ISRCTN76741621 https://doi.org/10.1186/ISRCTN76741621

Endovascular treatment for acute ischemic stroke; the use of periprocedural heparin or antiplatelet agents

Submission date
01/11/2017

Recruitment status
No longer recruiting

Registration date
06/12/2017

Overall study status
Completed

Last Edited
13/02/2025

Condition category
Circulatory System

[_] Prospectively registered
[X] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Background and study aims
When a blood clot blocks the flow of blood to the brain an ischemic stroke occurs. When this happens, the bloodstream leading to the blocked brain arteries can be entered using very small tubes (catheters) and mechanical devices (retrievable stents). By means of this procedure (intra-arterial treatment; IAT) the clot can be removed and the blocked brain areas can be reopened. This procedure has been proven safe and effective when performed within 6 hours after onset. However, despite clot removal a considerable proportion of patients do not recover. This is for a major part due to a disturbed circulation of the capillaries (Incomplete microvascular reperfusion; IMR). Antiplatelet drugs and heparin may reduce IMR. The aim of this study is to assess the effect of acetylsalicylic acid (ASA) and unfractionated heparin (UFH), alone or in combination, in patients with a stroke undergoing IAT.

Who can participate?
Patients aged 18 or older with acute ischemic stroke undergoing IAT

What does the study involve?
Participants are randomly allocated to be treated with either ASA, UFH, both or neither. When a patient is allocated to receive ASA a loading dose (a large initial dose) is given. When allocated to UFH, patients receive a loading dose and either a low or moderate continuous infusion for 6 hours. Every participant undergoes a brain scan of the cerebral vessels to assess the rate of recanalization (restoration of blood flow) at 24 hours and at 5-7 days to assess final infarct volume (the dead tissue resulting from lack of blood supply). During the hospital stay several blood samples are taken to look for blood clotting abnormalities. After 90 days, participants are contacted by telephone to check on their general condition.

What are the possible benefits and risks of participating?
There is a potential benefit of an improved functional outcome and a low risk, which includes the risk of bleeding inside the skull. The potential benefits of ASA and UFH are expected to outweigh the limited risks of harm of these study treatments.

Where is the study run from?
The study will run in about 19 stroke intervention centers in the Netherlands. The lead center is the Erasmus Medical Center.

When is the study starting and how long is it expected to run for?
May 2017 to April 2022

Who is funding the study?
1. Dutch Heart Foundation (Netherlands)
2. Dutch Brain Foundation (Netherlands)
3. Stryker (USA)

Who is the main contact?
Rob van de Graaf, MD

Study website
http://www.mrclean-med.nl

Contact information

Type(s)
Scientific

Contact name
Mr Rob van de Graaf

Contact details
Erasmus MC, University Medical Center
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Additional identifiers

EudraCT/CTIS number
2017-001466-21

IRAS number

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
NL61364.078.17

Study information

Scientific Title
Multicenter Randomized CLinical trial of Endovascular treatment for Acute ischemic stroke in the Netherlands: the effect of periprocedural MEDication: heparin, antiplatelet agents, both or neither

Acronym
MR CLEAN-MED

Study objectives
The use of unfractionated heparin and acetylsalicylic acid, alone, or in combination increases functional outcome within 3 months in patients who undergo intra-arterial treatment for an acute ischemic stroke caused by a confirmed intracranial large vessel occlusion of the anterior circulation.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Medisch Ethische Toetsings Commissie Erasmus MC (Medical Ethical Committee Erasmus MC), 09 /10/2017, ref: MEC-2017-366

Study design
Multicenter phase III clinical trial with randomized treatment allocation, open-label treatment and blinded endpoint assessment (PROBE), with a 2x3 factorial design

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
Not available in web format yet, please use the contact details to request a patient information sheet.

Health condition(s) or problem(s) studied
Acute ischemic stroke due to an intracranial large vessel occlusion of the anterior circulation

Interventions
Patients will be randomized either to receive acetylsalicylic acid, unfractionated heparin, both or none during intra-arterial treatment. The randomization procedure will be computer- and web-based, permuted blocks. Backup by telephone. Randomization will take place according to the 2x3 factorial PROBE design. Acetylsalicylic acid will be administered intravenously, in a loading dose of 300 mg. Unfractionated heparin will be administered intravenously in a low dose

(loading dose of 5000 IU followed by 500 IU/hour x 6 hours) or moderate dose (loading dose of 5000 IU followed by 1250 IU/hour x 6 hours). Both the IV acetylsalicylic acid and heparin treatment should be started prior to groin puncture when no IVT is administered or directly after /when the IV alteplase has been stopped.

Every participant will undergo a brain scan of the cerebral vessels to assess rate of recanalization at 24 hours and at 5-7 days to assess final infarct volume. During hospital stay several blood samples will be drawn to look for blood clotting abnormalities. After 90 days, participants are approached by telephone to check on their general condition.

Intervention Type
Drug

Pharmaceutical study type(s)
Not Applicable

Phase
Phase III

Drug/device/biological/vaccine name(s)
Unfractionated heparin, acetylsalicylic acid

Primary outcome measure
Functional outcome, measured by the modified Rankin Scale (mRS) at 90 days. Assessment of outcome on the mRS will be performed by independent assessors, blinded to the allocated and actually received treatment. Their assessment will be based on standardized reports of a telephone interview by trained research personnel who are not aware of treatment allocation.

Secondary outcome measures
1. Reperfusion grade, measured by the extended treatment in cerebral ischaemia (eTICI) score on final angiography of IAT
2. Symptomatic intra-cranial hemorrhage, according to the Heidelberg criteria
3. Clinical stroke severity, measured by the National Institutes of Health Stroke Scale score at 24 hours, and 5-7 days after randomization, or at discharge
4. Final infarct volume, measured on cranial non-contrast CT or MRI in a subset of 600 patients at 5-7 days after randomization. Infarct size at day 5-7 will be compared with plain CT and perfusion CT results (if available) at baseline
5. Dichotomization of functional outcome, measured by the modified Rankin Scale (mRS) at 90 days
6. Mortality at 90 days

Overall study start date
01/05/2017

Completion date
30/04/2022

Eligibility

Key inclusion criteria

1. A clinical diagnosis of acute ischemic stroke
2. Caused by a intracranial large vessel occlusion of the anterior circulation: distal intracranial carotid artery or middle (M1/proximal M2) cerebral artery, confirmed by neuro-imaging (CTA or MRA)
3. CT or MRI ruling out intracranial hemorrhage
4. Intra-arterial treatment (groin puncture) possible within 0-6 hours
5. A score of at least 2 on the NIH Stroke Scale
6. Age of 18 years or older
7. Written informed consent (deferred)

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
1500

Total final enrolment
663

Key exclusion criteria
1. Pre-stroke disability which interferes with the assessment of functional outcome at 90 days, i. e. mRS >2
2. Treatment with IV alteplase despite the following contra-indications for IV alteplase:
2.1. Cerebral infarction in the previous 6 weeks with residual neurological deficit or signs of recent infarction on neuroimaging
2.2. Previous intracerebral hemorrhage within the previous 3 months
2.3. INR exceeding 1.7
2.4. Prior use of direct oral anticoagulant (DOAC)
2.5. IV alteplase infusion >4.5 hours after symptom onset
3. Contra-indications for ASA/unfractionated heparin, for instance: allergy, recent surgery, heparin induced thrombocytopenia
4. INR exceeding 3.0
5. Thrombocyte count <100^9/L
6. Participation in trials other than current and MR ASAP

Date of first enrolment
01/11/2017

Date of final enrolment
01/11/2021

Locations

Countries of recruitment
Netherlands

Study participating centre
Erasmus MC, University Medical Center
Rotterdam
Netherlands
3000 CA

Study participating centre
Academic Medical Center
Amsterdam
Netherlands
1005 AZ

Study participating centre
University Medical Center Utrecht
Utrecht
Netherlands
3508 GA

Study participating centre
Maastricht University Medical Center
Maastricht
Netherlands
6202 AZ

Sponsor information

Organisation
Erasmus MC, University Medical Center

Sponsor details
Erasmus MC, University Medical Center
Department of Neurology
Room Ee2240
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Netherlands
3000 CA

Sponsor type
Charity

ROR
https://ror.org/018906e22

Funder(s)

Funder type
Charity

Funder Name
Hartstichting

Alternative Name(s)
Heart Foundation

Funding Body Type
Private sector organisation

Funding Body Subtype
Trusts, charities, foundations (both public and private)

Location
Netherlands

Funder Name
Hersenstichting

Alternative Name(s)
Hersenstichting Nederland, Nederlandse Hersenstichting

Funding Body Type
Private sector organisation

Funding Body Subtype
Trusts, charities, foundations (both public and private)

Location
Netherlands

Funder Name
Stryker

Alternative Name(s)
Stryker Corporation

Funding Body Type
Private sector organisation

Funding Body Subtype
For-profit companies (industry)

Location
United States of America

Results and Publications

Publication and dissemination plan
Additional documents (study protocol/statistical analysis plan) will be available approximately 1 year after the first patient's inclusion. Planned publication of results in a high-impact peer reviewed journal.

Intention to publish date
01/11/2023

Individual participant data (IPD) sharing plan
The data sharing plans for the current study are unknown and will be made available at a later date.

IPD sharing plan summary
Data sharing statement to be made available at a later date

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article		28/02/2022	04/03/2022	Yes	No
Other publications	Study progress abstract European Stroke Organisation Conference 2021	03/09/2021	29/03/2023	Yes	No
Protocol article		14/07/2020	13/02/2025	Yes	No