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.

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To assess the effect of acetylsalicylic acid (ASA) and unfractionated heparin, alone, or in combination, in patients with AIS, who undergo IAT for a confirmed intracranial anterior circulation occlusion.

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Central nervous system vascular disorders
Study type	Interventional

Summary

ID

NL-OMON53150

Source
ToetsingOnline

Brief title
MR CLEAN-MED

Condition

- Central nervous system vascular disorders
- Vascular therapeutic procedures
- Embolism and thrombosis

Synonym
Brain infarction, Ischemic Stroke

Research involving
Human

Sponsors and support

Primary sponsor: Erasmus MC, Universitair Medisch Centrum Rotterdam
Source(s) of monetary or material Support: Nederlandse Hartstichting en bedrijven via een unrestricted grant

Intervention

Keyword: Endovascular treatment, Ischemic stroke, Medication, Randomized Clinical Trial

Outcome measures

Primary outcome

The primary outcome is the score on the modified Rankin Scale (mRS) 90 days after inclusion in the study. The primary effect parameter is defined as the relative risk for improvement on the mRS estimated as an odds ratio with ordinal logistic regression. Multivariable regression analysis will be used to adjust for chance imbalances in main prognostic variables.

Secondary outcome

Secondary outcomes include mortality at 90 days, stroke severity measured with the National Institutes of Health Stroke Scale (NIHSS) at 24 hours and 5-7 days, recanalization on postprocedural DSA (measured with the extended treatment in cerebral ischemia (eTICI)) and on CTA at 24 hours +/- 12 hours or MRA at 24-48 hours and infarct size at 5-7 days, or 24-48 hours when MRI per performed, and dichotomized mRS, death, score on the EQ5D-5L and Barthel index at 90 days. In a subset of 600 patients we will assess reperfusion and infarct size with MRI. Safety endpoints include symptomatic intracerebral hemorrhage.

Tertiary objectives are 1) to collect (waste) biomaterials (including thrombo-emboli, aspirate blood) and to analyze biofactors in blood samples with respect to their potential for treatment effect modification, 2) to collect and analyze data regarding the deferred consent procedure and its association with patient recall and satisfaction at three months from randomization, and 3) to study the efficiency of national IAT implementation, given the availability of IAT hospitals and capacity, and travel times of ambulance services. To this end, we aim to collect data (time delays and diagnostics) from each step in the acute stroke pathway as input parameters for a simulation model. This way we can study the regional set-up of the IAT organizational model.

Other outcome measures are mRS, quality of life score (EQ5D-5L), major vascular events, health care amount and loss of productivity measured once at max 36 months after stroke, in patients who were included in the trial after august 1, 2020.

Study description

Background summary

Intra-arterial treatment (IAT) by means of retrievable stents, in patients with acute ischemic stroke (AIS) with confirmed proximal intracranial occlusion, in whom the procedure can be started within 6 hours from onset, has been proven safe and effective. Still, a considerable proportion of patients do not recover despite recanalization. This is for a major part attributable to incomplete microvascular reperfusion (IMR). Antiplatelet agents and heparin may reduce IMR. Yet, it is unknown whether periprocedural antiplatelet agents and anticoagulant medication in patients with acute ischemic stroke treated with IAT can improve clinical outcome.

Study objective

To assess the effect of acetylsalicylic acid (ASA) and unfractionated heparin, alone, or in combination, in patients with AIS, who undergo IAT for a confirmed intracranial anterior circulation occlusion.

Study design

This is a multicenter phase III randomized clinical trial with open-label treatment using a 2x2 factorial design, comparing IV ASA and one dose of unfractionated heparin as co-medication in IAT. It has blind assessment of primary outcomes and of neuro-imaging at baseline and follow-up.

Intervention

Treatment with unfractionated heparin in a low dose (loading dose of 5000 IU followed by 500 IU/hour x 6 hours). Treatment with IV acetylsalicylic acid (300 mg). At 24 hours after start of IAT, all patients will receive antiplatelet therapy or anticoagulation according to local protocol, at the discretion of the treating physician.

Study burden and risks

Clinical equipoise and considerable practice variation exist with respect to the periprocedural antiplatelet and anticoagulant treatment. There is a potential benefit, and a low risk which includes the risk of intracranial hemorrhage. However, every hour delay in reperfusion leads to 6-7% absolute risk reduction in good outcome. We therefore make use of deferred written informed consent (by proxy).

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

a clinical diagnosis of acute ischemic stroke; caused by proximal intracranial anterior circulation occlusion (distal intracranial carotid artery or middle (M1/proximal M2) or anterior (A1/A2) cerebral artery confirmed by neuro-imaging (CTA or MRA); CT or MRI ruling out intracranial hemorrhage; treatment possible (groin puncture) within 6 hours from symptom onset or last seen well; a score of at least 2 on the NIH Stroke Scale; age of 18 years or older; written informed consent (deferred).

Exclusion criteria

- Pre-stroke disability which interferes with the assessment of functional outcome at 90 days, i.e. mRS >2;
- Treatment with IV alteplase, despite the following contra-indications for IV alteplase: cerebral infarction in the previous 6 weeks with residual neurological deficit or signs of recent infarction on neuroimaging, previous intracerebral hemorrhage in the previous 3 months, INR exceeding 1.7, prior use of direct oral anticoagulant (DOAC)
- IV alteplase infusion >4.5 hours after symptom onset;
- Contra-indications for ASA/unfractionated heparin, for instance: allergy, recent hemorrhage, heparin induced thrombocytopenia;
- INR exceeding 3.0
- Known hemorrhagic diathesis or known thrombopenia (<90^9/L)
- Therapeutic heparin use

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)

Primary purpose: Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	22-01-2018
Enrollment:	1500
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Aspegic / Aspirin
Generic name:	Acetyl salicylic acid
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	heparin LEO
Generic name:	heparin
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	09-08-2017
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO Date:	19-10-2017
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	28-03-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	11-04-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	08-05-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	25-05-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	03-09-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	03-10-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	14-01-2019
Application type:	Amendment

Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	26-02-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	14-05-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	25-03-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2017-001466-21-NL
ISRCTN	ISRCTN76741621
CCMO	NL61364.078.17