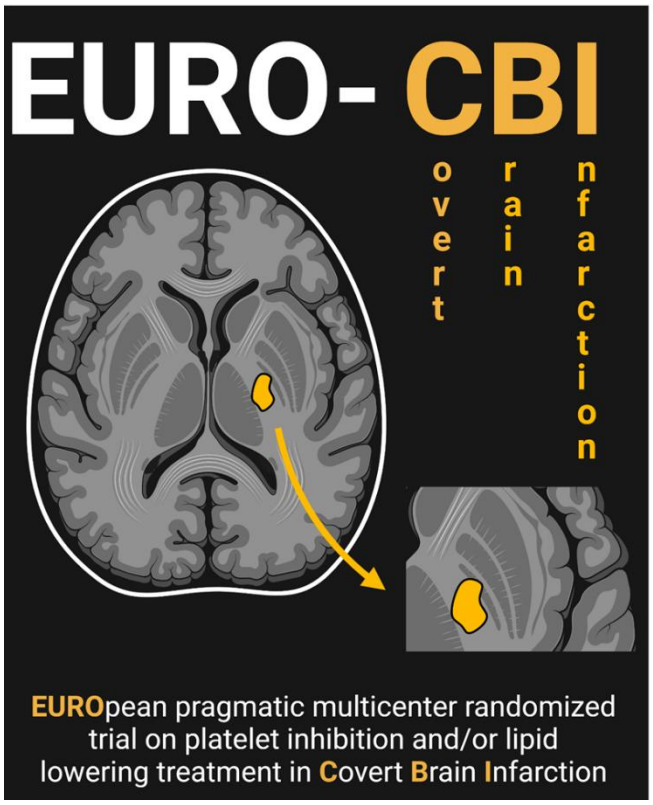
Synopsis



Title of study

EUROpean pragmatic multicenter randomized trial on platelet inhibition and/or lipid lowering treatment in Covert Brain Infarction (CBI) – EURO-CBI

Trial Management Groups (TMG)

Principal investigator/Sponsor (Aarhus University Hospital)

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Study Coordinator/Investigator

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Trial Steering Committee (TSC)

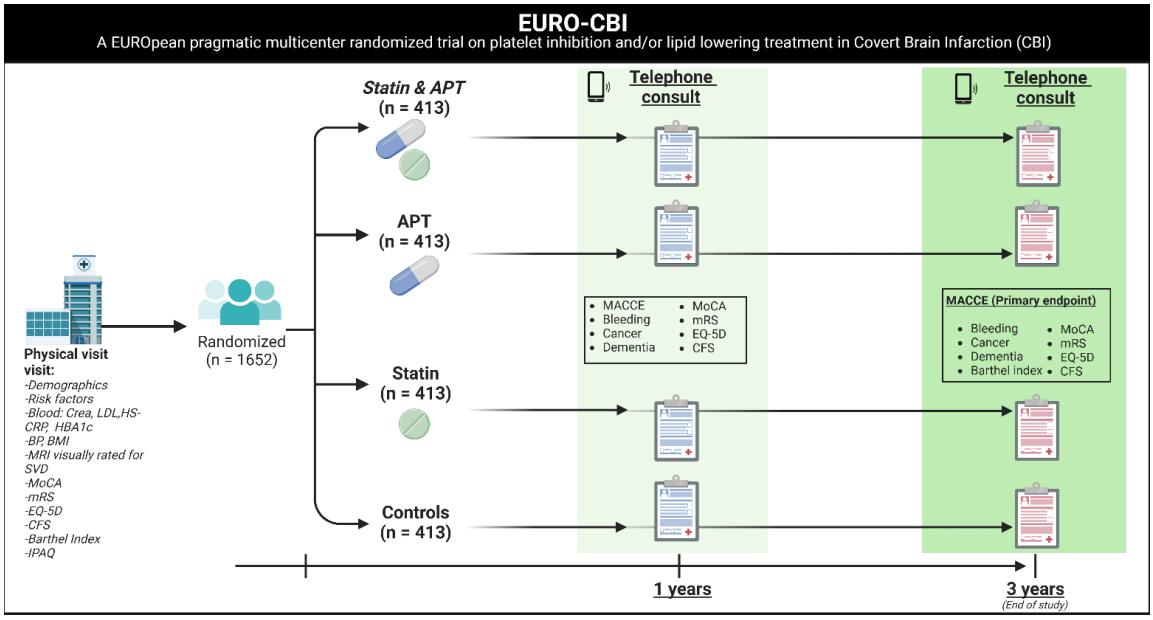
Rolf A. Blauenfeldt (Department of Neurology, Aarhus University Hospital), Ida Thingholm Norup (Department of Neurology, Aarhus University Hospital), Claus Z. Simonsen (Department of Neurology, Aarhus University Hospital), Søren Paaske Johnsen (Epidemiology, Aalborg University Hospital), Hanne Krarup Christensen (Department of Neurology, Bispebjerg and Frederiksberg Hospital), Yago Bundgaard (patient representative), David Gaist (Department of Neurology, Odense University Hospital), Janne K. Mortensen (Department of Neurology, Aarhus University Hospital), Thomas Raphael Meinel (Department of Neurology, Bern University Hospital), Jesper Petersson (Department of Neurology, Lund University Hospital), Anne Hege Aamodt (Department of Neurology, Oslo University Hospital), Götz Thomalla (Department of Neurology, University Medical Center Hamburg-Eppendorf)

Brief Description

Magnetic resonance imaging (MRI) is an important medical imaging technology and around 150 million scans are performed each year globally. Brain MRI often reveal Covert Brain Infarcts (CBIs) in patients being evaluated for e.g., headache or dizziness. These are ischemic brain lesions without stroke symptoms and are one of the most frequent incidental findings on a brain MRI. Despite the absence of symptoms, CBIs increase the risk of subsequent strokes and death. Current guidelines do not recommend specific treatments for CBIs due to limited evidence. Evidence from randomized trials on the effectiveness and safety of antiplatelet therapy and or statins in CBI are lacking, and clinical practice varies from a full secondary post-stroke preventive treatment (with antiplatelet treatment [APT] and statins) to no treatment at all.
At present, it is uncertain whether there is an annual undertreatment of millions of individuals with CBI or if a comparable number is subject to overtreatment without a net benefit.

Our hypothesis is that CBI confers a similar risk as a clinical stroke for recurrent ischemic events and death, and our aim is to investigate whether addition of antiplatelet treatment (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. Secondary we aim to explore whether CBI is a risk factor for dementia and whether the proposed treatments can reduce this risk.

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

Study centers

Department of Neurology, Aarhus University Hospital, Palle Juul-Jensens Boulevard 99, 8200 Aarhus N, Denmark
Department of Neurology, Bispebjerg Hospital, Bispebjerg Bakke 23, 2400 Kbh NV, Denmark
Department of Neurology, Rigshospitalet/Glostrup, Blegdamsvej 9, 2100 Kbh Ø / Valdemar Hansens Vej 13, 2600 Glostrup, Denmark
Department of Neurology, Aalborg University Hospital, Reberbansgade 15, 9100 Aalborg
Department of Neurology, Odense University Hospital, J. B. Winsløws Vej 4, 5000 Odense
Department of Neurology, Regional Hospital Goedstrup, Hospitalsparken 15, 7400 Herning
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Department of Neurology, Kolding Hospital, Sygehusvej 24, 6000 Kolding
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Department of Neurology, Skaane University Hospital, Entrégatan 7, 222 42 Lund
Department of Neurology, University Medical Center Hamburg-Eppendorf, Martinistraße 52, 20251 Hamburg

Planned study period: 2025-2035

Phase of development: Phase 3

Efficacy and safety of antiplatelet treatment (APT) and/or statins in patients with covert brain infarctions (CBI)

Objectives

To investigate whether 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 in patients with CBI.

Diagnosis

Covert Brain Infarctions

Methodology

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

Randomization

Eligible patients will be randomized at the initial physical screening visit

Study arms (1:1:1:1 randomization)

Patients will be randomized to *control group*, *APT alone*, s*tatin alone* or *APT and statin* treatment in combination in a 1:1:1:1 ratio

Number and subjects (planned):

1652 patients with CBI corresponding to 413 in each group.

Inclusion criteria

- Magnetic Resonance Imaging (MRI) demonstrating a covert **lacunar infarct** (chronic or sub-acute) without prior stroke/TIA symptoms.
- MRI demonstrating a covert **cortical infarct** (chronic or sub-acute) without prior stroke/TIA symptoms.
- Predominantly independent in actives of daily living (mRS score ≤ 3)
- Life expectancy > 12 months
- 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 (e.g., mechanical heart valve, antiphospholipid antibody syndrome etc.)
- Concurrent indication for platelet-inhibitors or statins (ischemic heart disease, recent stenting, ischemic stroke, transient ischemic attack, revascularization surgeries, lower-extremity atherosclerotic arterial disease etc.)
- Co-existing progressive neurodegenerative, dementia diagnosis or neoplastic condition that is uncontrolled, or associated with increasing risk of bleeding neoplastic disease
- Patient already on antiplatelet or anticoagulation agent, regardless of indication.
- Patient already on cholesterol-lowering treatment, regardless of indication.
- Women with a history of menopause below 12 months are only included after negative pregnancy test