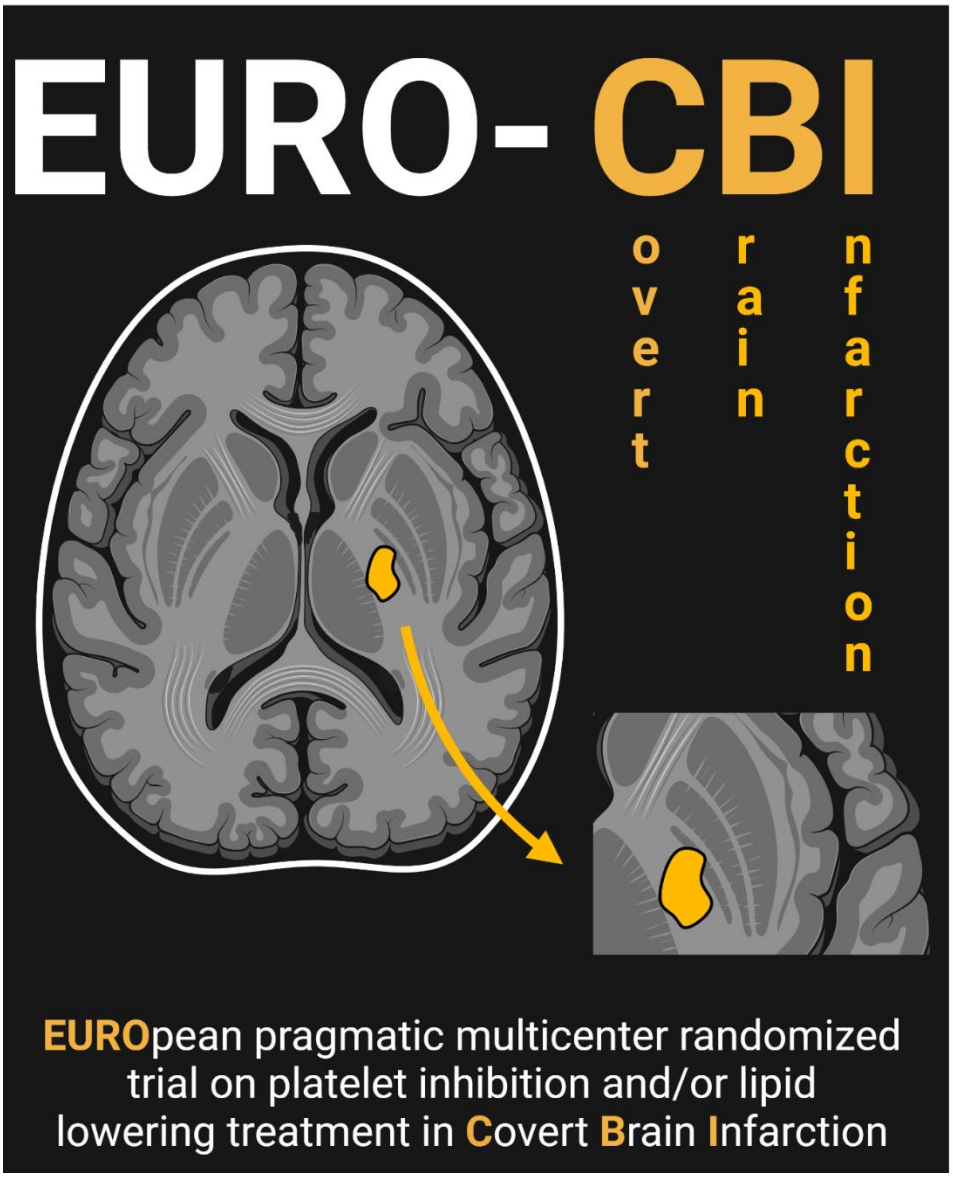

Project acronym	EURO-CBI
Protocol	**v 2.0 – 29-06-2025**
EU trial number	2025-521452-30-01
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Abbreviations

ASCVD Atherosclerotic Cardiovascular Disease

ADC Apparent diffusion coefficient

ADL Activities of Daily Living

AE Adverse event

AIS Acute ischemic stroke

ALAT Alanin aminotransferase

APT Antiplatelet therapy

ASA Acetylsalicylic Acid

BI Barthel Index

BMI Body-mass index

CBI Covert Brain Infarctions

CEC Clinical Event Committee

CFS Clinical Frailty Scale

eCRF Electronic Case Report Form

ccSVD covert cerebral SVD

CI Confidence intervals

CK Creatine kinase

CSF Cerebrospinal Fluid

cSVD Cerebral small vessel disease

CTIS Clinical Trials Information System

DICOM Digital Imaging and Communications in Medicine

DSMG Daily Study Management Group

DWI Diffusion-weighted imaging

DMC Data Monitoring Committee

ECG Electrocardiogram

ENT Ear, Nose and Throat Specialist

EOS End of Trial

GCA Global Cortical Atrophy

GCP Good Clinical Practice

GDPR General Data Protection Regulation

GP General practitioner

HR Hazard ratios

HBA1c Hemoglobin A1C

HDL High-density lipoprotein

Hs-CRP High-sensitivity C-reactive protein

ICD-10 International Classification of Diseases 10th Revision

ICD-11 International Classification of Diseases 11th Revision

IMP Investigational Medicinal Product

ITT Intention-to-treat

IPAQ International Physical Activity Questionnaire

ISMN Isosorbide Mononitrate

LDL Low Density Lipoprotein-cholesterol

MACCE Major Adverse Cardiac and Cerebral Events

MI Myocardial Infarction

MoCA Montreal Cognitive Assessment

MRI Magnetic resonance imaging

mRS Modified Rankin Scale

NSTEMI Non-ST elevation myocardial infarction

NPR Danish National Patient Register

OR Odds ratio

PROM Patient reported outcome

PI Pulsatility Index

RSI Reference Safety Information

SAE Serious Adverse Event

SmPC Summary of Product Characteristics

STEMI ST-elevation myocardial infarction

SUSAR Suspected Unexpected Serious Adverse Event/Reaction

SVD Small vessel disease

TG Triglyceride

TIA Transient ischemic attack

TMG Trial Management Group

TSC Trial Steering Group

T2-FLAIR T2 fluid-attenuated inverse recovery

WML White Matter Lesions

1. Introduction and rationale

With easy access to brain imaging, an increasing number of patients undergo magnetic resonance imaging (MRI) of the brain. A very common problem occurs when radiologists diagnose covert brain infarcts (CBI), e.g. on scans ordered in the work up of headache or dizziness. CBI are defined as focal cerebral lesions of presumed ischemic origin detected on MRI in patients without a fitting history of stroke or transient ischemic attack (TIA) and represent the most common incidental finding on brain MRI in clinical practice.[1,2] The majority are caused by asymptomatic cerebral small vessel disease. On T2-FLAIR (Fluid-Attenuated Inversion Recovery) MRI, a small round or ovoid, fluid-filled cavity usually with hyperintense rim of scaring (gliosis) can be seen[3]. These are called lacunes and the appearance of CBIs do not differ from the lacunes seen in symptomatic small vessel disease, where the patient experiences a clinical stroke syndrome.[4]

CBIs are found in 10-30% of healthy elderly populations and in up to 50% of populations with increased cardiovascular risk factors and are frequently seen together with other markers of cerebral small vessel disease (cSVD).[2] The lack of clinical manifestations in CBI might be related to their location in the brain, but the etiology is presumed to be the same as a clinical stroke. This is supported by results of the NOMAS (Northern Manhattan Study), in which the authors found a prevalence of CBI of 18% (236 out of 1290) and that CBIs where often located in non-eloquent areas of the brain and in the right brain hemisphere (lack of symptom awareness).[5]

In patients with CBI, the risk of recurrent ischemic events and vascular death are significantly elevated compared to individuals without CBI.[6] Due to the lack of clinical symptoms, CBI does not fulfill the definition of stroke. Nonetheless, CBI and cSVD stroke both lead to increased risk of recurrent stroke, vascular events, dementia and death.[2,7] In a recent study the presence of CBI in patients without a prior stroke conferred a similar risk of a subsequent stroke compared to patients with a prior clinical stroke history. Here, CBI in patients without prior stroke had a hazard ratio of 2.06 for recurrent stroke.[8,9]

Recommendations on preventive strategies for CBI, however, differ from guidelines on clinical stroke.[10,11] In patients with a prior stroke or TIA there is a net benefit of antiplatelet therapy (APT) and lipid lowering therapy in preventing recurrent ischemic events, despite an increased risk of hemorrhagic complications (for APT).[12,13] Currently, European guidelines recommend life style modification and treatment of additional risk factors in patients with CBI, but not platelet inhibitions treatment due to lack of evidence.[10] This recommendation relies heavily on the results of the ASPREE (Aspirin in Reducing Events in the Elderly) trial that did not show any benefit of acetylsalicylic acid in primary prevention in a healthy elderly population. Only one small, randomized trial (n=83) found no clear benefit or harm associated with aspirin vs placebo for patients with CBI. Currently, one ongoing Chinese trial (ANTISBI, NCT03318744, n=3400) investigates the effect of aspirin vs placebo in CBI. There are ethnic differences in the response to Aspirin and P2Y12 receptor inhibitors and the risk of intracerebral hemorrhage and gastrointestinal bleeding are higher in Asians compared to non-Asians treated with aspirin.[14] To date, there is not a single sufficiently powered preventive trial in stroke-free patients who present with CBI on MRI.

The net benefit of statin treatment as secondary prevention after acute ischemic stroke (AIS) and TIA is well documented[15]. A meta-analysis on statins used in primary prevention in patients at high risk for stroke, found an 18% reduction in all strokes over 5 years of statin treatment compared to placebo.[16] It is recommended to consider lipid lowering with statins in patients with covert cerebral SVD (ccSVD),

with the aim of delaying progression SVD, however trials are yet to prove this with effect on clinical endpoints.[10]

From a more general perspective, the research question at hand is whether CBI is a part of brain aging like cerebral white matter hyperintensities - or do CBI reflect a "missed stroke" and should be treated using the same secondary preventive treatment used to treat a clinical stroke. Evidence from randomized trials on the effectiveness and safety of antiplatelet therapy and/or statins in CBI is lacking and clinical practice varies.[17]

Our **hypothesis** is that CBI confers a similar risk as a clinical stroke for recurrent ischemic events and death, and we **aim to investigate** whether addition of APT and/or statins in addition to risk factor management will provide a net long-term benefit in reducing vascular events and death at 3 years.

2. Objectives and Endpoints

2.1 Objectives

2.1.1 Primary objectives

2.1.1.1 Primary efficacy objective

To evaluate whether APT and/or statins in addition to risk factor management will provide a net long-term benefit in reducing vascular events and death (Major Adverse Cardiac and Cerebral Events (MACCE)) at 3 years in patients with CBI.

2.1.1.2 Primary safety objective

To evaluate the cumulative risk of major and fatal bleeding at 36 months in patients with CBI.

2.1.2 Secondary objectives

1. **Dementia:** To determine the incidence of all-cause dementia at 36 months.

2. **Cardiovascular Mortality:** To evaluate the cumulative risk of cardiovascular-related mortality at 36 months.

3. **All-cause mortality:** To evaluate the cumulative risk of all-cause mortality at 36 months.

4. **Stroke (Ischemic and hemorrhagic):** To evaluate the cumulative risk of stroke (ischemic and hemorrhagic) at 36 months.

5. **Myocardial infarction (MI):** To evaluate the cumulative risk of myocardial infarction (MI) at 36 months.

6. **Cognitive Decline:** To determine the proportion of participants experiencing significant cognitive decline, defined as a ≥2-point reduction in Montreal Cognitive Assessment (MoCA) scores at 36 months.

7. **Adverse events:** To determine the difference in the proportion of patients experiencing at least one serious adverse event (SAE) over 36 months.

8. **Stratified MACCE:** To determine the incidence of MACCE at 36 months, stratified by baseline systolic blood pressure (≥130 mmHg), low-density lipoprotein cholesterol (LDL) levels (≥1.4 mmol/L), and high-sensitivity C-reactive protein (hs-CRP >3 mg/L).

9. **CBI subtype and infarct appearance:** To evaluate the cumulative risk MACCE, mortality, and dementia at 36 months based on CBI subtype (lacunar vs. cortical) and infarct appearance (acute vs. chronic)

10. **Cognitive Decline or Dementia Progression:** To evaluate the risk of progression to all-cause dementia or significant cognitive decline (≥2-point reduction in MoCA scores) at 36 months, stratified by baseline systolic blood pressure (≥130 mmHg), LDL levels (≥1.4 mmol/L), and hs-CRP (>3 mg/L)

11. **Cognitive function:** To assess the difference in MoCA scores from baseline to respectively 12 and 36 months.

12. **MRI Risk Markers:** To determine the association between baseline MRI risk markers, quantified using the ordinal simplified SVD (small vessel disease) score correlated to the risk of MACCE, mortality, and dementia.

13. **Inflammation Risk Markers:** To evaluate the association between baseline hs-CRP levels and the risk of MACCE, mortality, and dementia.

14. **Physical Activity and MACCE Risk:** To determine the association between baseline physical activity levels and the incidence of MACCE at 36 months.

15. **Functional status:** To determine the change in the Modified Rankin Scale (mRS) score from baseline to respectively 12 and 36 months.

16. **Frailty status:** To determine the change in the Clinical Frailty Scale (CFS) score from baseline to respectively 12 and 36 months.

17. **Functional independence in daily activities:** To determine the change in the Barthel Index (BI) for Activities of Daily Living (ADL) score from baseline to respectively 12 and 36 months.

18. **Quality of life:** To determine the change in quality of life (EQ-5D) from baseline to respectively 12 and 36 months.

2.1.2.1 Imaging Sub-studies

1. **Progression of total SVD score:** To determine the difference in progression of the total SVD score and the number of CBIs on follow-up MRI at 3 years.
2. **White matter lesion (WML) volume:** To determine the difference in the growth of WML volume between baseline and 3-year MRI.
3. **Plaque quantification on ultrasound:** To evaluate the association between carotid plaque quantification on ultrasound and the incidence of MACCE.
4. **Pulsatility index on ultrasound:** To evaluate the association between the middle cerebral artery pulsatility index on ultrasound and the risk of MACCE, mortality, and dementia.

2.1.2.1 Registry-based 5- and 10-years follow-up (Denmark only)

1. **MACCE:** To evaluate the cumulative risk of MACCE at 5 and 10 years.
2. **Major bleeding and fatal bleeding:** To evaluate the cumulative risk of major bleeding and fatal bleeding at 5 years and 10 years.
3. **Dementia**: To evaluate the incidence of all-cause dementia at 5 years and 10 years.
4. **Cardiovascular Mortality:** To evaluate the cumulative risk of cardiovascular-related mortality at 5 and 10 years.
5. **All-cause mortality:** To evaluate the cumulative risk of all-cause mortality at 5 and 10 years.

2.2 Endpoints and criteria for evaluation

2.2.1 Evaluation of primary endpoints

2.2.1.1 Primary efficacy endpoint

MACCE are defined as

- **All cause death:**
  - Death from any cause
- **Acute myocardial infarction:** Admission with a discharge diagnosis of
  - ST-elevation myocardial infarction (STEMI) and
  - non-ST elevation myocardial infarction (NSTEMI) and
- **Stroke:**
  - AIS*
  - Intracerebral hemorrhage (non-traumatic)

*****_Including Transient Ischemic Attack (TIA) with evidence of brain tissue infarction i.e. remission of symptoms within 24 hours but who have an acute ischemic lesion on diffusion weighted imaging MRI._

All events qualifying for a MACCE event will be adjudicated by the **Clinical event committee**

Accepted timeframe for evaluation is +/- 30 days

2.2.1.2 Primary safety endpoint

Fatal or major bleeding. Defined by the criteria established by the International Society on Thrombosis and Haemostasis. [18]

1) Fatal bleeding, and/or
2) Symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome, and/or
3) Bleeding causing a fall in hemoglobin level of 20 g/L^{-1} (1.24 $mmol/L^{-1}$) or more, or leading to transfusion of two or more units of whole blood or red cells.

All events qualifying for a major or fatal bleeding event will be adjudicated by the Clinical Event Committee.

2.2.2 Evaluation of secondary endpoints

2.2.2.1 Assessment of Dementia

Information about dementia is collected from telephone contacts and from the patient's electronic health record. Dementia is diagnosed according to national standards in each participating country. See the table below for diagnoses accepted according to ICD-10 (International Classification of Diseases 10th Revision) and ICD-11 (International Classification of Diseases 11th Revision).

Accepted time for evaluation is +/- 30 days

ICD-10 code and diagnosis	ICD-11 code and diagnosis
F00.0-00.9 and DG30.0-30.9: Dementia in Alzheimer disease	**6D80**: Dementia due to Alzheimer's disease
F01.0-01.9 and F00.2: Vascular dementia	**6D81**: Dementia due to cerebrovascular disease
F02.0-02.8: Dementia in other diseases classified elsewhere	**6D82:** Dementia due to Lewy body disease
F03.9: Unspecified dementia	**6D83:** Frontotemporal dementia
DG31.8E: Lewy body (dementia)	**6D8Z:** Dementia, unknown or unspecified cause
DG31.0A: Progressive isolated aphasia	**6D85.Y:** Dementia due to other specified diseases classified elsewhere
DG31.0B: Pick disease	
DG31.9: Degenerative disease of nervous system, unspecified	

2.2.2.2 Assessment of Cardiovascular Mortality

Information about cardiovascular mortality is collected from telephone contacts and from the patient's electronic health record. See the table below for the definition of cardiovascular mortality.

Cardiovascular Mortality[19]
▪ Acute MI ▪ Sudden cardiac death ▪ Heart failure ▪ Stroke: death as a direct consequence or complication of stroke ▪ Cardiovascular procedure ▪ Cardiovascular-related haemorrhage: non-stroke intracranial haemorrhage (subdural hematoma), non-procedural or non-traumatic vascular rupture (e.g. aortic aneurysm), or haemorrhage causing cardiac tamponade ▪ Death due to other cardiovascular causes: a cardiovascular death not included in the above categories but with a specific, known cause (e.g., pulmonary embolism or peripheral arterial disease)

2.2.2.3 Assessment of Cognitive Decline

The participant's score on the full 12 item in-person MoCA (30 points) at the initial visit is compared to the scores on the telephone administrated Tele-MoCA (items from MoCA not requiring the use of a pencil and paper or visual stimulus, 22 points) after 12 and 36 months. [20]
Accepted time for evaluation is +/- 30 days

2.2.2.4 Assessment of biomarkers of inflammation

Hs-CRP will be measured at baseline and correlated to the risk of future vascular events (MACCE), mortality (all-cause), and dementia (all-cause).

2.2.2.5 Assessment of Physical Activity

The association between baseline physical activity levels, as measured by the International Physical Activity Questionnaire (IPAQ), and the incidence of MACCE at 36 months will be evaluated to assess the potential impact of physical activity on cardiovascular and cerebrovascular outcomes.

2.2.2.6 Assessment of Clinician-reported outcome measure

1. **mRS:** The change in mRS score will be assessed from baseline to 12 and 36 months to evaluate shifts in functional independence and disability over time.
2. **CFS:** The change in CFS score will be assessed from baseline to 12 and 36 months to evaluate the progression of frailty and its impact on functional status and overall health over time.
3. **BI:** The change in BI score will be assessed from baseline to 12 and 36 months to evaluate the progression of functional independence in daily activities and overall disability status over time.

2.2.2.7 Assessment of Patient reported outcome (PROM)

1. **Quality of Life (EQ-5D)**: The change in EQ-5D score will be assessed from baseline to 12 and 36 months to evaluate variations in health-related quality of life over time.

2.2.2.8 Assessment of MRI markers

At baseline the MRI SVD score will be estimated, and the score will be compared to the risk of future

vascular events (MACCE), mortality (all-cause), and dementia (all-cause).
The CBI subtype and infarct appearance will be described by the enrolling physician, who has been trained to identify these findings on MRI.

The baseline MRI will be visually graded by the investigators and the total SVD score calculated. All investigators will receive training in assessing these items. The DICOM (Digital Imaging and Communications in Medicine) file containing the MRI will be downloaded and uploaded to the electronic case report form (eCRF) at redcap.au.dk, for later assessment by an imaging core lab.

MRI feauture	**Simple SVD score**
Microbleeds	0 microbleeds = 0 point ≥ 1 microbleed = 1 point
White matter hyperintensities (Fazekas)	Fazekas 0-1 = 0 point Fazekas 2-3 = 1 point
Lacunes	0-2 lacunes = 0 point >2 lacunes = 1 point
Total SVD score (range)	0-3

2.2.2.8.1 Repeated MRI after 3 years (sub-study)

At centers participating in the *extended imaging* sub-study, patients will be invited to a follow-up MRI after 3 years (+/- 1 months). The baseline MRI should be of sufficient quality and with a field strength of 3 Tesla. The follow-up MRI will contain diffusion-weighted imaging (DWI), apparent diffusion coefficient (ADC), Susceptibility Weighted Imaging (preferred) or T2* gradient-recalled echo (T2*GRE), and T2 fluid-attenuated inverse recovery (T2-FLAIR). Newly developed lacunar and/or cortical infarctions will be recorded and a SVD score will be calculated. If possible T1 weighted sequences will be performed. The MRI will be uploaded to eCRF.

The number of CBIs, number of cerebral microbleeds, deep white matter lesions (Fazekas grade)[a], MRI SVD score, and Global Cortical Atrophy (GCA) Scale will be assessed by two blinded assessors. If there is disagreement, a third and final blinded assessor will perform the assessment.

WML volume will be estimated using semiautomatic software, such as 3D Slicer (an open-source medical image analysis tool) or a similar alternative. WML will be segmented together with volume quantification. It will be performed by two blinded assessors, and the final volume will represent a consensus volume between the assessors.

[a] **Fazekas:** Grade 0: No lesions, Grade 1: Punctate foci, Grade 2: Beginning confluence of lesions, Grade 3: Large confluent areas)

[b] **GCA:** (0 = No atrophy, 1 = Mild widening of sulci without ventricular enlargement, 2 = Moderate widening of sulci with mild ventricular enlargement, 3 = Severe sulcal widening with obvious ventricular enlargement)

2.2.2.9 Ultrasonography assessment (sub-study)

At centers participating in the *extended imaging* sub-study, patients will be invited to an ultrasound examination at the baseline visit. The common- and internal carotid artery will be assessed for signs of atherosclerotic disease and presence, size and morphology of plaques, classifying them based on echogenicity (homogeneous or heterogeneous), surface characteristics (smooth or irregular), and calcification (presence or absence) ipsilateral to the CBI. If bilateral CBIs are present, the left side will be scanned. [21]

A plaque score will be calculated based on sum scores for each plaque identified in the carotid and intracranial arteries based on size and morphology. Plaque Grading Consensus will be used and range from no plaque (IMT < 1.5mm), protuberant/diffuse < 1.5mm IMT, protuberant/ diffuse with IMT 1.5-2.4mm or protuberant/ diffuse with IMT >2.5mm.[22]

Further, pulsatility Index (PI) of the mid- and distal middle cerebral artery (MCA) will be measured using transcranial Doppler ultrasound to assess blood flow resistance within cerebral vessels. It will be calculated based on the difference between peak systolic and end-diastolic blood flow velocities relative to the mean flow velocity:

PI=(Peak Systolic Velocity−End-Diastolic Velocity)/Mean Velocity.

PI has been associated with increased microvascular resistance, white matter disintegration, plaque burden[23]

2.3 Clinical event committee (CEC)

All events will be adjudicated by a clinical event committee, consisting of two neurologists and a cardiologist. The CEC will perform an independent and blinded assessment of events that are classified as MACCE by local investigators or in cases with doubt. Two CEC members can adjudicate an event, but if there is any doubt, a unanimous decision should be made, or a third CEC member will make the final decision. In the case of cardiological events, the cardiologist will make the final decision and similar a neurologist for neurological events. The CEC will receive event descriptions and associated prints from the electronic health records from national study coordinators. The events will be adjudicated online using redcap.au.dk.

3. Study plan and trial design

3.1 Trial Design

Investigator-initiated, multicenter, 2x2 factorial, randomized block, open-label, blinded endpoint (PROBE) pragmatic trial (phase III)

3.2 Number of subjects

1652 patients with CBI corresponded to 413 in each group.

3.3 Trial sites and investigators

Details regarding trial sites and investigators involved in the conduct of this clinical trial are registered in the Clinical Trials Information System (CTIS). Any updates to the list of trial sites and/or investigators will be managed within the CTIS platform.

3.4 Project timetable and recruitment feasibility

The study will be conducted at multiple European sites using a simple screening and single visit protocol. Prior to initiation and during the study: Information regarding the study will be sent to collaborators deemed relevant by each Department of Neurology, this could be neurologists, Ear, Nose and Throat Specialist (ENTs) and private practice neurologists and ENTs, private hospitals and neuroimaging clinics. These collaborators will, in agreement with the patient, refer to their local EURO-CBI trial site for further evaluation and screening.

Expected inclusion per site: 1650/20=83 patients included per site during a 3-year inclusion period.

Screening and inclusion-rate per site: 50% expected screen failures, 166 screened per site during a 3-year period = **4,6 patients screened per months and 2,3 patients included per months.**

Study start date: September 2025

Inclusion period: Patient recruitment: month 0-36

Expected inclusion end date: 30th of September 2028

Follow-up period: Month 37-72

Expected follow-up end date: 30th of June 2031

Last event in registries, analysis performed and presentation of results: Early in 2032

Last analysis and events are expected to be in 2042

3.5 Plan for patient participation

Patient advocates have in-depth insights into what it means to be diagnosed with a CBI and the uncertainty currently associated with its treatment. Patients and representatives from the Danish Stroke Association ("Hjernesagen") will be involved in the endpoint selection, study material and letters on the assigned treatment arm to be send for the General Practitioners (GPs) and patients.

4. Study population

4.1 Selection of subjects

All patients with a CBI who fulfill the study criteria will be invited to participate.

4.2 Study criteria

Inclusion criteria

Deep/Lacunar infarct

- MRI demonstrating a lacunar infarct (acute/subacute/chronic) without prior stroke/TIA symptoms*
  - A round or ovoid, subcortical, fluid-filled cavity (signal similar to cerebrospinal fluid (CSF)) between 3 and 15 mm in diameter and demonstrating a peripheral T2/FLAIR hyperintense rim of marginal gliosis. For infratentorial lesions the hyperintense rim may be less marked and a complete ring is not required. [24]

Or

Cortical infarct

- MRI demonstrating a cortical infarct (acute/subacute/chronic) without prior stroke/TIA symptoms*
  - A cortical infarct is defined as a fluid-filled cavity (signal similar to CSF) in the cortex, juxtacortical region or cerebellar cortex and with a ring of T2/FLAIR hyperintense lesions or as cortical T2/FLAIR lesions without a fluid-filled cavity with presumed vascular origin. Both supra- and infratentorial lesion will be included. [24]

And

- Life expectancy > 12 months

And

- Predominantly independent in actives of daily living (mRS score ≤ 3)

And

- Age ≥ 50 years

Exclusion criteria

- History of stroke/TIA
- High risk of bleeding (e.g., recent or recurrent gastrointestinal or genitourinary bleeding associated with a decrease in hemoglobin levels of at least 1 mmol/L, active peptic ulcer disease, MRI with cortical siderosis and/or prior lobar hemorrhage)
- Indication for long-term use of anticoagulants (e.g. deep vein thrombosis, pulmonary embolism, atrial fibrillation, and rarer indications; such as mechanical heart valve, antiphospholipid antibody syndrome etc.)
- Concurrent indication for lipid-lowering treatment and/or platelet-inhibitors for secondary cardiovascular prevention (ischemic heart disease, recent stenting, ischemic stroke, revascularization surgeries, lower-extremity atherosclerotic arterial disease etc.)
- Co-existing progressive neurodegenerative disease including dementia or Parkinson's disease.
- Neoplastic condition that is uncontrolled or associated with an increased risk of bleeding
- Patient already on antiplatelet or anticoagulation agent, regardless of indication
- History of peptic ulcer disease or symptoms suggestive of active gastritis
- Women of childbearing potential (WOCBP), defined as all women who have not undergone bilateral oophorectomy, hysterectomy, or medically confirmed ovarian failure, or who have not been postmenopausal for at least 12 consecutive months without an alternative medical cause, are excluded unless the following criteria are met: 1) A negative pregnancy test at baseline; and 2) Use of highly effective contraceptive measures throughout the study period.
- Breast-feeding
- Patients with myopathy and/or elevated creatine kinase (CK) >5 × upper limit of normal (ULN)
- A history of significant liver disease and/or excessive alcohol intake and/or unexplained persistent elevations of serum transaminases exceeding 3 times the upper limit of normal (excessive alcohol

intake defined as a history of alcohol-related liver dysfunction, including clinical signs such as ascites, spider naevi, caput medusae, or other stigmata of chronic liver disease.)

- Patients treated with the hepatitis C antivirals glecaprevir/pibrentasvir
- Patients receiving a combination of sofosbuvir/velpatasvir/voxilaprevis
- Patients receiving concomitant ciclosporin
- Severe renal impairment (creatinine clearance <30 ml/min)
- Hypersensitivity to the active substance or to any of the excipients

** Symptoms screened based on principles from the Questionnaire for Verifying Stroke-Free Status (QVSFS).* [25]

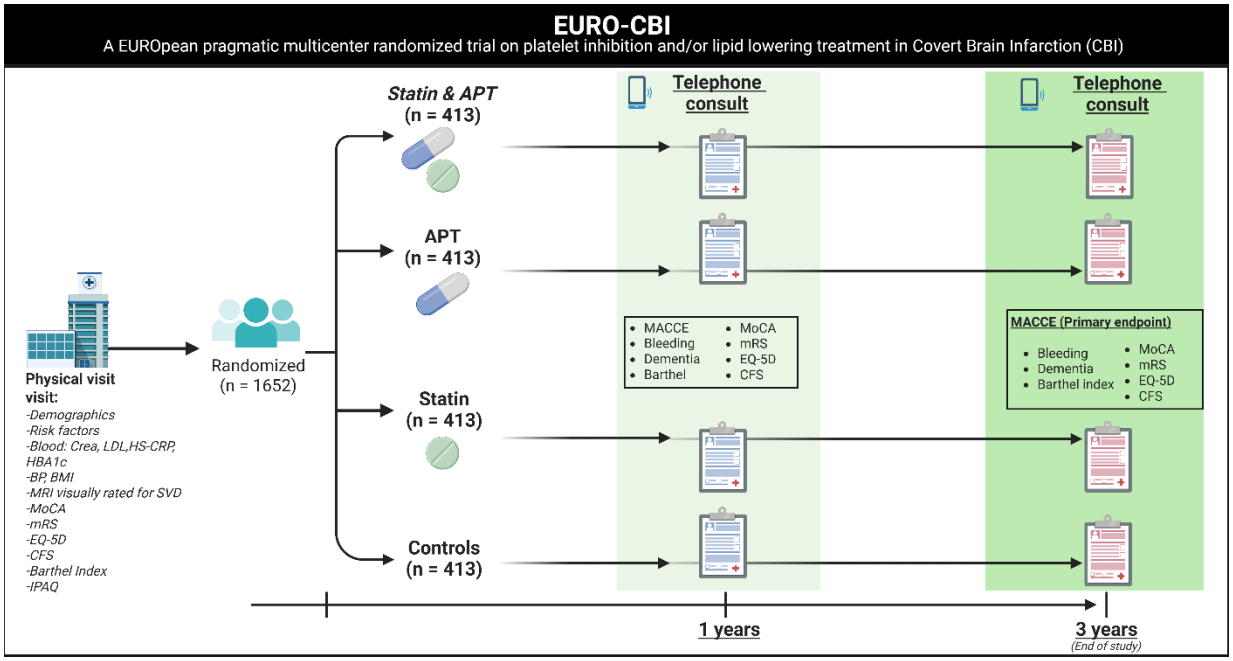
5. Study procedure and assessment

5.1 Screening procedure

We will screen for eligible patients in the referrals received at the stroke centers, tele-conferences, and MRIs performed in-house. Patients who meet the study criteria will be included upon informed consent. Collaborating specialists/departments that often perform head MRIs will be informed about the study and advised to refer eligible patients for assessment. This will include ENT specialists, neurosurgeons, private practice neurologists, private hospitals, neuroimaging clinics etc.

Patients will be invited for a single physical screening visit where consent will be obtained and baseline registrations performed. These include demographics, blood samples, ECG (Electrocardiogram), blood pressure and body-mass index (BMI) measurement (Table 1).

5.2 Study overview



Abbreviations: Crea: Creatinine, LDL: Low Density Lipoprotein-cholesterol, HBA1c: Hemoglobin A1c, BP: Blood pressure, BMI: Body Mass Index, MRI: Magnetic Resonance Imaging, SVD: Small Vessel Disease, APT: Antiplatelet treatment, MACCE: Major Adverse Cardiac and Cerebral Events. MoCA: Montreal Cognitive Assessment. CFS: Clinical Frailty Scale .EQ-5D: Quality of life scale. mRS: modified Rankin Scale, BI: Barthel Index., IPAQ: International Physical Activity Questionnaire

5.3 Randomization, blinding and treatment allocation

5.3.1 Randomization

Patients will be randomized to control group, *APT alone*, *Statin alone* or *APT and statin treatment in combination* in a 1:1:1:1 ratio by the study investigator. The randomization will be based on a secure web site providing computer-generated blocked randomization lists stratified by the center (redcap.au.dk). The online randomization will be stratified by simple SVD sum score (≤2 vs >2). All investigators will receive unique access and have no influence on the randomization process.

5.3.2 Method of blinding

The study drugs are open label, meaning that neither participants nor clinicians at sites are blinded. Information on treatment allocation will be registered in the electronic health records.

The 3-year MACCE endpoint will be blindly adjudicated by a clinical event committee.

5.3.3 Treatment allocation

1:1:1:1 Allocation

- **Platelet inhibitor - no Statin** (*"APT alone")* **(Group A)**
  Platelet inhibitor (APT) in monotherapy.
  All patients will initiate treatment with Aspirin *or* Clopidogrel. The decision on which of the two drugs to initiate is at the discretion of the treating physician/center.
  The dose of the treatment should adhere to the doses recommended in "*accepted Antiplatelet agents and doses*".
  If statins and/or platelet inhibitors are started during the study-period it should adhere to primary prevention guidelines [27]

- **Statins – no Platelet inhibitor** (*"Statin alone")*. **(Group B)**
  Patients will be treated with high-intensity statin therapy (Atorvastatin 40 mg once daily or Rosuvastatin 20 mg once daily). [26] The decision on which of the two drugs to initiate is at the discretion of the treating physician/center.
  After 1-3 months, creatine kinase (CK), alanin aminotransferase (ALAT) and cholesterol levels will be measured. If there is no safety concern in the blood-samples and the medication is well-tolerated, treatment will continue. The dose will not be adjusted based on LDL levels.

  If laboratory results indicate a potential safety concern or suggest a need for treatment discontinuation or dose adjustment, the investigator will contact the participant to discuss further management. If no action is required, participants will not be routinely contacted.
  As part of the baseline visit, participants are informed that they may contact the trial site at any time if they have questions regarding their test results or suspect adverse effects

  If a participant experiences adverse effects, the dose may be reduced to Atorvastatin 20 mg or Rosuvastatin 10 mg once daily or discontinued. The patient will continue for endpoint assessment as planned according to the intention to treat principle.

- **Statins – Platelet inhibitor** (*"APT and statin")* **(Group C)**
  Both types of medication are initiated as described in group A and B

- **No Statins – no Platelet inhibitor** *(standard treatment)* **(Group D)**
  This group follows the current European recommendations of primary prevention which do not include statins and APT agents. If statins and/or platelet inhibitors are started during the study-period it should adhere to primary prevention guidelines [27]

  All four groups receive advice on: Risk factor management from their GP. This will be communicated as a standard letter to the GP and as a "*risk factor management flyer*" given to each patient. These recommendations will align with the current European guidelines on cardiovascular disease and reflect standard clinical practice. Any treatment initiated as part of the study will be managed by the stroke center. The GP will not be responsible for additional study-related follow-up and will follow the patients according to standard operating procedure.

- Lifestyle optimizing
    - Daily physical activity
    - Nutrition and alcohol
    - Smoking cessation
    - Bodyweight
- Blood pressure management
    - Currently, CBIs are not classified as strokes and therefore do not indicate established atherosclerotic cardiovascular disease (ASCVD). Consequently, the blood pressure treatment goal follows updated guidelines for primary prevention i.e. <130/80 mmHg. [28]This applies to all four treatment arms and will be recommended and outlined in the standard letter to the GP, who will take care of blood pressure monitoring, risk assessment, and the initiation and selection of antihypertensive medication as needed[27]
      Notably, the routine care of the patients included in the study will not differ from the treatment they would otherwise require at their GP.
- Risk assessment and treatment targets for lipids
      For groups A and D: If, following the routine assessment of cardiovascular risk factors, there is an indication for initiating cholesterol-lowering medication it should adhere to the current guidelines for primary prevention[29]
    - At the 1- and 3-year follow-ups, data will be collected on any newly prescribed medications, including cholesterol-lowering treatments
- Treatment of diabetes if present

The general practitioner (GP) is therefore not involved in the trial as a treating physician, a co-investigator or as a contracted service provider, thus no formal arrangement is made between the GP and the sponsor.

The flyer is sent to the participant's GP for informational purposes only, to ensure awareness of the participant's involvement in the study and to support coordination of care if relevant. The flyer contains general information about the trial and an overview of cardiovascular risk factor management in accordance with current European guidelines and standard clinical practice, as outlined above.

If any adjustment of trial medication is necessary, or if the participant experiences adverse effects, the GP is instructed to contact the including trial site. The investigator retains full responsibility for all trial-related medical decisions, including initiation, modification, or discontinuation of treatment.

5.4 Baseline registrations

Demographics	**Objective measures**	**Cognitive test**	**Questionnaires and rating scales**
Age	Blood-samples - Creatinine - Hemoglobin A1C (HBA1c) -Cholesterol (Total, high-density lipoprotein (HDL), Triglyceride (TG), LDL) -Hs-CRP) *if possible, otherwise CRP* - Negative pregnancy test (WOCBP [9] only) and confirmation of highly effective contraceptive use[10]	MoCA	IPAQ [8]
Sex	12-lead ECG (any pathological findings registered)		Frailty Scale (CFS)
Ethnicity	Blood pressure (systolic, diastolic) & pulse		Functional status (mRS)
Educational level [4]	BMI		Quality of life (EQ-5D)
Living arrangement[5]	Visual assessment of the MRI with a quantitative assessment of cSVD [1]		Activities of Daily Living (Barthel Index)
Medical history[6]			
Medications [7]			
Smoking [2], alcohol [3]			

1) Visual assessment of MRI by study investigators for number of lacunar infarcts (1, 2,3-5, >5), white matter hyperintensities (Fazekas grade 0-3) and number of cerebral microbleeds (0, 1-5, 6-10,>10), cortical superficial siderosis (present/absent).[30] *All investigators will receive online training in study eligibility criteria including assessment of the index MRI, including calculating a total SVD score.*

2) Current/previous (if a patient has not smoked for at least one year)/never

3) Units per week

4) Years of education

5) Alone/with partner or familiy/shared residence and type of housing

6) Medical history including an assessment of vascular risk factors, such as hypertension, diabetes, atrial fibrillation, hyperlipidemia, and peripheral arterial disease, as well as a screening for previous stroke or TIA-suspected events based on principles from the Questionnaire for Verifying Stroke-Free Status (QVSFS).

7) Current and past medications

8) To be completed by the participant themselves

9) WOCBP is defined as all women who have not undergone bilateral oophorectomy, hysterectomy, or medically confirmed ovarian failure, or who have not been postmenopausal for at least 12 consecutive months without an alternative medical cause

10) The appropriate contraceptive measures are hormonal contraception associated with ovulation suppression, intrauterine devices (IUD), intrauterine hormone-releasing systems (IUS), or sterilisation. These methods must be maintained throughout the trial and for at least 4 weeks after the last dose of investigational medicinal product (IMP).

Electronic letters will be sent to each patient's GP (**Group A-D**) with information on the study, the treatment arm of the given patient and general risk factor management recommendations.

5.5 Follow-up registrations

Telephone consultation after 1 and 3 years*

- Any ischemic or hemorrhagic events and documentation of details
- Side-effects
- New medication
- Smoking and alcohol consumption
- Tele-MoCA (telephone administered)[31]
- Tele-mRS (telephone administered)[32]
- Tele- EQ-5D (telephone administered)[28]
- Tele-CFS (telephone administered)
- Tele-BI (telephone administered)[33]

**Accepted range +/- 1 month. While telephone-based follow-up remains the standard approach, follow-up visits can be conducted on-site if preferred by the study site or upon specific request from the participant. If so, the cognitive test should still be conducted as a tele-MoCA.*

At the telephone consultation after 3 years, a reminder is given to discontinue any medication initiated in connection with this trial.

Safety Follow-up Period

The safety follow-up period extends from the first administration of the IMP(s) until one month after the last administration of the IMP(s).

During this period, SAEs will be documented if reported. Trial participants are informed, both orally and in writing, that they may contact the investigator at any time during the safety follow-up period if they experience symptoms that could indicate a SAE. GPs will also be provided with an information sheet instructing them to notify the including trial site without delay if they become aware of a potential SAE during period.

No routine contact is scheduled during the safety follow-up period; however, spontaneous reports from participants or healthcare providers will be documented and managed in accordance with applicable safety reporting requirements.

5.6 Study procedure table

	On-site screening visit				Randomization	1 and 3 years (telephone)				5 and 10 years follow-up (registry-based)
	Demographics & Objective measures[1]	**Blood-samples[2]**	**MRI[3], MoCA[4] & mRS EQ-5D, IPAQ, CFS, BI[5]**	**Ultrasound (substudy)[6]**	**1:1:1:1**	**MRI (sub-study)[6]**	**MACCE (Primary Endpoint)[7]**	**t-MoCA & mRS, EQ-5D, CFS, BI[8]**	**Adherence, medicationside-effects, new risk factors**	
Centers in Denmark	x	x	x		x		x	x	x	x
Centers in Sweden	x	x	x		x		x	x	x	
Centers in Norway	x	x	x		x		x	x	x	
Centers in Germany	x	x	x		x		x	x	x	
Centers in Switzerland	x	x	x		x		x	x	x	
Centers participating in imaging sub-study	x	x	x	x	x	x	x	x	x	

1) Demographics including *Age, sex, ethnicity, educational level, living arrangement, known diseases, current medications, hypertension diabetes, peripheral arterial disease, smoking status, alcohol consumption. Objective measures: Body Mass Index (BMI), blood pressure, pulse, 12-lead ECG (any pathological findings registered).*

2) Blood-samples: *Routine lab results: Creatinine, HbA1c: Hemoglobin A1c, Cholesterol (Total, HDL, TG, LDL), (creatine kinase (CK), alanin aminotransferase (ALAT), high sensitivity CRP (HS-CRP) [if available, otherwise CRP]. For patients in group B and C a new bloodtest will be performed after 1-3 months after initiation of atorvastatin or rosuvastatin (CK, ALAT and cholesterol levels ((Total, HDL, TG, LDL)))*

3) Visual assessment of MRI *by study investigators for number of lacunar infarcts (1, 2,3-5, >5), white matter hyperintensities (Fazekas grade 0-3), number and distribution of cerebral microbleeds (0, 1-5, 6-10,>10), cortical superficial siderosis (present/absent).[22]*

4) Cognitive test: *Montreal cognitive assessment (MoCA)*

5) Questionnaires and rating scales: *physical activity level (IPAQ), Modified Rankin Scale (mRS), Clinical Frailty Scale (CFS), quality of life (EQ-5D) and Barthel Index (BI)*

6) Ultrasound *of carotid artery quantifying atherosclerosis and pulsatility index.: Plaque Grading be performed and range from no plaque (IMT < 1.5mm), protuberant/diffuse < 1.5mm IMT, protuberant/ diffuse with IMT 1.5-2.4mm or protuberant/ diffuse with IMT >2.5mm. Further, the Pulsatility Index (PI) of the mid- and distal middle cerebral artery (MCA) is measureed using transcranial Doppler ultrasound.*
MRI*: Diffusion-weighted imaging (DWI), apparent diffusion coefficient (ADC), Susceptibility Weighted Imaging (preferred) or T2* gradient-recalled echo (T2*GRE), and T2 fluid-attenuated inverse recovery (T2-FLAIR)*

7) Endpoints (MACCE) *will be validated by a clinical endpoint committee.*

8) Telephone *administered MoCA, mRS, EQ-5D, CFS and BI*

Abbreviations:

ECG: Electrocardiogram MRI: Magnetic Resonance Imaging, HbA1c: Hemoglobin A1c, t-MoCA: telephone Montreal cognitive assessment

5.7 Administration of study medication

The enrolling site will coordinate the distribution of the investigational drugs.
At the initial on-site visit, medication for one year of the trial will be dispensed. If there are no contraindications to continuing the medical treatment at the one-year telephone follow-up, the patient will receive medication for an additional year. This can be done either by the patient attending the enrolling site or, if circumstances prevent the patient from attending the site to collect the medication, it may be sent to the patient's home by mail, as individually agreed upon with each patient.
After two years, the patient will be contacted to arrange how the medication for the final year of the trial will be dispensed—either in person or by mail. No additional clinical assessments will be conducted during contact after 2 years.

After three years, the patient will be contacted for the final clinical follow-up. At this time, they will be reminded to discontinue the medical treatment, unless events occurred during the study period that have provided a clinical indication for continued use of the prescribed medication.

5.8 Handling of Clinically Relevant Incidental Findings

If clinically relevant incidental findings are detected on follow-up MRI (sub-study), the patient will be informed, and if necessary, referred to the appropriate medical department for further evaluation and management.
If the cognitive test (MoCA) raises suspicion of cognitive impairment or dementia, the participant will be advised to follow up with their general practitioner for further assessment. In all cases, participants will receive guidance and support to ensure necessary follow-up and clinical care.

5.9 Minimizing Participant Burden

To reduce participant burden, this trial primarily relies on telephone follow-ups at 1 and 3 years, replacing frequent on-site visits while allowing structured assessments and clinical data collection. On-site visits are limited to a single baseline visit, during which essential procedures such as blood sampling, ECG, blood pressure measurement, and risk assessment are conducted. Sample collection is minimal, with blood samples taken only at baseline and after 1–3 months for statin groups. No additional invasive tests are planned. To further reduce the participation burden, medication can be collected by the patients by an on-site visit or shipped by mail.

5.9.1 Decentralized trial procedures

As this trial incorporates three decentralized elements to reduce participant burden and administrative workload: telephone follow-ups, Investigational medicinal product (IMP) shipment, and home administration, we recognize that these elements may also be considered as critical-to-quality factors.
Therefore, we will ensure:

- That telephone interviews follow structured and clearly defined data collection methods.
- That IMP shipment complies with strict distribution
- That participants receive clear instructions on medication administration and storage

The following sections provide further details on these aspects

5.9.1.1 Decentralized Delivery of IMPs

Participants may opt to have IMPs delivered directly to their homes for storage and self-administration. This approach increases accessibility and convenience for participants, supporting a more flexible and patient-centered study participation while ensuring compliance with regulatory and quality requirements and maintaining high standards in IMP administration.

Procedures for Delivery by Shipment

The IMPs used in this study (Aspirin, Clopidogrel, Atorvastatin and Rosuvastatin) are chemically stable at room temperature and do not require special handling such as refrigeration or controlled humidity; therefore, it is assessed that shipment under normal conditions does not exceed regulatory requirements regarding storage and transportation.

Authorized distributors will handle IMP delivery while complying with General Data Protection Regulation (GDPR) standards. Medication will be shipped directly to participants' home addresses to minimize transport steps and reduce risks related to product quality and dispensing errors.

Investigator's Responsibility

The investigator remains accountable for treatment decisions, documented through a prescription issued before the IMP is dispatched.

Delivery Options

IMP shipment will be conducted according to national regulations, through

- Directly from the investigator's site pharmacy.
- Via a delegated pharmacy unit.
- From a central depot.

Data Protection and Consent

Participants' personal data will be processed in accordance with GDPR and will only be accessible to individuals directly involved in the delivery process. The information will not be stored for purposes other than delivery and will be restricted in availability as soon as the final delivery is completed. Participants will be informed during the informed consent process that their contact details will be used for this purpose as well.

Receipt of IMP

Upon delivery, the IMP will only be handed over to the study participant or a designated relative if the participant has provided consent for this. If the participant or their relative is not present to receive the IMP, the product will be returned to the original dispensing site.

5.9.1.2 Self-Administration of IMP at Home

As these medications are commonly self-administered, it is assumed that participants can maintain appropriate storage conditions at home. Upon inclusion, participants will receive clear instructions regarding IMP use, storage, and administration.

5.9.1.3 Telephone Follow-Ups and Compliance Monitoring

Ensuring the Quality of Telephone Follow-Up

The content of clinical telephone follow-ups will be clearly defined. To maintain consistency, data

related to clinical endpoints will be collected using structured questionnaires and rating scales or verified through other sources, such as patient records.

Compliance monitoring

Investigators will be in annual contact with the patient; after 1 and 3 years as a full clinical follow-up. After 2 years, there will be a brief contact to plan the distribution strategy for the upcoming year. During these contacts, proper adherence to the prescribed IMP regimen will be ensured.

If the measured compliance at one and/or two years is below 70%, an additional telephone contact at 6 months will be implemented for subsequent participants to assess and reinforce adherence early in the treatment course. This will include brief counselling and reminder on the importance of continued medication.

Returning of remaining IMPs

During the follow-up after 3 years, the patient will be reminded to discontinue the medical treatment (unless an indication for the medication has emerged during the study period). Plans will be made for the return of any remaining IMP to the site to ensure that no IMP remains in participants' homes beyond the intended treatment period. Mechanisms for IMP return and destruction will be established.

6. Study discontinuation

6.1 Definition End of Trial

End of Trial (EOS) is defined as the last visit of the last patient.

The end of trial participation for each individual participant is defined as the last scheduled visit (physical or telephone) for each participant. However, if a participant requires continued follow-up due to an unresolved adverse event, EOS will be extended until the event is deemed stable or resolved. Once the condition is assessed as stable or resolved, the participant's EOS will be recorded accordingly.

6.2 Criteria for temporary halt and early termination of the clinical trial

The trial may be discontinued in part or entirely due to safety concerns, lack of efficacy, ethical considerations, regulatory requirements, or feasibility issues. If terminated prematurely, all enrolled participants will be informed, and appropriate follow-up procedures will be conducted to ensure their safety. Regulatory authorities and ethics committees will be notified as required. Data collection will be completed as far as possible, and an analysis of available data will be performed. In cases of early termination due to participant safety, immediate measures will be taken to mitigate risks, and participants will receive necessary medical care.

6.3 Discontinuation/withdrawal of individual participants

A patient can withdraw from the study at any time. Patients can be withdrawn from the study at the principal investigator's discretion. In case we are unable to reach the patient by telephone at 1 and 3 years, every effort will be made to contact the patient or to document the outcome regarding new vascular events via electronic health records. If the patient ultimately cannot be contacted, and electronic health records provide insufficient data on outcomes, the patient will be excluded from the per-protocol analysis. If a patient withdraws from the study, the date of withdrawal will be recorded.

Participants are free to withdraw without providing any reason. However, they will be invited to share any experienced adverse effects (AEs) and, if they wish, the reason for withdrawal, in order to support participant safety and data interpretation.

7. Study treatments

7.1 Investigational Medicinal Product(s) (IMP(s))

The study drugs prescribed will depend on the assigned treatment arm.
The IMP is defined solely by its active substance, allowing the use of any authorized brand and formulation.
All four IMPs are well-known and commonly used in clinical practice. They are administered at the same dosage and for the same indication as their approved use.

Responsibility for detecting and managing intolerance to IMP(s) lies with the investigator at the including trial site. Participants are thoroughly informed about potential side effects and explicitly instructed to contact the site directly if they experience symptoms that may indicate intolerance or adverse drug reactions.
Based on the participant's report and relevant clinical information (blood samples after 1-3 months and follow-ups), the investigator will assess the need for dose adjustment, temporary discontinuation, or withdrawal of the IMP. GPs are not responsible for treatment decisions related to the trial; if approached, they are instructed to refer the participant back to the including site.

These procedures are further described in Section 5.3.3.

Accepted Antiplatelet agents and doses:
Active Substance: **Acetylsalicylic acid** (ASA) (ETC code B01AC) Daily dose 75 mg to 100 mg p.o.
Active Substance: **Clopidogrel** (ETC code B01AC04) Daily dose 75 mg p.o.

Accepted lipid lowering agents and doses:
Active Substance: **Atorvastatin** (ATC code C10AA05) Daily dose 40 mg p.o.
SmPCs for atorvastatin from different manufacturers vary in their recommendations regarding the starting dose.
In current clinical practice for secondary prevention following symptomatic stroke, atorvastatin 40 mg once daily is frequently initiated without prior titration in order to achieve effective LDL-cholesterol reduction from the outset.

The selection of 40 mg as the starting dose in this trial is intended to:

- Reflect standard clinical practice in secondary stroke prevention
- Ensure alignment with evidence-based treatment intensity recommended in current guidelines
- Support the pragmatic design of the trial by avoiding an artificial titration scheme not typically used in routine care

Active Substance: **Rosuvastatin** (ATC code C10AA07) Daily dose 20 mg p.o. (10 mg once daily for the first 4 weeks, then 20 mg once daily for the remainder of the study period if tolerated).

If Atorvastatin 40 mg is not tolerated, a dose reduction to 20 mg is allowed.
If Rosuvastatin 20 mg is not tolerated, a dose reduction to 10 mg is allowed.

7.2 Auxiliary medicinal products
No other auxiliary medicinal products will be expected to be used in the trial.

7.3 Study drug labelling
No additional labeling will be used, as Aspirin, Clopidogrel, Rosuvastatin and Atorvastatin are open label drugs.

7.4 Study drug storage and traceability
The study drug will be stored in a locked room, only accessible by the respective center's nurses. They will be stored in a restricted access area where the temperature is monitored and maintained below 25°C.
The IMPs are authorised. To ensure traceability, routinely maintained pharmacy documentation on receipt, storage, and handling will be used, and normal prescribing practices and documentation will be followed. Specific documentation of prescribed amounts and doses taken will be recorded in the patient's medical records.

7.5 Adherence to study drug
Adherence will be documented at study sites using electronic medication charts (this may differ between sites/countries). These charts will track the number of prescriptions (daily doses) actually collected, divided by the total number of study days. The main outcome of the trial will be according to intention to treat and disregarding adherence to treatment.
If there is any unused medication, it must be returned to the enrolling site.

8. Other treatments and restrictions
Once the patient is included in the study, there are no specific medications prohibited from the perspective of the study. However, as always, potential drug interactions with the study medication should be considered if new medication is initiated. This assessment must be made by the prescribing physician.

Patients will receive general lifestyle advice at the time of inclusion, but no specific lifestyle restrictions apply during the study.

If the patient undergoes surgery or dental extractions during the study, it is the responsibility of the operating physician to take appropriate precautions based on this information.

9. Safety reporting
9.1 Definitions
9.1.1. Adverse Events (AEs)
Adverse events are defined as any untoward medical occurrence in a participant to whom a medicinal product is administered and which does not necessarily have a causal relationship with this treatment.

An adverse event can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Since this clinical trial involves the use of four authorised marketed products with well-established safety profiles, and no increased risk is anticipated for the study population , safety recording,reporting and follow-up of participants will be simplified, following a risk-proportionate approach.

Consequently, adverse events (AEs) will not be documented.

9.1.2 Serious Adverse Events (SAEs)

AE that:

a) led to death, injury or permanent impairment to a body structure or a body function.

b) led to a serious deterioration in health of the subject, that either resulted in:

- a life-threatening event, or
- a permanent impairment of a body structure or a body function, or
- in-patient hospitalization or prolongation of existing hospitalization, or
- results in persistent or significant disability/incapacity,
- a medical or surgical intervention to prevent life threatening illness

c) led to a congenital anomaly or birth defect.

In accordance with the HMA/EMA Recommendation Paper on Decentralised Elements in Clinical Trials, and to ensure adequate detection and reporting of Serious Adverse Events (SAEs) between scheduled follow-up contacts, the following procedures are implemented:

- Trial participants will receive training and clear written information on what constitutes a Serious Adverse Event (SAE), including examples. They will be instructed to immediately contact the including trial site if they experience or suspect an SAE.
- General practitioners (GPs) will be provided with an information sheet that defines an SAE and instructs them to notify the including trial site without delay if they become aware of a potential SAE affecting a participant.

These measures are intended to ensure that SAEs are reported to the investigator in a timely manner.

SAEs must be reported from the investigator to the sponsor within 24 hours**If the SAE is unexpected (based on the investigators brochure for the particular drug) it will be defined as Suspected Unexpected Serious Adverse Event/Reaction (SUSAR)**

The Summary of Product Characteristics (SmPC) for the relevant drug will be used as Reference Safety Information (RSI), when assessing whether a SAE becomes a SUSAR.

9.2 Event reporting and causality assessment

The relationship between each adverse event and the study drug will be assessed and categorized. It will be evaluated whether the study drug is causally related to the adverse event or if it is deemed not related. All events will be registered in the eCRF (REDCap). Event reporting will follow standards from the Clinical Trials Information System (CTIS). SUSARs will be reported through the EudraVigilance system. An annual safety report will be submitted to the authorities through the CTIS.

SAEs must be reported to the sponsor within 24 hours.

The assessment of causality for each SAE is the responsibility of the investigator.

SUSARs that are life threatening or fatal will be reported within 7 days, and all other SUSARS reported within 15 days.

9.3 Data Monitoring Committee (DMC)

The trial safety will be monitored by a DMC consisting of independent neurologist and a statistician and include a signed DMC charter. The DMC will ensure the safety and wellbeing of trial patients and to assist and advise the Trial Steering Committee (TSC), so as to protect the validity and credibility of the trial. Further, it will ensure that the benefit/risk ratio remains acceptable for participating patients and assess the safety and efficacy of the interventions during the trial and monitor the overall conduct of the clinical trial.

The DMC will make recommendations to the sponsor regarding study modification, continuation or termination.

The trial should be stopped, paused, or modified if any of the following criteria are met in one of the treatment arms:

A significant increase in major bleeding ($p<0.01$)

A significant increase in all-cause mortality ($p<0.01$)

The detailed agreements are outlined in the DMC charter.

10. Statistical analysis

10.1 Interim analysis

We will perform an interim analysis for evaluation of the actual event rate after inclusion of 50% of the patients. Furthermore, the DMC will perform an independent safety analysis and will review the overall safety and efficacy according to the DMC charter (planned in the early phase of the trial, at 12 months and hereafter at least every 12^{th} month. Interim analyses are assessed using a level of significance of 1%. The main reason for stopping the trial will be efficacy or safety reasons. The following analysis will be performed at each DMC meeting and at the interim analysis.

Difference in MACCE (Efficacy)

Difference in cumulative risk of major and fatal bleeding (Safety)

Difference in all-cause mortality (Safety)

However, the trial may be stopped if there is very low recruitment, which could lead to insufficient funding due to an extended inclusion period. Any such decision will be made with careful consideration by the DMC and the trial steering committee.

10.2 Participant demographics and other baseline characteristics

Demographic and baseline disease characteristic data will be summarized for each treatment group by presenting frequency distributions and/or descriptive statistics.

10.3 Sample size determination and Power analysis

10.3.1 Sample size

In the Northern Manhattan MRI study, participants ≥ 55 years old without a prior clinical stroke were randomly invited to participated in MRI sub study.[34] The yearly event rate for vascular death, myocardial infarction and stroke (MACCE) were 2.06% per year in the no-CBI group and 6.9% in the CBI group. A total of 24-41% were on statins and 42-55% on APT at baseline which may underestimate the event rates in patients without any medication. Supporting this, yearly stroke and dementia rates in patients with CBIs detected on routine clinical imaging were 3.2% and 2.9%, respectively.[35,36] To make an estimate on the needed sample size we used this as the base event-rate for the control group. The assumed differences in proportion of patients reaching the primary endpoint are presented below.

Event rates

Group	Yearly event rate (MACCE)	Percent with Recurrent Event over 3 years (MACCE)	Percent without Recurrent Event over 3 years (MACCE)
Controls	6.9%	20.7%	79.3%
Platelet inhibitor only[a]	5.6%	16.8%	83.2%
Statin only[b]	5.2%	15.5%	84.5%
Platelet inhibitor + Statin[c]	4.4%	13.2%	86.8%

[a]APT arm: assuming a 19% reduction over 3 years from the base rate of 6.9%[13]

[b]Statin arm: assuming a 25% reduction over 3 years from the base rate of 6.9%[15,37,38]

[c]APT + Statin: The combination is estimated to provide additional 20% relative risk reduction compared to single treatment[39]

We expect to include up to 300 patients who are already on statin therapy when entering the trial and thus cannot be randomized to the statin arms of the trail. While this will slightly reduce the statistical power of the statin comparisons, the overall power remains sufficient to detect meaningful treatment effects.

Sample size in comparison with other trials

In the most recent, comparable trial (LACI-2 trial, 2023), patients with a lacunar stroke were randomized in a 2x2 factorial design to Isosorbide mononitrate (ISMN) and/or cilostazol on top of standard treatment after AIS.[40] A total of 363 patients were recruited and more than 90% received APT and statins. The overall composite event rate for stroke, MI, death was 6% at 12 months. The event-rate of 6% may be affected by Isosorbide mononitrate (ISMN) or Cilostazol use but corresponds well to the rates found in CBI patients in Northern Manhattan study.

10.3.2 ANOVA Power Analysis

Assuming a difference in proportion of events as described above, we need a sample size of 385 patients in each group, to reach a 80% power at an alpha level of 0.05 (two-way ANOVA). The power analysis was performed using ANOVA, as we are using a split-plot design. Since the outcome is a proportion, the variance was estimated using the Bernoulli distribution. ANOVA is considered more conservative than a Cox model; however, since we aim to compare cumulative risk, no standard power calculation package exists for this purpose in a factorial trial. As a result, the required sample size may

be slightly overestimated. To account for loss to follow-up and withdrawal of consent (5-6%) and emigration (1%), we plan to include 1652 patients in total with 413 in each group.

10.4 Planned analysis

Data will be reported as numbers (percentage), median (IQR), or mean (SD). Any missing data, including outcome variables, are assumed to be missing at random and will be addressed using multiple imputation by chained equations. The primary analyses will be performed as intention to treat according to randomization status, disregarding adherence to assigned treatments. For the primary endpoint we will use Cox proportional hazards regression (adjusted hazard ratios [aHRs]) with corresponding 95% confidence intervals. We will compare treatment with vs without APT, with vs without statins, and with APT+statin vs no drug. Analyses will be adjusted for the minimization variable: simple SVD score (≤2 vs >2). As appropriate binary logistic regression (presented as adjusted odds ratios [aORs]), ordinal logistic regression (aORs) will be used and presented with 95% CIs. Country-wise analyses will be performed to explore potential heterogeneity between countries. Secondary endpoints will not adjust for multiple comparisons and these results will be used for hypothesis testing or inference.

10.4.1 Primary Efficacy End Point Analysis

The cumulative risk of the primary endpoint, MACCE at 36 months, will be analyzed using a Cox proportional-hazards model to estimate the hazard ratio.

Analysis will be performed as intention-to-treat disregarding adherence to treatment, or treatment discontinuation by a treating physician. Adherence to treatment will be used for a secondary per-protocol analysis.

10.4.2 Primary Safety End Point Analysis

The cumulative risk of major bleeding and fatal bleeding will be assessed at 36 months using a Cox proportional-hazards model under an intention-to-treat (ITT) approach. Hazard ratios (HR) and 95% confidence intervals (CI) will be estimated to compare treatment groups.

10.4.3 Secondary end point analysis

1. **Dementia**: The incidence of all-cause dementia at 36 months will be analyzed using a Cox proportional-hazards model, adjusted for treatment assignment, under an ITT approach. HRs with 95% CI will be estimated to compare the risk of dementia between treatment groups.
2. **Cardiovascular-related mortality:** The cumulative risk of cardiovascular-related mortality at 36 months will be analyzed using a Cox proportional-hazards model under an ITT approach. HRs with 95% CI will be estimated to compare treatment groups.
3. **All-cause mortality:** The cumulative risk of all-cause mortality at 36 months will be analyzed using a Cox proportional-hazards model under an ITT approach. HRs with 95% CI will be estimated to compare treatment groups.
4. **Stroke (Ischemic and hemorrhagic):** The cumulative risk of stroke (ischemic and hemorrhagic) at 36 months will be analyzed using a Cox proportional-hazards model under ITT approach. HRs with 95% CI will be estimated to compare treatment groups. Separate analyses will be performed for ischemic stroke and hemorrhagic stroke.
5. **Myocardial infarction (MI):** The cumulative risk of myocardial infarction (MI) at 36 months will be analyzed using a Cox proportional-hazards model under an ITT approach. HRs with 95% CI will be estimated to compare treatment groups.
6. **Cognitive Decline:** The proportion of participants experiencing significant cognitive decline, defined as a ≥2-point reduction in MoCA scores at 36 months, will be analyzed using a mixed-effects logistic regression model with a random intercept, adjusted for treatment assignment, under an ITT approach.
7. **Adverse events:** The difference in the proportion of patients experiencing at least one serious adverse event (SAE) during 36 months between treatment groups will be analyzed using a logistic regression model, adjusted for treatment assignment, under an ITT approach. The model will estimate ORs with 95% CI to compare the risk of SAEs between groups
8. **Incidence of MACCE:** The incidence of MACCE at 36 months will be analyzed using a Cox proportional-hazards model under an ITT approach. The analysis will be stratified by baseline systolic blood pressure (≥130 mmHg), LDL levels (≥1.4 mmol/L), and hs-CRP >3 mg/L. The model will be adjusted for treatment assignment and baseline systolic BP, LDL, and hs-CRP, with interaction terms included for stratification factors as necessary. HRs with 95% CI will be estimated to compare treatment groups.
9. **CBI sub-type:** The cumulative risk of MACCE, mortality, and dementia at 36 months will be analyzed using a Cox proportional-hazards model. The analysis will be stratified based on CBI sub-type (lacunar vs. cortical) and infarct appearance (acute vs. chronic). HRs with 95% CI will be estimated to compare risk between groups.
10. **Cognitive Decline or Dementia Progression**: The risk of progression to all-cause dementia or significant cognitive decline (defined as a ≥2-point reduction in MoCA scores) at 36 months will be analyzed using a Cox proportional-hazards model under an ITT approach. The analysis will be stratified by baseline systolic blood pressure (≥130 mmHg), LDL levels (≥1.4 mmol/L), and hs-CRP >3 mg/L. The model will be adjusted for treatment assignment, baseline systolic BP, LDL, and hs-CRP, and HRs with 95% CI will be estimated to compare treatment groups.
11. **Cognitive function:** The difference in MoCA scores from baseline to 12 and 36 months will be analyzed using a linear mixed-effects model with repeated measures, adjusted for treatment assignment.

12. **MRI Risk Markers:** The association between baseline MRI risk markers, quantified using the ordinal simplified SVD score, and the risk of future vascular events, mortality, and dementia will be assessed using a multivariable Cox proportional-hazards model. The ordinal simplified SVD score will be incorporated as a categorical or ordinal predictor, depending on distribution and proportionality assumptions. The model will be adjusted for treatment assignment, with inclusion of main effects and interaction terms if necessary.
13. **Inflammation Risk Markers:** The association between baseline hs-CRP levels and the risk of future vascular events (MACCE), mortality, and dementia will be evaluated using a Cox proportional-hazards model. Baseline hs-CRP will be analyzed as a continuous variable, modeled using restricted cubic splines to account for potential nonlinear associations. The model will be adjusted for treatment assignment.
14. **Physical Activity and MACCE Risk:** The association between baseline physical activity levels, as measured by the IPAQ, and the incidence MACCE at 36 months will be assessed using a Cox proportional-hazards model. The baseline IPAQ score will be analyzed as a continuous variable, modeled using restricted cubic splines. The model will be adjusted for treatment assignment

10.4.4 Clinician-reported outcome measure

1. **mRS:** The change in mRS score from baseline to 12 and 36 months will be analyzed using a linear mixed-effects model with repeated measures, adjusted for treatment assignment.
2. **CFS:** The change in CFS score from baseline to 12 and 36 months will be analyzed using a linear mixed-effects model with repeated measures, adjusted for treatment assignment.
3. **BI:** The change in BI score from baseline to 12 and 36 months will be analyzed using a linear mixed-effects model with repeated measures, adjusted for treatment assignment.

10.4.5 Patient reported outcomes (PROMs)

1. **Quality of life (EQ-5D):** The change in EQ-5D score from baseline to 12 and 36 months will be analyzed using a linear mixed-effects model with repeated measures, adjusted for treatment assignment.

10.4.6 Imaging Sub-studies (secondary objectives)

1. **Progression of SVD:** The difference in SVD score and the number of CBIs on follow-up MRI at 3 years will be analyzed using a mixed-effects model, adjusted for treatment assignment.
2. **WML volume:** The difference in the growth of WML volume between baseline and 3-year MRI will be analyzed using a mixed-effects model, adjusted for treatment assignment
3. **Plaque quantification:** The association between plaque quantification on ultrasound and the incidence of MACCE will be analyzed using a Cox proportional-hazards model, with plaque quantification as an ordinal predictor. The model will be adjusted for treatment assignment, and HRs with 95% CI will be estimated to assess the relationship between plaque burden and MACCE risk.
4. **Pulsatility index:** The association between pulsatility index on ultrasound and the risk of future vascular events, mortality, and dementia will be analyzed using a Cox proportional-hazards model, with pulsatility index as a continuous predictor. Restricted cubic splines will be applied if needed to account for nonlinearity. The model will be adjusted for treatment assignment, and HRs with 95% CI will be estimated to assess the relationship between pulsatility index and clinical outcomes.

10.4.7 5- and 10-years follow-up (secondary objectives)

1. **MACCE:** The cumulative risk of MACCE at 5 and 10 years will be analyzed using a Cox proportional-hazards model under an ITT approach. HRs with 95% CI will be estimated to compare treatment groups.
2. **Major bleeding and fatal bleeding:** The cumulative risk of major bleeding and fatal bleeding at 36 months, 5 years, and 10 years will be analyzed using a Cox proportional-hazards model under an ITT approach. HRs with 95% CI will be estimated to compare treatment groups.
3. **All-cause dementia:** The incidence of all-cause dementia at 36 months, 5 years, and 10 years will be analyzed using a Cox proportional-hazards model, adjusted for treatment assignment, under an ITT approach. HRs with 95% CI will be estimated to compare treatment groups.
4. **Cardiovascular-related mortality:** The cumulative risk of cardiovascular-related mortality at 5 and 10 years will be analyzed using a Cox proportional-hazards model under an ITT approach. HRs with 95% CI will be estimated to compare treatment groups
5. **All-cause mortality:** The cumulative risk of all-cause mortality at 5 and 10 years will be analysed using a Cox proportional-hazards model under an ITT approach. HRs with 95% CI will be estimated to compare treatment groups.

11. Ethical considerations

11.1 Declaration of Helsinki

The sponsor will ensure that this study is conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki.

11.2 Recruitment and informed consent

Being informed that a brain MRI, performed for other diagnostic purposes, has revealed an old asymptomatic infarction can be overwhelming. During the initial consultation, it is therefore essential that patients are thoroughly informed about the nature of CBIs and our current medical understanding of such findings.

APT and cholesterol-lowering medications are well-documented and effective treatments already used by several million patients worldwide. It is important to ensure that the participants understand the purpose of this trial, the associated risks, and the potential benefits. Participants must also be informed about the specific implications of receiving either APT (a slightly increased risk of bleeding, i.e. gastrointestinal and intracranial bleeding), cholesterol-lowering medication (myalgia, elevated liver enzymes and in rare cases myopathy and rhabdomyolysis), or no treatment (a possible increased risk of new symptomatic strokes).
All participating individuals are treated according to current European guidelines for the primary prevention of cardiovascular events. Therefore, patients will not be deprived of any existing treatments deemed necessary for their health condition.

11.2.1 Informed consent

Participants will be contacted by letter/e-letter or telephone, informed about the study and receive study material. Before this, the participant will have been referred to the study site for evaluation based on the CBI finding or will have agreed to be contacted by the research team. The participant will be invited for an on-site screening visit where study information will be repeated and any questions answered. There will be at least 24 hours between first contact and the screening visit. Every participant must be able to provide informed consent independently. If the person consents to

participate, they will give a written consent based on study material. We will ask for consent to perform follow-up (for up to 10 years) and use of baseline data (including MRI). Every effort will be made to inform the participant and their relatives in quiet and undisturbed settings, this will be at a designated room at the hospitals. We will prioritize the presence of nearest relatives at time of study information and inclusion. Consent will be obtained in accordance with national legislation in each participating Member State. For example, in Denmark, informed consent must be obtained by a qualified medical doctor. Assessment of study eligibility will always be performed by a physician/investigator. All participants will also be asked for acceptance of a later contact in case of follow-up sub-studies to the present study. All patients will have the ability to provide their own consent.

11.3 Benefit of the study

11.3.1 Potential benefits

Participants randomized to APT or lipid lowering may experience a reduced risk of vascular events and dementia in the study period. All costs associated with the assigned treatments will be covered.

11.3.2 Potential disadvantage

Participants randomized to APT may experience side effects to the treatment and will experience a slightly increased bleeding risk. This can be serious and in rare cases fatal. Participants randomized to lipid lowering treatment may experience primarily transient side effects to the treatment, such as myalgia, rash, abdominal discomfort, insomnia, and headache. Both treatments are well tolerated and used as a part of routine treatment after AIS and MI. Blood samples at screening and after 1-3 months will be performed and may be associated with a slight discomfort. Participants in the *imaging sub-study* will receive additional ultrasonography of the neck and brain vessels at baseline and a follow-up MRI at 3 years. There is no radiation exposure associated with these examinations.

11.3.3 Expected outcome of the trial

This trial is designed to estimate the treatment effects and harms associated with starting lipid lowering and/or APT in patients with a CBI. CBI is a very frequent finding. Therefore, the results of the present trial will provide important quantitative data to clinicians worldwide treating patients with a CBI, irrespective of the direction of the trial results.

11.4 Insurance cover and indemnification for trial participants

All research participants are covered by the national compensation scheme for drug injuries.

11.5 Compensation for trial participants

The sponsor will cover all costs associated with the investigational drugs used in this trial. No additional compensation will be provided to participants for their involvement in the study.

11.6 Financing and compensation for investigators and trial sites

Study initiator is Rolf A. Blauenfeldt, Neurologist, MD, PhD, Associate Professor of Neurology at Department of Neurology, Aarhus University Hospital.

The study is funded by the Novo Nordisk Foundation (Investigator Initiated Clinical Trial grant, NNF 0094646 on 6.962.505 DKK) and Lundbeck Foundations (Ascending Investigator Grant, id: R467-2024-633 on 4.983.390 DKK). The research grants are transferred directly to a research account

administered by the financial department of Aarhus University Hospital. None of the involved doctors or research nurses has any conflict of interest or economic advantages regarding the study. There is no economic compensation or reimbursement for patients participating in the study. Study medication is paid for by the sponsor. Each site will be reimbursed 2000 Danish kroner (approx. 270 EUR) per inclusion. Legal agreements between sponsor and other participating sites will be made before study initiation at each site.

12. Administrative aspects, monitoring and confidentiality

12.1 Approval initial application and substantial modifications

The clinical trial will be conducted in compliance with the Regulation (EU) No 536/2014 (CTR), the protocol and with the principles of good clinical practice.

The trial protocol, informed consent form, participant information sheet, investigational medicinal product dossier, investigators brochure and any other documents required by the Regulation will be submitted for the regulatory approval before the clinical trial is started via CTIS.

The sponsor will also submit and obtain approval for substantial modifications to the original approved documents via CTIS.

12.2 Monitoring

The trial will be monitored in accordance with the requirements set by each member state's national requirements/Good Clinical Practice (GCP) units.

12.3 Recording, handling and storage of information

All data will be collected and processed in accordance with the General Data Protection Regulation (EU) 2016/679. Neither personal data nor biological material will be transferred outside the EU.

All study data are recorded in an eCRF with blinded data and identification via a study identification number.

The study will apply to the specifications of the Data Protection Act and GDPR. The database(e-CRF) is handled by REDCap (hosted at Aarhus University). The investigator permits direct access to all source data/documents (including electronic patient records) at monitoring visits, audits and/or inspections by the regional ethics committee and Medicines Agencies.

Data collection from medical records

The following trial-relevant data will be collected from the participants' medical records:

- At baseline: clinical data corresponding to the parameters listed in the table "*Baseline registrations*", including prior diagnoses, cardiovascular risk factors, ongoing medication, and relevant medical history. Further, physiological measurements (blood pressure), baseline brain magnetic resonance imaging and biochemical results will be collected.

- During the follow-up period: information on any hospital admissions, changes in medication and new medical diagnoses relevant to cerebrovascular, cardiovascular, or neurological health will be collected, as these may represent endpoints or safety-related events.

The purpose of collecting this information is to ensure accurate characterization of the study population at inclusion, and to identify relevant clinical outcomes during the study period.

Use of registry data

Prior to the initiation of follow-up activities involving registry data, the sponsor will ensure that approval from the Danish Health Data Authority (Sundhedsdatastyrelsen) is obtained in accordance with national data protection regulations and applicable legislation.

12.4 Clinical trial master file and data archiving

The sponsor and the investigator will keep a clinical trial master file. The clinical trial master file will at all times contain the essential documents relating to the clinical trial which allow verification of the conduct of a clinical trial and the quality of the data generated

The sponsor and the investigator will archive the content of the clinical trial master file for at least 25 years after the end of the clinical trial, unless longer storage is dictated by national laws.
The content of the clinical trial master file will be archived in a way that ensures that it is readily available and accessible, upon request It will be stored at the designated rooms at the participating sites.

12.5 Audits and inspections and direct access to source data/documents

This trial may be participant to internal or external monitoring, auditing or inspections procedure to ensure adherence to GCP. Access to all trial-related documents including direct access to source data will be given at that time.

12.6 Reporting of serious breaches

The sponsor will notify the Member States concerned about a serious breach of the Regulation or of the version of the protocol applicable at the time of the breach through CTIS without undue delay but not later than **7 days** of becoming aware of that breach

In the event of a data security breach, the following measures will be implemented to mitigate potential adverse effects:

1. Immediate Identification and Containment
    - The breach will be identified and contained as quickly as possible to prevent further unauthorized access or data loss.
    - Access to the compromised system will be restricted, and any vulnerabilities will be addressed promptly.
2. Notification of Relevant Authorities and Stakeholders
    - The relevant data protection authorities will be informed in accordance with applicable regulations (e.g., GDPR if applicable).
    - All affected participants will be notified, ensuring transparency about the nature and extent of the breach.

- Together with the data protection authorities further risk mitigation, actions and reporting of the incident will be performed.

12.7 Notification of Recruitment Start and End

The sponsor will notify each Member State via CTIS within 15 days of:

- The start of a clinical trial in that Member State.
- The first participant's first visit in that Member State.
- The end of participant recruitment in that Member State (notified through the EU).

12.8 Temporary Halt / (Early) Termination

The sponsor will notify each Member State through CTIS within 15 days of:

- The end of a clinical trial in that Member State.
- The trial's conclusion in all Member States and third countries.

12.8.1 Temporary Halt / Early Termination (Administrative reasons not affecting benefit-risk balance)

The sponsor will notify each Member State via CTIS within 15 days of:

- A temporary halt in all concerned Member States.
- The trial's resumption following a temporary halt.
- Early termination, including reasons and follow-up measures.

12.8.2 Temporary Halt / Early Termination (Participant safety reasons)

The sponsor will suspend the study if continuation poses a health or safety risk for the participants. Temporary halt or early termination due to a benefit-risk balance change will be reported via CTIS without undue delay, and no later than 15 days. The notification will include reasons and follow-up measures. The notification must include reasons and follow-up measures. Restarting the trial after such a halt is considered a substantial modification and will therefore require a new approval process under Chapter III of the Clinical Trial Regulations.

12.9 Publication policy and plan for data-sharing

The results of the study, both negative, inconclusive, and positive, will be disseminated as widely as possible - through publication in an international peer-reviewed journal, as conference presentations and on www.clinicaltrials.gov

The trial will be registered on ClinicalTrials.gov with Identifier: *to be determined.*

The trial data will be uploaded to the CTIS database within one year after the end of study. Individual participant data underlying the baseline screening visit and 3 years outcome can be shared after de-identification, upon reasonable request and proposals should be directed at the study investigator. To gain access to these data, data requestors will need to sign a data processing agreement. Further, anonymized data will be available through public databases such as the Zenodo open data repository (CERN) or other equivalent databases after trial completion.

Aggregated baseline and 5 to 10 years outcome data may be based on the Danish health registries and individual level data cannot be shared due to national regulations. However, summary statistics in addition to the results provided in the results section and supplementary material, may be provided upon request.

13. Collaborations

The proposed project is a collaboration between major stroke centers in Denmark, Norway, Sweden Germany and Switzerland with a high expertise in stroke diagnostics and treatment, and Danish Center for Health Services Research. Principal investigator (Rolf A. Blauenfeldt) will, assisted by the Trial Steering Committee, be in charge of the overall trial conduct, including study initiation, patient inclusion, and collection of data.

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