ISRCTN80619088 https://doi.org/10.1186/ISRCTN80619088

Is intravenous alteplase still of added benefit in patients with acute ischaemic stroke who undergo intra-arterial treatment?

Submission date
31/10/2017

Recruitment status
No longer recruiting

Registration date
09/11/2017

Overall study status
Completed

Last Edited
17/06/2025

Condition category
Nervous System Diseases

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

Plain English summary of protocol

Background and study aims
Stroke is a major cause of death and disability. Eighty percent of stroke cases are ischemic (caused when there is a restriction in blood supply to the brain) in nature, meaning that a clot blocks a cerebral artery. In the Netherlands (16.7 million inhabitants), each year more than 20,000 individuals are admitted to hospital and up to 8500 patients die because of ischaemic stroke. Until recently, intravenous thrombolysis (IVT) with alteplase (injections to try to dissolve blood clots) was the only proven therapy for stroke. In 2015, however, studies showed that mechanical removal of the clot with a stent retriever/aspiration device (intra-arterial treatment, or IAT) improved functional outcome compared to IVT alone. However, all of these studies included patients who also received IVT, unless they had a contra-indication for IVT. Also, 67% of patients treated with IVT followed by IAT remained functionally dependent. Furthermore, the effect of IAT on functional outcome appears not to be influenced by IVT. This raises the question whether IVT is still of added benefit to stroke patients who are treated with IAT. The aim of this study is to assess whether direct IAT is more effective than IVT followed by IAT on improving functional outcome at 3 months.

Who can participate?
Adult patients with a clinical diagnosis of acute ischemic stroke and a confirmed clot in a major cerebral artery, who are eligible for IVT and IAT.

What does the study involve?
Participants are randomly allocated to one of two groups. Those in the first group receive the standard treatment, which is IVT followed by IAT. Those in the second group receive direct intra-arterial treatment. At three months, the functional outcome of both groups are measured and compared to asses which type of treatment is most effective. All patients undergo a follow-up cranial non-contrast CT scan at 5-7 days or at discharge, and three extra blood samples are taken from all patients.

What are the possible benefits and risks of participating?
There are benefits and risks with both procedures. IVT is a standard treatment, however, it is

associated with bleeding complications. It might cause the clot to move to where it cannot be reached by the stent retriever. Conversely, it is an ultra-fast mode of treatment and it may help soften the clot for mechanical removal. IAT is also a standard treatment, but is associated with a slightly higher risk of infarctions in new vascular territories in treatment with IAT and groin hematomas.

Where is the study run from?
This study is being run by the Academic Medical Centre (AMC) (Netherlands).

When is the study starting and how long is it expected to run for?
May 2017 to February 2021

Who is funding the study?
Stryker (Netherlands)
Hartstichting (Netherlands, Dutch Heart Foundation)
Hersenstichting (Netherlands, Dutch Brain Foundation)

Who is the main contact?
1. Professor Yvo Roos (Scientific)
2. Professor Charles Majoie (Scientific)

Contact information

Type(s)
Scientific

Contact name
Prof Yvo Roos

Contact details
Academic Medical Centre Amsterdam
Department of Neurology
PO Box 22660
Amsterdam
Netherlands
1100 DD

Type(s)
Scientific

Contact name
Prof Charles Majoie

Contact details
Academic Medical Centre Amsterdam
Department of Radiology and Nuclear Medicine
PO box 22660
Amsterdam
Netherlands
1100 DD

Additional identifiers

Protocol serial number
NL58320.078.17

Study information

Scientific Title
MR CLEAN-NO IV: Intravenous treatment followed by intra-arterial treatment versus direct intra-arterial treatment for acute ischaemic stroke caused by a proximal intracranial occlusion

Acronym
MR CLEAN-NO IV

Study objectives
Direct intra-arterial treatment will lead to a better functional outcome compared to intravenous thrombolysis with alteplase followed by intra-arterial treatment in patients with acute ischaemic stroke based on a large vessel occlusion.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Medical Ethics Committee Erasmus MC University Medical Centre Rotterdam, 19-10-2017, ref: MEC-2017-368.

Study design
Multicentre phase III prospective randomised clinical trial with open-label treatment and blinded outcome assessment (PROBE).

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Acute ischaemic stroke based on an intracranial large vessel occlusion of the anterior circulation.

Interventions
Participants are randomly allocated using acomputer- and web-based programme, using permuted blocks, to receiving either direct intra-arterial treatment, or intravenous thrombolysis with alteplase followed by intra-arterial treatment. Back-up by telephone is provided. Randomisation is allowed when the occlusion has been established by CTA or MRA and isstratified by center and inclusion in the active treatment arm of the MR ASAP trial (Multicentre randomised trial of Acute Stroke treatment in the Ambulance with a nitroglycerin Patch: pre-hospital augmentation of collateral blood flow and blood pressure reduction).

Intra-arterial treatment involves catheterisation, after which intracranial thrombectomy is performed with a stent-retriever or other device approved by the steering committee. Every

participant undergoes a CTA of the cerebral vessels to assess rate of recanalisation at 24 hours after randomisation, and a cranial non-contrast CT to assess final infarct volume 5-7 days after randomisation. Three months after inclusion, all participants are interviewed by telephone to determine functional outcome.

Intervention Type
Other

Primary outcome(s)
Functional outcome measured by the score on the modified Rankin Scale (mRS) at 90 days.

Key secondary outcome(s))
1. Death, defined as a score of 6 on the mRS, within 90 days (± 14 days)
2. Pre-interventional recanalisation, defined as an extended treatment in cerebral ischaemia (eTICI) score of 2b or more on first angiography
3. Reperfusion as measured by an eTICI score of 2b or more on final angiography of IAT
4. Recanalisation rate assessed with CT-angiography at 24 hours
5. Clinical stroke severity, measured by the National Institutes of Health Stroke Scale score at 24 hours and 5-7 days, or at discharge
6. Final infarct volume measured on cranial non-contrast CT at 5-7 days after randomisation
7. Dichotomised clinical outcome on the mRS at 90 days
8. Quality of life as measured on the EQ5D-5L at 90 days (± 14 days)
9. Functional independence as measured by the Barthel index at 90 days (± 14 days)

Safety outcome measures
1. Hemorrhages according to the Heidelberg criteria
2. Symptomatic intracerebral hemorrhages, according to the Heidelberg criteria
3. Embolisation in new territory on angiography during IAT
4. Occurrence of aneurysma spurium
5. Occurrence of groin haematoma
6. Infarction in a new territory on cranial non-contrast CT at 5-7 days
7. Death from all causes within 90 days (± 14 days).

Completion date
05/02/2021

Eligibility

Key inclusion criteria
1. A clinical diagnosis of acute ischaemic stroke
2. Caused by a large vessel occlusion of the anterior circulation (distal intracranial
3. Carotid artery or middle (M1/proximal M2) cerebral artery confirmed by neuroimaging (CTA or MRA)
4. CT or MRI ruling out intracranial hemorrhage
5. Eligible for IVT (within 4.5 hours after symptom onset)
6. Ascore of at least 2 on the NIH Stroke Scale
7. Age of 18 years or older
8. Written informed consent (deferred)

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
All

Total final enrolment
539

Key exclusion criteria
1. Pre-stroke disability which interferes with the assessment of functional outcome at 90 days i.e. mRS >2
2. Participation in trials other than current and MR ASAP
3. Any contra-indication for IVT, according to national guidelines, which are in accordance with guidelines of the American Heart Association, i.e.:
3.1. Arterial blood pressure exceeding 185/110 mmHg
3.2. Blood glucose less than 2.7 or over 22.2 mmol/L
3.3. Cerebral infarction in the previous 6 weeks with residual neurological deficit or signs of recent infarction on neuro-imaging
3.4. Recent head trauma
3.5. Recent major surgery or serious trauma
3.6. Recent gastrointestinal or urinary tract hemorrhage
3.7. Previous intracerebral hemorrhage
3.8. Use of anticoagulant with INR exceeding 1.7
3.9. Known thrombocyte count less than 100 x 109/L
3.10. Treatment with direct thrombin or factor X inhibitors
3.11. Treatment with therapeutic dose of (low-molecular weight) heparin

Date of first enrolment
24/01/2018

Date of final enrolment
28/10/2020

Locations

Countries of recruitment
Belgium

France

Netherlands

Study participating centre
Amsterdam UMC, location AMC
Meibergdreef 9
Amsterdam
Netherlands
1105 AZ

Study participating centre
Maastricht University Medical Centre
P. Debyelaan 25
Maastricht
Netherlands
6229 HX

Study participating centre
Erasmus MC University Medical Centre Rotterdam
's-Gravendijkwal 230
Rotterdam
Netherlands
3000 CA

Study participating centre
University Medical Centre Utrecht
Heidelberglaan 100
Utrecht
Netherlands
3584 CX

Sponsor information

Organisation
Academic Medical Centre Amsterdam

Funder(s)

Funder type
Industry

Funder Name
Stryker

Alternative Name(s)
Stryker Corporation, Orthopedic Frame Company

Funding Body Type
Government organisation

Funding Body Subtype
For-profit companies (industry)

Location
United States of America

Funder Name
Hartstichting (Netherlands, Dutch Heart Foundation)

Funder Name
Hersenstichting (Netherlands, Dutch Brain Foundation)

Results and Publications

Individual participant data (IPD) sharing plan
The de-identified dataset generated during and/or analysed during the current study will be available upon request through www.contrast-consortium.nl/data-request-form/ from 18 months after the trial publication date until 15 years after publication. The data will be made available to researchers who are CONTRAST consortium members or collaborators, and whose proposed use of the data has been approved by the CONTRAST data access and writing committee. The data will only be made available for specified purposes, as defined in the sub-study proposal and approved by the CONTRAST data access and writing committee. To ensure transparency and quality, researchers should adhere to the CONTRAST publication policy, accessible on https://www.contrast-consortium.nl/publication-policy-contrast/.

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article		01/07/2020	14/04/2021	Yes	No
Results article		11/11/2021	11/11/2021	Yes	No
		13/07	14/07		

Results article		/2022	/2022	Yes	No
Results article	Infarct evolution between baseline and follow-up imaging	23/03 /2023	17/06 /2025	Yes	No
Protocol article	CONTRAST consortium rationale and design of five large acute stroke trials to test novel treatment strategies	07/01 /2020	16/02 /2021	Yes	No
Protocol article	Protocol for MR CLEAN-NO IV	15/02 /2021	17/06 /2025	Yes	No
Other publications	Post hoc analysis of association between outcomes in patients with high systolic blood pressure and prior intravenous thrombolysis		29/08 /2023	Yes	No
Other publications	Retrospective post hoc analysis of patients from the MR CLEAN-NO IV with available CTP data	08/03 /2023	17/06 /2025	Yes	No
Participant information sheet	Participant information sheet	11/11 /2025	11/11 /2025	No	Yes
Statistical Analysis Plan	version V1.0	22/10 /2020	23/11 /2020	No	No
Statistical Analysis Plan	version V2.0	16/01 /2021	18/01 /2021	No	No
Study website	Study website	11/11 /2025	11/11 /2025	No	Yes