Protocol for the MR CLEAN-Registry (MR CLEAN-R)

A multicenter registry of endovascular treatment for acute ischemic stroke

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ACKNOWLEDGMENTS

The study is designed, and will be conducted, analyzed and interpreted by the investigators independently of all sponsors.

SUMMARY

RATIONALE AND AIM

After the last inclusion in the MR CLEAN trial there is a momentum in endovascular treatment (EVT) for acute anterior circulation ischemic stroke in the Netherlands. The international guidelines and recommendations allowed endovascular treatment as a rescue treatment, but since early 2015,abundant proof of a beneficial effect of endovascular treatment on functional outcome has become available.

The purpose of the MR CLEAN-R is a post-trial Registry of the Multicenter Randomized Clinical trial of Intra-arterial treatment for acute ischemic stroke in the Netherlands is to monitor implementation and safety of the new endovascular treatment.

MR CLEAN-R is a multicenter registry. In the period following the last inclusion of the MR CLEAN trial this study will register all patients with acute ischemic stroke caused by intracranial occlusion who undergo endovascular treatment.

STUDY POPULATION

All patients undergoing endovascular treatment for acute ischemic stroke will be registered. The core study population, however, will consist of patients with a clinical diagnosis of acute ischemic stroke due to a proximal arterial occlusion in the anterior cerebral circulation demonstrated by neuro-imaging and endovascular treatment started within 6.5 hours after stroke onset. Intracerebral hemorrhage should be ruled out by CT or MRI.

INTERVENTION

Endovascular treatment may consist of intra-arterial thrombolysis with urokinase or alteplase, mechanical treatment or both. Mechanical treatment refers to retraction or aspiration of the thrombus with a catheter guided device, including use of a retrievable stent. The exact choice of endovascular treatment modality for each patient is left to the discretion of the local investigator and treating physicians. Medical management will be delivered according to national standards and guidelines. It may include treatment with intravenous alteplase before inclusion in the registry.

MAIN OUTCOME MEASURES

The primary outcome is the score on the modified Rankin Scale (mRS) 90 days after inclusion in the study; this categorical scale measures the functional outcome. Secondary clinical measures are the National Institutes of Health Stroke Scale (NIHSS) score pre- and post (<48 hours) treatment and time points of onset, groin puncture and first substantial reperfusion. Secondary imaging-based measurements are pre- and posttreatment collateral status on DSA (TICI), infarct volume on CT and evaluation of the carotid arteries with respect to atherosclerotic disease on CT angiography (CTA). Safety parameters include intra- and extracranial hemorrhagic complications, neurological deterioration, arterial dissection or perforation due to IAT, embolism in other vascular territories, allergic contrast medium reaction, pneumonia, cardiac ischemia and venous thromboembolism.

BURDEN AND RISKS ASSOCIATED WITH PARTICIPATION.

Patients participating in the registry will undergo a second CT scan after 2 days, if clinically indicated. All patients will have an interview at three months. Patients undergoing endovascular treatment may need sedation or anesthesia and intubation during the procedure. Finally, endovascular treatment is associated with increased risk of intra-cerebral hemorrhage. The decision for endovascular treatment in a patient will be made by the treating physician on the basis of a professional estimate of the risk and benefits involved.

DISCUSSION

MR CLEAN-R is a post-trial registry of the MR CLEAN trial. Enrollment has been started after the last inclusion in the MR CLEAN trial (March 17 2014) and will continue after the start of the MR CLEAN II trials in the (COllaboration for New TReatments of Acute STroke (CONTRAST) consortium.

Key words: alteplase, endovascular treatment, endovascular thrombectomy, acute ischemic stroke, post-trial cohort registry.

1. INTRODUCTION AND RATIONALE

1.1 GENERAL INTRODUCTION

In Western Europe and the US, the annual incidence of ischemic stroke is 1-2 per 1000.[1, 2] Half of all patients with stroke die or remain severely disabled. Stroke is one of the major causes of death and the first cause of dependency in the western world. Treatment with intravenous (IV) alteplase, aiming at early reperfusion has been proven effective for these patients, when they are treated within 4.5 hours, and when there are no contra-indications.[3-5] The absolute reduction in the chance of poor outcome in patients treated with IV alteplase within 3 hours from onset amounts to 10%; the number needed to treat is 10.[6] For the patients treated within 3 to 4.5 hours, this effect is reduced to 7%, for a number needed to treat of 14.[4]

In general, the number of patients eligible for treatment with IV alteplase is limited because of the restricted time window and contra-indications for systemic administration of alteplase. In about 25% of the patients with acute ischemic stroke, symptoms are caused by a proximal occlusion of one of the major intracranial arteries, i.e. the distal intracranial internal carotid artery, the proximal segments of the middle cerebral artery and the anterior cerebral artery.[7] The likelihood of a proximal intracranial occlusion increases with severity of the neurological deficit at presentation.[8-10] The effect of IV alteplase in these patients with a symptomatic intracranial arterial occlusion is limited as treatment with IV alteplase leads to recanalization in up to 33% of treated patients only.[11] In those without recanalization, outcome is generally poor.[12, 13]

1.2 EFFECTIVENESS AND SAFETY OF ENDOVASCULAR TREATMENT IN RECENT TRIALS

After the last inclusion in the MR CLEAN trial and the start of this Registry there was a momentum in endovascular treatment for acute anterior circulation ischemic stroke in the Netherlands. The international guidelines and recommendations allowed endovascular treatment as a rescue treatment. During inclusion of patients in this Registry, since early 2015, proof of a beneficial effect of endovascular treatment on functional outcome has become available.[14-18] Since then guidelines worldwide have been updated, recommending endovascular treatment with stent retrievers as standard therapy in patients with neuro-imaging –confirmed intracranial large vessel occlusion confirmed.[19, 20]

1.4 RATIONALE: NEED FOR A REGISTRY OF ENDOVASCULAR TREATMENT

The purpose of the MR CLEAN-R is a post-trial registry of the Multicenter Randomized Clinical trial of Intra-arterial treatment for acute ischemic stroke in the Netherlands is to monitor intra-arterial interventions for acute ischemic stroke, in order to assess the safety and outcome in clinical practice, in a well-defined set of patients.. For further evaluation of endovascular treatment, a core dataset – comparable to the MR CLEAN trial population- will be used.

2. OBJECTIVES

To study safety and functional outcome after endovascular treatment for acute ischemic stroke caused by thrombo-embolic intracranial occlusion in everyday practice. To identify associations of baseline clinical and neuro-imaging parameters with outcome and complications.

3. STUDY DESIGN

This a prospective national multicenter registry. At least 17 large hospitals will start registering patients in April 2014. Data of prospectively registered patients after this date, and of patients who died will be entered retrospectively into the database. Actual prospective enrollment will start in January 2015.

4. STUDY POPULATION

4.1 PATIENTS

All patients with acute ischemic stroke of the anterior or posterior circulation who are treated endovascular treatment will be registered and followed. Patients who have been included in Randomized Clinical trials will be registered but not data on intervention, clinical and long term follow-up will be entered into the database, in order to maintain the blind.

Patients meeting the inclusion and exclusion criteria as set out below will be entered in the core dataset.

4.2 REGISTRY INCLUSION & EXCLUSION CRITERIA

All patients who underwent EVT for acute ischemic stroke will be registered. We will create a core dataset of patients who conform to specific criteria.

GENERAL INCLUSION CRITERIA FOR REGISTRATION IN THE MR CLEAN REGISTRY

- A clinical diagnosis of acute ischemic stroke
- CT or MRI scan ruling out intracranial hemorrhage.
- Extracranial carotid and intracranial arterial occlusion demonstrated with CTA, MRA or DSA.
- Endovascular treatment was initiated; defined as groin puncture.

GENERAL EXCLUSION CRITERIA FOR REGISTRATION IN THE MR CLEAN REGISTRY

- Inclusion in the BASICS trial.

INCLUSION CRITERIA FOR CORE DATA SET

- Groin puncture within 6.5 hours of symptom onset
- Intracranial proximal arterial occlusion (intracranial carotid artery (ICA, ICA-T) or middle (M1/M2) or anterior (A1/A2) cerebral artery), demonstrated by CTA, MRA or DSA
- Endovascular treatment in a MR CLEAN center (list in appendix)
- Age of 18 or above

EXCLUSION CRITERIA FOR CORE DATA SET

- Violation of one of the preceding in- and exclusion criteria
- Pre modified Rankin Scale score > 2

4.3 PARTICIPATING CENTERS AND CENTER ELIGIBILITY

As the purpose of the registry is to include all patients who had endovascular treatment since termination of the MR CLEAN trial. All centers that participated in the MR CLEAN trial now participate in the MR CLEAN registry. We will also register patients treated in other centers, who started EVT after the MR CLEAN trial (appendix). These patients will be entered into the extended registry, while we are awaiting a formal procedure for recognition and certification of stroke-intervention centers.

5. TREATMENT OF SUBJECTS

5.1 ENDOVASCULAR TREATMENT

Endovascular treatment may consist of mechanical thrombectomy, aspiration and/or the delivery of a thrombolytic agent. The choice of treatment is up to the interventionist.

6. METHODS

6.1 STUDY OUTCOMES

PRIMARY OUTCOME

The primary outcome is the score on the modified Rankin Scale at 90 days (Appendix 1).

SECONDARY OUTCOMES

CLINICAL PARAMETERS

- NIHSS at within 48 hours or at discharge.

IMAGING PARAMETERS

- Infarct size assessed by CT at 2 days, when available. This includes manual tracing of the infarct perimeter and semi-automated pixel thresholding.[21, 22]
- Pre-treatment and post-treatment TICI-score assessed on DSA acquired intervention.
- Evaluation of atherosclerotic carotid disease assessed by CTA at baseline.

WORKFLOW

-
- Time points of onset or last seen well), admission to ER, intervention center, imaging, groin puncture and first substantial reperfusion and end of procedure.

SAFETY PARAMETERS

Safety is an issue of concern, as the experience with the intervention, overall, and within the participating centers, is limited. Safety parameters include , neurological deterioration, symptomatic intracranial hemorrhage, arterial dissection or perforation due to IAT, embolism in other vascular territories, extracranial hemorrhage, allergic contrast medium reaction, pneumonia, cardiac ischemia and venous thromboembolism and short-term outcome (mortality). As we will make use of web-based data-entry, these data will be available on short notice.

The primary safety parameter will be neurological deterioration within 24 hours from inclusion in the registry. Neurological deterioration is defined as any decline in NIHSS of 4 points or more. In these patients, urgent brain CT is mandatory. This serious complication will be further classified as due to intracranial hemorrhage, ischemia or other (undetermined) cause. A full list of serious adverse events is provided in Appendix 5.

6.2 BLINDING FOR ASSESSMENT

Blinding refers to the assessment of outcome data without knowledge of baseline characteristics or treatment details. Results of neuroimaging will be assessed in a blinded manner, except for symptomatic side.

6.3 STUDY PROCEDURES

BASELINE DATA OBTAINED AT ADMISSION

Clinical data, neuro-imaging data, data that might be related to treatment effect or to complications caused by the intervention, as well as several stroke risk factors, will be recorded in order to illustrate the representativeness of the study population (Table 1.1).

INCLUSION AND REGISTRATION

The registry office will be notified when a new patient is entered into the web-based database. Personal data will be sent to the registry office separately, through encrypted email.

FOLLOW-UP DATA

NIHSS scores at baseline and after procedure (<48 hours) will be scored constructed from clinical data when missing. All patients will undergo CT or MR imaging at 2 days, if clinically indicated. Raw anonymous data will be forwarded to the trial office for blind evaluation. When there was no three month follow-up to determine mRS at three months, mRS score will be derived of discharge data or data from closed follow-up at another moment.[23]

WITHDRAWAL

Patients can stop compliance with the registry at any time for any reason if they wish to do so without any consequences.

7. SAFETY REPORTING

7.1 SERIOUS COMPLICATIONS

A serious complication is any untoward medical occurrence or effect that can cause mortality, is life-threatening, requires prolonged hospitalization, or results in persistent significant disability.

Expected serious complications are neurologic deterioration, symptomatic intracranial hemorrhage, extracranial hemorrhage, technical complications or vascular damage at the target lesion such as perforation or dissection and mortality in the first week of stroke, aspiration pneumonia, and death from any cause until assessment of the 90-day follow-up.

A cumulative log will be kept of all serious complications and evaluated by the executive committee.

8. STATISTICAL ANALYSES

Baseline characteristics and outcomes will be summarized by means of simple descriptive statistics. The main analysis of this study concerns the primary outcome at 90 days. Associations between baseline demographic and clinical characteristics and intervention details with the primary and secondary outcome will be analyzed. Associations are defined as the relative risk for improvement on the mRs and estimated as an odds ratio with (adjusted) ordinal logistic regression taking the whole range of the modified Rankin Scale (mRS) into account.[24] Similar associations of demographic and clinical characteristics and intervention details with secondary outcomes will be analyzed with standard statistical tests and multiple regression models to adjust for other prognostic factors.

9. ETHICAL CONSIDERATIONS, ACCESS TO APPROPRIATE TREATMENT

All patients will receive best medical treatment according to national and local guidelines and current insights. The decision to carry out the intervention will be made the local stroke team and investigators. The steering committee will issue recommendations with regard to treatment and medical management of the patients in the registry.

9.1 REGULATION STATEMENT

The registry will be conducted in accordance with the principles of the Declaration of Helsinki, as amendended by the World Medical Association General Assembly in October 2008, and with the guidelines for Good Clinical Practice.

9.2 RECRUITMENT AND CONSENT

All patients will be provided with a written explanation of the study. The patients or their representatives will be given the opportunity to refuse participation. In that case all data will be deleted from the database and clinical material will be destroyed.

This registry makes use of "waste material" only, such as blood aspirated during intervention and retrieved thrombi. No additional blood will be drawn. However, substudies may require additional activities, for which separate written informed consent will have to be obtained.

Data of patients who died before they were asked for consent and data of patients who were recruited retrospectively since April 2014 will be entered anonymously in the study base. Patient material and data will be stored anonymously.

The study physician will inform the patient orally and in writing. In case the patient is legally incompetent, for example because of aphasia or anosognosia, the information will be given to a legal representative. Because the study physicians are also involved in the clinical care of patients with acute ischemic stroke, it appears inevitable that in some occasions the study physician and treating physician will be the same person.

9.3 BURDENS TO THE PATIENT

All patients will undergo an additional CT scan after 2 days to assess infarct size, if clinically indicated. Radiation exposure for this CT scan is 2.1-2.3 mSV (milliSievert).[25]

Patients may be asked to participate in substudies (see section 10.2). Also, during the intervention aspirated blood may be kept and stored, as well as the thrombo-embolic material which is retrieved from the retraction devices (THRAPS substudy).

10. ADMINISTRATIVE ASPECTS AND PUBLICATION

10.1 PRIVACY

All included patients will be assigned a unique number. Name and address will be stored separately from the study data. The study physician will inform the patient orally and in writing. The information describes the purpose of the study, interventions, potential hazards and benefits and the procedures for recording of clinical information and three month follow up.

10.2 SUBSTUDIES

Within the framework of the MR CLEAN-R, several observational substudies are carried out. They were also active within the framework of the MR CLEAN trial itself. They will be summarized below. For each substudy the patients' written consent will be asked. For a full description of the study procedures see the appendices with study protocols.

THRAPS

THRAPS is an observational study of the thrombo-emboli and aspirate blood (waste material) that is retrieved during the intervention. We will relate histopathologic parameters with the effect of the procedure (recanalization, no reflow and functional recovery).

10.3 PUBLICATION POLICY

The writing committee consists of executive committee members and PIs of centers including more than 50 patients in the first full year of the registry. The writing committee will coordinate authorship for the main results paper (all PIs and committee members are eligible for authorship), and for subsequent papers. All scientific publications will be made on behalf of the MR CLEAN Registry investigators, who will be mentioned by name in an appendix. All investigators will have the opportunity to read and comment on a manuscript before it will be submitted for publication.

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12. TABLES

1. STUDY PARAMETERS

1.1 Baseline characteristics	
Demographics	Age, sex
Clinical	NIHSS, NIHSS supplemental motor score, pre-stroke mRs, blood pressure, GCS, weight, height, body temperature.
Medical history	Previous stroke, previous MI, PAD, diabetes mellitus
Medication	Antiplatelet agents, coumarines, heparin(oids), oral thrombin antagonists, oral factor Xa inhibitors , statins
Vascular risk factors	Hypertension, atrial fibrillation, diabetes mellitus, smoking, hypercholesterolemia
Laboratory parameters	INR, kreatinine, GFR (Cockroft-Gault), serum glucose, CRP.
Neuroimaging	Thin slice and standard CT and CTA: location, ASPECT score, hemorrhagic transformation (Heidelberg classification)[26], and hyperdense artery sign, and assessment of carotid arteries.
Treatment	Intended mode of endovascular treatment

1.2 Procedural/treatment	
Time window	time points of onset (last seen well), admission to intervention center ER, imaging, groin puncture and first substantial reperfusion and end of procedure.
Treatment	Performed intervention, pre- and post-intervention TICI-score on anterior-posterior and lateral DSA images, medication during procedure, anesthesia during procedure
Complications	Complications will be registered. See also Appendix 5.

1.3 Follow-up		
Clinical assessment at 24-48 hours	Clinical status, NIH Stroke Scale, NIHS supplemental motor scale	
Neuro-imaging at 2 days (if clinically indicated)	Plain CT: location, ASPECTS score, hemorrhagic transformation (Heidelberg classification)[26]	
Clinical assessment at 90 days	Modified Rankin Scale score	
Serious complications	See appendix 5	

13. APPENDICES

1. MODIFIED RANKIN SCALE (MRS)[23]

Category	Short description	Long description
0	No symptoms	No symptoms
1	Symptoms, no Disability	Minor symptoms that do not interfere with lifestyle
2	Slight disability	Slight disability, symptoms that lead to some restriction in lifestyle, but do not interfere with the patient's capacity to look after himself.
3	Moderate disability	Moderate disability, symptoms that significantly restrict lifestyle and prevent totally independent existence
4	Moderately severe disability	Moderately severe disability, symptoms that clearly prevent independent existence though not needing constant attention
5	Severe disability	Severe disability, totally dependent patient requiring constant attention day and night.
6	Dead	Death

2. STUDY PERSONNEL

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3. Maastricht Medical Center
4. UMC Utrecht
5. LUMC Leiden
6. UMC Nijmegen
7. Haaglanden Ziekenhuis Den Haag
8. Haga Ziekenhuis Den Haag
9. UMC Groningen
10. St. Elisabeth Ziekenhuis Tilburg
11. Isala klinieken Zwolle
12. Catharina Ziekenhuis Eindhoven
13. St. Antonius Nieuwegein
14. Rijnstate Ziekenhuis Arnhem
15. Medisch Spectrum Twente
16. Atrium Heerlen (close collaboration with Maastricht Medical Center)
17. Reinier de Graaf Groep Delft (close collaboration with Haga Ziekenhuis Den Haag)

OTHER PARTICIPATING CENTERS

1. Albert Schweitzer Ziekenhuis, Dordrecht
2. Amphia Ziekenhuis, Breda

4. PARTICIPATING NON-INTERVENTION CENTERS

1. VU Medisch Centrum Amsterdam

2. St. Lucas Andreas Ziekenhuis Amsterdam

5. SERIOUS COMPLICATIONS

1. Neurological deterioration	Defined as any decline in NIHSS of 4 points or more regardless of the reason of deterioration. Urgent brain CT is mandatory for further classification.
2. Symptomatic new ischemic stroke	Imaging of new brain infarction with corresponding clinical neurologic deficit
3. Symptomatic intracranial hemorrhage	Symptomatic intracranial hemorrhage is defined as a decline in NIHSS of 4 points or more, and corresponding hemorrhage confirmed on brain CT. Also box 'neurological deterioration' will be ticked.
4. Extracranial hemorrhage requiring surgery or blood transfusion	Examples: gastrointestinal bleeding, inguinal bleeding after arterial puncture. Aneurysm spurium will registered as 'Other'.
5. Technical complications at the target lesion such as perforation or dissection	Evidence of vascular injury,: perforation, or dissection, vasospasm, new clot in different vascular territory or distal thrombus confirmed with imaging .
6. Pneumonia, aspiration pneumonia and other infections.	Defined as any infection occurring within 7 days after the onset of stroke. Definitions of infections were based on CDC/NHSN surveillance definition of health care-associated infection and criteria for specific types of infections in the acute care setting.[27]
7. Deep venous thrombosis and pulmonary embolism	Documented deep venous thrombosis and pulmonary embolism
8. Allergic reaction towards contrast fluid	Clinical suspicion of anaphylactic reaction to contrast fluid.
9. Cardiac ischemia	Myocardial ischemia confirmed by ECG, and release of appropriate biomarkers.

10. Death from any cause within the registry period	All causes of death that are related or not to endovascular treatment.

A complication is considered serious when it causes mortality, is life-threatening, requires prolonged hospitalization, or results in persistent significant disability.