential risks related to lumbar puncture will be minimized in the following manner:
• Post-lumbar puncture headaches
We will use atraumatic spinal needles and will take out the needle with the stylet reinserted. To further reduce the risk, we will advise the patients to drink ample water and drinks with caffeine. A prospective study to investigate possible predictors for postdural puncture headache revealed young age and low BMI as significant risk factors.[23] Our study population will consist of middle-aged or older participants for the most part.
• Risk of infection
We will minimize the risk of infection by working under sterile conditions.

There is no benefit for the patients except for more general insight into the underlying pathophysiology of the hemorrhages related to their disease.

9.4 Compensation for injury

Subjects are insured by the insurance of the LUMC. The LUMC has a liability insurance which is in accordance with article 7, subsection 6 of the WMO. The insurance covers an amount of € 650.000 per participant, € 5.000.000 for the entire study, and € 7.500.000 per year for all studies from the same sponsor.

9.5 Incentives

All participants will be compensated for traveling costs.

10. ADMINISTRATIVE ASPECTS AND PUBLICATION

10.1 Handling and storage of data and documents

All study data will be handled confidentially. All data will be coded. The investigator will retain the originals of all source documents generated at LUMC for a period of 2 years after the report of the study has been finalized, after which all study-related documents will be archived for 15 years. The handling of personal data complies with the EU General Data Protection Regulation and the Dutch Act on Implementation of the General Data Protection Regulation (in Dutch: Uitvoeringswet AVG, UAVG). The person responsible for the processing of personal data will be Prof. Wermer and drs. E.S. van Etten.. Blood products and CSF for future biomarker research will be stored with coded medical information into the LUMC Biobank under ‘Neurologische Ziekten’. Results of the Neuropsychological testing will be sent and stored in the digital CASTOR EDC database. CASTOR is

compliant with 21 CFR Part 11, ICH E6 GCP, GDPR, and HIPAA. ISO27001 and ISO9001 certified. Informed consents will be stored at the Neurology department of the LUMC at K5-106.

Participants may withdraw from this study at any time, without any consequences. This also accounts for the blood products and CSF, which will be destroyed after withdrawal. When measurements already have been performed, these data will still be used.

10.2 Monitoring and Quality Assurance

This study will be monitored by a research group-independent monitor. The monitor will visit the site at the end of the study and will assess informed consent procedures, protocol compliance / protocol violations, source document verification, reporting of (serious) adverse events in 1-10% of included patients. Available data management systems will be evaluated for privacy, security, completeness and back-ups. The monitor may visit the site on additional occasions, in case the investigators request to do so. For each monitoring visit, a written report will be made up, which will be stored in the trial master file.

10.3 Amendments

Amendments are changes made to the research after a favourable opinion by the accredited METC has been given. All amendments will be notified to the METC that gave a favourable opinion.

10.4 Annual progress report

The investigator will submit a summary of the progress of the trial to the accredited METC once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events/serious adverse reactions, other problems, and amendments.

10.5 End of study report

The investigator will notify the accredited METC of the end of the study within a period of 8 weeks. The end of the study is defined as the last patient's visit. The study will be terminated prematurely in case of safety problems. Also, the study will be terminated if it is temporarily suspended for reasons of subjects' safety and the accredited METC gives a negative decision after assessing the reasons that led to the temporary suspension. Within one year after the end of the study, the investigator will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC.

10.6 Public disclosure and publication policy

Results of this study will be published in international peer-reviewed scientific journals and will be presented on (inter)national scientific conferences and meetings. This will be in accordance to the CCMO statement on publication policy.

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APPENDIX A

The Modified Boston Criteria for Cerebral Amyloid Angiopathy

1. Definite CAA

Full post-mortem examination demonstrating:

- Lobar, cortical, or cortical-subcortical hemorrhage
- Severe CAA with vasculopathy
- Absence of other diagnostic lesion

2. Probable CAA with supporting pathology

Clinical data and pathologic tissue (evacuated hematoma or cortical biopsy) demonstrating:

- Lobar, cortical, or cortical-subcortical hemorrhage (including ICH, CMB, or cSS)
- Some degree of CAA in specimen
- Absence of other diagnostic lesion

3. Probable CAA

Clinical data and MRI or CT demonstrating:

- Multiple hemorrhages (ICH, CMB) restricted to lobar, cortical, or cortical-subcortical regions (cerebellar hemorrhage allowed), OR single lobar, cortical, or cortical-subcortical hemorrhage and cSS (focal or disseminated)
- Age≥55 years
- Absence of other cause of hemorrhage*

4. Possible CAA

Clinical data and MRI or CT demonstrating:

- Single lobar, cortical, or cortical-subcortical ICH, CMB, or cSS (focal or disseminated)
- Age ≥55 years
- Absence of other cause of hemorrhage*

*__Other causes of hemorrhage (differential diagnosis of lobar haemorrhages):__ antecedent head trauma, hemorrhagic transformation of an ischemic stroke, arteriovenous malformation, haemorrhagic tumour, warfarin therapy with international normalisation ratio > 3, vasculitis