Insights in acute endovascular treatment in ischemic stroke

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Insights in acute endovascular treatment in ischemic stroke

Debbie Beumer

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Insights in acute endovascular treatment in ischemic stroke

PROEFSCHRIFT

ter verkrijging van de graad van doctor aan de Universiteit Maastricht,
op gezag van de Rector Magnificus, Prof. dr. Rianne M. Letschert,
volgens het besluit van het College van Decanen,
in het openbaar te verdedigen
op donderdag 10 oktober 2019 om 12.00 uur

door

Debbie Beumer

Promotores

Prof. dr. R.J. van Oostenbrugge

Prof. dr. D.W.J. Dippel, Erasmus Universiteit Rotterdam

Copromotor

Dr. W.H. van Zwam

Beoordelingscommissie

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Dr. H.D. Boogaarts, Radboud Universiteit Nijmegen

Prof. dr. M.W. de Haan

Prof. dr. A.W.J. van 't Hof

Prof. dr. M.J.H. Wermer, Leids Universitair Medisch Centrum

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Abbreviations

acOR	adjusted common Odds Ratios
AF	atrial fibrillation
AIS	acute ischemic stroke
aOR	adjusted Odds Ratio
APTT	Activated Partial Tromboplastin Time
ASPECTS	Alberta Stroke Program Early CT Score
BA	Basilar Artery
BMI	Body Mass Index
CE	Conformité Européenne
CI	Confidence Interval
CT	Computed Tomography
CTA	Computed Tomography Angiography
DMC	Data Monitoring Committee
DSA	Digital Subtraction Angiography
ECG	Electro Cardio Gram
ED	Emergency Department
ER	Emergency Room
ESS	Erasmus Stroke Study
EVT	Endovascular Treatment
FDA	Food and Drug Administration
HERMES	Highly Effective Reperfusion Evaluated in Multiple Endovascular Stroke Trials
IAT	Intra-Arterial Treatment
ICA	Internal Carotid Artery
IMS	Interventional Management of Stroke
INR	International Normalized Ratio
IQR	Interquartile Range
IV	intravenous
IVT	intravenous thrombolysis
LVO	Large Vessel Occlusion
MDCT	Multidetector Computed Tomography
MEC	Medical Ethical Committee
MRA	Magnetic Resonance Angiography
MR CLEAN	Multicenter Randomized CLinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands
MRI	Magnetic Resonance Imaging

MR RESCUE	Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy
mRS	modified Rankin Scale
mTICI	modified Thrombolysis in Cerebral Infarction
NASA	North American SOLITAIRE Stent-Retriever Acute Stroke Registry
NIHSS	National Institutes of Health Stroke Scale
OR	Odds Ratio
PROACT	Prolyse in Acute Cerebral Thromboembolism
RCT	randomized clinical trial
rtPA	recombinant tissue Plasminogen Activator
SD	standard deviation
SICH	Symptomatic Intracranial Haemorrhage
TICI	Thrombolysis In Cerebral Infarction
TIMI	Thrombolysis In Myocardial Infarction

Chapter 1

General introduction

General introduction

Stroke is a neurological disorder caused by disturbance in cerebral blood flow in a particular region of the brain. Although the brain makes up only 2 percent of total body weight, it uses 20 percent of the cardiac output. Any problem in the cerebral blood flow disturbs energy and oxygen delivery to the brain tissue causing graceless local ischemia. The clinical neurological signs and symptoms depend on the region of the brain in which the disturbance of cerebral blood flow takes place. It is important to recognize stroke symptoms as quickly as possible in order to instigate potential therapeutic options as soon as possible. Stroke is divided in ischemic stroke (80%) and hemorrhagic stroke (20%). In hemorrhagic stroke a local defect in the arterial wall causes bleeding in the brain parenchyma or around the brain in the subarachnoid space, which leads to neurological symptoms. In ischemic stroke the disturbance in cerebral blood flow is caused by an obstruction of the blood flow in the blood vessels.

This thesis is on ischemic stroke and endovascular treatment (EVT) in the acute setting. EVT is possible in ischemic strokes caused by an intracranial large vessel occlusion (LVO). These occlusions can be caused by a dislodged thrombus from the heart or the proximal carotid artery, or by local thrombus formation, often due to local vessel pathology as is seen in atherosclerosis.

Acute ischemic stroke (AIS) is estimated in about 28 to 61% of cases to be caused by an occlusion of a large blood vessel,¹⁻⁵ interfering with the local cerebral blood flow.

Epidemiology

Stroke is one of the major causes of death and severe disability in the Western world affecting mainly the older population. The annual incidence of ischemic stroke is 1-2 per 1000.⁶ In The Netherlands with over 17 million inhabitants annual incidence was estimated 41.000 in 2008.⁷ In 2015 in total 26.266 patients were treated in the hospital due to ischemic stroke of which 5631 patients died from ischemic stroke.^{7,8}

The Dutch population is growing older with in total 1.2 million persons over 75 years in 2011 and an expected 2.6 million persons in 2040 being older than 75 year. With this the expected increase of older persons the incidence of ischemic stroke will also increase.

Treatment of acute ischemic stroke

Since more than 20 years patients with AIS are treated with intravenous thrombolysis (IVT) i.e. by administering recombinant tissue plasminogen activator (rtPA).⁹ However, this is only indicated within 4.5 hours after symptom onset and many contra-indications are known. Moreover, in LVO, which is the cause of AIS in about one third of the

patients,¹ recanalization rate is low and good functional outcome in these patients was seen in approximately 10% only.^{10,11}

Since the 1980s various endovascular treatment options were explored, first by administering local intra-arterial thrombolytics, later combined with mechanical clot removal techniques.

The first randomized clinical trial (RCT) to study the efficacy and safety of endovascular admitted recombinant pro-urokinase versus placebo in patients with AIS in 1998, was the Prolyse in Acute Cerebral Trombo embolism (PROACT Trial). In this study, in which 46 patients were randomized, recanalization rate was significantly higher in the intervention arm, without increase of intracranial hemorrhage and no significant difference was found on functional outcome expressed by mRS (0-1).¹² This study was followed by the PROACT II trial in which 180 patients with AIS were randomized between recombinant pro-urokinase with heparin versus heparin alone. Functional independence (mRS 0-2) at 90 days was reached in 40% of the patients in the intervention group versus 25% in the control arm, without difference in mortality or intracranial hemorrhage.¹³ In the following years devices for mechanical clot removal were developed with variable success. The endovascular use of the Merci device (Concentric Medical corp.) e.g. showed better technical and clinical results than intravenous thrombolytics alone.^{14,15}

The discovery in 2008 that a stent used for aneurysm treatment was able to remove clots,^{16,17} led to the development of so called stent retrievers. They appeared to have better results on recanalization, safety and functional outcome in patients with a large vessel occlusion in AIS than previous devices.^{18,19} However, all these positive results came from relatively small single-device industry driven studies. Larger independent randomized trials were needed to establish the efficacy of EVT in AIS.

Three large independent multicenter RCTs were published in 2013.²⁰⁻²² Unfortunately they were not able to show better functional outcome and safety of EVT over standard therapy, including IV rtPA.

The Interventional Management of Stroke (IMS-III) was the largest study that assessed IVT with EVT compared to IVT alone.²⁰ This study was stopped earlier than planned after 656 inclusions of the 900 planned, due to futility. Similar results were found on functional independence and safety. In the Local versus Systemic Thrombolysis for Acute Ischemic Stroke (Synthesis Expansion) trial IVT alone was compared to EVT without IVT, and again no difference was found between both groups.²¹

The third RCT, the Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy (MR RESCUE), randomized patients based on neuroimaging penumbral pattern but could not find a specific penumbral pattern identifying patients who may benefit from EVT.²² Also no differences on functional outcome were found between IVT and EVT.

Several concerns were raised about the design and conduct of these trials, as confirmation of LVO on vascular imaging was not required and the newest generation of mechanical devices were not allowed to be used in these trials. In the meantime a new trial was designed in The Netherlands in which LVO confirmed on CT or MR angiography was required before randomization and use of the latest generation mechanical devices was allowed. This Dutch trial was called ‘The Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in The Netherlands’ (MR CLEAN) in which EVT additional to standard care, including IVT, was compared to standard care alone in patients 18 years or older with a confirmed LVO of the anterior circulation, who could be treated within 6 hours after symptom onset.

Outline of the thesis

In The Netherlands, all patients treated with EVT before the start of MR CLEAN were registered in the so called “MR CLEAN pretrial registry” to gain insight in the way patients were endovascularly treated and to gain information about radiological and functional outcome after EVT in The Netherlands. This data was gathered from 2002 until the intervention center started to participate in MR CLEAN.

Patient enrollment in the MR CLEAN trial started in 2010. Eighteen Dutch centers, participated in this trial. During the inclusion period, which ended in April 2014, virtually no potentially eligible patient was treated with EVT outside the trial.

The design and protocol of the MR CLEAN trial are described in Chapter 5.

Main results of the MR CLEAN trial are presented in Chapter 6.

Experience of the interventionist in the MR CLEAN pretrial registry

Endovascular treatment of patients with AIS is a team effort. In this team the operator (interventionist) performs the endovascular procedure. In the setting of a new treatment technique experience of the operator with the procedure might modify the effect of this treatment. Operator experience has been studied before in carotid artery surgery and an association between life time experience and outcome was not observed.²³ It is unclear whether the level of operator experience influences clinical and radiological patient outcome in endovascular AIS treatment. The MR CLEAN pretrial registry offered a unique opportunity to study the effect of operator experience on clinical and radiological outcome. In chapter 4 the results of this pretrial registry study on operator’s experience are described.

Large vessel occlusion in endovascular treatment

Knowledge of the number of patients with a radiologically confirmed LVO in AIS is important to estimate the number of patients eligible for EVT. Observational studies report ranges of 10-61% of patients who present at the emergency department suffering from a LVO.¹⁻⁴ Unfortunately these studies did not include unselected, consecutive patients and different time windows from symptom onset to start of the endovascular procedure were used. Also, not all patients received an angiography to confirm the presence of a LVO. As such, precise numbers were not available at the moment of the design of MR CLEAN. As these numbers were needed to determine the feasibility of MR CLEAN,

The number of patients potentially eligible for EVT was determined in Chapter 2. Data was obtained from the Erasmus Stroke Study (ESS) of the Erasmus Medical Center Rotterdam.

Age and endovascular treatment

Age is known as a strong predictor for outcome after stroke. Older ischemic stroke patients suffer more frequent from comorbid conditions, achieve less often good functional outcome and have higher mortality after AIS. This may influence clinical decision making in EVT.^{24,25}

The efficacy and safety of intravenous alteplase in older patients (i.e. >80 years) has been demonstrated. A recent meta-analysis of individual patient data of 6756 patients in 9 randomized trials in IVT showed that IVT in the elderly significantly improved functional outcome compared to no IVT (OR 1.56, 1.17-2.08).²⁶ It was debated whether older aged patients would benefit from EVT as well.

A number of RCT's on EVT excluded older patients. It was thought that treatment effect of EVT would be minimal due to expected technical difficulties by advanced atherosclerosis, vessel tortuosity and lower quality of collateral circulation.^{27,28} Some intervention trials included older patients and treatment effect in these older patients appeared to be similar to that in younger patients. Selection bias in these cannot be excluded in view of the small number of included older patients.^{29,30}

Chapter 3 describes the effect of older age on outcome after EVT using observational data from the MR CLEAN pretrial registry.

Chapter 7 describes the interaction of older age with EVT in the MR CLEAN randomized controlled trial.

Neurological outcome in AIS

Patients with AIS who present at the emergency department suffer from a variety of neurological symptoms ranging from very mild to severe neurological deficit. In general, higher severity of symptoms is associated with LVO although low severity does not exclude the presence of LVO.^{27,30,31} So far it remains unclear whether patients with low NIHSS scores do benefit from EVT. In the MR CLEAN study an attempt to assess interaction of low baseline NIHSS with EVT was made. In Chapter 8 this study on interaction between baseline neurological condition and EVT is described.

The last chapter 9 contains a general discussion with future implications and research recommendations.

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Chapter 2

Occurrence of intracranial large vessel occlusion in
consecutive, non-referred patients with
acute ischemic stroke

D Beumer*, MJHL Mulder*, G Saiedie, S Fonville, RJ van Oostenbrugge, WH van Zwam,
PJ Homburg, A van der Lugt, DWJ Dippel

* Equal contributors

Neurovascular Imaging 2016;2:11

Abstract

Background

The relative frequency of acute intracranial large vessel occlusion (LVO) in patients with acute ischemic stroke (AIS) who could be candidate for intra-arterial treatment (IAT) is not well known. In this study, we determined clinical variables associated with LVO and the proportion of patients with LVO among patients presenting with AIS within 6 h of symptom onset.

Methods

Data of consecutive patients with AIS presenting at the emergency department (ED) of the Erasmus University Medical Center, in the Netherlands, was used. Referrals from other hospitals were excluded.

Results

From 2006 January 1st to 2012 April 30th, 1063 non-referred patients presented at our ED with AIS. 445 (42%) arrived within 6 h of onset of symptoms. Computed tomography angiography was not performed or was of insufficient quality in 50 patients (11%) and performed late (≥ 1 day) in 57 patients (13%). The remaining 338 with AIS were included in the final analysis. 106 patients (31%) had LVO, mostly in the anterior circulation (72%). National Institutes of Health Stroke Scale score was the only variable associated with the presence of LVO (adjusted OR 1.23 per point [95% Confidence interval: 1.17-1.29]).

Conclusion

Of all patients with acute ischemic stroke who arrive within 6 h of symptom onset at the emergency department, almost one out of three have a intracranial large vessel occlusion and may be candidate for intra-arterial treatment.

Background

Recently published randomized clinical trials showed that intra-arterial treatment (IAT) with retrievable stents for acute ischemic stroke (AIS) was safe and effective in patients with acute intracranial large vessel occlusion (LVO) if they were treated within 6 h of symptom onset.¹⁻⁶ Updated guidelines indicate that IAT is now standard of care for AIS patients with LVO.^{7,8} This has great impact on stroke care providers, as the number of performed procedures increases rapidly and resources are limited. To estimate the number of candidates for IAT, it is important to know how many patients with AIS present with LVO.

Observational studies report that 10-61% of the patients who present at the emergency department (ED) with presumed AIS have LVO. However, these studies did not include unselected, consecutive patients,⁹ did not use appropriate neuro-imaging in all patients, 10 included patients who were transferred from other hospitals,^{11,12} or used a restricted time window.¹³

Knowledge of the occurrence of LVO is important clinically, for manpower planning and for resource allocation. In this study we describe the occurrence of LVO cases in a consecutive population of all AIS patients admitted to emergency department (ED) within 6 h after onset of symptoms. Moreover, we evaluate clinical predictors of LVO.

Methods

Patients

This retrospective single center study of a consecutive patient cohort was executed by the Erasmus University Medical Center, Rotterdam, the Netherlands. The patient population represents an urban population in a large city, where stroke patients are referred from general practitioners and other centers. Patients with AIS were identified from our Erasmus Stroke Registry, which is operational since 1990. All patients admitted to the ED with a presumed diagnosis of acute stroke are seen by a neurologist or a resident in neurology as part of clinical routine. Patients with AIS were entered into the registry after review and confirmation of the diagnosis by a vascular neurologist. For the present study electronic medical charts and imaging were used. No additional data collection was performed and institutional review board was not needed. All non-referral patients with AIS in the period of From 2006 January 1st to 2012

April 30th who were admitted to the ED were included. Patients had to be 18 years or older. Patients arriving later than 6 h after onset of symptoms at the emergency department were excluded. Patients who did not receive a Computed Tomography

Angiography (CTA) or in whom the CTA was of insufficient quality, and patients in whom a CTA was made more than 24 h after intravenous alteplase treatment (IVT) or more than 48 h after stroke onset were also excluded from the present study. Magnetic resonance imaging was never used instead of CTA.

Clinical variables

We determined the clinical location of the occlusion by categorizing symptoms, described by the attending neurologist or resident in neurology in the medical chart, as belonging to occlusion in the territory of the right or left carotid artery or the vertebrobasilar arteries. Furthermore, the National Institutes of Health Stroke Scale (NIHSS) on admission and time from onset of symptoms to arrival at the ED were assessed. Data on medical history were collected from medical records of the patients. The diagnosis of atrial fibrillation (AF) could be based on pre-existing AF, identified through medical history and de novo AF during hospitalization. All patients were monitored during the first 24 h after AIS and the diagnosis of de novo AF was confirmed by 12-lead ECG. The diagnosis of previous stroke was based on history, transient ischemic attack was not included.

CTA acquisition and analysis

CTA was performed with a 16-slice multidetector CT (MDCT) scanner (Siemens, Sensation 16, Erlangen, Germany), a 64-slice MDCT scanner (Siemens, Sensation 64, Erlangen, Germany) or a 128 slice MDCT scanner (Siemens, Definition AS, Erlangen, Germany) with a standardized optimized contrast-enhanced protocol (100–120 kVp, collimation 16×0.75 mm, 64×0.6 mm, or 128×0.6 mm, pitch ≤1).^{14,15} The CTA scan ranged from the ascending aorta to the intracranial circulation. Contrast material was given in a bolus of 80 ml (Iodixanol 320 mg/ml, Visipaque, Amersham Health, Little Chalfont, UK), followed by a 40 ml saline bolus chaser. The injection rate was 4 ml/s for both Iodixanol and saline. At the level of the ascending aorta contrast material passage was detected by real time bolus tracking followed by data acquisition. The images were reconstructed by a 100 mm field of view, matrix size 512×512 (real in-plane resolution 0.6×0.6 mm), slice thickness ≤1.0 mm, increment ≤0.6 mm and with an intermediate reconstruction algorithm.

CTA images were sent to a stand-alone workstation (Leonardo, Siemens Medical Solutions, Forchheim, Germany) with dedicated 3D analysis software, and were assessed by experts (GS, PH, AL) who had no clinical information other than a clinical diagnosis of AIS. Of all CTAs the extracranial and intracranial circulation were evaluated blinded without knowledge of the clinical data with multiplanar reformatting software, which

allows also reconstruction of sagittal, coronal, and oblique maximum intensity projections from axial sections.

The location of LVO was categorized as: intracranial internal carotid artery (ICA), anterior cerebral artery (A1 segment), proximal middle cerebral artery (M1 segment), distal middle cerebral artery (M2 segment), intracranial vertebral artery (IVA), basilar artery (BA), proximal posterior cerebral artery (P1 segment), distal posterior cerebral artery (P2 segment). Patients suffering from occlusions in multiple segments were categorized by their most proximal intracranial occlusion at the level of the circle of Willis. In addition, occlusions in the extracranial carotid artery and vertebral artery were assessed.

Outcome

LVO was defined as an occlusion in one of the intracranial arteries (ICA, A1, M1, M2, IVA, BA, P1 and P2), accompanied by clinical symptoms that could be attributed to ischemia in the territory of the occluded artery.

Statistical analysis

We used cross tabulation, univariable and multivariable logistic regression analysis. We expressed associations as odds ratios with 95% confidence intervals (CIs). Statistical analyses were performed with Stata/SE 14.1 (Stata-Corp. Texas. USA). We considered NIHSS, previous ischemic stroke and AF as possible predictors of occlusion, and we adjusted for age, gender and time to ED.

Results

Over a 6-year period 1063 patients with AIS were admitted to our ED. Of these 1063 patients, 618 (53%) were excluded because they arrived more than 6 h after onset of symptoms at the emergency department (Figure 2.1).

Figure 2.1 Inclusion chart of the patients. ED = emergency department, CTA = computer tomography angiography, AIS = acute ischemic stroke.

Of the 445 patients who presented within 6 h after onset of symptoms CTA was not performed or of insufficient quality in 50 patients (11%), and CTA was performed ≥ 24 h after IVT or ≥ 48 h after stroke onset in 57 patients (13%) (Figure 2.1). Most of these 107 patients with no or late CTA were admitted in the early phase after implementation of acute CTA in AIS patients (2006–2008). Clinical characteristics, including NIHSS at baseline in these 107 patients (median=5; IQR:2-12) were similar to the total 338 patients (median=5; IQR:2-11) with CTA in the acute phase ($p=0.67$). Of the remaining 338 patients with clinical symptoms of AIS, 106 patients (31%) had LVO. These patients had a mean age of 64 ± 15 years and 53 patients (50%) were male (Table 2.1). The median NIHSS on admission was 13 (6-18). Of these, 77 patients (73%) had an occlusion in the anterior circulation and 29 patients (27%) had an occlusion in the posterior circulation (Table 2.2).

Clinical predictors of LVO

Only admission NIHSS was associated with LVO (adjusted Odds Ratio (aOR)=1.23 per NIHSS point increase [95% CI: 1.17-1.29]) (Table 2.1). Patients with NIHSS of 1 or 2 had a

10% likelihood of LVO (Figure 2.2). A score of exactly 12 points on NIHSS indicates a likelihood of 50% for LVO. When NIHSS ≥ 12 , likelihood of LVO is 75%. NIHSS of 7 and above corresponds with a $>50\%$ likelihood of LVO. When NIHSS ≥ 20 , 21 (91%) of 23 patients had LVO. Of the two patients with NIHSS ≥ 20 without LVO, one had a previous stroke, with consequently a pre-stroke modified Rankin Scale score of 3 with a spastic hemiparesis; new stroke symptoms were aphasia and facial palsy. The other patient who had a NIHSS score of 22, experienced rapid recovery without IVT. No association was found between the presence of LVO and AF (aOR=1.10 [95% CI: 0.43-2.79]) or previous ischemic stroke (aOR=0.69 [95% CI: 0.34-1.44]) (Table 2.1).

Table 2.1 Baseline characteristics of the study population with and without acute intracranial large vessel occlusion (LVO).

	LVO (n=106)	No LVO (n=232)	P-value
Age (years), mean (SD)	64 (15)	62 (16)	0.26
Male sex, n (%)	53 (50%)	116 (50%)	1.00
Caucasian ethnicity, n (%)	81 (76%)	184 (79%)	0.55
Systolic blood pressure, mean (SD)	161 (38)	167 (33)	0.16
Diastolic blood pressure, mean (SD)	85 (21)	89 (19)	0.11
BMI (kg/m ²), mean (SD)	28 (3.8)	27 (5.1)	0.50
Glucose (mmol/L), mean (SD)	7.6 (2.4)	7.3 (2.8)	0.33
Previous ischemic stroke, n (%)	18 (17%)	52 (23%)	0.22
Previous heart disease, n (%)	14 (13%)	41 (18%)	0.28
Atrial fibrillation, n (%)	14 (13%)	19 (8%)	0.16
NIHSS on admission, median (IQR)	13 (6-18)	3 (2-7)	<0.01

All patients arrived at the emergency department within 6 h after onset of symptoms and received a CT-angiography of the intracranial circle of Willis in the acute phase. NIHSS on admission significantly differed between both groups. BMI body mass index, NIHSS National Institutes of Health Stroke Scale. NIHSS on admission significantly differed between both groups.

Table 2.2 Distribution and location of acute intracranial large vessel occlusion (LVO).

Anatomical location LVO	Number and percentage of total LVO (n=106)
Anterior circulation (n=77)	
Anterior cerebral artery A1 segment, n (%)	0
Intracranial carotid artery, n (%)	23 (22%)
Middle cerebral artery M1 segment, n(%)	38 ((36%)
Middle cerebral artery M2 segment, n(%)	16 (15%)
Posterior circulation (n=29)	
Intracranial vertebral artery, n (%)	9 (9%)
Posterior cerebral artery, P1 segment, n (%)	8 (8%)
Posterior cerebral artery, P2 segment, n (%)	3 (2%)
Basilar artery, n (%)	9 (%)

A1 first segment of anterior cerebral artery, M1 first segment of middle cerebral artery, M2 second segment of middle cerebral artery, P1 first segment of posterior cerebral artery, P2 second segment of the posterior cerebral artery.

Figure 2.2 The association between National Institutes of Health Stroke Scale (NIHSS) and the likelihood of the presence of acute intracranial large vessel occlusion (LVO) confirmed by CTA, in 338 patients with acute ischemic stroke, admitted within 6 h of symptom onset. For each point increase in NIHSS, aOR is 1.23 (95% CI: 1.17-1.29) for having LVO. At NIHSS 12 the chance of having LVO is 0.5 (50%).

Discussion

This study of an unselected non-referred consecutive cohort of AIS patients arriving at the ED within 6 h of symptom onset, showed that almost one out of three have LVO and may be IAT candidate.

Clinical practice

Our study suggests that almost one third of all patients with AIS may be candidates for IAT, since they had LVO in the proximal anterior or posterior circulation and these LVO locations are currently treated in clinical practice in the Netherlands and registered in the MR CLEAN Registry (www.mrclean-trial.org). This is in concordance with data from Copenhagen where 29% had LVO. The population in the latter study was different from ours, since only IVT candidates were studied, which implies a restricted time window and extra criteria for candidates in comparison to IAT candidates.¹³ However, both these estimates are based on a consecutive AIS population presenting at EDs. In two large and well documented studies from Bern, using an overlapping population, 40-61% of patients had LVO.¹² However, these studies included patients who were referred from other centers, which implies selection and at least partly explains the higher proportion

of patients with LVO. This makes it difficult to extrapolate these estimates to other settings.

Our results confirm that NIHSS score at baseline is the most important predictor of LVO, as reported previously.^{12,13,16} We found that a vast majority (91%) of patients with NIHSS ≥ 20 had LVO. This high percentage of occlusion in patients with severe clinical symptoms is in concordance with other studies, where more than 95% of patients with NIHSS ≥ 20 had an occlusion.^{12,13} However, our study also emphasizes that patients with low NIHSS could have LVO.

Limitations

Several limitations may influence the generalizability of our study results. First, our study was a single center study in an academic hospital. However, our center is a centrally located comprehensive stroke center and it has no restrictions on access to the ED. We present a consecutive series of non-referred patients, which we believe is representative for any urban population in a large city like Rotterdam. Second, 107 patients (24%) who presented at the ED within 6 h after symptom onset did not get a CTA in the acute phase. Most of these patients were admitted to our hospital in the first years after implementation of acute CTA in AIS patients, in 2006. In that early period CTA was sometimes performed later or not at all, despite being part of standard protocol. Most importantly there was no selection bias based on stroke severity as there was no difference in baseline NIHSS between the patients with and without CTA. Since NIHSS at baseline is the most important predictor of LVO, there is no reason to assume that the rate of LVO in these patients differs from in those who had CTA in the acute phase and were included in our analysis.

Conclusion

Of all patients with acute ischemic stroke who arrive within 6 h of symptom onset at the emergency department, almost one out of three will have an intracranial large vessel occlusion and may be eligible for intra-arterial treatment.

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Chapter 3

The effect of age on outcome after intra-arterial
treatment in acute ischemic stroke:
a MR CLEAN pretrial study

D Beumer, AD Rozeman, GJ Lycklama à Nijeholt, PA Brouwer, SFM Jenniskens, A Algra,
J Boiten, W Schonewille, RJ van Oostenbrugge, DWJ Dippel, WH van Zwam, and for the
MR CLEAN Pretrial Investigators

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Abstract

Background

In recent randomized controlled trials (RCTs) intra-arterial treatment (IAT) has been proven effective and safe for patients with acute ischemic stroke (AIS). So far, there seemed to be no interaction between older age (>80) and main treatment effect. We studied the association of older age with outcome and adverse events after IAT in a cohort of intra arterially treated patients.

Methods and findings

Data from all AIS patients with proven proximal anterior circulation cerebral artery occlusion who were intra arterially treated between 2002 until the start of the MR CLEAN trial were studied retrospectively. Duration of the procedure, recanalization (Thrombolysis In Cerebral Infarction score (TICI)), early neurological recovery (i.e. decrease on NIHSS of ≥ 8 points) after one week or at discharge, good functional outcome at discharge by modified Rankin Scale ($mRS \leq 2$) and the occurrence of neurological and non-neurological adverse events were assessed and the association with age was investigated. In total 315 patients met our inclusion criteria. Median age was 63 years (range 22-93) and 17 patients (5.4%) were over 80. Age was inversely associated with good functional outcome (adjusted Odds Ratio (aOR) 0.80, 95% CI: 0.66-0.98) for every 10 years increase of age. Age was not associated with longer duration of the procedure, lower recanalization rate or less early neurological recovery. The risk of all adverse events (aOR 1.27; 95% CI: 1.08-1.50) and non-neurological adverse events (aOR 1.34; 95% CI: 1.11-1.61) increased, but that of peri-procedural adverse events (aOR 0.79; 95% CI: 0.66-0.94) decreased with age.

Conclusion

Higher age is inversely associated with good functional outcome after IAT in patients with AIS. However, treatment related adverse events are not related to age. These findings may help decision making when considering treatment of older patients with AIS.

Background

Stroke is one of the leading causes of death and disability. Risk of stroke increases with age.¹ Higher age is often an exclusion criterion in randomized trials especially in those evaluating acute treatment. This applied to the first trials evaluating the effect of intravenous thrombolysis.²

Later studies and meta-analyses, however, demonstrated the effect of intravenous alteplase in older patients.³⁻⁵ Recently, the safety and efficacy of intra-arterial treatment (IAT) was established in several large trials.⁵⁻⁹ Although not all trials included patients aged >80 years,^{6,7} in those intervention trials that included older patients treatment effect seemed similar in the young and the old, but the proportions of older patients were small, suggesting selection bias.^{8,10,11} In older patients, longer procedure time and higher complication rates may be expected, due to technical difficulties such as advanced atherosclerosis and vessel tortuosity. Low quality collateral circulation and brain tissue vulnerability may lead to delayed or diminished neurological recovery.

We studied the association between age and procedure duration, rate of recanalization, occurrence of adverse events, neurological recovery and functional outcome after IAT in patients with acute ischemic stroke (AIS) due to a large vessel occlusion in the anterior circulation. We analysed data from the Multicenter Randomized CLinical trial of Endovascular treatment for Acute ischemic stroke in the Netherlands (MR CLEAN) pretrial registry.

Methods

Patients

In this cohort study, we selected patients with a clinical diagnosis of AIS similar to criteria of MR CLEAN¹² from the prospective patient registries of the participating centers. Approval for this retrospective study was obtained by the central medical ethical committee of the Erasmus University Medical Center Rotterdam and because of the retrospective nature of the study no written informed consent was obliged from each participant. Patients were treated intra-arterially in 16 large stroke hospitals in The Netherlands between October 2002 and start of participation of the hospital in the MR CLEAN trial, between 2010 and 2012. We selected all patients with a neurological deficit on the National Institutes of Health Stroke Scale (NIHSS) of at least two points. Intracranial haemorrhage was ruled out by Computed Tomography (CT) or Magnetic Resonance Imaging (MRI). Intracranial arterial occlusion was confirmed by Computed Tomography Angiography (CTA), Magnetic Resonance Angiography (MRA) or Digital

Subtraction Angiography (DSA) and was located in the distal part of the internal carotid artery, the middle cerebral artery (M1 and M2 segment), or the anterior cerebral artery (A1 segment). Intra-arterial treatment had to be started within 6 h from onset of symptoms and patients had to be 18 years or older. There was no upper age limit. Patients were excluded if systolic blood pressure was > 185 mmHg or diastolic blood pressure was >110 mmHg, if blood glucose level was <2.7 or >22.2 mmol/l, if intravenous treatment with alteplase was given in a dose exceeding 0.9 mg/kg or 90 mg, or if intravenous alteplase was given despite contraindications such as major surgery, gastro-intestinal bleeding or urinary tract bleeding within the previous 2 weeks, or arterial puncture at a non-compressible site within the previous 7 days. Specific exclusion criteria applied for patients treated mechanically or with intra-arterial thrombolysis. Patients treated with mechanical devices were excluded when there was laboratory evidence of coagulation abnormalities (platelet count <40*10⁹/l, APTT>50 s or INR>3.0). Patients treated with intra-arterial thrombolysis were excluded when the platelet count was <90 * 10⁹/l, APTT>50 s, or INR>1.7.

We obtained all clinical and radiological data of the patients who were prospectively registered in the participating centres and all patient data were anonymized prior to analysis. Missing values of NIHSS were reconstructed with the help of a validated algorithm.¹³

Intervention

Intra-arterial treatment consisted of arterial catheterization with a microcatheter to the level of occlusion. At the level of the occlusion the interventionist could decide to deliver a thrombolytic agent, perform mechanical thrombectomy or both. This choice was left to the discretion of the interventionist. Pre- and post-intervention angiograms were made to assess location and grade of occlusion and final recanalization.

Outcomes

We tabulated baseline risk factors and results by tertiles of age.

Functional outcome was assessed by means of the modified Rankin Scale (mRS) at discharge. Good functional outcome was defined as a mRS score of 0, 1 or 2. Neurological status after the intervention was evaluated with the NIHSS, assessed at one week after the procedure (or at discharge in case discharge was within the first week). Early neurological recovery was defined as a decrease on the NIHSS of 8 points or more after one week or at discharge compared with baseline NIHSS.

The duration of the procedure was determined by the time interval between the first and last angiographic series plus 5 min. Occlusion status was assessed with the TIC1

score, at the start and at the end of the procedure. Recanalization was defined as a TICl score of 2b or 3 at the end of the procedure. Digital subtraction angiography images were assessed by one of three experienced neuroradiologists (PB, GL, SJ). They were blinded for clinical data of the patient, and did not assess angiograms from their own centre.

Adverse events

We defined symptomatic intracerebral haemorrhage (SICH) as intraparenchymal blood on cranial CT being compatible with neurological deterioration. Symptomatic haemorrhagic transformation was defined as CT detected haemorrhagic transformation of the acute infarct accompanied by neurological deterioration. Recurrent ischemic stroke, stuttering stroke, brain herniation and craniotomy accompanied with neurological deterioration were all clustered as progression of ischemic stroke.

Adverse events were categorized as neurological adverse events, neurological serious adverse events, nonneurological adverse events and peri-procedural adverse events. Neurological adverse events were any symptomatic intracerebral haemorrhage, haemorrhagic transformation, progression of ischemic stroke, intracranial haemorrhage and transient neurological dysfunction including seizures. Neurological serious adverse events were symptomatic intracranial haemorrhage, haemorrhagic transformation of the infarct and progression of ischemic stroke with an increase on the NIHSS of 4 points or more. Nonneurological adverse events, without neurological sequelae, were pneumonia, urinary tract infections, cardiac rhythm disturbances, and other complications. Other complications included pulmonary embolism, cerebral venous thrombosis, bacteraemia, use of antibiotics without a confirmed infection, oral mycosis, delirium, acute kidney failure and falls. Peri-procedural adverse events included development of distal micro-emboli, technical problems including unfolding of stent retriever, iatrogenic damage of arterial vessel wall, groin hematoma and peri-procedural seizures.

Statistical analysis

We analysed the association of age with good functional outcome (mRS 0-2) with regression models expressed as odds Ratio (OR). Multiple linear regression was used to determine the association of age with the duration of the procedure and the neurological outcome (NIHSS) after the procedure. We analyzed the association of age with recanalization and occurrence of adverse events, with logistic regression models. In all regression models, age was a continuous variable, and effect parameters were expressed per 10 years of age. Precision of effect estimates was described by 95%

confidence intervals. We always adjusted for sex, onset to treatment time, stroke severity at baseline (NIHSS), use of a retrievable stent and presence of intracranial carotid T occlusions. Values missing at random were imputed with their mean or modus. Statistical analyses were carried out with Stata statistical software (release 12.0 College Station, Texas).

Results

During the study period 529 patients with ischemic stroke were treated with IAT in the participating centers. Of these, 160 had a posterior circulation stroke and were not included in this study. From the remaining 369 patients, we excluded 19 (5.1%) who underwent IAT more than 6 h after symptom onset, 15 (4.1%) because of AIS secondary to a surgical procedure, 1 patient (0.3%) in whom carotid artery dissection was the cause and 1 patient (0.3%) who had a distal anterior circulation cerebral artery occlusion (M3 segment). We also excluded 2 patients (0.5%) because of age <18 years, 4 patients (1.0%) because systolic blood pressure >185 mmHg or diastolic blood pressure >110 mmHg, 11 patients (3.0%) because of coagulation disturbances and 1 patient (0.3%) because of pre-treatment glucose level >22.2 mmol/l.

As a result 315 patients were included. Median age of the included patients was 63 years (range 22–93) and 17 patients (5%) were older than 80. Median NIHSS was 16 (IQR 12–18) and 245 patients (78%) were treated with intravenous alteplase prior to IAT (Table 3.1).

Table 3.1 Baseline characteristics of the included patients

	Overall 22–93 years	Tertile 1 22–55 years	Tertile 2 56–70 year	Tertile 3 71–93 years
Number of patients	315	106	113	96
Age, median (IQR)	63 (52–72)	48 (40–52)	64 (60–68)	77 (73–80)
Male sex, n (%)	168 (53 %)	52 (49 %)	75 (66 %)	41 (43 %)
Systolic blood pressure, mean (SD)	146 (23)	138 (21)	149 (24)	152 (20)
Diastolic blood pressure, mean (SD)	82 (16)	78 (16)	85 (15)	84 (17)
Stroke severity at admission (NIHSS) mean (SD) ^a	16 (6.0)	15 (5.0)	16 (5.0)	16 (7.0)
Prior treatment with intravenous rtPA, n (%) ^b	245 (78 %)	77 (73 %)	91 (81 %)	75 (80 %)
Time from onset symptoms to intra-arterial treatment (minutes), mean (SD) ^c	93 (58)	96 (70)	87 (67)	77 (53)
Use of stent, n (%) ^d	132 (42 %)	41 (39 %)	52 (46 %)	39 (41 %)
Carotid T top occlusion, n (%) ^e	25 (8.0 %)	11 (10 %)	11 (10 %)	3 (3.0 %)

SD standard deviation, IQR interquartile range, ER emergency room. ^a65 unknown (21%); ^b13 unknown (4.1%); ^c177 unknown (56%); ^d4 unknown (0.6%); ^e2 unknown (0.6%)

IAT consisted of stent thrombectomy in 132 (42%). The median duration of the procedure was 116 min (IQR 80-153). At the end of the procedure a TIC1 2b or 3 was reached in 119 patients (43%) (see Table 3.2). SICH occurred in 23 patients (7.0%) and prevalence of SICH was highest in the third age tertile (10/96, 10%). Mortality was higher in older patients, 22% in the third tertile versus 9% in the first tertile.

Table 3.2 Clinical and radiological outcomes in patients with IAT for acute ischemic stroke caused by proximal arterial intracranial occlusion of the anterior circulation by age

	Overall 22–93 years	Tertile 1 22–55 years	Tertile 2 56–70 year	Tertile 3 71–93 years	P for trend
N patients	315	106	113	96	
Procedural duration in minutes, median (IQR)	116 (80–153)	125 (81–160)	110 (78–143)	116 (82–158)	0.19
Recanalization (TICI 2b and TICI 3)	119 (43 %)	41 (34 %)	45 (38 %)	33 (28 %)	0.46
TICI 0, <i>n</i> (%)	38 (14 %)	12 (12 %)	12 (12 %)	14 (17 %)	
TICI 1, <i>n</i> (%)	18 (6.0 %)	10 (10 %)	5 (5.0 %)	3 (4.0 %)	
TICI 2a, <i>n</i> (%)	103 (37 %)	36 (36 %)	35 (36 %)	32 (39 %)	
TICI 2b, <i>n</i> (%)	36 (13 %)	13 (13 %)	17 (18 %)	6 (7.0 %)	
TICI 3, <i>n</i> (%)	83 (30 %)	28 (28 %)	28 (29 %)	27 (33 %)	
NIHSS after IAT, mean (SD)	13 (12)	12 (10)	13 (11)	15 (13)	0.14
Neurological recovery (decrease in NIHSS of 8 points or more), <i>n</i> (%)	133 (42 %)	47 (44 %)	49 (43 %)	37 (39 %)	
Functional outcome, mRS, <i>n</i> (%)					0.03
mRS 0–1, <i>n</i> (%)	37 (12 %)	15 (14 %)	9 (8 %)	13 (14 %)	
mRS 0–2, <i>n</i> (%)	78 (25 %)	29 (27 %)	27 (24 %)	22 (23 %)	
mRS 0–3, <i>n</i> (%)	132 (42 %)	46 (43 %)	49 (43 %)	37 (39 %)	
mRS 0–4, <i>n</i> (%)	222 (70 %)	80 (75 %)	82 (73 %)	60 (63 %)	
mRS 0–5, <i>n</i> (%)	261 (83 %)	96 (91 %)	92 (81 %)	73 (76 %)	
Death, <i>n</i> (%)	51 (16 %)	10 (9 %)	20 (18 %)	21 (22 %)	0.01
All adverse events, <i>n</i> (%)	177 (56 %)	46 (43 %)	71 (63 %)	60 (63 %)	0.004
Serious adverse events, <i>n</i> (%)	47 (15 %)	13 (12 %)	18 (16 %)	16 (17 %)	0.11
Symptomatic intracranial hemorrhage, <i>n</i> (%)	23 (7.0 %)	5 (5.0 %)	8 (7.0 %)	10 (10 %)	
Hemorrhagic transformation infarct, <i>n</i> (%)	6 (2.0 %)	2 (2.0 %)	4 (4.0 %)	0 (0.0 %)	
Progression of ischemic stroke, <i>n</i> (%)	32 (10 %)	8 (8.0 %)	13 (12 %)	11 (12 %)	
Neurological adverse events, <i>n</i> (%)	119 (38 %)	38 (36 %)	48 (42 %)	33 (34 %)	0.60
Asymptomatic intracranial hemorrhage	22 (7 %)	2 (2.0 %)	15 (13 %)	5 (5.0 %)	
hemorrhage, <i>n</i> (%)					
Seizures, <i>n</i> (%)	16 (5.0 %)	4 (4.0 %)	4 (4.0 %)	8 (8.0 %)	
Non-neurological adverse events, <i>n</i> (%)	101 (32 %)	20 (19 %)	40 (35 %)	41 (43 %)	0.002
Pneumonia, <i>n</i> (%)	41 (13 %)	9 (8.0 %)	16 (14 %)	16 (17 %)	
Urinary tract infection, <i>n</i> (%)	18 (6.0 %)	5 (5.0 %)	5 (4.0 %)	8 (8.0 %)	
Cardiac arrhythmias, <i>n</i> (%)	35 (11 %)	3 (3.0 %)	17 (15 %)	15 (16 %)	
Other, <i>n</i> (%)	29 (9.0 %)	8 (8.0 %)	9 (8.0 %)	12 (13 %)	

We found a significant inverse association between age and good functional outcome (mRS 0-2) (aOR 0.80; 95% CI: 0.66-0.98) for every 10 years increase of age. Furthermore, we found a significant association between age and the occurrence of all adverse events (aOR 1.27, 95% CI: 1.08-1.50) as well as the occurrence of non-neurological adverse

events (aOR 1.34, 95% CI: 1.11-1.61) (Table 3.3). Age was significantly associated with less peri-procedural adverse events (aOR 0.79, 95% CI: 0.66-0.94) (Table 3.4). We found no association between age and neurological recovery after IAT (aOR 0.88, 95% CI: 0.75-1.04). No associations were observed between age and duration of the procedure (regression coefficient -2.96 95% CI: -7.35-1.44), recanalization (aOR 0.94, 95% CI: 0.79-1.11), neurological serious adverse events (aOR 1.22, 95% CI: 0.96-1.56) and neurological adverse events (aOR 1.05, 95% CI: 0.89-1.24).

Table 3.3 Age in association with clinical neurological and radiological outcomes. Effect parameters are expressed per 10 years of age

	Association	Unadjusted	Sex adjusted	Fully adjusted
Intervention				
Duration of procedure, minutes	BC	-2.80 [-7.10 to 1.45]	-2.80 [-7.10 to 1.45]	-2.96 [-7.35 to 1.44]
Recanalization (TICI 2b-3)	OR	0.94 [0.80 to 1.11]	0.94 [0.8. to 1.11]	0.94 [0.79 to 1.11]
Clinical outcome				
Neurological recovery (decrease on NIHSS > 7 points)	OR	0.92 [0.79 to 1.08]	0.92 [0.79 to 1.08]	0.88 [0.75 to 1.04]
Functional outcome, mRS 0-2	OR	0.85 [0.71 to 1.01]	0.85 [0.71 to 1.01]	0.80 [0.66 to 0.98]
Safety outcome				
Peri-procedural adverse events	OR	0.79 [0.67 to 0.93]	0.79 [0.67 to 0.93]	0.79 [0.66 to 0.94]
All adverse events	OR	1.27 [1.08 to 1.49]	1.27 [1.08 to 1.49]	1.27 [1.08 to 1.50]
Neurological serious adverse events	OR	1.04 [0.89 to 1.22]	1.04 [0.89 to 1.22]	1.05 [0.89 to 1.24]
Neurological adverse events	OR	1.04 [0.89 to 1.22]	1.04 [0.89 to 1.22]	1.05 [0.89 to 1.24]
Non-neurological adverse events	OR	1.37 [1.14 to 1.64]	1.37 [1.14 to 1.64]	1.34 [1.11 to 1.61]

Discussion

In the present study we show that the likelihood of good functional outcome after IAT was inversely associated with age, whereas we did not find an increased risk for neurological (serious) adverse events after IAT in older patients although the likelihood of developing non-neurological adverse events increased with age. Interestingly, the risk of developing peri-procedural adverse events decreased with increasing age.

Our results are in line with recent studies that also showed lower rates of good clinical outcome in elderly stroke patients treated with IAT. These retrospective nonrandomized studies do not allow conclusions about the treatment effect of IAT in older aged

patients. Therefore results of randomized controlled trials are needed. Several large randomized controlled trials have investigated the effect of IAT in AIS, but only three of these had no upper age limit.^{10,14,15} In two of those no effect modification by age was present,^{8,10} but a more refined analysis on age has not been performed so far. Selection bias, by including only the relatively healthier older patients in the trials, cannot be excluded.

Table 3.4 Clinical and radiological outcome in patients younger than 80 years and patients 80 years or over

	<80 years	≥80 years
N patients	298	17
Procedural duration in minutes, median (IQR)	121 (55)	108 (54)
Recanalization (TICI 2b and TICI 3)	113 (43%)	6 (46%)
Neurological recovery (decrease in NIHSS of 8 points or more), n (%)	9 (53%)	8 (47%)
Good functional outcome at discharge, mRS 0–2, n (%)	75 (25%)	3 (18%)
Death, n (%)	47 (16%)	4 (26%)
All adverse events, n (%)	164 (55%)	13 (76%)
Non-neurological adverse events, n (%)	91 (31%)*	10 (59%)*
Neurological adverse events, n (%)	113 (38%)	6 (35%)
Neurological serious adverse events, n (%)	44 (15%)	3 (18%)

* $p=0.02$

Our study has several limitations. First, although patients were prospectively registered, all patient data had to be assessed retrospectively from the hospital records. However, we are confident that all intra-arterially treated patients are included and that there are no missing data on important medical information as the occurrence of adverse events, because all centers kept prospective registries of intra-arterially treated patients and our research team had access to all data. Second, we did not systematically register comorbidity, such as previous myocardial infarction and previous ischemic stroke. However, it is well known that comorbidity increases with age and this may explain some of the excess mortality and poor outcome. Third, the relatively low percentage of recanalization might be explained by the relative low percentage of treatments with latest generation thrombectomy devices, as these devices only entered the market halfway the inclusion period.¹⁶ These so called stent retrievers have a proven better recanalization success rate than the first generation devices.^{11,17} Fourth, the small percentage of patients above 80 years old (5%) in this cohort suggests a strong selection bias. This might explain the lower peri-procedural adverse event rate in the older patients: exclusion from treatment of patients with hostile vessels is more likely when patients are older. Fifth, the lack of a reference population to compare with and to know if there was a selection bias for the higher aged subjects who underwent IAT. However, the goal of this study was to describe a relation between age and outcome in intra-arterially treated patients to assess whether an upper age limit in randomized controlled

trials is indicated. To have the best comparison between age and treatment effect in age in IAT we need the results of randomized controlled trials.

Our study has several strengths: First, we could make use of prospective registries of the participating hospitals in which all IAT treated patients were documented. As such, all patients treated in these centers are included in this study. Second, all stroke intervention centers in the Netherlands participated in this study what makes it very unlikely that more than just a few patients were not registered and included in this study. And thirdly, all participating centers were comprehensive stroke services with a central function for acute stroke treatment for regional hospitals.

Conclusion

In summary, we confirm that older age is inversely associated with good functional outcome after IAT in patients with AIS. Furthermore age is associated with increased non-neurological adverse events. Our results, however, do not confirm an increased risk of treatment related events nor an increase of neurological adverse events. This might explain the findings in recent RCTs that older age does not interact with treatment effect of IAT. Knowledge about the effect of age on clinical outcome, procedure related features and adverse events of IAT may enhance proper decision making in treatment of older patients with AIS.

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Chapter 4

The relationship between interventionists' experience and clinical and radiological outcome in intra-arterial treatment for acute ischemic stroke. A MR CLEAN pretrial survey

D Beumer, TH van Boxtel, S Schipperen, WH van Zwam, GJ Lycklama à Nijeholt, PA Brouwer, SFM Jenniskens, WJ Schonewille, JA Vos, A van der Lugt, Y Roos, CB Majoie, RJ van Oostenbrugge, DWJ Dippel, The MR CLEAN Pretrial Investigators

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Abstract

Background

Intra-arterial treatment in acute ischemic stroke is safe and effective as recently shown in several randomized clinical trials. The level of experience of the interventionist performing the IAT procedure has not been studied. The present study investigates effects of interventionists' experience on technical aspects of the procedure and clinical outcome of the patient.

Methods

In this study of 313 patients with a proximal intracranial arterial anterior circulation occlusion, treated in the Netherlands from 2002 until participation in the Multicenter Randomized Clinical trial of Endovascular treatment for acute ischemic stroke (MR CLEAN), data were collected retrospectively. The association of the senior interventionists' experience with duration of the procedure, adverse events, recanalization, neurological outcome, and functional outcome at discharge was analyzed. Multiple regression models adjusted for age, sex, stroke severity, carotid terminus occlusion, use of a retrievable stent and onset to door time were used.

Results

No association between interventionists' experience and recanalization, neurological outcome, or functional outcome was observed in a strict selection of patients. This strict selection include a start of intra-arterial treatment within 6 h, no coagulation disturbances, systolic blood pressure ≤ 185 mmHg and diastolic blood pressure ≤ 110 mmHg, blood glucose level between 2.7 and 22.2 mmol/L and the existence of a proximal intracranial occlusion. However, significant shorter procedure times were found with more experienced interventionists' [adjusted beta coefficient -0.67 , 95% CI: -1.24 to -0.11], when using less strict inclusion criteria.

Conclusion

No significant relation between the level of experience and either serious neurologic adverse events or poor outcomes was observed in this study of treatments by interventionists with experience of ≤ 50 previous procedures. We need further research to explore the relation of much higher levels of interventionists' and team experience with procedure times, results and patient outcomes.

Introduction

Several large randomized clinical trials have proven intra-arterial treatment (IAT) acute ischemic stroke (AIS) to be effective and safe.¹⁻⁶ The evolution of thrombectomy devices for IAT has improved efficacy.⁷ The level of experience of the interventionist performing the IAT procedure has not been studied. The present study investigates the effect of interventionists' experience on duration of the intra-arterial procedure, recanalization, clinical outcomes, and adverse events.

Materials and methods

Patients

Patient data were retrieved from the MR CLEAN pretrial registry. All patients with acute ischemic stroke who received IAT in 16 large stroke centers in the Netherlands were included. The registry started in October 2002 and continued until a center started participation in the MR CLEAN trial, which was in 2010 or 2011. For the primary analysis in- and exclusion criteria of the MR CLEAN trial were used. (Table 4.1) A second analysis of high risk patients with a less confined protocol was also performed.

Study procedures and clinical definitions

Data were retrospectively obtained by trained medical researchers, who passed a medical PhD program. Definitions of serious adverse events were applied retrospectively containing clinical deterioration in accordance with radiological features as intracranial hemorrhage and hemorrhagic transformation of the infarcted zone. NIHSS at baseline and follow-up was reconstructed with a modified algorithm.⁸ A total of 80 interventionists have been treating the included patients.

Intervention

Patients were treated intra-arterially with a thrombolytic agent, a retrievable stent, another mechanical device or combinations of these methods. Choice of method and device type was at the discretion of the treating interventionist. Pre- and post-intervention angiograms were made available to assess location and grade of thromboembolic occlusion. Recanalization was defined as a Thrombolysis In Cerebral Infarction (TICI) score of 2b or 3.⁹

Table 4.1 Inclusion and exclusion criteria of study population.

Inclusion criteria
<ul style="list-style-type: none"> • Age of 18 years or older. <ul style="list-style-type: none"> • A neurological deficit on the NIHSS scale of at least 2 points. • Intracranial hemorrhage ruled out by CT or MRI. • Proximal occlusions could be located in the supraclinoid intracranial segment of the internal carotid artery, the M1 or M2 segments of the middle cerebral artery, or the A1 or A2 segment of the anterior cerebral artery confirmed with CTA, MRA or DSA. • Intra-arterial treatment started within 6 h of symptom onset.
General exclusion criteria
<ul style="list-style-type: none"> • A systolic blood pressure >185 mmHg or a diastolic blood pressure >110 mmHg. • Venous blood glucose level <2.7 mmol/L or >22.2 mmol/L. • Intravenous alteplase in a dose exceeding 0.9 mg/kg or 90 mg in total. • Pre-treatment with intravenous alteplase despite known contraindications (major surgery, gastrointestinal bleeding, urinary tract bleeding within the previous 2 weeks, arterial puncture at a non-compressible site within the previous 7 days). • Cerebral infarction in the distribution of the relevant occluded artery in the previous 6 weeks.
Specific exclusion criteria for intended mechanical thrombectomy
<ul style="list-style-type: none"> • Platelet count <40 × 10⁹/L. • Activated partial thromboplastin time (APTT) >50 s. • International Normalized Ratio (INR) >3.0.
Specific exclusion criteria for intended intra-arterial thrombolysis
<ul style="list-style-type: none"> • A history of cerebral hemorrhage. • Severe head injury (contusion) in the previous 4 weeks. • Clinical laboratory evidence of coagulation abnormalities (that is, platelet count <90 × 10⁹/L, APTT N 50 s or INR N 1.7). • Treatment with oral thrombin or factor X antagonists

Outcomes

Duration of procedure was defined as the time in minutes between the first and last angiographic runs added with 5 min to account for average time between groin puncture and first image acquisition. All angiographic runs were assessed by one of three experienced observers. Observers were blinded for patient data and the participating institution. Neurological outcome after the procedure was assessed within one week after IAT by means of the national institutes of health stroke scale (NIHSS). Functional outcome at discharge was assessed with the modified Rankin Scale (mRS).¹⁰ Serious neurologic adverse events included: symptomatic intracranial hemorrhage (SICH), hemorrhagic transformation of the infarct, and progression of ischemic stroke. Symptomatic intracranial hemorrhage was defined as parenchymal hemorrhage at any site in the brain on the CT-scan, being compatible with documented neurological deterioration of at least 4 points on the NIHSS. Neurologic adverse events included: symptomatic intracranial hemorrhage (SICH), hemorrhagic transformation of the infarct, and progression of ischemic stroke without neurological deterioration. Progression of ischemic stroke denoted recurrent ischemic stroke, stuttering stroke, brain herniation

and craniotomy. Non-neurological adverse events included pneumonia, urinary tract infections, cardiac rhythm disturbances, pulmonary embolism, cerebral venous thrombosis, bacteremia, antibiotics usage without an infection cause, oral mycosis, delirium, acute kidney failure, and iatrogenic falling of the patient.

Statistical analysis

We related interventionists' experience with the occurrence of (serious) adverse events and with recanalization (i.e. TICl 2b or 3) in logistic regression models, and expressed the association as adjusted odds ratios (aOR) with 95% confidence interval. The association of functional outcome on the modified Rankin Scale (mRS) with experience was estimated with ordered logistic regression (shift analysis). The association of interventionists' experience with duration of the procedure and with neurological outcome (NIHSS) was estimated with linear regression models. In all models, adjustments were made for age and sex, and full adjustments were made for age, sex, occlusion site, stroke severity on admission, use of a retrievable stent, and time since onset of symptoms to arrival at the emergency department. Due to the retrospective nature of the study, some data points were not obtainable. These variables included; NIHSS at the emergency department (26 missing values), time of onset of symptoms to arrival at emergency department (77 missing values), prior treatment with intravenous rtPA (2 missing values), presence of carotid terminus occlusion (1 missing value), use of a retrievable stent (1 missing value). These values were adjusted with a mean or mode, where applicable. Statistical analyses were performed with Stata statistical software, release 12.0. (College Station, Texas).

Sensitivity analysis

In order to investigate the association between experience and clinical and radiological outcome in a less limited protocolled setting, a second selection of high risk patients was made. These patients had a time of symptom onset till start of intra-arterial treatment exceeding 6 h, coagulation disturbances (i.e. thrombocyte count <40 , activated partial thromboplastine time (APTT) >50 s, INR >3.0), hypertension (systolic blood pressure >185 mmHg, diastolic blood pressure >110 mmHg), blood glucose level <2.7 mmol/L or >22.2 mmol/L and the presence of an M3 segment occlusion.

Ethics

The Medical Ethical Committee of the Erasmus University Medical Center Rotterdam gave permission to perform this study without obtaining written informed consent, due to the retrospective nature of this study. All patient data were analyzed anonymously.

Results

A total of 527 patients with acute ischemic stroke treated with IAT were registered. We excluded 214 patients (Figure 4.1).

Figure 4.1 Inclusion scheme of the patient selection.

The mean age was 61 years ($SD \pm 14$), 167 patients (53%) were men and mean baseline NIHSS was 16 ($SD \pm 5.8$). We categorized the level of experience in tertiles, as 'low' (0-5 procedures), 'minimal' (6-15 procedures), and 'moderate' (>16 procedures). Baseline prognostic factors predicting a good functional outcome by experience level category were similar. Patients in the group with low experience operators had shorter

onset to door times ($p=0.20$), and patients in the minimal and moderate experience level groups were more often treated with retrievable stents ($p\leq 0.05$) (Table 4.2).

The median experience of the senior interventionist in each patient was 11 procedures (IQR 4–20). The smallest number of performed procedures was one and the largest number of performed procedures was 49.

Median duration of the procedure was 116 min (IQR 80–154) (Table 4.2). A trend was seen for the association of experience with the duration of the procedure in a univariable analysis [adjusted beta coefficient -0.71, 95% CI: -1.25 to -0.17] but after full adjustment the association was no longer statistically significant (Table 4.3).

Table 4.2 Baseline characteristics of study population.

	Overall	Group 1	Group 2	Group 3
Experience level		Low	Minimal	Moderate
N of procedures	0–49	0–5	6–15	16–49
N (patients)	313	103	103	107
Age (years), mean (SD)	61 (14)	61 (16)	62 (15)	62 (13)
Men, n (%)	167 (53%)	51 (50%)	59 (57%)	57 (53%)
Systolic blood pressure, mean (SD)	145 (23)	148 (23)	142 (22)	146 (22)
Diastolic blood pressure, mean (SD)	82 (16)	82 (15)	81 (16)	84 (17)
NIH stroke scale score, mean (SD) ^a	16 (5.8)	16 (6.0)	16 (4.7)	15 (6.4)
Prior treatment with intravenous rtPA, n (%) ^b	244 (78%)	79 (78%)	80 (78%)	83 (78%)
Onset to door time (minutes), mean (SD) ^c	93 (58)	77 (42)	93 (73)	92 (75)
Use of retrievable stent, n (%) ^d	131 (42%)	18 (18%)	48 (47%)	65 (61%)
Use of other mechanical device, n (%)	82 (26%)	24 (23%)	29 (28%)	29 (27%)
Use of intra-arterial urokinase, n (%)	145 (46%)	46 (45%)	49 (48%)	50 (47%)
Use of intra-arterial alteplase, n (%)	57 (18%)	29 (28%)	21 (20%)	7 (7%)
Carotid T/L occlusion, n (%) ^e	24 (7.7%)	6 (5.8%)	9 (8.7%)	9 (8.4%)

^a 26 Unknown (8.3%); ^b 2 Unknown (0.6%); ^c 77 Unknown (25%); ^d 1 Unknown (0.3%); ^e 1 Unknown (0.3%).

Recanalization was reached in 119 of 313 patients (43%). We did not observe an association between experience level and recanalization [aOR 0.99, 95% CI: 0.97 to 1.02] (Table 4.3). We found no significant association between the experience level and functional outcome after IAT [adjusted beta coefficient -0.07, 95% CI: -0.18 to 0.05]. No association was observed between interventionists' experience and functional outcome at discharge [adjusted beta coefficient 0.99, 95% CI: 0.97 to 1.01] (Table 4.3).

In total we observed 46 patients (15%) with serious neurological adverse events. Patients treated by interventionists with low experience had the highest percentage of serious neurological adverse events, 18% (19/103 patients) (Table 5.4). The frequency of symptomatic intracranial hemorrhage was lower when interventionists were more experienced (Table 4.4). The association between experience and occurrence of serious neurological adverse events however, was not statistically significant [aOR 0.99, 95% CI: 0.96 to 1.02].

Table 4.3 Association of experience with clinical and radiological outcomes.

	Unadjusted	Age-sex adjusted	Fully adjusted
Duration of procedure	- 0.71 (- 1.25 to - 0.17)*	- 0.70 (- 1.24 to - 0.16)*	- 0.55 (- 1.14 to 0.04)
Recanalization (TICI 2b-3)	1.00 (0.98 to 1.02)	1.00 (0.98 to 1.02)	0.99 (0.97 to 1.02)
Neurological outcome (NIHSS)	- 0.10 (- 0.21 to 0.02)	- 0.09 (- 0.21 to 0.02)	- 0.07 (- 0.18 to 0.05)
Good functional outcome (mRS)	0.99 (0.97 to 1.00)	0.99 (0.97 to 1.00)	0.99 (0.97 to 1.01)
All adverse events	1.00 (0.98 to 1.02)	1.00 (0.98 to 1.02)	1.00 (0.98 to 1.02)
All serious neurological adverse events	0.99 (0.96 to 1.02)	0.99 (0.96 to 1.02)	0.99 (0.96 to 1.02)
All neurological adverse events	0.99 (0.97 to 1.01)	0.99 (0.97 to 1.01)	0.99 (0.97 to 1.01)
All non-neurological adverse events	1.00 (0.97 to 1.02)	1.00 (0.98 to 1.02)	1.01 (0.99 to 1.03)

Associations are expressed as odds ratios (OR), common OR (cOR) or Beta coefficients (BC) where applicable, with corresponding 95% confidence intervals. * Statistically significant (p < 0.05) associations.

Table 4.4 Outcomes in patients with intra-arterial treatment for acute ischemic stroke caused by proximal anterior intracranial occlusion (n=313), by level of experience in tertiles.

	Overall	Group 1	Group 2	Group 3
Experience level				
N (procedures)	0-49	Low	Minimal	Moderate
N (patients)	313	0-5 103	6-15 103	16-49 107
Duration of procedure				
Procedural duration in minutes, median (IQR)	116 (80-154)	125 (90-164)	110 (73-152)	116 (75-144)
Radiological outcome				
Recanalization (TICI 2b and TICI 3)	119 (43%)	34 (41%)	46 (50%)	39 (39%)
Neurological outcome				
NIHSS median (IQR)	10 (5-16)	12 (6-19)	10 (4-15)	11 (5-16)
Functional outcome				
mRS 0-1, n (%)	37 (12%)	16 (16%)	11 (11%)	10 (9%)
mRS 0-2, n (%)	78 (25%)	27 (26%)	23 (22%)	28 (26%)
mRS 0-3, n (%)	131 (42%)	39 (38%)	44 (43%)	48 (45%)
mRS 0-4, n (%)	221 (71%)	63 (61%)	77 (75%)	81 (76%)
mRS 0-5, n (%)	260 (83%)	81 (79%)	89 (86%)	90 (84%)
mRS 6, n (%)	50 (16%)	21 (21%)	14 (14%)	15 (14%)
Safety outcome				
All adverse events, n (%)	176 (56%)	59 (57%)	55 (53%)	62 (58%)
Neurological serious adverse events, n (%)	46 (15%)	19 (18%)	12 (12%)	15 (14%)
Symptomatic intracranial hemorrhage, n (%)	22 (7%)	9 (9%)	8 (8%)	5 (5%)
Neurological adverse events, n (%)	118 (38%)	41 (40%)	37 (36%)	40 (37%)
Non-neurological adverse events, n (%)	121 (39%)	31 (30%)	35 (34%)	35 (33%)

TICI= thrombolysis in cerebral infarction score, NIHSS= National Institutes of health Stroke Scale, mRS = modified Rankin Scale.

Sensitivity analysis

In the sensitivity analysis, which included high risk patients, we analyzed 350 patients with acute ischemic stroke, who received IAT outside our MR CLEAN criteria.

In this larger group of patients, we observed a significant association between experience level and the duration of the procedure in a univariable [adjusted beta coefficient -0.82, 95% CI: -1.34 to -0.29] as well as multivariable analysis [adjusted beta coefficient -0.67, 95% CI: -1.24 to -0.11], with shorter procedure times by more experienced interventionists. No other significant associations were found. (Table 45.5).

Table 4.5 Association of experience with clinical and radiological outcomes in a less limited protocol setting with high risk patients (N=350).

	Unadjusted	Fully adjusted
Duration of procedure	-0.82 (-1.34 to -0.29)*	-0.67 (-1.24 to -0.11)*
Recanalization (TICI 2b-3)	1.00 (0.98 to 1.02)	1.00 (0.98 to 1.03)
Neurological outcome (NIHSS)	-0.08 (-0.19 to 0.03)	-0.10 (-0.24 to 0.05)
Good functional outcome (mRS)	0.98 (0.97 to 1.00)	0.98 (0.96 to 1.00)
All significant neurological adverse events	0.98 (0.95 to 1.00)	0.98 (95% (0.95 to 1.01)

Discussion

In this study no significant effect of interventionists' experience on the duration of the procedure, occurrence of serious adverse events, neurological outcome and functional outcome could be found, when strictly using the 'MR CLEAN criteria'. However in a larger cohort with less strict inclusion criteria, we observed a statistically significant association between interventionists' experience and the duration of the procedure as a higher level of experience was associated with shorter duration of the procedure.

To our knowledge, this is the first large study to examine interventionists' experience in intra-arterial acute stroke treatment. Recently it was shown that the presence of a learning curve in IAT with mechanical thrombectomy with the solitaire stent was significantly associated with operator experience and CT to recanalization times. However, measurements on clinical outcome were not reported.¹¹ A study on operator experience in carotid artery stenting suggested that operators who performed 6 carotid artery stenting procedures annually had better outcomes compared to colleagues who performed these procedures less often. An association with lifetime experience was not observed.¹²

Our study has limitations. First, the patient data was collected retrospectively from the medical records in different hospitals. We tried to solve this, by applying strict definitions of adverse events and outcomes.

We used the number of acute stroke procedures performed by the interventionist. All procedures in our registry were performed by interventionists with experience in performing endovascular procedures. However, we did not take into account intra- or extracranial endovascular procedures for other indications. This might have led to underestimation of observed experience. We focused on the experience of the senior interventionist, because we considered this parameter most appropriate as it bears directly on the intervention, because the senior interventionist decides how the procedure was executed by giving instructions to the junior interventionist. However, annual caseload per center might be an important predictor of outcome as well.^{13,14} This deserves further analysis.

In our study, the experience indicator ranged from 1 to 49 procedures. We consider it not unlikely that patients treated by teams with much larger experience may do better on our outcome measures.

Second, the power of this observational study was limited. We cannot for example exclude the existence of a 1% relative increase in likelihood of good outcome with every point experience in this cohort. This would accumulate to large outcome differences between patients treated by the very experienced and patients treated by the less experienced.

However, within the range of levels of experience we were testing in our study, the effect would be limited and further research to the effect of operator experience has to be fulfilled in larger patients groups with interventionists who have treated a larger number of patients.

In our analysis we adjusted for several factors predicting a good functional outcome. This may have led to over-adjustment because patient selection could have been influenced by experience itself. However, in this particular study, adjustment did not lead to gross changes in the observed associations.

Conclusions

No significant relation between the level of experience and either serious neurologic adverse events or poor outcomes was observed in this study of treatments by interventionists with experience of <50 previous procedures. We need further research to explore the relation of much higher levels of interventionists' and team experience with procedure times, results and patient outcomes.

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Chapter 5

MR CLEAN, a multicenter randomized clinical trial of
endovascular treatment for acute ischemic stroke in the
Netherlands: study protocol for a randomized
controlled trial

PSS Fransen, D Beumer, OA Berkhemer, LA van den Berg, H Lingsma, A van der Lugt,
WH van Zwam, RJ van Oostenbrugge, YBWEM Roos, CB Majoie, DWJ Dippel and
for the MR CLEAN Investigators

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Abstract

Background

Endovascular or intra-arterial treatment (IAT) increases the likelihood of recanalization in patients with acute ischemic stroke caused by a proximal intracranial arterial occlusion. However, a beneficial effect of IAT on functional recovery in patients with acute ischemic stroke remains unproven. The aim of this study is to assess the effect of IAT on functional outcome in patients with acute ischemic stroke. Additionally, we aim to assess the safety of IAT, and the effect on recanalization of different mechanical treatment modalities.

Methods/design

A multicenter randomized clinical trial with blinded outcome assessment. The active comparison is IAT versus no IAT. IAT may consist of intra-arterial thrombolysis with alteplase or urokinase, mechanical treatment or both. Mechanical treatment refers to retraction, aspiration, sonolysis, or use of a retrievable stent (stent-retriever). Patients with a relevant intracranial proximal arterial occlusion of the anterior circulation, who can be treated within 6 hours after stroke onset, are eligible. Treatment effect will be estimated with ordinal logistic regression (shift analysis); 500 patients will be included in the trial for a power of 80% to detect a shift leading to a decrease in dependency in 10% of treated patients. The primary outcome is the score on the modified Rankin scale at 90 days. Secondary outcomes are the National Institutes of Health stroke scale score at 24 hours, vessel patency at 24 hours, infarct size on day 5, and the occurrence of major bleeding during the first 5 days.

Discussion

If IAT leads to a 10% absolute reduction in poor outcome after stroke, careful implementation of the intervention could save approximately 1% of all new stroke cases from death or disability annually.

Background

Intravenous thrombolysis

Treatment with intravenous (IV) alteplase, aiming at early reperfusion, has been proven effective for patients with acute ischemic stroke when they are treated within 4.5 hours after stroke onset. The number of patients eligible for treatment with IV alteplase is limited because of the restricted time window.¹⁻³ In approximately 33% of the patients with acute anterior circulation ischemic stroke, symptoms are caused by a proximal occlusion of one of the major intracranial arteries - that is, the distal intracranial carotid artery, the proximal segment of the middle cerebral artery and the anterior cerebral artery.⁴ The likelihood of a proximal occlusion increases with severity of neurological deficit at presentation.^{5,6} In these patients the effect of IV alteplase is limited and leads to recanalization in only 33% of the cases. In patients without recanalization outcome is generally poor.⁷

Intra-arterial treatment

Delivery of the thrombolytic agent at the site of the occlusion may improve the likelihood of recanalization, reperfusion of still viable tissue and, hence, recovery of neurological deficits. Several randomized clinical trials of intra-arterial treatment (IAT) for acute ischemic stroke have been conducted and published.⁸⁻¹⁰ Although the results of these trials suggested a benefit, they have to be interpreted with care and cannot be extrapolated to the current clinical situation since IV alteplase was not an option, neither as pre-treatment nor as part of the control treatment. In the Middle cerebral artery Embolism Local fibrinolytic intervention Trial, mechanical treatment was allowed,¹⁰ but this was not available in Prolyse in Acute Cerebral Thromboembolism (PROACT) I or PROACT II.^{8,9} The Interventional Management of Stroke III (IMS-III) trial was an international randomized, multicenter, open label trial of the effect of combined IV/IAT versus IV treatment only, when treatment is initiated within 3 hours in patients with a National Institutes of Health stroke scale (NIHSS) score ≥ 10 . The sponsor terminated the trial prematurely because of futility; there were no safety concerns. The IMS-III included 656 patients who were all treated intravenously. The increase in absolute risk of good outcome (modified Rankin Scale (mRS) ≤ 2) at 3 months follow-up was 1.5% (95% CI -6.1 to 9.1%). Several factors may have contributed to the absence of a treatment effect: confirmation of occlusion was not required at the time of randomization; in the IV/IAT group, 23% of the patients did not receive IAT due to the absence of an arterial occlusion; time from onset of symptoms to IAT was rather long (249 minutes on average); and only five patients (1.2%) were treated with a stent-retriever.¹¹

SYNTHESIS Expansion was a head-to-head comparison of IAT with IV treatment in 362 patients. In the intervention group, 4.4% fewer patients recovered (95% CI −14.6 to 5.8%) than in the group with standard treatment. Time from onset of symptoms to treatment was on average 225 minutes in the IAT group, but patients receiving the standard treatment with IV recombinant tissue Plasminogen Activator (rtPA) were treated 60 minutes earlier. In this study, confirmation of an occlusion at the time of randomization was not required and only a small group of patients was treated with a stent-retriever (23 patients, 12.7%).¹²

Intravenous and intra-arterial thrombolytic treatment

The combination of IV and intra-arterial alteplase has been described in observational studies and in one other randomized controlled trial.¹³ Some studies adjusted the intravenous dose to 0.6 mg/kg, with a maximum dose of 60 mg. The incidence of hemorrhages was no larger than in studies of treatment with IV thrombolysis only.¹⁴⁻¹⁸ In case series, IAT with low dose intraarterial alteplase was preceded by full dose IV alteplase (that is, 0.9 mg/kg). Risk of symptomatic intracerebral hemorrhage ranged from 0 to 13%.¹⁹⁻²¹ These studies suggest that, in patients who have been treated this way, recanalization rates can be high without unacceptably high risks of complications.

Mechanical thrombectomy

The Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy trial compared mechanical thrombectomy with the MERCI Retriever (Concentric Medical, Mountain View, USA) with standard therapy in 118 patients who had undergone IV thrombolysis. All patients underwent computed tomography (CT) perfusion or magnetic resonance imaging (MRI) diffusion/perfusion, and randomization was stratified for the presence of penumbra. This study showed no beneficial effect of the intervention overall, or in the pre-stratified subgroup of patients with penumbra.²²

Since the first application of IAT for acute ischemic stroke, new techniques for mechanical treatment have been developed. Mechanical treatment is a promising approach, either as a primary intervention or as secondary treatment in patients who fail IV thrombolysis, or in patients for whom thrombolytic agents are contraindicated. Mechanical techniques include retraction, aspiration, stenting and other techniques, such as local ultrasound-augmented fibrinolysis. Studies suggest that, in experienced hands, mechanical thrombectomy devices can be safe and may lead to substantial recanalization rates.²³ The results of two randomized clinical trials comparing retrievable stents with a retraction device suggest that use of a retrievable stent leads to

recanalization more often than use of a retraction device. No comparison was made with standard treatment.^{24,25}

Research question

The MR CLEAN aims to assess the effect of IAT on functional outcome in patients with acute ischemic stroke caused by a proximal intracranial arterial occlusion.

Patients and methods

Design

The Multicenter Randomized Clinical trial of Endovascular treatment for Acute ischemic stroke in the Netherlands (MR CLEAN) is a multicenter clinical trial with randomized treatment allocation, open-label treatment and blinded endpoint evaluation (PROBE design) (Figure 5.1). The active comparison is IAT (intra-arterial alteplase or urokinase, and/or mechanical treatment) versus no IAT.

The treatment is provided in addition to best medical management according to national and international guidelines, and may include IV thrombolysis. The study currently runs in 17 large hospitals in the Netherlands for a total period of 5 years (4 years of patient inclusion). Patient inclusion started in December 2010.

Figure 5.1 Trial logo.

Patient inclusion and exclusion criteria

Patients aged 18 years or older with acute ischemic stroke and a symptomatic anterior proximal artery occlusion, which can be treated within 6 hours after stroke onset, are eligible for participation in this trial.

General inclusion criteria are: a clinical diagnosis of acute stroke with a deficit on the NIHSS of at least 2 points, CT or MRI ruling out intracranial hemorrhage, occlusion of distal intracranial carotid artery or middle (M1 or M2 or anterior cerebral artery (A1) demonstrated with CT angiography (CTA), magnetic resonance angiography (MRA) or digital subtraction angiography (DSA), the possibility to start treatment within 6 hours of onset, aged 18 years or over and informed consent given in writing.

We use three sets of exclusion criteria: general exclusion criteria for IAT, a specific exclusion criterion for mechanical treatment and specific exclusion criteria for intra-arterial thrombolysis.

General exclusion criteria are: arterial blood pressure exceeding 185/110 mmHg, blood glucose less than 2.7 or over 22.2 mmol/L, treatment with IV thrombolysis in a dose exceeding 0.9 mg/kg or 90 mg or treatment with IV thrombolysis despite contraindications, and, finally, cerebral infarction in the distribution of the relevant occluded artery in the previous 6 weeks.

A specific exclusion criterion for intended mechanical thrombectomy is laboratory evidence of coagulation abnormalities (that is, platelet count $<40 \times 10^9/L$, activated partial Thromboplastin time (APTT) >50 seconds or International normalized ratio (INR) >3.0).

Specific exclusion criteria for intended intra-arterial thrombolysis are: a history of cerebral hemorrhage, severe head injury (contusion) in the previous 4 weeks and clinical laboratory evidence of coagulation abnormalities, (that is, platelet count $<90 \times 10^9/L$, APTT >50 seconds or INR >1.7), or treatment with oral thrombin or factor X antagonists.

These hierarchically ordered exclusion criteria make it possible that patients with contraindications for IV or IAT with alteplase but no contraindication for mechanical thrombectomy are included in the study. Also, patients who cannot be treated within the 4.5-hour time window may still be included in the trial. Enrolment was not limited according to the Alberta Stroke Program Early CT Score (ASPECTS) or extension of early signs of infarction at baseline.

Eligibility criteria for participating centers

To be fully eligible for participation in the trial and to include patients in the trial, centers should meet the following minimum criteria. The intervention team should have ample experience with intra-arterial interventions for cerebrovascular disease (carotid stenting or aneurysm coiling), peripheral artery disease, or coronary artery disease. In order to include and randomize patients who may be treated with mechanical thrombectomy, the intervention team should make use of one or more of the devices that have been approved by the trial steering committee. Other devices are not allowed into the trial. At least one member of the intervention team should have sufficient experience with IAT

for acute ischemic stroke and with the particular device that is being used (sufficient experience in this context is defined as the completion of at least five procedures with the particular device or procedure). Compliance with these criteria is checked by the data-monitor.

Randomization

The randomization procedure is computer- and web-based, using permuted blocks. Full-time back-up by telephone is provided. Randomization is allowed when the intracranial occlusion has been established by CTA, MRA or DSA. Randomization is stratified for center, use of IV alteplase, planned treatment modality (mechanical thrombectomy or not) and stroke severity (NIHSS >14 or not).

Intervention

IAT will consist of arterial catheterization with a microcatheter to the level of occlusion and delivery of a thrombolytic agent and/or mechanical thrombectomy. The decision for intubation or conscious sedation was left to the treating physicians. Time from onset to treatment (needle in groin) was recorded. The trial steering committee has issued recommendations that interventional procedures should be stopped at 8 hours from onset of symptoms.

Both alteplase and urokinase for intra-arterial thrombolysis are allowed into the trial, a dose of 1 mg alteplase is considered to be equivalent to 10,000-15,000 U urokinase. Patients who are pre-treated with IV alteplase should not receive more than 30 mg alteplase or 400,000 U urokinase intra-arterially. The maximum allowed dose of urokinase is 1,200,000 U urokinase.²⁶ Mechanical treatment may consist of thrombus retraction, aspiration, sonolysis or use of a retrievable stent. Specific recommendations with regards to procedures and devices will be issued regularly by the trial steering committee.

The steering committee will make recommendations for dosages of thrombolytic agents, procedures, and for devices that will be allowed in the trial based on proposals by the executive committee or local investigators. The requirements for a device to be allowed in the trial are Conformité Européenne (CE) marking or Food and Drug Administration (FDA) registration, documented evidence of safety in experienced hands, recanalization rates that are similar to rates with other mechanical devices, and published case series of at least 20 patients with one particular type of device in a representative series of patients.

Blinding

Both patient and treating physician will be aware of the treatment assignment. Treatment assignment cannot be determined before inclusion and randomization. Information on outcome at 3 months will be assessed with standardized forms and procedures, in a structured telephone interview by an experienced research nurse at the central trial office who is not aware of treatment allocation. Assessment of outcome on the mRS will be based on this information, by assessors who are blind to the allocated and actually received treatment. Results of neuroimaging will also be assessed by blinded observers. Information on treatment allocation and primary outcome will be kept separate from the main study database. The steering committee will be kept unaware of the results of interim analyses of outcomes, efficacy and safety. The trial statistician (HL) will combine data on treatment allocation and outcomes in order to report to the data monitoring committee (DMC).

Study outcomes

The primary outcome is the score on the mRS at 90 days. Secondary outcomes are the imaging parameter vessel recanalization at 24 hours (Clot Burden score and collateral score), infarct size at 5 days assessed with ASPECTS, and final infarct volume calculation.²⁷ For clinical outcome, the NIHSS and NIH supplemental motor scale²⁸ at 24 hours and at 1 week or discharge will be assessed. To further assess functional outcome at 90 days, the score on the EuroQol 5D measurement tool for health-related quality of life and Barthel index will be used (Table 5.1).^{29,30} DSA runs are evaluated by a separate independent central core laboratory because the assessors of DSA will not be blinded to treatment allocation.

Safety aspects

Safety is an issue of concern, as experience with the intervention overall and within the participating centers is limited. Adverse events are undesirable experiences occurring to subjects during the study, whether or not they are considered to be related to the experimental treatment. All adverse events reported spontaneously by the subject or observed by the investigators are recorded. A serious adverse event is defined as any untoward occurrence or effect that causes death, is life-threatening, requires prolonged hospitalization or results in persistent significant disability. The primary safety parameter will be neurologic deterioration during the first 24 hours from inclusion. This is defined as an increase in NIHSS of 4 points or more. Expected serious adverse events are neurologic deterioration, symptomatic intracranial hemorrhage, extracranial hemorrhage, technical complications or vascular damage at the target lesion, such as

perforation or dissection, distal emboli in non-involved arteries, aspiration pneumonia, and allergic reactions to contrast agents.

Table 5.1 Clinical assessment and neuroimaging at baseline and follow-up.

Baseline	
Clinical assessment	Demographics, risk factors, medication, medical history, NIHSS
Neuro-imaging	Unenhanced CT and CT angiography*
Follow-up	
Clinical assessment at 24 hours	NIHSS. Adverse events.
Neuro-imaging at 24 hours	CT angiography*
Neuro-imaging at 5-7 days	Unenhanced CT or MRI
Clinical assessment at 1 week or discharge	NIHSS; Barthel index
Clinical assessment at 90 days	Modified Rankin score, Barthel index, EQ5D

*Magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA) are allowed; computed tomography (CT) perfusion is recommended but not obligatory. EQ-5D, EuroQol 5D measurement tool for health-related quality of life; NIHSS, National Institutes of Health stroke scale.

Data monitoring committee

The DMC is chaired by a neurologist, and includes a neuro-interventionist and a statistician (see Appendix 5.1). The DMC meets at least annually, and is provided with structured unmasked reports, prepared by the trial statistician, for their eyes only. The DMC assesses the occurrence of unwanted effects by center and by allocated treatment. During the period of intake to the study, interim analyses of mortality and of any other information that is available on major endpoints (including serious adverse events believed to be due to treatment) will be supplied, in strict confidence, to the chairman of the DMC along with any other analyses that the Committee may request. In the light of these analyses, the DMC will advise the chairman of the Steering Committee if, in their view, the randomized comparisons in MR CLEAN have provided both (1) "proof beyond reasonable doubt" that for all, or for some specific types of patients, one particular treatment is clearly indicated or clearly contraindicated in terms of a net difference in outcome, and (2) evidence that might reasonably be expected to materially influence patient management. Appropriate criteria of proof beyond reasonable doubt cannot be specified precisely, but a difference of at least 3 standard deviations in an interim analysis of a major endpoint may be needed to justify halting, or modifying, the study prematurely. This criterion has the practical advantage that the number of interim analyses is of little importance.

There are no detailed safety stopping rules. Safety criteria for individual centers include the following. If the local investigator or other member of the team at a trial center has a concern about the outcome of their trial procedures, they should inform the MR CLEAN trial office, which will organize a blinded assessment of the relevant outcome events.

This will be submitted by the central office to the chairman of the DMC, who may recommend further action, such as suspending randomization at the center. Similarly, the database manager at the trial office will monitor outcome events and if there are three consecutive deaths or three consecutive serious adverse events at a single center within 30 days of treatment in the same arm of the study, then assessment of the events will be triggered. A cumulative death rate of more than 50% or a cumulative serious adverse event rate exceeding 20% over 10 cases during hospital admission would also trigger careful assessment of the relevant outcome events.

Statistical analyses

Baseline characteristics will be summarized by means of simple descriptive statistics. The main analysis of this trial consists of a comparison of the primary outcome after 90 days between the trial treatment groups. The analysis will be based on the intention-to-treat principle. The primary effect parameter takes the whole range of the mRS into account and is defined as the relative risk for improvement on the mRS. It is estimated as an odds ratio with ordinal logistic regression.^{31,32} In this primary analysis, multivariable regression analysis will be used to adjust for chance imbalances in main prognostic variables between intervention and control group, such as age, stroke severity (NIHSS), time since onset, previous stroke, atrial fibrillation, carotid top occlusion and diabetes mellitus. Accordingly, treatment effect modification will be explored in subgroups defined by (tertiles of) these prognostic variables.

Secondary effect parameters will be the improvement according to the classic dichotomizations of the mRS scale at 0-1 versus 2-6 and 0-2 versus 3-6, vessel patency on CTA, MRA or DSA at 24 hours, and the score on the NIHSS at 24 hours and 1 week or discharge.

For the analysis of the secondary outcomes, simple 2 × 2 tables, two-group t-tests, Mann–Whitney tests, and multivariable linear and logistic regression models will be used, where appropriate. In all analyses, statistical uncertainty will be expressed by means of 95% CI. A detailed statistical analysis plan can be found in Additional File 5.1.

Sample size

A moderate effect on the distribution of mRS scores, resulting in a 10% absolute increase in the cumulative proportion of patients with mRS 0-3 in the intervention group is assumed, compared with controls. The distribution of outcome categories is based on the results of the PROACT-II trial.⁹ A total study size of 500 patients (2×250 patients) allows for a power (1- α) of 82% at a significance level of 0.05, taking into account 10% cross-over rate.³³ This sample size should also be sufficient to assess the effect of

the intervention on secondary endpoints: analysis of a meaningful reduction on NIHSS at 1 week of 3-4 points (Cohen's $d=0.33$) would require a sample of 400 patients, assuming that at 24 to 48 hours mean NIHSS would be 12, with a standard deviation of 10. A doubling of the recanalization rate from 30% to 60% would require 126 patients to achieve a power of 0.90.

Study organization and funding

See Appendix 5.1 for the study investigators. The trial steering committee is the main decision-making body. It consists of local principal investigators, a stroke neurologist and a neuro-interventionist from each participating center, the members of the executive committee, and the trial statistician. The steering committee meets at least once a year. The trial executive committee consists of a team of six principal investigators, the three coordinating junior researchers and the trial statistician. The trial executive committee also forms the writing committee for the trial. Publications will be made on behalf of all investigators.

All incoming data are reviewed by the trial coordinator at the central trial office. Imaging data are reviewed at the secondary imaging center. All data were entered into a web-based trial management system that allowed for edit and audit trails, by trained local research nurses. All local data were carefully reviewed and first three, as well as every 10th patient case report form was fully checked against source data. Subcommittees exist for outcome assessment, adverse event adjudication and imaging assessment.

Ethical considerations

Informed consent will be obtained from all participants or their legal representative, in writing, before inclusion in the trial. The MR CLEAN trial protocol has been approved for the Netherlands by the central medical ethics committee and research board of Erasmus MC University Medical Center (MEC-2010-041).

Discussion

MR CLEAN is a pragmatic multicenter randomized clinical trial of IAT for acute ischemic stroke versus no IAT. The study is a pragmatic phase III trial with a PROBE design. This trial will primarily evaluate the effect of IAT on functional outcome; secondarily it will assess the safety of IAT, and recanalization rates. MR CLEAN also aims to collect data for a cost-effectiveness evaluation. Furthermore, this trial will provide a basis for the further implementation of IAT in the Netherlands and other countries.

For the trial results to be generalizable and representative of the state-of-the-art approach in IAT, the trial design is pragmatic. This implies the possibility to use several local thrombolytic agents and mechanical devices for a broad range of patients with acute ischemic stroke caused by a proximal thrombo-embolic occlusion of one of the intracranial arteries belonging to the anterior circulation.

The trial's pragmatism is also apparent from the clinical situations it addresses: patients who have been treated unsuccessfully with IV thrombolysis, patients who can be treated within 6 hours, but do not meet the time window requirements for IV thrombolysis, and patients with contraindications for IV or intra-arterial thrombolytic treatment (thrombectomy only).

This trial's design is based on the existence of clinical equipoise, meaning that there is genuine uncertainty in the expert medical community over whether IAT will be beneficial.³⁴ The trial design accommodates the grey area of uncertainty principle; we allow different ranges of uncertainty with regard to eligibility related to age, stroke severity and other clinical or radiological criteria. We presume that all grey areas eventually overlap and will allow us to analyze the full clinical spectrum of acute ischemic stroke caused by intra-arterial occlusion.³⁵

Limitations and concerns

We estimated a sample size of 500 patients. Although the sample size seems rather small, especially for a phase III intervention trial, it allows us to estimate the primary effect parameter with sufficient precision. Indeed, we made a quite conservative estimate of the treatment effect (10% absolute reduction in death and dependence), which is similar in size to the average effect of IV alteplase.

We do not restrict the use of multiple IAT modalities per patient. This is a limitation of the trial design, because it will restrict the possibilities of comparing different treatment modalities and only allows us to give a global judgment whether or not IAT is effective. On the other hand, this pragmatism allows us to follow current practice closely, and allows new mechanical devices and treatment strategies into the trial, even after the start of the study.

A concern with phase III trials of new interventions is the possibility of a "learning curve" - that is, an increase in effectiveness or decrease in the occurrence of procedure-related complications during the conduct of the trial. We therefore required a certain amount of experience with intra-arterial interventions from each group of devices and the number of procedures done by the interventionist. Moreover, we carefully gathered information on consecutive patients treated in each center before the start of the trial, in order to document the experience with the procedures. These data will be used to test for the presence of a learning curve in the trial data and before the start of the trial. Also, all

participating centers register consecutive patients with acute ischemic stroke and record IATs given outside the trial protocol. These will be reported.³⁶

Time since onset is a serious concern. The arguments for a 6-, or even 8-hour time window from onset of stroke symptoms to treatment are mostly based on tradition (previous studies of IAT also used this window), and the absence of an association of complications and treatment effect with time since onset in previous, mostly neutral trials. However, we consider it likely that a treatment effect, if present, will be stronger in patients who can be treated early after onset of symptoms and we will encourage our investigators to act accordingly.

The primary effect parameter is defined as the relative risk for improvement on the mRS estimated as an odds ratio with ordinal logistic regression. The method is also called “shift analysis”, as it takes changes along the full range of the modified Rankin scale into account.^{31,32} It is therefore more sensitive to differences in outcome between the intervention and control groups, and also more relevant, as improvements will be taken into consideration that would not be registered as such in an analysis of dichotomized outcomes.

We assess recanalization on CTA because it is available in intervention and control patients. We will use a combination of Clot Burden Score and collateral flow score to assess the presence and extent of recanalization, because Thrombolysis in Myocardial Infarction (TIMI) or Thrombolysis in Cerebral Infarction (TICI) scores do not apply, as they require information concerning flow, which is not provided by CTA. We do not repeat DSA at 24 hours, as this would pose an additional risk to the patients in the study.

MR CLEAN has started in the Netherlands. We see no problems in generalizing our results to other countries in Western Europe and beyond. We strive to collaborate with other investigators and combine our data in a systematic review for effect estimates and prognostic modeling.

Other ongoing trials

Several randomized clinical trials of intra-arterial therapy for acute ischemic stroke are ongoing. One trial exclusively concerns the treatment of patients with basilar artery occlusion.³⁷ Several other studies compare mechanical thrombectomy with standard treatment, both including, or preceded by IV alteplase.³⁷⁻⁴² Several other trials include patients who are ineligible for IV alteplase treatment exclusively⁴³ or additionally.^{44,45} Several trials have an upper age limit,^{39,38,42,43,45,46} some exclude patients with a large ischemic core,⁴⁴⁻⁴⁶ and some require perfusion mismatch on baseline imaging.^{41,45,46}

Compared to these ongoing trials, MR CLEAN has the advantage of a short time window for inclusion and treatment and no restrictions in age, stroke severity or in penumbral

imaging, all of which have not been validated sufficiently in our view. Moreover, the intervention is not restricted to one type or make of mechanical device.

Expected benefit

In the Netherlands more than 44,000 patients suffer from stroke each year, 80% of these concern ischemic stroke. About a third of these patients arrive within 6 hours in a hospital. Of these, we expect about 33% to have a proximal intracranial occlusion.⁴ A positive trial result could lead to at least a 10% absolute reduction in poor outcome. This implies that after successful implementation of the treatment in routine practice, almost 10% of all stroke patients could be treated and benefit. For the Netherlands, more than 400 patients would thus be saved from death or a disabled life, but for Europe as a whole this could amount to more than 10,000 patients annually.⁴⁷ We expect that MR CLEAN will increase our knowledge of the effects of IAT for acute ischemic stroke, and facilitate the further development and implementation of this potentially beneficial treatment.

Trial status

Patient recruitment started in December 2010. Inclusion was completed with 500 patients on 16 March 2014 (Figure 5.2).

Figure 5.2 Observed and expected accrual. As of 16 March 2014, 500 patients were included in the trial.

Appendix 5.1 The MR CLEAN investigators

Local principal investigators

Diederik W Dippel, Patrick A Brouwer, Erasmus MC Rotterdam; Yvo B Roos, Charles B Majoie, Academisch Medisch Centrum Amsterdam; Robert J van Oostenbrugge, Wim H van Zwam, Maastricht UMC. Jelis Boiten, Geert J Lycklama à Nijeholt, MC Haaglanden Den Haag; Marieke J Wermer, Marianne A van Walderveen, Leids Universitair Medisch Centrum Leiden; L Jaap Kappelle, Rob T Lo, UMC Utrecht; Ewoud J van Dijk, Joost de Vries, UMC St Radboud Nijmegen; Wouter J Schonewille, Jan Albert Vos, St Antonius Ziekenhuis Nieuwegein; Jeannette Hofmeijer, Jacques A van Oostayen, Rijnstate Ziekenhuis Arnhem; Patrick C Vroomen, Omid Eshghi, UMC Groningen; Paul L de Kort, Willem Jan van Rooij, St Elisabeth Ziekenhuis Tilburg; Koos Keizer, Xander Tielbeek, Catharina Ziekenhuis Eindhoven; Bas F de Bruijn, Lukas C van Dijk, Haga Ziekenhuis Den Haag; JS Peter van den Bergh, Boudewijn A van Hasselt, Isala Klinieken, Zwolle; Leo A Aerden, René J Dallinga, Reinier de Graaf Gasthuis, Delft; Tobien H Schreuder, Roel J Heijboer, Atrium MC Heerlen; Heleen M den Hertog, Dick G Gerrits, Medisch Spectrum Twente Enschede; Marieke C Visser, Joost C Bot, VUMC Amsterdam.

Executive committee

Diederik WJ Dippel, Erasmus MC Rotterdam; Aad van der Lugt, Erasmus MC Rotterdam; Charles B Majoie, AMC Amsterdam; Yvo BWEM Roos, AMC Amsterdam; Robert J van Oostenbrugge, Maastricht UMC; Wim H van Zwam, Maastricht UMC.

Imaging assessment committee

Charles B Majoie, chair; Wim H van Zwam; Geert J Lycklama à Nijeholt; Marianne A van Walderveen, Joost C Bot; Henk A Marquering; Ludo F Beenen; Marieke E Sprengers; Sjoerd Jenniskens, René van den Berg; Aad van der Lugt.

Independent DSA reader: Albert J Yoo, Massachusetts General Hospital, Boston, USA.

Outcome assessment committee

Yvo B Roos, chair; Peter J Koudstaal; Jelis Boiten; Ewoud J van Dijk.

Adverse event committee

Robert J van Oostenbrugge, chair; Marieke J Wermer; H Zwenneke Flach.

PhD-students and study coordinators

Puck SS Fransen, Erasmus MC Rotterdam; Debbie Beumer, UMC Maastricht; Olvert A Berkhemer, AMC Amsterdam, Lucie van den Berg, AMC Amsterdam.

Trial statisticians

Ewout W Steyerberg, Dept of Public Health, Center for Clinical Decision Sciences, Erasmus MC Rotterdam. Hester F Lingsma, Dept of Public Health, Center for Clinical Decision Sciences Erasmus MC Rotterdam.

Data Monitoring Committee

Martin M Brown (Chair), professor of stroke medicine, Institute of Neurology, University College London, UK. Thomas Liebig, professor of neuroradiology, department of Radiology, Uniklinik Köln, Germany; Theo Stijnen, professor of medical statistics, department of Medical Statistics and Bioinformatics at Leiden University Medical Center, The Netherlands.

Trial managers

Esther S van der Heijden; Erasmus MC Rotterdam. Nadine M Fleitour, AMC Amsterdam

Additional File 5.1: Statistical analysis plan.

Abbreviations

ASPECTS: Alberta Stroke Program Early CT Score; CT: computed tomography; CTA: computed tomography angiography; DMC: data monitoring committee; DSA: digital subtraction angiography; IAT: intra-arterial treatment; IMS: Interventional Management of Stroke; IV: intravenous; MR CLEAN: Multicenter Randomized Clinical trial of Endovascular treatment for Acute ischemic stroke in the Netherlands; MRA: magnetic resonance angiography; MRI: magnetic resonance imaging; mRS: modified Rankin Scale; NIHSS: National Institutes of Health stroke scale; PROACT: Prolyse in Acute Cerebral Thromboembolism.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

DWJD, AvdL, CBM and YBWEMR designed the study and obtained funding. HL contributed to the methodology chapters of the protocol. DWJD and AvdL wrote the study protocol. PSSF drafted the first version of this manuscript. DB, OAB, LAvdB, HL, AvdL, WHvZ, RJvO, YBWEMR, CBM and DWJD critically reviewed the manuscript for intellectual content. All authors read and approved the final manuscript.

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Author details

¹Department of Neurology, Erasmus MC University Medical Center, PO Box 2040, 3000 CA, Rotterdam, the Netherlands. ²Department of Radiology, Erasmus MC University Medical Center, PO Box 2040, 3000 CA, Rotterdam, the Netherlands. ³Department of Neurology, Maastricht University Medical Centre, PO Box 5800, 6202 AZ, Maastricht, the Netherlands. ⁴Department of Radiology, Academisch Medisch Centrum, PO Box 22660, 1100 DD, Amsterdam, the Netherlands. ⁵Department of Neurology, Academisch Medisch Centrum, PO Box 22660, 1100 DD, Amsterdam, the Netherlands. ⁶Department of Public Health, Erasmus MC University Medical Center, PO Box 2040, 3000 CA, Rotterdam, the Netherlands. ⁷Department of Radiology, Maastricht University Medical Centre, PO Box 5800, 6202 AZ, Maastricht, the Netherlands.

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Chapter 6

A randomized trial of intraarterial treatment for acute ischemic stroke

OA Berkhemer*, PSS Fransen*, D Beumer*, LA van den Berg, HF Lingsma, AJ Yoo, WJ Schonewille, JA Vos, PJ Nederkoorn, MJH Wermer, MAA van Walderveen, J Staals, J Hofmeijer, JA van Oostayen, GJ Lycklama a Nijeholt, J Boiten, PA Brouwer, BJ Emmer, SF de Bruijn, LC van Dijk, LJ Kappelle, RH Lo, EJ van Dijk, J de Vries, PLM de Kort, WJJ van Rooij, JSP van den Berg, BAAM van Hasselt, LAM Aerden, RJ Dallinga, MC Visser, JCJ Bot, PC Vroomen, O Eshghi, THCM Schreuder, RJJ Heijboer, K Keizer, AV Tielbeek, HM den Hertog, DG Gerrits, RM van den Berg-Vos, GB Karas, EW Steyerberg, HZ Flach, HA Marquering, MES Sprengers, SFM Jenniskens, LFM Beenen, R van den Berg, PJ Koudstaal, WH van Zwam, YBWEM Roos*, A van der Lugt*, RJ van Oostenbrugge*, CBLM Majoie*, and DWJ Dippel*, for the MR CLEAN Investigators

* Contributed equally

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Abstract

Introduction

In patients with acute ischemic stroke caused by a proximal intracranial arterial occlusion, intraarterial treatment is highly effective for emergency revascularization. However, proof of a beneficial effect on functional outcome is lacking.

Methods

We randomly assigned eligible patients to either intraarterial treatment plus usual care or usual care alone. Eligible patients had a proximal arterial occlusion in the anterior cerebral circulation that was confirmed on vessel imaging and that could be treated intraarterially within 6 hours after symptom onset. The primary outcome was the modified Rankin scale score at 90 days; this categorical scale measures functional outcome, with scores ranging from 0 (no symptoms) to 6 (death). The treatment effect was estimated with ordinal logistic regression as a common odds ratio, adjusted for prespecified prognostic factors. The adjusted common odds ratio measured the likelihood that intraarterial treatment would lead to lower modified Rankin scores, as compared with usual care alone (shift analysis).

Results

We enrolled 500 patients at 16 medical centers in the Netherlands (233 assigned to intraarterial treatment and 267 to usual care alone). The mean age was 65 years (range, 23 to 96), and 445 patients (89.0%) were treated with intravenous alteplase before randomization. Retrievable stents were used in 190 of the 233 patients (81.5%) assigned to intraarterial treatment. The adjusted common odds ratio was 1.67 (95% confidence interval [CI], 1.21 to 2.30). There was an absolute difference of 13.5 percentage points (95% CI, 5.9 to 21.2) in the rate of functional independence (modified Rankin score, 0 to 2) in favor of the intervention (32.6% vs. 19.1%). There were no significant differences in mortality or the occurrence of symptomatic intracerebral hemorrhage.

Conclusion

In patients with acute ischemic stroke caused by a proximal intracranial occlusion of the anterior circulation, intraarterial treatment administered within 6 hours after stroke onset was effective and safe.

Introduction

Intravenous alteplase administered within 4.5 hours after symptom onset is the only reperfusion therapy with proven efficacy in patients with acute ischemic stroke.¹ However, well-recognized limitations of this therapy include the narrow therapeutic time window and contraindications such as recent surgery, coagulation abnormalities, and a history of intracranial hemorrhage.² Moreover, intravenous alteplase appears to be much less effective at opening proximal occlusions of the major intracranial arteries, which account for more than one third of cases of acute anterior-circulation stroke.^{3,4} Early recanalization after intravenous alteplase is seen in only about one third of patients with an occlusion of the internal-carotid-artery terminus,⁵ and the prognosis without revascularization is generally poor for such patients.⁶ For these reasons, intraarterial treatment is regarded as a potentially important component of the therapeutic armamentarium.

Intraarterial therapy can be broadly divided into chemical dissolution of clots with locally delivered thrombolytic agents and clot retrieval or thrombectomy with mechanical devices. Although early randomized trials and subsequent meta-analyses⁷ showed a benefit of treatment with prourokinase^{8,9} or urokinase,¹⁰ their results are not directly applicable to current decision making about treatment because the control groups did not include intravenous alteplase, and mechanical approaches have largely replaced locally applied thrombolytic agents as first-line therapy.¹¹

The neutral results of the recent randomized, controlled trials of intraarterial treatment have contributed to uncertainty regarding the efficacy of the catheter-based approach.¹²⁻¹⁴ Numerous questions have been raised concerning the design and conduct of these trials, including a relatively long interval before intraarterial treatment, the absence of pretreatment vascular imaging to confirm a proximal intracranial occlusion, and the limited use of third-generation mechanical thrombectomy devices such as retrievable stents. In the Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands (MR CLEAN), we assessed whether intraarterial treatment plus usual care would be more effective than usual care alone in patients with a proximal arterial occlusion in the anterior cerebral circulation that could be treated intraarterially within 6 hours after symptom onset.

Methods

Study design and participants

MR CLEAN was a pragmatic, phase 3, multicenter clinical trial with randomized treatment-group assignments, open-label treatment, and blinded end-point evaluation. Intraarterial treatment (intraarterial thrombolysis, mechanical treatment, or both) plus usual care (which could include intravenous administration of alteplase) was compared with usual care alone (control group) in patients with acute ischemic stroke and a proximal intracranial arterial occlusion of the anterior circulation that was confirmed on vessel imaging.

The study protocol (available with the full text of this article at [NEJM.org](https://www.nejm.org)) was approved by a central medical ethics committee and the research board of each participating center. All patients or their legal representatives provided written informed consent before randomization.

Members of the executive committee and the local investigators designed the study, collected and analyzed the data, wrote the manuscript, and made the decision to submit the manuscript for publication. The authors vouch for the accuracy and completeness of the data and for the fidelity of this report to the study protocol. The study sponsors were not involved in the study design, study conduct, protocol review, or manuscript preparation or review.

Patients and participating centers

The study was conducted at 16 centers in the Netherlands. Patients were 18 years of age or older (no upper age limit) with acute ischemic stroke caused by an intracranial occlusion in the anterior circulation artery. Initiation of intraarterial treatment had to be possible within 6 hours after stroke onset. Eligible patients had an occlusion of the distal intracranial carotid artery, middle cerebral artery (M1 or M2), or anterior cerebral artery (A1 or A2), established with computed tomographic (CT) angiography (CTA), magnetic resonance angiography (MRA), or digital-subtraction angiography (DSA), and a score of 2 or higher on the National Institutes of Health Stroke Scale (NIHSS; range, 0 to 42, with higher scores indicating more severe neurologic deficits). Inclusion of patients with an additional extracranial internal-carotid-artery occlusion or dissection was left to the judgment of the treating physician. Detailed inclusion and exclusion criteria are listed in the study protocol. We did not keep a log of patients who were screened for eligibility.

Randomization

The randomization procedure was Web-based, with the use of permuted blocks. We stratified randomization according to medical center, use of intravenous alteplase (yes or no), planned treatment method (mechanical or other), and stroke severity (NIHSS score of ≤ 14 or >14).

Intervention

Intraarterial treatment consisted of arterial catheterization with a microcatheter to the level of occlusion and delivery of a thrombolytic agent, mechanical thrombectomy, or both. The method of intraarterial treatment was left to the discretion of the local interventionist.

The use of alteplase or urokinase for intraarterial thrombolysis was allowed in this trial, with a maximum dose of 90 mg of alteplase or 1,200,000 IU of urokinase. The dose was restricted to 30 mg of alteplase or 400,000 IU of urokinase if intravenous alteplase was given. Mechanical treatment could involve thrombus retraction, aspiration, wire disruption, or use of a retrievable stent.

Only devices that had received U.S. Food and Drug Administration approval or a Conformite Europeenne (CE) marking and were approved by the steering committee could be used in the trial. One or more members of each intervention team had to have completed at least five full procedures with a particular type of device.¹⁵

Outcome and safety measures

The primary outcome was the score on the modified Rankin scale at 90 days. The modified Rankin scale is a 7-point scale ranging from 0 (no symptoms) to 6 (death). A score of 2 or less indicates functional independence.¹⁶

Secondary outcomes included the NIHSS score at 24 hours and at 5 to 7 days or discharge if earlier, activities of daily living measured with the Barthel index, and the health-related quality of life measured with the EuroQol Group 5-Dimension Self-Report Questionnaire at 90 days.^{17,18} We examined the following prespecified dichotomizations of the modified Rankin score: 0 or 1 versus 2 to 6, 0 to 2 versus 3 to 6, and 0 to 3 versus 4 to 6. Imaging outcomes included arterial recanalization measured with CTA or MRA at 24 hours and the final infarct volume on noncontrast CT at 5 to 7 days.

Safety variables included hemorrhagic complications, progression of ischemic stroke, new ischemic stroke into a different vascular territory, and death. If neurologic deterioration developed, additional neuroimaging was required. Symptomatic intracranial hemorrhage was defined as neurologic deterioration (an increase of 4 or more points in the score on the NIHSS) and evidence of intracranial hemorrhage on

imaging studies. Local neurologists were aware of the treatment-group assignments and reported serious adverse events through our Web-based database or by fax or e-mail.

Clinical and radiologic assessment

All patients underwent clinical assessment (including determination of the NIHSS score) at baseline, after 24 hours, and at 5 to 7 days or at discharge if earlier. A single experienced trial investigator, who was unaware of the treatment-group assignments, conducted the follow-up interviews at 90 days by telephone with the patient, proxy, or health care provider. This interview provided reports for the assessment of the modified Rankin score by reviewers who remained unaware of the treatment-group assignments.¹⁶⁻¹⁸

The imaging committee evaluated the findings on baseline noncontrast CT for the Alberta Stroke Program Early Computed Tomography Score (ASPECTS; range, 0 to 10, with 1 point subtracted for any evidence of early ischemic change in each defined region on the CT scan),¹⁹ baseline vessel imaging (CTA, MRA, or DSA) for the location of the occlusion, and follow-up CTA or MRA at 24 hours for vessel recanalization. Recanalization was classified as complete or not complete and was further evaluated with the use of the modified Arterial Occlusive Lesion score (see the Supplementary Appendix, available at NEJM.org, for details about scales).^{20,21} Followup CT scans obtained at 5 days were assessed for the presence of intracranial hemorrhage.²² All neuroimaging studies were evaluated by two neuroradiologists who were unaware of the treatment-group assignments. The final infarct volume on the follow-up CT scan was assessed with the use of an automated, validated algorithm.²³ An independent core laboratory assessed angiographic outcomes on DSA imaging, using the modified Thrombolysis in Cerebral Infarction (TICI) score, which ranges from 0 (no reperfusion) to 3 (complete reperfusion).²¹

Statistical analysis

All analyses were based on the intention-to-treat principle. The primary effect variable was the adjusted common odds ratio for a shift in the direction of a better outcome on the modified Rankin scale; this ratio was estimated with multivariable ordinal logistic regression.²⁴ We calculated an adjusted odds ratio for all possible cutoff values on the modified Rankin scale to assess the consistency of effect and the plausibility of proportionality of the odds ratio. The adjusted common odds ratio and all secondary effect variables were adjusted for potential imbalances in the following major prognostic variables between the intervention group and the control group: age; stroke severity (NIHSS score) at baseline; time from stroke onset to randomization; status with respect

to previous stroke, atrial fibrillation, and diabetes mellitus; and occlusion of the internalcarotid-artery terminus (yes vs. no).²⁵ We imputed missing values of baseline variables that were used to adjust the regression models of treatment effect on primary and secondary outcomes with mean or mode, as applicable. No outcomes were imputed, except for single missing values of items on the NIHSS at 24 hours and at 5 to 7 days or discharge. Patients who died were not assigned NIHSS scores and were not included in analyses of such scores.

The adjusted and unadjusted common odds ratios are reported with 95% confidence intervals to indicate statistical precision. Binary outcomes were analyzed with logistic regression and are reported as adjusted and unadjusted odds ratios with 95% confidence intervals. All P values are two-sided.

Treatment-effect modification was explored in prespecified subgroups of patients, defined by NIHSS score (2 to 15, 16 to 19, or ≥ 20), age (≥ 80 years or < 80 years), occlusion of the internalcarotid-artery terminus (yes or no), additional extracranial internal-carotid-artery occlusion (yes or no), time from stroke onset to randomization (≤ 120 minutes or > 120 minutes), and ASPECTS (0 to 4, 5 to 7, or 8 to 10). The statistical significance of possible differences between subgroups in the treatment effect was tested with interaction terms. No adjustments for multiple tests were made. All analyses were performed with the use of the Stata/SE statistical package, version 13.1 (StataCorp).

Assuming a 10% crossover rate,²⁶ we calculated that a sample of 500 patients (250 patients in each group) would yield a power of 82%, at a significance level of 0.05, to detect a treatment effect that resulted in an absolute increase of 10 percentage points in the proportion of patients with a modified Rankin score of 0 to 3 in the intervention group as compared with the proportion in the control group.

Results

Randomization and baseline characteristics

Between December 2010 and March 2014, a total of 502 patients underwent randomization in 16 Dutch centers. Two patients, whose representatives withdrew consent immediately after randomization and assignment to the control group, could not be included in the intention-to-treat analysis.

The mean age of the 500 study participants was 65 years (range, 23 to 96); 292 participants (58.4%) were men. Risk factors for a poor outcome, clinical risk factors for stroke, and aspects of prerandomization treatment were evenly distributed between the two treatment groups (Table 6.1, and Table S6.1 in the Supplementary Appendix).

Table 6.1 Baseline characteristics of the 500 patients.*

Characteristic	Intervention (N=233)	Control (N=267)
Age — yr		
Median	65.8	65.7
Interquartile range	54.5–76.0	55.5–76.4
Male sex — no. (%)	135 (57.9)	157 (58.8)
NIHSS score†		
Median (interquartile range)	17 (14–21)	18 (14–22)
Range	3–30	4–38
Location of stroke in left hemisphere — no. (%)	116 (49.8)	153 (57.3)
History of ischemic stroke — no. (%)	29 (12.4)	25 (9.4)
Atrial fibrillation — no. (%)	66 (28.3)	69 (25.8)
Diabetes mellitus — no. (%)	34 (14.6)	34 (12.7)
Prestroke modified Rankin scale score — no. (%)‡		
0	190 (81.5)	214 (80.1)
1	21 (9.0)	29 (10.9)
2	12 (5.2)	13 (4.9)
>2	10 (4.3)	11 (4.1)
Systolic blood pressure — mm Hg§	146±26.0	145±24.4
Treatment with IV alteplase — no. (%)	203 (87.1)	242 (90.6)
Time from stroke onset to start of IV alteplase — min		
Median	85	87
Interquartile range	67–110	65–116
ASPECTS — median (interquartile range)¶	9 (7–10)	9 (8–10)
Intracranial arterial occlusion — no./total no. (%)		
Intracranial ICA	1/233 (0.4)	3/266 (1.1)
ICA with involvement of the M1 middle cerebral artery segment	59/233 (25.3)	75/266 (28.2)
M1 middle cerebral artery segment	154/233 (66.1)	165/266 (62.0)
M2 middle cerebral artery segment	18/233 (7.7)	21/266 (7.9)
A1 or A2 anterior cerebral artery segment	1/233 (0.4)	2/266 (0.8)
Extracranial ICA occlusion — no./total no. (%) **	75/233 (32.2)	70/266 (26.3)
Time from stroke onset to randomization — min††		
Median	204	196
Interquartile range	152–251	149–266
Time from stroke onset to groin puncture — min		
Median	260	NA
Interquartile range	210–313	

* The intervention group was assigned to intraarterial treatment plus usual care, and the control group was assigned to usual care alone. Plus–minus values are means $\pm$ SD. ICA denotes internal carotid artery, IV intravenous, and NA not applicable. † Scores on the National Institutes of Health Stroke Scale (NIHSS) range from 0 to 42, with higher scores indicating more severe neurologic deficits. The NIHSS is a 15-item scale, and values for 30 of the 7500 items were missing (0.4%). The highest number of missing items for a single patient was 6. ‡ Scores on the modified Rankin scale of functional disability range from 0 (no symptoms) to 6 (death). A score of 2 or less indicates functional independence. § Data on systolic blood pressure at baseline were missing for one patient assigned to the control group. ¶ The Alberta Stroke Program Early Computed Tomography Score (ASPECTS) is a measure of the extent of stroke. Scores range from 0 to 10, with higher scores indicating fewer early ischemic changes. Scores were not available for four patients assigned to the control group: noncontrast computed tomography was not performed in one patient, and three patients had strokes in the territory of the anterior cerebral artery. || Vessel imaging was not performed in one patient in the control group, so the level of occlusion was not known. ** Extracranial ICA occlusions were reported by local investigators. †† Data were missing for two patients in the intervention group.

Treatment assignments and crossovers

In total, 233 patients (46.6%) were assigned to the intervention group and 267 patients (53.4%) were assigned to the control group. One patient received intraarterial treatment after being assigned to the control group. Intraarterial treatment was never initiated in 17 patients (7.3%) assigned to the intervention group (Figure S6.1 in the Supplementary Appendix).

Intervention details

Actual intraarterial therapy (with or without mechanical thrombectomy) was performed in 196 of the 233 patients in the intervention group (84.1%). In 88 patients (37.8%), general anesthesia was used. A simultaneous second revascularization procedure (acute cervical carotid stenting) was performed in 30 patients (12.9%).

Mechanical treatment was performed in 195 of the 233 patients (83.7%). Retrievable stents were used in 190 patients (81.5%), and other devices were used in 5 patients (2.1%) (Table S6.2 in the Supplementary Appendix). Additional intraarterial thrombolytic agents were given to 24 patients (10.3%).

Intraarterial thrombolytic agents were used as monotherapy in 1 of the 233 patients (0.4%). No intervention was given in 37 patients (15.9%) (Figure S6.1 in the Supplementary Appendix).

Primary outcome

Data on the primary outcome (the score on the modified Rankin scale at 90 days) were complete. There was a shift in the distribution of the primary-outcome scores in favor of the intervention. The adjusted common odds ratio was 1.67 (95% confidence interval [CI], 1.21 to 2.30) (Table 6.2). The shift toward better outcomes in favor of the intervention was consistent for all categories of the modified Rankin scale, except for death (Figure 6.1). The absolute between-group difference in the proportion of patients who were functionally independent (modified Rankin score, 0 to 2) was 13.5 percentage points (95% CI, 5.9 to 21.2) in favor of the intervention (32.6% vs. 19.1%), with an adjusted odds ratio of 2.16 (95% CI, 1.39 to 3.38) (Table 6.2).

Secondary outcomes

All clinical and imaging secondary outcomes favored the intervention (Table 6.2, and Table S6.3 in the Supplementary Appendix). The NIHSS score after 5 to 7 days was, on average, 2.9 points (95% CI, 1.5 to 4.3) lower in the intervention group than in the control group.

Figure 6.1 Modified Rankin Scale Scores at 90 Days in the Intention-to-Treat Population. Shown is the distribution of scores on the modified Rankin scale. Scores range from 0 to 6, with 0 indicating no symptoms, 1 no clinically significant disability, 2 slight disability (patient is able to look after own affairs without assistance but is unable to carry out all previous activities), 3 moderate disability (patient requires some help but is able to walk unassisted), 4 moderately severe disability (patient is unable to attend to bodily needs without assistance and unable to walk unassisted), 5 severe disability (patient requires constant nursing care and attention), and 6 death. There was a significant difference between the intervention group and the control group in the overall distribution of scores in an analysis with univariable ordinal regression (common odds ratio, 1.66; 95% CI, 1.21 to 2.28), as well as after adjustment of the treatment effect for age; National Institutes of Health Stroke Scale score at baseline; time from stroke onset to randomization; status with respect to previous stroke, atrial fibrillation, and diabetes mellitus; and occlusion of the internal-carotid-artery terminus (yes vs. no) in an analysis with multivariable regression (adjusted common odds ratio, 1.67; 95% CI, 1.21 to 2.30). In the control group, only 1 patient (0.4%) had a modified Rankin score of 0.

Data on recanalization after 24 hours, assessed by means of CTA, were available for 394 patients. An absence of residual occlusion at the target site was more common in the intervention group (141 of 187 patients [75.4%]) than in the control group (68 of 207 patients [32.9%]) (Table 6.2). Data on infarct volume were available for 298 of 500 patients; the between-group difference in volume (19 ml; 95% CI, 3 to 34) favored the intervention group (Table 6.2). Good reperfusion (modified TICl score, 2b or 3) was achieved in 115 of 196 patients (58.7%) in the intervention group (Table S6.4 in the Supplementary Appendix).

Safety

There was no significant between-group difference in the occurrence of serious adverse events during the 90-day follow-up period ($p=0.31$) (Table 6.3). However, 13 of the 233 patients (5.6%) in the intervention group had clinical signs of a new ischemic stroke in a different vascular territory within 90 days, whereas only 1 of the 267 patients (0.4%) in the control group did so. There was no significant difference in mortality at 7, 30, or 90 days of follow-up.

Table 6.2 Primary and secondary outcomes and treatment effects. *

Outcome	Intervention (N=233) 3 (2 to 5)	Control (N=267) 4 (3 to 5)	Effect variable	Unadjusted value (95% CI)	Adjusted value (95% CI) [†]
Primary outcome: modified Rankin scale score at 90 days — median (interquartile range)			Common odds ratio	1.66 (1.21 to 2.28)	1.67 (1.21 to 2.30)
Secondary outcomes					
Clinical outcomes					
Modified Rankin score of 0 or 1 at 90 days — no. (%)	27 (11.6)	16 (6.0)	Odds ratio	2.06 (1.08 to 3.92)	2.07 (1.07 to 4.02)
Modified Rankin score of 0–2 at 90 days — no. (%)	76 (32.6)	51 (19.1)	Odds ratio	2.05 (1.36 to 3.09)	2.16 (1.39 to 3.38)
Modified Rankin score of 0–3 at 90 days — no. (%)	119 (51.1)	95 (35.6)	Odds ratio	1.89 (1.32 to 2.71)	2.03 (1.36 to 3.03)
NIHSS score after 24 hr — median (interquartile range) [‡]	13 (6 to 20)	16 (12 to 21)	Beta	2.6 (1.2 to 4.1)	2.3 (1.0 to 3.5)
NIHSS score at 5–7 days or discharge — median (inter-quartile range) [§]	8 (2 to 17)	14 (7 to 18)	Beta	3.2 (1.7 to 4.7)	2.9 (1.5 to 4.3)
Barthel index of 19 or 20 at 90 days — no./total no. (%) [¶]	99/215 (46.0)	73/245 (29.8)	Odds ratio	2.0 (1.3 to 2.9)	2.1 (1.4 to 3.2)
EQ-5D score at 90 days — median (interquartile range)	0.69 (0.33 to 0.85)	0.66 (0.30 to 0.81)	Beta	0.08 (0.00 to 0.15)	0.06 (–0.01 to 0.13)
Imaging outcomes					
No intracranial occlusion on follow-up CT angiography	141/187 (75.4)	68/207 (32.9)	Odds ratio	6.27 (4.03 to 9.74)	6.88 (4.34 to 10.94)
Final infarct volume on CT ⁺⁺					
Patients evaluated — no. (%)	138 (59.2)	160 (59.9)			
Median (interquartile range) — ml	49 (22 to 96)	79 (34 to 125)	Beta	20 (3 to 36)	19 (3 to 34)

* CT denotes computed tomography. † Values were adjusted for age; NIHSS score at baseline; time from stroke onset to randomization; status with respect to previous stroke, atrial fibrillation, and diabetes mellitus; and occlusion of the internal-carotid-artery terminus (yes vs. no). ‡ The NIHSS score was determined for survivors only. The score was not available for 20 patients: 12 died before assessment was finished, and 8 had missing scores. § The NIHSS score was determined for survivors only. The score was not available for 74 patients: 56 died before assessment was finished, and 18 had missing scores. ¶ The Barthel index is an ordinal scale for measuring performance of activities of daily living. Scores range from 0 to 20, with 0 indicating severe disability and 19 or 20 indicating no disability that interferes with daily activities. The EuroQoL Group 5-Dimension Self-Report Questionnaire (EQ-5D) is a standardized instrument for the measurement of health status. Scores range from –0.33 to 1.00, with higher scores indicating a better quality of life. ** Data for follow-up CT angiography were not available for 106 patients owing to imminent death or death (24 patients), decreased kidney function (13 patients), insufficient scan quality (5 patients), and other reasons (64 patients). †† Data for final infarct volume on noncontrast CT (performed at 3 to 9 days) were missing for 202 patients because of death (52 patients), hemicraniectomy (21 patients), technical errors with automated assessment (14 patients), or insufficient scan quality (5 patients) or because CT was not performed for reasons other than death (110 patients).

Procedure-related complications in the intervention group included embolization into new territories outside the target downstream territory of the occluded vessel in 20 of the 233 patients (8.6%), procedure-related vessel dissections in 4 patients (1.7%), and vessel perforations in 2 patients (0.9%).

Table 6.3 Safety variables and serious adverse events within 90 days after randomization.

Variable	Intervention (N=233) no. of patients (%)	Control (N=267) no. of patients (%)
Safety variables		
Death		
Within 7 days	27 (11.6)	33 (12.4)
Within 30 days	44 (18.9)	49 (18.4)
Hemicraniectomy	14 (6.0)	13 (4.9)
Serious adverse events*		
Any serious adverse event	110 (47.2)	113 (42.3)
Symptomatic intracerebral hemorrhage		
Any type	18 (7.7)	17 (6.4)
Parenchymal hematoma†		
Type 1	0	2 (0.7)
Type 2	14 (6.0)	14 (5.2)
Hemorrhagic infarction‡		
Type 1	1 (0.4)	0
Type 2	1 (0.4)	1 (0.4)
Subarachnoid hemorrhage	2 (0.9)	0
New ischemic stroke in a different vascular territory§	13 (5.6)	1 (0.4)
Progressive ischemic stroke	46 (19.7)	47 (17.6)
Pneumonia	25 (10.7)	41 (15.4)
Other infection	16 (6.9)	9 (3.4)
Cardiac ischemia	1 (0.4)	4 (1.5)
Extracranial hemorrhage	0	2 (0.7)
Allergic reaction	1 (0.4)	0
Other complication	22 (9.4)	33 (12.4)

* Only first events of a type are listed. Patients having multiple events of one type were counted once. † For parenchymal hematoma, type 1 was defined by one or more blood clots in 30% or less of the infarcted area with a mild space-occupying effect, and type 2 was defined by blood clots in more than 30% of the infarcted area with a clinically significant space-occupying effect. ‡ For hemorrhagic infarction, type 1 was defined by small petechiae along the margins of the infarction, and type 2 was defined by more confluent petechiae within the infarction area. § $p < 0.001$.

Subgroup analyses

There were no significant interactions between subgroups and treatment effect. The treatment effect remained consistent in all predefined subgroups, including those based on age (<80 years or ≥80 years), NIHSS score (2 to 15, 16 to 19, or ≥20), and ASPECTS (0 to 4, 5 to 7, or 8 to 10) (Figure S6.2 in the Supplementary Appendix). The point estimate for treatment effect in the subgroup with ASPECTS of 0 to 4 was close to unity but with a wide confidence interval (adjusted common odds ratio, 1.09; 95% CI, 0.14 to 8.46).

Discussion

Our results show that patients with acute ischemic stroke caused by a proximal intracranial arterial occlusion of the anterior circulation have a benefit with respect to functional recovery when intraarterial treatment is administered within 6 hours after stroke onset. This treatment leads to a clinically significant increase in functional independence in daily life by 3 months, without an increase in mortality.

Our findings stand in clear distinction to those of recent randomized, controlled trials that failed to show a benefit of intraarterial treatment.^{12,13} Approximately 90% of patients in each treatment group of MR CLEAN received intravenous alteplase, making our cohort similar to that in the Interventional Management of Stroke (IMS) III trial, in which intravenous alteplase alone was compared with intravenous alteplase plus intraarterial treatment.¹² However, in the IMS III trial, patients had to be enrolled and undergo randomization within 40 minutes after the start of intravenous alteplase. This requirement may have led to the inclusion of more patients who had a favorable response to intravenous alteplase than in MR CLEAN, which had a median time from the start of intravenous alteplase to randomization that was considerably longer than the maximum time in the IMS III trial. It is likely that intraarterial treatment will not alter the natural history of acute ischemic stroke in the absence of a proximal arterial occlusion. Unlike the IMS III trial and the Local versus Systemic Thrombolysis for Acute Ischemic Stroke (SYNTHESIS Expansion) trial,¹³ MR CLEAN required a radiologically proven intracranial occlusion for study eligibility. When the IMS III trial was designed, the availability of CTA was still limited, and the presence of a proximal arterial occlusion was therefore uncertain in a subgroup of patients in that trial (47% of the study population).¹²

Our study benefited from the widespread availability of retrievable stents, which were used in 82% of the patients in the intervention group. These devices were recently shown to be superior to the first-generation Merci device for both revascularization and clinical outcomes.^{27,28}

Previous trials have been criticized because investigators could have treated many patients outside the trials. This was reflected in the low recruitment rates in the IMS III trial and the Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy (MR RESCUE) trial,¹⁴ which had an average enrollment of 1 to 2 patients per center per year. In contrast, all stroke centers in the Netherlands that provided intraarterial treatment during the execution of MR CLEAN participated in the trial, and from 2013 onward, reimbursement by insurance companies required participation in a trial.

Our trial had several limitations. First, randomization was slightly unbalanced, resulting in more patients in the control group than in the intervention group. This imbalance was the result of block size and multiple stratifications.

Second, the reperfusion rate in MR CLEAN (modified TICl score of 2b or 3, 58.7%) was relatively low as compared with the rates in recent case series, which were 80% or higher.^{29,30} However, the rate of a modified TICl score of 2b or 3 in the IMS III trial was 23 to 44%, depending on the location of the occlusion. The two recently published phase 2 trials of retrievable stents showed reperfusion rates of 61% and 86%, but these rates were based on end points of a modified TICl score of 2a to 3 and a Thrombolysis in Myocardial Ischemia score of 2 or 3, respectively.^{27,28} Differentiation between a modified TICl score of 2a and a score of 2b or 3 is difficult when lateral DSA images are not available. This applied to 15 patients in MR CLEAN, who were subsequently given a modified TICl score of 2a. This may have led to an underestimation of the actual reperfusion rate among patients with a modified TICl score of 2b or 3.

Third, despite the positive result of this trial, almost 9% of the patients in the intervention group had embolization into new vascular territories on DSA. A total of 30 patients (13%) assigned to intraarterial treatment also underwent a simultaneous second revascularization procedure (acute cervical carotid stenting), and this complexity needs to be considered when interpreting our trial results.

Fourth, a relatively low proportion of patients in the control group had a modified Rankin score of 0 to 2 at the 90-day follow-up assessment. This may be explained by our broad inclusion criteria, which allowed contraindications for intravenous alteplase, nonresponse to intravenous alteplase, octogenarians and even nonagenarians, and patients with extracranial internal-carotidartery occlusions or dissections. Taken together, this resulted in a population with a relatively poor prognosis at baseline. The advantage is a wide generalizability of our results.

Finally, although the outcome assessment was blinded, patients were aware of the treatmentgroup assignments, and this might have influenced their opinions about their health and functional condition. However, modified Rankin scores at 90 days were based on assessment by reviewers who were unaware of the treatment-group assignments, to avoid biased assessments, and the results of blinded assessments of neuroimaging corroborated our findings.

In conclusion, we found that intraarterial treatment in patients with acute ischemic stroke caused by a proximal intracranial occlusion of the anterior circulation was effective and safe when administered within 6 hours after stroke onset.

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Chapter 7

Patient age and the effect of endovascular
treatment for ischemic stroke caused by
intracranial large vessel occlusion

D Beumer, PSS Fransen, WH van Zwam, OA Berkhemer, H Lingsma, L van den Berg,
A van der Lugt, CB Majoie, YB Roos, DWJ Dippel, RJ van Oostenbrugge,
for the MR CLEAN investigators

Submitted

Abstract

Introduction

Age is a strong predictor of poor outcome after ischemic stroke but whether and how age should be taken into account in the decision process for endovascular treatment (EVT) is still under debate. We therefore analyzed the effect of age on outcome and its possible modification of treatment effect in the Multicenter Randomized CLinical trial of Endovascular treatment for Acute ischemic stroke in the Netherlands (MR CLEAN) trial.

Methods

This subgroup analysis included all 500 patients in MR CLEAN , which was a multicenter, randomized, open label trial of EVT versus no EVT in patients with acute ischemic stroke of the anterior intracranial circulation due to proven large vessel occlusion. We used ordinal and binary logistic regression models to assess the association of age as a continuous variable with functional outcome (modified Rankin Scale; mRS) and modification of treatment effect in relative terms (Odds Ratio) and absolute terms (absolute risk difference) for the distribution of categories of the mRS: dependency (3-6) versus independence (0-2), and unfavorable (4-6) versus favorable (0-3).

Results

Age was related to functional outcome in treated and untreated patients (adjusted common odds ratio; acOR 0.96 95% CI 0.94 to 0.98 per year). There was no modification of treatment effect by age ($p=0.87$). EVT induces a smaller absolute increase in likelihood of becoming independent (mRS 0-2) in the elderly compared to younger patients, but there is still an 8% increase in becoming independent with advanced age (number needed to treat: 12).

Conclusion

There was no interaction of age with the effect of EVT in ischemic stroke, although the chance of good outcome by treatment decreased with increasing age. Age affects outcome, but not treatment effect. Moreover, treatment did not cause an increased chance of complications. Age by itself should therefore not be an argument to withhold EVT from patients with acute ischemic stroke caused by intracranial large vessel occlusion.

Introduction

Age is strongly related to poor outcome in patients with ischemic stroke [8-27]. Whether the reduced likelihood of good outcome is an argument for withholding endovascular treatment (EVT) in older patients has been debated for a long time.¹⁻⁵

Increased frequencies of comorbid conditions, more severe stroke symptoms, higher chance for hemorrhagic complications^{6,7} and poor rehabilitation capabilities compared to younger patients have been put forward as argument for restrictive use of EVT for older patients.⁸

Currently, data regarding the effect of EVT in older patients is scarce. Several observational studies and randomized trials made use of an upper age limit for inclusion.⁹⁻¹¹ Two randomized controlled EVT trials reported that patients older than 80 years undergoing EVT showed a similar relative treatment effect on outcome compared to the overall treatment effect of the trial.^{12,13} In a pooled analysis of 5 published EVT trials which was the Highly Effective Reperfusion Evaluated in Multiple Endovascular Stroke Trials (HERMES) collaboration older people more often suffered from multiple comorbid conditions, which further complicates clinical decision making.¹⁴ This study did not indicate interaction between age and treatment, so uncertainty remains about treatment effect in elderly patients and also in those aged under 50.¹⁴

The primary aim of this study was therefore to assess treatment effect modification by age in acute ischemic stroke (AIS) in MR CLEAN trial. We aim to determine the influence of age on the effect of treatment in terms of relative and absolute effects on the likelihood of good outcome.

Methods

Study design and participants

All 500 patients of Multicenter Randomized CLinical trial of Endovascular treatment for Acute ischemic stroke in the Netherlands (MR CLEAN) were included. Patient eligibility and methods of MR CLEAN have been reported previously.^{13,15} In short, MR CLEAN was a randomized clinical trial with a PROBE (prospective open label with blinded outcome assessment) design, of standard care plus EVT (intervention group) versus standard care alone (control group) in patients with an intracranial large vessel occlusion (LVO) in the anterior circulation demonstrated on vessel imaging, who could be treated within 6 hours after symptom onset. The study had no upper age limit for inclusion. The study protocol was approved by a central medical ethics committee and by the research board of each participating center. Members of the executive committee and the local

investigators of each participating center contributed to the design of the study and data collection.

Outcomes

The primary outcome was functional outcome defined by the score on the modified Rankin Scale (mRS) at 90 days. Secondary outcome comprised neurological deficits assessed by the National Institutes of Health Stroke Scale (NIHSS) at 24 hours and at 5-7 days or at discharge if earlier. Radiological outcome included recanalization grade at 24 hours, which could be evaluated on Computed Tomographic Angiography (CTA) or Magnetic Resonance Angiography (MRA). In the intervention group reperfusion was assessed with the modified Thrombolysis in Cerebral Infarction (mTICI) Score on Digital Subtraction Angiography (DSA) at the end of the procedure.

Safety

Safety parameters were occurrence of intracranial hemorrhage (sICH), procedural related complications, progression of ischemic stroke, hemicraniectomy, other complications such as pneumonia or cardiac ischemia, and death. sICH was defined as neurological deterioration of 4 or more points on the NIHSS and confirmed intracranial hemorrhage on imaging.

Statistical analysis

All analyses were based on the intention-to-treat-principle. Baseline patient characteristics were presented (median and IQR for continuous and absolute variables and proportions for numeric variables) for age in quintiles to illustrate the data properly. The primary effect parameter was the adjusted common odds ratios (acOR) for a shift on the mRS in the direction of better outcomes. Modification of treatment effect with age as a continuous factor was analyzed by means of a multiplicative interaction term, in which considered both relative and absolute treatment effect modifications were considered.¹⁶ The latter were visualized by plotting the distribution of mRS categories as function of age for treatment and no treatment, and by plotting the differences in likelihood per category between the two distributions. Outcomes by quintiles of age for illustration and better understanding were also reported.

The effects on primary and secondary effect parameters were adjusted for potential imbalances in prognostic variables at baseline: baseline stroke severity (NIHSS) and collateral score. Statistical uncertainty was expressed by 95% confidence intervals. Stata/SE statistical software (StataCorp, release 13.0 College Station Texas, USA) was used for all analyses.

Role of the funding source

The study sponsors were not involved in the study design, study conduct, protocol review, manuscript preparation or review.

Results

Patients in the highest quintile, more often suffered from myocardial infarction (20% versus 6%), peripheral artery disease (8% versus 2%), diabetes mellitus type II (21% versus 2%), hypertension (67% versus 17%), atrial fibrillation (42% versus 6%) and hyperlipidemia (33% versus 9%) compared to the lowest quintile (Table 7.1). Patients in the highest quintile smoked less often (7% versus 43%) and more frequently used antiplatelet agents (39% versus 14%) and anticoagulants (15% versus 4%) compared with those in the lowest quintile. In patients in the highest quintile EVT was started a few minutes later compared to the lowest quintile, but the difference was not statistically significant.

Primary outcome

No patients were lost to follow-up. Overall, the effect of treatment on the distribution of the mRS was substantial, with an acOR of 1.67 [95% CI; 1.22-2.30]. Age was strongly associated with outcome as the likelihood of moving at least one point on the mRS towards good outcome decreased with an OR of 0.96 per year of age (95% CI: 0.94-0.98), for both treated and untreated patients. Advancing age was associated with a decreased likelihood of independence and favorable outcome, both for patients in the intervention arm and the control arm (Figure 7.1). The interaction of age with EVT was not significant ($p=0.87$). However, for patients younger than 80 years a positive shift occurred in the categories 0-2, while for patients aged 80 and older, this shift occurred predominantly in the mRS categories 3-4 (Figure 7.2).

Table 7.1 Baseline characteristics of the study population. No percentages are given, as quintiles consist of 100 patients each.

Characteristic	Q1 N=100	Q2 N=100	Q3 N=100	Q4 N=100	Q5 N=100
Age –range (years)	23-52	52-61	61-69	69-77	77-96
Male sex – n	53	70	67	57	45
History of ischemic stroke – n	6	9	12	12	15
History of myocardial infarction – n	6	10	19	20	20
History of peripheral artery disease – n	2	2	3	9	8
Diabetes Mellitus – n	2	16	15	14	21
History of hypertension – n	17	34	52	57	67
History of atrial fibrillation – n	6	10	32	45	42
History of hyperlipidemia – n	9	28	29	30	33
Current smoking – n	43	35	29	29	7
Current antiplatelet use – n	14	19	30	42	39
Current anticoagulants use – n	4	2	7	11	15
Current statins use – n	10	27	33	38	35
Weight in kg – mean (SD)	79 (17)	85 (16)	83 (16)	78 (12)	75 (12)
NIHSS score – mean (SD)	17 (8)	17 (7)	18 (7)	18 (9)	19 (7)
Systolic blood pressure mmHg – mean (SD)	132 (23)	140 (32)	145 (27)	150 (34)	157 (32)
Diastolic blood pressure mmHg – mean (SD)	79 (17)	80 (18)	80 (18)	82 (20)	85 (27)
Intracranial occlusion*					
ICA without ICA-T – n	0	1	0	0	3
ICA-T - n	28	28	32	21	25
M1 segment – n	67	61	58	71	62
M2 segment – n	4	9	8	8	10
A1/2 segment – n	1	1	1	0	0
ASPECTS 0-4 - n	8	6	9	5	2
ASPECTS 5-7 - n	25	27	15	10	16
ASPECTS 8-10 - n	66	66	74	85	82
Collateral score after consensus					
Absent collaterals - n	3	4	3	10	6
Filling < 50% of occlusion	27	20	28	30	30
Filling > 50% but less < 100% of occlusion – n	35	44	44	35	41
100% of occluded area – n	34	30	24	25	21
Time from onset to tPA minutes –mean (SD)	77 (50)	87 (40)	82 (46)	90 (36)	96 (52)
Time from onset to CTA minutes– mean (SD)	156 (143)	164 (141)	164 (120)	140 (122)	122 (112)
Time from onset to randomization minutes – mean (SD)	200 (109)	219 (117)	205 (103)	209 (98)	190 (120)
Time from onset to EVT Minutes–mean (SD)	265 (71)	269 (62)	253 (67)	264 (61)	272 (78)

n=number; SD=standard deviation, kg=kilogram; IQR=interquartile range; NIHSS=National Institutes of Health Stroke Scale range 0 to 42, higher scores indicate more severe neurological deficits, SD=standard deviation; IV=intravenous; ASPECTS=Alberta Stroke Program Early CT Score, range 0 to 10. Higher scores indicate less early ischemic changes; ICA=Internal Carotid Artery (intracranial segment); ICA-T=Internal Carotid Artery with involvement of the M1 segment; M1/M2- Middle cerebral artery segments; A1/A2=Anterior cerebral artery segments; EVT=endovascular treatment. * =vessel imaging was not performed in one patient and level of occlusion is not available. mRS=Modified Rankin Scale, NIHSS=national Institutes of Stroke Health Scale, CTA=Computed Tomographic Angiography, SICH=symptomatic intracranial hemorrhage.

Figure 7.1 Distribution of mRS outcome categories as a function of age, estimated from an ordinal multiple logistic regression model, in the intervention group and control group.

Secondary outcomes

Functional independence (mRS 0-2) was reached more often in the intervention group with a 13% increase compared to the control group in all quintiles of age and modification of treatment effect by age was not found ($p=0.71$) (Table 7.2). In the highest quintile (age 77-96) 8% more patients reached functional independency in the intervention group compared to the control group. Neurological improvement on the NIHSS was in favor of intervention in all quintiles after 24 hours and after 5-7 days or discharge (Table 7.2). There was no significant modification of treatment effect by age for NIHSS at 24 hours ($p=0.37$), and NIHSS at 5-7 days or discharge ($p=0.34$). Recanalization rate on follow-up imaging was higher in the intervention group compared

to the control group, which was consistent for all quintiles of age ($p=0.95$). Rate of successful revascularization on post-treatment DSA (mTICI 2b-3) measured in patients undergoing IAT was differed between quintiles of age (resp 21/43 [49%] vs. 26/35 [74%] vs 26/38 [68%] vs. 24/40 [60%] vs. 18/40 [45%]), with lower recanalization rates in the youngest and oldest quintile.

Figure 7.2 Absolute percentage shift in probabilities of mRS categories induced by treatment (Y-axis), at 5-year age points (X-axis), estimated in a multiple ordinal logistic regression model. For young patients the positive shift occurs in mRS categories 0, 1 and 2, for patients aged 80 and older, half or more of the positive shift occurs in the categories 3 and 4

Procedural related outcomes and safety

There is a relation between age and mortality, aOR 1.07 [95% CI; 1.03-1.10] adjusted for stroke severity and collateral score. There was no interaction with treatment, $p=0.23$. Higher age was associated with higher serious adverse event rates, but this was not due to treatment (P -interaction=0.37), also patients in higher age quintiles suffered more often from pneumonia and sICH's, but again there was no interaction with treatment (Table 7.3).

Table 7.2 Clinical outcome table; secondary clinical and secondary radiological

	Q1C	Q1I	Q2C	Q2I	Q3C	Q3I	Q4C	Q4I	Q5C	Q5I	P for interaction
Age-range (years)	23-52				61-69		69-77		77-96		
Number of patients, N	49	51	56	44	58	42	50	50	54	46	
Secondary – clinical											
mRS 0-1 at 90 days – n. (%)	5 (10)	7 (14)	2 (4)	4 (9)	6 (10)	4 (10)	1 (2)	7 (14)	2 (4)	5 (11)	0.53
mRS 0-2 at 90 days – n. (%)	14 (29)	24 (47)	10 (18)	16 (36)	14 (24)	15 (36)	9 (18)	14 (28)	4 (7)	7 (15)	0.71
mRS 0-3 at 90 days – n. (%)	28 (57)	34 (67)	21 (38)	29 (66)	24 (41)	22 (52)	15 (30)	21 (42)	7 (13)	13 (28)	0.94
NIHSS 24 hrs –median (IQR) †	16 (9-18)	12 (3-21)	17 (11-21)	10 (6-18)	18 (12.5-22)	11 (8-15.5)	17 (12-21)	15 (5-20)	16 (13-20.5)	18 (9-25)	0.37
NIHSS 7 days or discharge-median (IQR) *	13 (6-18)	8.5 (1-18)	14 (9-17.5)	7 (2-13)	14 (6-18)	6 (3-16)	15 (5-20)	10 (2-17)	14 (8-18)	10 (2-17)	0.34
Secondary-radiological											
Recanalization on follow-up CTA [‡] – n.	13 (32)	32 (68)	12 (26)	31 (78)	17 (40)	26 (84)	17 (45)	28 (80)	9 (23)	24 (71)	0.95
/ total n. (%)											

QC=control group; QI=intervention group; cOR = common Odds Ratio; OR = Odds Ratio; mRS = modified Rankin Scale; NIHSS = National Institutes of Health Stroke Scale; CTA = Computed Tomography Angiography; NCCT = Non Contrast Computed Tomography. †NIHSS was measured in survivors only. The score was not available in 20 patients, 12 died before assessment was done and 8 were missing. *NIHSS was measured in survivors only. The score was not available in 74 patients, 56 died before assessment was done and 18 were missing. ‡CTA was not available in 106 patients. Reasons for absence were: imminent death/death 24, decreased kidney function in 13, scan quality (movement or contrast load) in 5 and other/missing in 64 patients.

Discussion

Summary

Our study shows a constant relative treatment effect of EVT for age in patients with intracranial large vessel occlusion of the anterior circulation treated within 6 hours after stroke onset. In younger patients (<80 years), we report a positive shift in mRS due to treatment, mostly in mRS categories 0-2. In the elderly (≥80 years) the positive shift occurs towards categories 3 and 4. This could be explained by the higher prior chance of worse outcome after ischemic stroke by increasing age and the difficulty to remain completely independent at high age. However, a shift from nursing home care to living at home with some help for daily activities will increase quality of life, and diminish both burden of disease for the patient and costs for society substantially. EVT induces a smaller absolute increase in likelihood of becoming independent (mRS 0-2) in the elderly compared to younger patients, but there is still an 8% increase in becoming independent in the highest quintile of age, which means a number needed to treat of 12. This implies that older age by itself should not be an argument to withhold EVT.

Internal validity

In this study we demonstrate that patients benefit from EVT regardless of their age in both relative and absolute treatment effect. No patients were lost to follow up. There were no major safety concerns in the elderly, there were more complications in the elderly and mortality was higher, but this was not related to treatment.

External validity and other studies

Our findings agree with other recently published studies in which patients of 80 years or older do benefit from EVT.¹⁴

Several cohort studies describe outcome after EVT in elderly patients, although these uncontrolled studies could not by design, explore the relation of age with treatment effect.^{17,18} However, they do confirm that good recovery is possible after EVT. In that sense these studies corroborate our findings.

The North American Solitaire-FR Stent-Retriever Acute Stroke (NASA) Registry found age over 80 years to be predictive for poor clinical outcome and reported increased mortality compared with younger patients, though no control group was available.¹⁹

Another study on predictors of functional outcome after mechanical thrombectomy for LVO of the anterior circulation in patients 80 years or over reported good recanalization rates and acceptable rates of intracranial hemorrhage in these patients, although the number of patients with good functional outcome (mRS 0-2) was low (17.4%).²⁰ The

ENDOSTROKE study reported a good functional outcome (mRS 0-2) of 17% in patients aged 77-94 years undergoing EVT.⁸

Limitations

In this study we focused on age and its effect on EVT regarding clinical and radiological outcome, but predicting outcome in individual patients will be multivariable, especially in older patients suffering from comorbid conditions that influence outcome.²¹

Patients in MR CLEAN were relatively young (median age 65 years) compared to the general ischemic stroke population. As we did not keep track records of all eligible patients a bias in selection of patients with higher age cannot be excluded, which may influence generalizability of our results. However, in our study 70/500 patients (14%) were older than 80 years, and comorbidity and mortality was substantially higher than in younger patients, which suggests only limited selection bias. The absence of interaction with treatment and the consistency of our results with other studies suggest that generalizability is not an issue.

Conclusion

There was no interaction of age with the effect of EVT in ischemic stroke, although the chance of good outcome by treatment decreased with increasing age. Age affects outcome, but not treatment effect. Moreover, treatment did not cause an increased chance of complications. Age by itself should therefore not be an argument to withhold EVT from patients with acute ischemic stroke caused by intracranial large vessel occlusion.

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Chapter 8

Baseline stroke severity and effect of intra-arterial treatment in acute stroke in MR CLEAN

PSS Fransen, D Beumer, OA Berkhemer, LA van den Berg, AJ Yoo, HF Lingsma, WH van Zwam, CBLM Majoie, RJ van Oostenbrugge, YBWEM Roos, DWJ Dippel, A van der Lugt, on behalf of the MR CLEAN investigators

Submitted

Abstract

Background

MR CLEAN showed a clear benefit of intra-arterial therapy (IAT) in patients with acute ischemic stroke (AIS) caused by a proximal intracranial occlusion of the anterior circulation. This effect was reproduced by four other RCT's. One important difference in the inclusion criteria was the lower cut-off of baseline stroke severity during presentation on the emergency department. For decades there was a general understanding patients with low stroke severity would not benefit from intra-arterial treatment due to their natural history. In MR CLEAN the cut-off NIHSS was only 2 points. The aim of this study was to assess treatment effect modification by NIHSS at baseline. Our second aim was to assess treatment effect in patients with low stroke severity ($\text{NIHSS} \leq 10$) and higher stroke severity ($\text{NIHSS} 10+$) at presentation.

Methods

Full methods of the MR CLEAN trial have been described earlier. We looked at clinical, radiological and safety parameters in three predefined subgroups of NIHSS (2-15/16-19/20+)

As a primary analysis we assessed treatment effect modification by NIHSS by means of a multiplicative interaction variable. Treatment effect and interaction were also assessed for all the secondary and safety effect parameters for the three predefined subgroups. To compare our results to historical results we also looked at $\text{NIHSS} \leq 10$ and $10 >$.

Results

There was no significant modification of treatment effect on the primary outcome by baseline NIHSS ($P=0.65$), adjusted for age and collateral score. There was a shift in the distribution on the mRS in favor of the intervention group across all baseline NIHSS subgroups (Figure 8.1). The strongest shift (acOR 1.9 [95%CI; 1.1 to 3.2]) was seen in patients with baseline NIHSS 20+. Though patient numbers are rather small in the $\text{NIHSS} \leq 10$ group ($N=57$), both clinical and radiological outcomes were all in favor of the intervention group.

Conclusion

Patients who suffer acute ischemic strokes by a proximal intracranial occlusion and have relative low stroke severity should be treated intra-arterially. There is no clinical, radiological or safety argument to withheld treatment from them.

Introduction

MR CLEAN showed a clear benefit of intra-arterial therapy (IAT) in patients with acute ischemic stroke (AIS) caused by a proximal intracranial occlusion of the anterior circulation. The intervention contrast was IAT versus no IAT against a background of best medical care including intravenous (IV) alteplase if indicated. The trial demonstrated a shift in the distribution of functional outcomes on the modified Rankin Scale (mRS) in favor of the intervention, which was consistent in almost all subgroup analyses. With IAT the rate of patients being independent (mRS 0-2) increased from 19% to 33%.¹ After publication of MR CLEAN, four other trials confirmed the effect of IAT.²⁻⁵

Apart from their common denominator, which is the presence of a proven vessel occlusion on imaging, patient selection for inclusion differed between studies. One important difference in the inclusion criteria was the lower cut-off of baseline stroke severity during presentation on the emergency department. Stroke severity, measured with the National Institutes of Health Stroke Scale (NIHSS)⁶, is an important independent predictor of functional outcome in patients with AIS.⁷ After publication of PROACT-II, which demonstrated no effect of IAT in the subset of patients presenting with NIHSS 4-10, these patients were believed to have no additional benefit from IAT due to a good natural course.⁸ However, in MR CLEAN also patients were included with low NIHSS scores, cut-off NIHSS was 2, while the other recently published positive studies on the effect of IAT included patients with baseline NIHSS of at least 5 points or more.²⁻⁵

The aim of this study is to assess treatment effect modification by NIHSS at baseline in acute ischemic stroke. We also studied treatment effect and interaction for three predefined subgroups of baseline NIHSS (NIHSS; 2-15, 16-19 and ≥ 20). Additionally our aim was to assess treatment effect in patients with mild stroke severity (NIHSS ≤ 10) and high stroke severity (NIHSS 10+) at presentation.

Methods

MR CLEAN showed a clear benefit of intra-arterial therapy (IAT) in patients with acute ischemic stroke (AIS) caused by a proximal intracranial occlusion of the anterior circulation. The intervention contrast was IAT versus no IAT against a background of best medical care including intravenous (IV) alteplase if indicated. The trial demonstrated a shift in the distribution of functional outcomes on the modified Rankin Scale (mRS) in favor of the intervention, which was consistent in almost all subgroup analyses. With IAT the rate of patients being independent (mRS 0-2) increased from 19% to 33%.¹ After publication of MR CLEAN, four other trials confirmed the effect of IAT.²⁻⁵

Apart from their common denominator, which is the presence of a proven vessel occlusion on imaging, patient selection for inclusion differed between studies. One important difference in the inclusion criteria was the lower cut-off of baseline stroke severity during presentation on the emergency department. Stroke severity, measured with the National Institutes of Health Stroke Scale (NIHSS)⁶, is an important independent predictor of functional outcome in patients with AIS.⁷ After publication of PROACT-II, which demonstrated no effect of IAT in the subset of patients presenting with NIHSS 4-10, these patients were believed to have no additional benefit from IAT due to a good natural course.⁸ However, in MR CLEAN also patients were included with low NIHSS scores, cut-off NIHSS was 2, while the other recently published positive studies on the effect of IAT included patients with baseline NIHSS of at least 5 points or more.²⁻⁵

The aim of this study is to assess treatment effect modification by NIHSS at baseline in acute ischemic stroke. We also studied treatment effect and interaction for three predefined subgroups of baseline NIHSS (NIHSS; 2-15, 16-19 and ≥ 20). Additionally our aim was to assess treatment effect in patients with mild stroke severity (NIHSS ≤ 10) and high stroke severity (NIHSS 10+) at presentation.

Results

Patient characteristics

Between December 2010 and March 2014, 500 patients were included in the MR CLEAN study. In total, 233 patients (46.6%) were allocated to intervention, and 267 patients (54.4%) were assigned to control. All patients from MR CLEAN were included in the current study and all received neurological assessment, including NIHSS at baseline. The NIHSS is a 15-item scale, and values for 30 of the 7500 items in the follow up moments, 24 hrs and 1 week, were missing (0.4%). The highest number of missing items for a single patient was 6.

Baseline characteristics were evenly distributed across the three NIHSS groups (Table 8.1), apart from occlusion level, with more ICA-T occlusions in the higher NIHSS subgroups ($p=0.003$).

Primary outcome

No patients were lost to follow-up. There was no significant modification of treatment effect on the primary outcome by baseline NIHSS ($p=0.65$), adjusted for age and collateral score. There was a shift in the distribution on the mRS in favor of the intervention group across all baseline NIHSS subgroups (Figure 8.1). The strongest shift

(acOR 1.9 [95%CI; 1.1 to 3.2]) was seen in patients with baseline NIHSS 20+. In the group with moderate NIHSS (NIHSS 16-19) the acOR was 1.7 [95% CI; 0.9 to 3.0]. The acOR was 1.7 [95%CI; 0.9 to 2.9] in patients with lower NIHSS (2-15). (Figure 8.2a,b,c)

Table 8.1 Clinical characteristics at baseline of patients included in MR CLEAN in patients with mild stroke severity (NIHSS 2-15) at presentation, moderate stroke severity (NIHSS 16-19) at presentation, and high stroke severity (NIHSS >20+) at presentation

Characteristic	NIHSS subgroup		
	NIHSS 2-15 (n=164)	NIHSS 16-19 (n=153)	NIHSS 20+ (n=183)
Age in years - median (IQR)	64 (52-76)	65 (56-75)	66 (59-77)
Male sex – n (%)	88 (54%)	91 (59%)	113 (62%)
NIHSS score - median (IQR)	12 (9-14)	17 (16-19)	23 (21-25)
Clinical localization: Left hemisphere – n (%)	67 (41%)	52 (34%)	150 (82%)
History of ischemic stroke – n (%)	20 (12%)	19 (12%)	15 (8%)
History of hypertension – n (%)	75 (46%)	71 (46%)	81 (44%)
Diabetes mellitus – n (%)	23 (14%)	19 (12%)	26 (14%)
History of myocardial infarction – n (%)	18 (11%)	27 (18%)	30 (16%)
History of peripheral artery disease – n (%)	7 (4%)	6 (4%)	11 (6%)
History of hyperlipidemie – n (%)	43 (26%)	40 (26%)	46 (25%)
Current smoking – n (%)	50 (30%)	41 (27%)	52 (28%)
Current statins use – n (%)	49 (30%)	42 (27%)	52 (28%)
Current anticoagulants use – n (%)	15 (9%)	10 (7%)	14 (8%)
Current antiplatelet use – n (%)	45 (27%)	51 (33%)	48 (26%)
Pre-stroke mRS – n (%)			
0	127 (77%)	129 (84%)	148 (81%)
1	22 (13)	11 (7%)	17 (9%)
2	6 (4%)	8 (5%)	11 (6%)
>2	9 (5%)	5 (4%)	7 (4%)
Treatment with IV alteplase - n (%)	146 (89%)	139 (91%)	160 (87%)
Onset to IV alteplase in min - median (IQR)	90 (65-112)	88 (69-115)	80 (65-110)
Level of Occlusion - n (%)			
ICA	1 (1%)	3 (2%)	0 (0%)
ICA-T	29 (18%)	40 (26%)	65 (36%)*
M1	116 (71%)	101 (66%)	102 (56%)
M2	17 (10%)	7 (5%)	15 (8%)
Onset to randomization in min - median (IQR)	193 (150-257)	212 (159-272)	197 (146-253)
Onset to IAT in min - median (IQR)	251 (206-300)	270 (225-327)	260 (214-315)

* p=0.003.

Secondary outcomes

When functionally independent status at 90-days (mRS 0-2) was considered as outcome, the clinical independence (mRS 0-2) was reached more often in the intervention group compared to the control group in all three NIHSS subgroups, but modification of treatment effect by baseline stroke severity was not found (p=0.83). This was consistent for mRS 0-1 and mRS 0-3 (Table 8.2).

Neurological improvement on the NIHSS was in favor of intervention in all subgroups after 24 hours and after 5-7 days or discharge (Table 8.2). There was no significant modification of treatment effect by baseline NIHSS for NIHSS at 24 hours ($p=0.74$), or NIHSS 5-7 days or discharge ($p=0.83$) on good functional outcome. Recanalization rate on follow-up imaging was higher in the intervention group compared to the control group, which was consistent for all baseline NIHSS subgroups ($p=0.27$).

The median final infarct volumes on 5-7 day NCCT (range 3 to 9 days) were 40 ml, 75 ml and 73 ml for mild, medium and high baseline NIHSS subgroup. We did find a significant ($p=0.04$) treatment effect modification by baseline NIHSS subgroup when follow-up infarct volume was a secondary outcome (Table 8.2). The difference between follow up infarct volume between intervention and control group increased with an increase in NIHSS (Table 8.2). Rate of successful revascularization on post-treatment DSA (mTICI 2B-3) only measured in patients undergoing IAT was comparable between the three baseline NIHSS subgroups (resp 62% vs. 55% vs. 60%).

Primary outcomes and secondary outcomes are for patients with mild stroke severity (NIHSS ≤ 10) and higher stroke severity (NIHSS >10) are listed in Table 8.3. Though patient numbers are rather small in the NIHSS ≤ 10 group ($N=57$), all clinical and radiological outcomes are in favor of the intervention group.

Procedural related outcomes and safety

There was a difference in overall mortality ($p=0.001$) across the different baseline NIHSS groups (Table 8.4). The proportion of patients with at least one serious adverse event was higher in patients with higher baseline NIHSS ($p=0.03$). We did find a trend ($p=0.09$) for proportion of patients with a symptomatic intracranial hemorrhage across baseline NIHSS subgroups, with proportion of ICH's increasing with stroke severity. In addition, there was no trend in proportion of patients with progression of ischemic stroke across baseline NIHSS subgroups (Table 8.4).

Table 8.2 Clinical outcome table; primary clinical, secondary clinical and secondary radiological

	NIHSS 2-15 controls (n=85)	NIHSS 2-15 intervention (n=79)	NIHSS 16-19 Controls (n=77)	NIHSS 16-19 Intervention (n=76)	NIHSS 20+ Controls (n=105)	NIHSS 20+ Intervention (n=78)	P for interaction	P for interaction adjusted
Secondary – clinical								
mRS 0-1 at 90 days – n. (%)	9 (11%)	14 (18%)	2 (3%)	6 (8%)	5 (5%)	7 (9%)	0.69	0.67
mRS 0-2 at 90 days – n. (%)	27 (32%)	39 (49%)	13 (17%)	21 (28%)	11 (10%)	16 (21%)	0.78	0.83
mRS 0-3 at 90 days – n. (%)	43 (51%)	52 (66%)	27 (35%)	36 (47%)	25 (24%)	31 (40%)	0.88	0.92
NIHSS 24 hrs	11 (7-15)	8 (3-15)	16 (14-19)	13.5 (8.5-19)	21 (17-24)	18 (11-24)	0.94	0.92
NIHSS 7 days or discharge	9 (2-15)	2.5 (1-12)	14 (10-18)	10.5 (5-15)	18 (13-22)	14.5 (4.5-20)	0.61	0.63
Secondary-radiological								
Recanalization on follow-up CTA [^]	27 (38%)	50 (75%)	15 (27%)	48 (77%)	26 (33%)	43 (74%)	0.45	0.52
– n. / total n. (%)								
Final infarct volume on follow-up	55/85 (65%)	50/79 (63%)	47/77 (61%)	47/76 (62%)	61/105 (58%)	48/78 (62%)		
NCCT – n. / total n. (%)								
Volume in millilitres – mean (SD)	64 (66)	62 (71)	99 (63)	79 (72)	116 (79)	77 (77)	0.07	0.04

Table 8.3 Primary and secondary outcomes in patients included in MR CLEAN in patients with low stroke severity (NIHSS ≤ 10) at presentation, and higher stroke severity (NIHSS >10), subdivided per treatment allocation.

	NIHSS ≤ 10 control (n=34)	NIHSS ≤ 10 intervention (n=23)	>10 control (n=233)	>10 intervention (n=210)
Secondary – clinical				
mRS 0-1 at 90 days – n. (%)	5 (15%)	5 (22%)	11 (5%)	22 (11%)
mRS 0-2 at 90 days – n. (%)	14 (41%)	13 (56%)	37 (16%)	63 (30%)
mRS 0-3 at 90 days – n. (%)	22 (65%)	16 (70%)	73 (31%)	103 (49%)
NIHSS at 24 hrs [†]	8 (3-12)	5 (1-11)	17 (14-22)	14 (7.5-20)
NIHSS at 1 week or discharge [‡]	5 (1-9)	1 (0-6)	16 (9-19)	9 (3-17)
Secondary-radiological				
Recanalization on follow-up CTA [^] – n. / total n. (%)	13 (45%)	14 (64%)	55 (31%)	127 (77%)
Final infarct volume on follow-up	22/34	13/23	141/233	132/210
NCCT – n. / total n. (%)				
Volume in millilitres – mean (SD)	42 (41)	41 (36)	101 (74)	76 (75)

The table lists numbers of patients and percentages in each treatment group, type of effect. [†]NIHSS was measured in survivors only. [^]Final infarct volume on NCCT after 5 days (range 3-9 days)

Discussion

Summary

In this study, there was no significant modification of treatment effect on shift on the mRS by baseline NIHSS. Also our results showed a positive effect of intra-arterial treatment in all NIHSS subgroups for primary and secondary clinical outcomes and radiological outcomes. Based on these findings we state that patients should not be excluded from intra-arterial treatment based on stroke severity.

Internal validity

In this study we demonstrate that patients benefit from IAT regardless of their NIHSS at baseline.

In MR CLEAN, by including patients with mild stroke severity, we created a unique opportunity to study the effect of IAT in this group, and though patient numbers were small (N=57 in NIHSS ≤ 10) we still found favorable outcomes for both clinical and radiological outcomes for the intervention group compared to controls. The acOR for shift on the mRS was 1.57 in favor of the intervention group in the NIHSS ≤ 10 group (95% CI 0.56-4.31). Lack of statistical significance is due to small patient numbers. We adjusted all analyses for age and collateral score at CTA baseline, since these appeared to be the most influencing prognostic factors.

External validity

Since MR CLEAN four other trials have shown the beneficial effect of intra-arterial treatment.¹⁻⁵ As a result, IAT is now implemented in every day stroke care in many parts of the world. We are still searching for clinical en radiological predictors to select patients for IAT in order to optimize treatment effect. Based on PROACT II, in which a beneficial effect of intra-arterial thrombolysis in patients with mild stroke severity (NIHSS ≤ 10)¹¹ was not observed, expert opinion was to exclude patients with mild stroke severity from IAT, because natural course of mild strokes was thought to be quite positive and risk of treatment should be avoided in this group. We must be aware though, that patients who suffer language disturbances due to a mild stroke, can be highly disabled in daily life, while their actual NIHSS could easily be below 10 points, or 5 for that matter. Current techniques have made it possible to select patients with a proximal intracranial arterial anterior circulation occlusion while having a mild NIHSS. In MR CLEAN we included only patients with a proven intracranial occlusion on CTA and we had a NIHSS cut off of ≥ 2 . This low cut off was different from other recent positive trials that had their NIHSS cut off at 5 or more. At this moment a study is conducted in the US and results can be expected this year.¹² In this study researchers address the controversy about the effect of intravenous alteplase in patients with mild AIS (NIHSS 5 or less) and who are not clearly disabled according to the treating physician, why patients consult a first aid post has been subordinated.

Other studies

Recently the HERMES study group¹³ published the results of the pooled data analysis of the 5 positive trials. They also looked at different strata for baseline stroke severity, 177/1287 (13.8%) patients in total had a baseline NIHSS of 10 or less and treatment effect was in favor of the intervention group (cOR 1.20, 95% CI 0.81-1.78) with a P-interaction of 0.47. The results we found are comparable, and in our study we had about the same amount of patients with mild-stroke severity, compared to the total number of patients, 57/500(11.4%).

The SEER-collaboration looked at different strata of stroke severity in all patients who were treated with the solitaire device. They found a P-interaction of 0.72. Treatment effect in all three strata of baseline NIHSS arranged from OR 2.84 in NIHSS 2-15, and OR 3.25 in NIHSS >20 .¹⁴

Limitations

As already stated there is controversy about the degree of aggressive treatment approach in patients with mild stroke severity. If we aim to put an end to these

controversies forever we need more data and larger patient numbers. Therefore it is of great essence to state that also patients with mild stroke severity and a large vessel occlusion continue to receive treatment in the absence of contraindications. And not the treating physician should be the one to judge the degree of disability but only the fact a patient is seeking for help at an emergency side should be reason for treatment.

High NIHSS scores are more often associated with large anterior vessel occlusions.⁷ Especially in large countries with in some areas mild population densities there is a need to do a pre-hospital patient selection in order to take patients to an IAT center as soon as possible. A recent study showed that best gaze, as an item from the NIHSS score, together with FAST (face-arm-speech-time), G-FAST, is a good predictor for a large vessel occlusion and could be used by paramedics as well.¹⁵ Our findings that approximately 10-13% of the patients have mild stroke severity (NIHSS ≤ 10) but do benefit from IAT will probably not attribute to a quick solution in better patient selection.

Although interrater reliability for the NIHSS score is high as well as the test-retest reliability⁶ it never is a perfect tool. Especially in acute stroke setting where every minute is counting, there is a fair change of under-or overestimation of the NIHSS score. This could most easily be the case in our study, but probably in all acute stroke studies so may therefore be rejected.

Conclusion

Our results show no clinical, radiological or safety argument to withheld intra-arterial treatment from patients with mild stroke severity. Moreover, patients with mild baseline NIHSS scores and proven large vessel occlusion benefit from IAT in a similar way as patients with high stroke severity.

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Chapter 9

General discussion

General discussion

The general discussion of this thesis focuses on clinical and organizational aspects of endovascular treatment (EVT) in patients with acute ischemic stroke and on future directions for research within the field of EVT.

The first part is related to clinical aspects: the overall results of the MR CLEAN trial are discussed as well as subgroup analyses on the effect of EVT in older patients and in patients with mild neurological symptoms at onset.

The second part relates to the reorganization of acute stroke care in The Netherlands as a result of the implementation of the results of MR CLEAN in clinical practice. Finally, the third part concerns future directions of EVT related research.

I. Endovascular treatment a ‘gamechanger’

Results of the MR CLEAN trial

Until 2015, acute ischemic stroke patients were treated with intravenous thrombolytics (alteplase) only, which has been proven effective when given within 4.5 hours after symptom onset.^{1,2} However, the treatment benefit is limited, especially if started beyond 3 hours after symptom onset with an number needed to treat of 14, and even more if a proximal or large intracranial vessel is occluded.³

The MR CLEAN trial investigated the effect of EVT in patients with acute ischemic stroke caused by large vessel occlusion (LVO) of the anterior circulation treated up to 6 hours after symptom onset. The study showed a significant improvement, expressed as a shift on the modified Rankin Scale (mRS) after 3 months, after EVT compared to standard treatment (acOR 1.67 [95%CI 1.21 to 2.30]).⁴ Functionally this implies that one third of the patients undergoing EVT are disability free (mRS 0-2) three months after treatment, compared to one fifth of the patients who do not undergo EVT. The results of MR CLEAN were confirmed by several other RCT's⁵⁻¹¹ and a pooled individual patient data meta-analysis.¹² Soon after, Dutch guidelines and guidelines of the American Heart Association / American Stroke Association were adjusted recommending EVT for all eligible patients.^{13,14} In The Netherlands where annually about 40.000 patients are admitted with ischemic or hemorrhagic stroke, it is estimated that about 2000 patients (5%) are eligible for EVT.¹⁵ With the results of MRCLEAN this would mean that annually around 300 more patients can live independently after a stroke.

Subgroups that do benefit from EVT

Older aged patients and EVT

Several randomized clinical trials excluded older aged patients.^{6,7,10} Other trials, like MR CLEAN, had no upper age limit for patient inclusion but the proportion of octogenarians in these trials was small.^{4,5,8,9} Outcome after stroke strongly depends on age of the patient¹⁶ and in IVT high percentages of unfavorable outcome in patients 80 years or older were found.^{17,18} In our MR CLEAN pre-trial study worse outcome with higher age was found, as expected, but in the MR CLEAN trial we found no modification of treatment effect by age ($p=0.87$). Though the relative treatment effect remained constant over all age groups, absolute benefit of EVT decreased with age; for example, absolute benefit for patients 50 years of age is 13% compared to 8% for patients 80 years old.

However, patients in MR CLEAN were relatively young compared to the general stroke population, as the median age in the MR CLEAN population was 65 years. This suggests a selection bias in the older aged patients. Benefit in the elderly occurred mostly in mRS categories 3 and 4. Furthermore, pre-stroke mRS scores in MR CLEAN also showed that of the patients over 70 years 93% had a pre-stroke mRS scores of 0-2, which indicates that relatively healthy seniors were included in MR CLEAN. This could influence the generalizability of the results.

The results of age subgroup analysis in the HERMES collaboration confirmed the findings in MR CLEAN, with a benefit of EVT in all patients with a LVO of the anterior circulation irrespective of age (cOR 3.68 [95% CI: 1.95-6.92] for patients of 80 years or older.¹² Therefore, there is no reason to withhold EVT in older aged patients based on age alone. In current guidelines EVT is recommended without age restrictions, which will have important implications in light of the aging population.^{14,19}

Stroke severity at symptom onset

Most EVT trials that showed benefit of EVT, used a minimum NIHSS score for inclusion, mostly ≥ 5 .^{5-7,10} In MR CLEAN inclusion of patients with a NIHSS score as low as 2 was allowed. We found no interaction between baseline stroke severity and treatment effect, but the number of patients with a NIHSS <5 was very small. In other words, we found no indication to withhold EVT for patients with low stroke severity scores at onset.

II. Re-organization of acute stroke care

Number of patients eligible for EVT

The positive results on EVT initiated a reorganization of acute stroke care in the Netherlands, nationally and regionally, in order to transfer patients eligible for EVT fast and efficiently to a comprehensive stroke center able to perform EVT. To anticipate on this logistical challenge, it was needed to know the number of patients who suffer from a stroke caused by a LVO of the anterior circulation. In several studies different numbers of patients eligible for EVT were reported, presumably because not all centers in these studies reported consecutive, not referred patients.²⁰⁻²⁴ One study found LVO to be present in 40 to 61% of the patients, but the main limitation was the high number of referred patients to the study hospital from over 40 other hospitals, probably showing an overrepresentation of patients with a LVO.²⁴ In a single-center study in which 1063 non-referred patients with presumed ischemic stroke were assessed, almost one third (31%) suffered from a LVO of the anterior or posterior circulation and were eligible for EVT (Chapter 2).

Implications and centralization of acute stroke care in The Netherlands

Because of the relatively low numbers of patients eligible for EVT and the complexity of EVT due to logistics, infrastructural needs and the EVT itself, there is a need to centralize this treatment. In order to warrant good patient care, centers are to conform to protocolled guidelines, minimum annual number of treatments, benchmarked door-to-groin-times and registration of procedures in a database as defined quality criteria.^{25,26}

Interventionists' experience for EVT

Experience of an interventionist performing EVT may improve patient care. The question is what number of endovascular procedures is needed to treat patients with acute ischemic stroke optimally and which number of performed procedures is needed to keep sufficient operator skills.

Before the start of MR CLEAN, during the MR CLEAN pretrial phase, in several Dutch centers interventionists and neurosurgeons already treated patients endovascularly. In this pretrial period we studied the effect of interventionist's experience on patients outcome in a cohort of 500 patients. We also aimed to define a minimum number of procedures a center has to perform before this center was allowed to participate in the MR CLEAN trial.

Contrary to e.g. carotid stenting trials in which a 30 day risk of stroke or death was significantly higher in patients treated by operators with low mean of performed

procedures (≤ 3.2) compared to operators with a mean of 5.6 procedures per year,²⁷ we found no relation between interventionists' experience and patient outcome. However, we did find a positive trend on the procedural time with increased experience, although this was not statistically significant. Further research to study effects of interventionist's experience with much higher numbers of endovascular procedures per interventionist, needs to be done for better judgement of the effect of operator experience. In such studies the effect of multidisciplinary team discussions and feedback about procedure performances could also be evaluated.

Despite lack of scientific evidence for an association between interventionist's experience and patient outcome in acute ischemic stroke, we proposed a pragmatic minimum of 5 acute stroke procedures performed by an interventionist before participating in MR CLEAN. (Chapter 4).

A recent study presented data about low versus high volume centers on outcome after EVT. It showed that patients who were endovascularly treated in high volume centers, compared to low volume centers, had better outcomes.²⁸ Data about interventionist's experience were not reported. These data may suggest more impact of institutional experience than interventionist's experience alone on outcome after EVT.

After the results of MR CLEAN and other RCTs quality criteria were developed by the Minister of Health and it was recommended that each interventionist should perform at least 20 EVT procedures annually to maintain a sufficient level of expertise.

Subsequently, this has led to the registration of specialized intervention centers by the Minister of Health with 24/7 available treatment by a dedicated intervention team, consisting of a vascular neurologist, interventionist and anesthesiologist.

III. Future research

Improving outcome after EVT

So far, it is proven that EVT in patients with a LVO of the anterior circulation is effective and safe.

However, there are still patients in whom quick and adequate recanalization after EVT (i.e. mTICI score 2b or 3 on angiography at the end of the procedure) is reached, but who remain severely neurologically and functionally disabled.⁴ In cardiology this failure of treatment has been described as the 'no-reflow' phenomenon.²⁹⁻³¹

This phenomenon is described as a local cellular based hypoperfusion of the microvasculature in which various mechanisms play a role, like microvascular obstruction, inflammatory response, edema, endothelial swelling and vasospasm.³² In acute stroke incomplete reperfusion can be linked to several mechanisms as distal

microvascular damage, dysfunction due to tissue necrosis and cell death, presence of distal embolization, or a delayed start of the EVT procedure. Distal embolization might be the result of pericyte contraction, distal occlusion of a microthrombus as part of the original thrombus or newly in situ formation of microthrombi and cellular plugs caused by platelet activation and increased hemostasis, activated by formation of neutrophil extracellular traps (NETs).³³ NETs cannot be resolved by recombinant tissue plasminogen activator and some studies have revealed the presence of NETs added to the structure of the thrombus. In human specimen thrombi are found to have a heterogenous composition consisting of calcium-phosphate, fibrin, cholesterol crystals, erythrocytes, platelets, connective tissue, and leukocytes.^{34,35}

Thrombi that mainly result from areas with reduced blood flow, as in atrial fibrillation, heart failure and in the venous system, are formed by activation of plasmatic coagulation cascade and have high hematocrit levels,³⁶ whereas thrombi resulting from endothelial damage, often from atherosclerotic vessels, contain high levels of fibrin.³⁷ Furthermore, the interaction between thrombi and mechanical devices, which are mainly adhesive, are influenced by thrombus surface and content.³⁸

Apart from this, impaired fibrinolysis, increased clot formation and thrombogenesis due to dysregulation on a genetical level may also play a role.³⁹ Due to impaired hemostasis and endothelial dysfunction intraluminal filling occurs by sticking of thrombocytes and leukocytes to the damaged lamina interna of the vessel wall, which can cause unwanted re-occlusion.

Therefore, it is important to further improve treatment of acute ischemic stroke patients. In The Netherlands the COLlaboration for New TReatments in Acute Stroke (CONTRAST) outcome in patients with acute stroke is developed to further assess and improve treatment of acute stroke.

MR CLEAN MED as part of CONTRAST will investigate the effect of antithrombotic or antiplatelet agent administered directly before the start of EVT on outcome.⁴⁰

In older studies, where no imaging was performed to confirm presence of a LVO, NIHSS was used to select and include patients.^{41,42} Higher NIHSS scores increase the chance of suffering from a LVO. Derex *et al* reported a 25% chance of suffering from a LVO with a NIHSS of 10⁴³ and the odds for having a LVO was 1.28 (95% CI: 1.11-1.46) per one point increase on the NIHSS. We found a similar aOR of 1.23 (95 % CI: 1.17–1.29) per point increase on the NIHSS for the presence of LVO (chapter 2). This implies that NIHSS can be a tool for identifying patients with a high likelihood of having a LVO and who potentially may be directly transferred to intervention hospitals. However, stroke mimics and patients with intracranial hematoma first need to be excluded and use of the NIHSS in a prehospital setting is impractical compared to available simplified scoring systems like the Face-Arm-Speech test (FAST). The Multicenter Randomized trial of Acute Stroke

treatment in the Ambulance with a nitroglycerin Patch (MR ASAP) will investigate the effect of administering transdermal nitroglycerin, by a patch given in the ambulance, on final clinical outcome of patients with an acute stroke. One of the inclusion criteria is a score of 2-3 on the FAST.

Expanding indication for EVT.

In acute ischemic stroke the area with severe reduced blood flow will develop irreversible damage, which leads to cell death. This area is called the ischemic core. The ischemic core is surrounded by an area which is called the ischemic penumbra. The ischemic penumbra is a zone in which neuronal cells are at risk for permanent cell death, but can be saved if adequate reperfusion takes place.⁴⁴ Factors that are expected to influence the transition from the ischemic penumbra to definite ischemic core are for example 1) collateral blood supply, 2) size of the infarct core and 3) time from onset to the start of reperfusion therapy.^{45,46}

Patients with a large penumbra and a small ischemic core are expected to improve by EVT more than patients with a large ischemic core and a relatively smaller penumbra. In a recent study, DEFUSE3, it was shown that patients known to be last seen well or having a symptom onset 6-16 hours before treatment, with an infarct core <70 ml and a minimal core-penumbra mismatch on CTP or MRI-DWI, benefit from EVT.⁴⁷ Another trial, the DAWN trial in which a strict patient selection was used, namely small infarct core being, determined by CT- or MR perfusion, in combination with relatively severe neurological deficit (of at least 10 points on NIHSS), also showed that selected 'late patients' (6-24 hours after symptom onset) benefit from EVT.⁴⁸

In The Netherlands MR CLEAN LATE investigates the effect of EVT in patients who present between 6-24 hours after symptom onset or last seen well with a pragmatic patient selection. Compared to the DAWN trial, in MR CLEAN LATE patients are not selected based on infarct volume but on presence of collaterals in the infarcted area. Collaterals can be assessed with the standard CTA, already performed in these patients to confirm an LVO. Although patients meeting DAWN or DEFUSE 3 patient characteristics (small ischemic core and severe neurological deficit) will be treated directly, conform Dutch guidelines, and can therefore not be randomized in the trial, still a substantial number of patients can be included in MR CLEAN LATE due to broad inclusion criteria.⁴⁹

Improving efficiency in EVT

Before EVT became available for acute ischemic stroke, intravenous thrombolysis (IVT) with alteplase was the only proven effective therapy^{50,51} and therefore, in the large RCTs assessing EVT all eligible patients received IVT prior to EVT. The benefits of IVT given

before EVT may include early recanalization, fewer passes with a stent retriever, improved microvascular reperfusion, and lysis of distal thrombi. However, potential disadvantages are delayed start of EVT, risk for hemorrhagic complications and thrombus fragmentation with the risk of developing distal microthrombi. Therefore, it is questioned whether IVT should be given prior to EVT. MR CLEAN NO-IV investigates the effect of immediate EVT compared to IVT followed by EVT on outcome.

Implementation of EVT and health care

Now endovascular treatment has been established as the first-line therapy, acute stroke care can be further improved by focusing on the implementation of EVT, in particular on prehospital care with adequate triage of patients. One option could be sending EVT eligible patients directly to an intervention center, bypassing the nearest primary stroke center. Such a strategy is currently being investigated in the “Direct Transfer to an Endovascular Center Compared to Transfer to the Closest Stroke Center in Acute Stroke Patients With Suspected Large Vessel Occlusion (RACECAT)” study, but its results may be difficult to generalize and extrapolate to other regions and settings.⁵² To allow fast and adequate pre-hospital assessment of patients’ neurological status current neurological stroke scales need to be simplified and better reproducible. At this moment the NIHSS is the most commonly used score, but for fast pre-hospital assessment it is probably too long, and not well known among a wide number of physicians and nurses and could be replaced by for shorter test as the FAST test or the RACE scale .

Another important point for improvement of logistics for EVT includes improved speed of transport of patients in rural areas located far from intervention hospitals . Shorter times to the start for EVT have been found in studies on mobile stroke services and telemedicine. However, no difference in outcome has been found yet and further research is needed.^{53,54}

Conclusion

In patients with acute ischemic stroke with a LVO of the anterior circulation EVT has been proven effective and safe. This is also true for older patients and patients with mild stroke symptoms. Unfortunately, not all patients fully recover after EVT and its effect is proven only for a small proportion of stroke patients, which is reflected in the recommendations in current guidelines. Further research is needed to improve the effect of EVT and to expand the indication for EVT.

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Valorization

Introduction

In general, a PhD project in medicine embraces a specific discipline. This thesis embraces vascular neurology and focuses on clinical aspects of endovascular treatment of patients with acute ischemic stroke due to large vessel occlusion of the anterior circulation. Therefore, it will be of specific interest for vascular neurologists and radiologist and especially interventionists, who treat these patients. Nevertheless, it will be important to exhibit the results in a social and economic perspective. For this reason a chapter on valorization of the results of the studies in respect to its social and economic value next to research perspectives is added to this thesis.

Impact of acute ischemic stroke and social and economic relevance

Patients with acute ischemic stroke (AIS) presenting at the emergency department often suffer from severe symptoms consisting for example of facial palsy, language disturbances and paralyzed arm or leg. These neurological symptoms can have severe impact on the life of patients and their relatives. AIS can even be life threatening. In The Netherlands every year about 40.000 patients are affected by AIS of whom 8.500 die. Intravenous thrombolysis (IVT) has been standard therapy in the acute phase since it was proven effective and safe in 1995 by the NINDS rtPA Stroke Trial. However, only 10% percent of patients benefit from IVT, which is just a small part of this severely disabling illness. Apart from the positive effect of IVT in AIS, a positive effect on the prognosis after cerebral ischemia has also been proven for aspirin 160-300 milligram as well as for post-stroke care on a specialized Stroke Care Unit.

In this thesis the results of the Multicenter Randomized CLinical trial on Endovascular treatment of Acute ischemic stroke in the Netherlands (MR CLEAN) are presented. MR CLEAN was the first study to demonstrate the safety and effectiveness of endovascular treatment (EVT) in AIS caused by large vessel occlusion (LVO) in the anterior cerebral circulation. After MR CLEAN, 6 other trials presented the same results for the effect of EVT in patients with an LVO. This has led to an enormous change in the care for patients with AIS worldwide.

From a societal point of view these results may have a strong positive effect, because patients suffering a severe stroke now have a significantly higher chance to regain independency. This is a major advancement compared to the situation before where many patients who were moderately or severely disabled required intensive nursing care. So, from both individual and societal perspective these results have major impact on patient survival with good quality of life and less usage of long term health facilities as home care and nursing homes. Results from economic evaluation analysis demonstrates that EVT added to usual care is cost effective over a period of two years of follow up. The

initial investment of a rather expensive therapy as EVT treatment pays off in reduced costs of rehabilitation, physiotherapy and nursing home stay in the end.

Furthermore, more patients will be able to participate in daily working life, which will also have a positive economic effect.

The importance of logistics and intervention centers

In The Netherlands infrastructure and logistics for patients with AIS have changed drastically. Transfer of patients by ambulance services is now better accepted as an urgent procedure and patients are transferred as quickly as possible to a nearby hospital. Apart from the change in view and practice of ambulance services, another important change is the development of specialized Dutch stroke intervention centers in which dedicated teams, consisting of experienced neurologists, radiologists, interventionists and anesthesiologists, are able to treat patients immediately endovascularly 24/7 with adequate post stroke care.

Medical devices in acute ischemic stroke

With the implementation of endovascular treatment as a standard novel therapy, several new medical devices have been developed. The results of the MR CLEAN study evoked renewed interest by the industry to improve or develop new thrombectomy devices, in order to better remove the clot.

Valorization for research

The results of MR CLEAN that were confirmed by several other large randomized clinical trials led to an enormous change in the treatment of patients with AIS and an LVO. This led also to new ideas for future research. One of the questions raised was whether the time window in which patients should be treated could be extended. This will be investigated in a new trial with an extension of the inclusion window up to 24 hours after symptom onset or last seen well where patients are included if collaterals are (still) present on pretreatment CT Angiography. This study has been called MR CLEAN Late. Another important question was if direct EVT without prior IVT would lead to better patient's outcome; this will be assessed in a study called MR CLEAN NO IV. Since local hemostatic processes around the clot might influence outcome the question whether peri-procedural administration of anti-thrombotic medication has an effect on outcome will be assessed in MR CLEAN Med. Another study, MR CLEAN ASAP, will investigate the effect of prehospital transdermal nitroglycerin on patient outcome. Apart from these very interesting topics a lot of other topics deserve attention, for example effect of the interventionist's skills level, optimal anesthetic management, treatment effect in

patients with mild symptoms or with large infarct at baseline. With these future research topics a new scientific domain has developed in acute vascular neurology.

Conclusion

The results of the studies presented in this thesis have shown that endovascular treatment in acute ischemic stroke in patients with a large vessel occlusion in the anterior circulation is effective and safe. This has led to enormous changes in acute stroke care for patients and clinicians nationally and globally, and has provided a basis for new research in vascular neurology.

Summary

Summary

Cerebral ischemia develops through any form of disturbance in blood flow in brain tissue. Acute ischemic stroke (AIS) is caused by a sudden disruption of cerebral blood flow. Due to this sudden disruption of blood flow, brain tissue does not receive the needed oxygen and nutrients and with that, is at risk for permanent damage and loss of millions of neurons. An important cause for major AIS due to a sudden disruption in blood flow is occlusion of a large cerebral blood vessel or 'large vessel occlusion' (LVO) due to thrombo-emboli. To prevent patients from permanent cerebral ischemia, it is important to recognize neurological symptoms rapidly and to restore cerebral blood supply as quickly as possible. In The Netherlands approximately 40.000 patients suffer from acute cerebral ischemia annually, of whom 8.500 patients die.

Until a few years ago, patients with acute ischemic stroke were treated with a drug (recombinant tissue plasminogen activator) admitted intravenously. Unfortunately, recanalization is reached in about one third of these patients only. In patients with ischemic stroke due to LVO this number is even lower as only 1 in 10 reaches recanalization.

Already for several decades patients with acute myocardial ischemia were endovascularly treated with special catheters to reopen the blood vessels that were occluded. Knowing this treatment in cardiology, the question raised if this form of catheter treatment which is also called 'endovascular treatment' (EVT) could be used in patients with acute ischemic stroke. For decades physicians searched for opportunities to reopen acutely occluded arterial cerebral blood vessels in ischemic stroke, but this appeared more difficult than in myocardial ischemia or peripheral arterial disease. We aimed to assess the effect of EVT on outcome in patients with a LVO of the anterior circulation. In this thesis two cohorts were studied. The first group consisted of patients who were endovascularly treated prior to the start of the so called 'Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in The Netherlands' (MR CLEAN), in the MR CLEAN pretrial study. The second group related to MR CLEAN patients and aimed to investigate the effect of EVT on functional outcome.

Chapter 1 describes a general introduction to the studies of this thesis.

Chapter 2 investigates the occurrence of an LVO in patients who present with acute ischemic stroke at the emergency department of a large urban hospital in the Netherlands. We found about one third of the patients suffering from an LVO. Knowing the numbers of patients with an LVO in acute ischemic stroke helps to estimate the number of patients that could be treated endovascularly.

Before the start of the MR CLEAN study, older aged patients were often denied EVT because it was thought that older patients would not benefit from EVT. Moreover,

physicians assumed that blood vessels of older aged patients showed more often elongation and atherosclerosis with subsequent higher chance of periprocedural risks.

Chapter 3 describes the relation between age and adverse events and functional outcome after EVT in the so called 'MR CLEAN Pretrial study'. This study found that high age is inversely related with good functional outcome after EVT. Age was not associated with complications during the endovascular procedure.

The relation between the experience of the interventionist and EVT is described in **chapter 4**. It is to be expected that increased experience will lead to better patient results in terms of functional outcome and complications. In this study this relationship could not be confirmed. However, the maximum number of procedures performed per interventionist in The Netherlands at that moment was 49. Experience effect may only come to light with a higher number of procedures performed by interventionists which may be an interesting research topic in future.

In **chapter 5** the MR CLEAN protocol is described in detail.

Chapter 6 describes the results of the MR CLEAN study. In summary, MR CLEAN investigated the effect of EVT in patients with acute ischemic stroke due to LVO in the anterior cerebral blood circulation. Patients were 18 years or older and EVT was started within 6 hours after symptom onset. The results of MR CLEAN showed that EVT was effective and safe. In contrast with previously published neutral large randomized controlled trials, all patients in MR CLEAN had a proven LVO. In MRCLEAN also older aged patients and patients with mild neurological deficit or signs of large infarcts at baseline CT were included.

Chapter 7 describes the relation between age and EVT in acute ischemic stroke in MR CLEAN. The study approves that older age does influence outcome, but treatment effect remains. In other words, older patients do also benefit from EVT.

Chapter 8 describes the association between severity of neurological deficit and effect of EVT in MR CLEAN. The existence of a LVO is related to severity of neurological deficit. However, it is unknown whether this severity influences treatment effect of EVT. We found no significant association between the severity of neurological deficit and effect of EVT, meaning that patients with severe neurological deficit as well as patients with mild neurological deficit both benefit from EVT.

In **chapter 9** a general discussion of the results of the studies in this thesis and perspectives for future research are given. The most important finding was that EVT in patients with acute ischemic stroke from LVO of the anterior circulation is safe and very effective. Furthermore, older aged patients and patients with mild neurological deficit do benefit from EVT as well. Due to these positive results EVT has become standard treatment in the Netherlands and worldwide, giving new hope to many patients suffering from a devastating disease.

Nederlandse samenvatting

Nederlandse samenvatting

Een herseninfarct ontstaat doordat hersenweefsel verstoken blijft van de toevoer van bloed. Hierdoor krijgt het hersenweefsel niet de benodigde zuurstof en voedingsstoffen uit het bloed. Eén van de oorzaken hiervoor is de afsluiting van een toevoerend bloedvat door een stolsel. Het is belangrijk dat patiënten die klachten ontwikkelen welke kunnen passen bij een acuut herseninfarct –zoals een scheve mond, gestoorde spraak of verlamde arm- zo snel mogelijk behandeld worden om de bloedtoevoer te herstellen. Jaarlijks worden in Nederland zo'n 40.000 patiënten getroffen door een acuut herseninfarct waarvan er 8.500 overlijden. De acute behandeling van het herseninfarct bestond tot voor kort alleen uit het oplossen van het bloedstolsel met een medicijn (recombinant tissue plasminogen activator) dat wordt toegediend via een ader. Deze therapie noemt men ook wel intraveneuze therapie. Echter deze intraveneuze therapie leidt slechts bij een derde van de patiënten tot herstel. Bij patiënten met een afgesloten aanvoerend bloedvat is dit aantal nog veel lager, namelijk slechts 1 op de 10.

Derhalve vroeg men zich af of een katheter behandeling, zoals die ook plaatsvindt bij een hartinfarct, ook zou kunnen helpen bij een herseninfarct. Bij deze behandeling wordt een katheter via een bloedvat in de lies opgevoerd tot het niveau van het stolsel in de hersenen, waarna dit stolsel verwijderd wordt. Dit noemt men ook wel endovasculaire behandeling of intra-arteriële behandeling. Het doel is om met deze methode het achterliggende hersenweefsel weer zo snel mogelijk van bloed te voorzien voordat er onomkeerbare schade ontstaan is.

In dit proefschrift zijn patiënten met een acuut herseninfarct met een afsluiting van één van de grote hersenvaten, ook wel "large vessel occlusion" (LVO) genoemd, bestudeerd. We onderzochten hiertoe twee cohorten. De eerste groep bestond uit patiënten die endovasculair behandeld waren vóór de start van de zogenaamde 'Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in The Netherlands' (MR CLEAN). De tweede groep patiënten betrof de patiënten van de MR CLEAN studie zelf.

In **hoofdstuk 1** van dit proefschrift wordt een algemene introductie van de studies in dit proefschrift beschreven.

In **Hoofdstuk 2** wordt onderzoek gedaan naar de frequentie van het voorkomen van een LVO bij mensen die zich presenteren op de spoedeisende hulp met een herseninfarct. Informatie hierover ontbrak tot op heden. Het is van belang om dit te weten om zo een realistische schatting te kunnen maken hoeveel patiënten daadwerkelijk voor een endovasculaire behandeling in aanmerking komen. Voor dit onderzoek werd in een

groep patiënten die zich op de eerste hulp van een ziekenhuis met een acuut herseninfarct presenteerden de frequentie van het voorkomen van een LVO bestudeerd met behulp van een CT-scan van de hersenvaten. In deze groep vonden we in bijna een derde van de patiënten een LVO.

In vele grote internationale studies werden oudere patiënten met een acuut herseninfarct vaak niet geïnccludeerd, omdat men dacht dat ouderen geen baat zouden hebben van een endovasculaire behandeling. Men veronderstelde dat het vaatstelsel van de oudere patiënt vaak moeilijker te benaderen is met een katheter omdat het bijvoorbeeld meer bochtig is en meer atherosclerose bevat. Hierdoor was er geen consensus over hoe om te gaan met de oudere patiënt met de verschijnselen van een acuut herseninfarct op basis van een LVO. In hoofdstuk 3 en hoofdstuk 7 wordt ingegaan op de endovasculaire behandeling van het acute herseninfarct bij de oudere patiënt.

Hoofdstuk 3 beschrijft de relatie tussen leeftijd en nadelige uitkomsten met betrekking tot het zelfstandig functioneren en complicaties na een endovasculaire behandeling in de zogenaamde MR CLEAN-pretrial studie. De studie laat zien dat bij hoge leeftijd er weliswaar een kleinere kans op zelfstandig functioneren van de patiënt met een acuut herseninfarct is, maar het risico op complicaties die direct het gevolg zijn van de katheter behandeling niet geassocieerd is met leeftijd. In **hoofdstuk 7** wordt de relatie bestudeerd tussen leeftijd en het effect van de endovasculaire behandeling van het acute herseninfarct in de MR CLEAN studie. Het toont aan dat leeftijd niet het behandel-effect van een endovasculaire behandeling beïnvloedt. Met andere woorden, ouderen hebben net zo veel baat bij de endovasculaire behandeling als jongere patiënten, maar de kans op een goede uitkomst neemt met het stijgen van de leeftijd af.

In **hoofdstuk 4** wordt de associatie van de ervaring van de interventionist met functionele uitkomst en het optreden van complicaties bestudeerd in de MR CLEAN pretrial studie. Het is te verwachten dat meer ervaring van de behandelaar, dus het verricht hebben van meer endovasculaire procedures van het herseninfarct, zou leiden tot betere resultaten voor de patiënt. Het effect van ervaring van de interventionist op de uitkomst van de patiënt kon in deze studie niet worden vastgesteld. Echter, het maximaal aantal endovasculaire procedures dat was uitgevoerd door één interventionist was in deze studie 49. Naar verwachting zouden verschillen pas duidelijk worden bij hogere aantallen procedures, zoals bijvoorbeeld 100 of 200 procedures.

In **hoofdstuk 5** worden het studie protocol en de opzet van de MR CLEAN studie beschreven.

Hoofdstuk 6 beschrijft de resultaten van de MR CLEAN studie. Kort samengevat onderzocht MR CLEAN de effectiviteit van de endovasculaire behandeling bij patiënten met een acuut herseninfarct met een LVO van de voorste hersencirculatie. Patiënten werden hierbij in twee groepen verdeeld. Beide groepen kregen de standaard behandeling, dus ook intraveneuze trombolysie (IVT) als dat geïndiceerd was, en de interventiegroep kreeg tevens de endovasculaire behandeling. De twee groepen werden met elkaar vergeleken, waarbij de mate van zelfstandig functioneren na 3 maanden de primaire uitkomstmaat was. MR CLEAN toonde aan dat de endovasculaire behandeling veilig was en leidde tot betere functionele uitkomst van de patiënt. In tegenstelling tot eerdere internationale grote studies konden alle patiënten met een herseninfarct en een LVO, welke was aangetoond op een hersenscan, meedoen aan de studie, dus ook patiënten met milde klachten of juist met ernstige neurologische uitval.

De mate van neurologisch uitval bij aankomst in het ziekenhuis is van belang voor het eventuele herstel van de patiënt. In **hoofdstuk 8** wordt de associatie tussen de mate van neurologisch uitval en de effectiviteit van de endovasculaire behandeling beschreven. De resultaten van deze analyse toonden dat zowel patiënten met weinig als met veel neurologisch uitval baat hebben bij een endovasculaire behandeling.

In **hoofdstuk 9** wordt een algemene beschouwing en discussie van de resultaten van de verschillende hoofdstukken gegeven.

De belangrijke conclusie van dit proefschrift is dat patiënten met een acuut herseninfarct met een arteriële afsluiting door een stolsel in de voorste circulatie van de hersenen baat hebben bij een endovasculaire behandeling binnen 6 uur na het ontstaan van de klachten. Dit geldt ook voor oudere patiënten en patiënten met milde neurologische verschijnselen. Op basis van dit onderzoek is de endovasculaire behandeling opgenomen in nationale en internationale richtlijnen als standaard behandeling van het acute herseninfarct.

Dankwoord

Dankwoord

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List of publications

List of publications

1. Campbell BCV, Majoie CBLM, Albers GW, Menon BK, Yassi N, Sharma G, van Zwam WH, van Oostenbrugge RJ, Demchuk AM, Guillemin F, White P, Dávalos A, van der Lugt A, Butcher KS, Cherifi A, Marquering HA, Cloud G, Macho Fernández JM, Madigan J, Oppenheim C, Donnan GA, Roos YBWEM, Shankar J, Lingsma H, Bonafé A, Raoult H, Hernández-Pérez M, Bharatha A, Jahan R, Jansen O, Richard S, Levy EI, Berkhemer OA, Soudant M, Aja L, Davis SM, Krings T, Tisserand M, San Román L, Tomasello A, **Beumer D**, Brown S, Liebeskind DS, Bracard S, Muir KW, Dippel DWJ, Goyal M, Saver JL, Jovin TG, Hill MD, Mitchell PJ; HERMES collaborators. Penumbra imaging and functional outcome in patients with anterior circulation ischaemic stroke treated with endovascular thrombectomy versus medical therapy: a meta-analysis of individual patient-level data. *Lancet Neurol.* 2019;18(1):46-55.
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Curriculum vitae

Curriculum vitae

Debbie Beumer was born on March 12th, 1980 in Velp, The Netherlands. After finishing her pre-university education at Graafschap College in Doetinchem, she started medical school at Erasmus University, Rotterdam, the Netherlands where she obtained her medical degree in 2007.

Apart from the medical school, she followed a 'Master of Science in Neuroscience' program under supervision of Prof. dr. C.I. de Zeeuw, neuroscientist and Prof. dr. G.J. Kleinrensink, neuro-anatomist for which she graduated at the Erasmus University, Rotterdam. The subject of her thesis was neuro-anatomy combined with neurosurgical approaches under supervision of Prof. dr. A.F. Krisht, neurosurgeon in Little Rock, United States of America, together with Dr. E.J. Delwel, neurosurgeon at the Erasmus University Rotterdam.

From 2007 till 2008 she started working as a medical doctor at the neurosurgical department of the Erasmus University Medical Center under supervision of Prof. dr. C. Dirven after which she continued at the neurological department till 2009. From 2009 till 2010 she worked as a resident family medicine in Oostvoorne under supervision of Frank de Kok, general practitioner. In 2010 she went back to the neurological department of the Erasmus University Medical Center for clinical training after which she started vascular research under supervision of Prof. dr. D.W.J. Dippel, neurologist and Prof. dr. R.J. van Oostenbrugge in Maastricht and collaborated as one of the three residents in the coordination of the MR CLEAN trial. In 2013 she started her training as a resident neurology under supervision of Prof. dr. R.J. van Oostenbrugge and later Prof. dr. C.G. Faber in Maastricht.

Today she lives in Maastricht, together with her partner Hans Ubben and their three children, Elin, Karlijn and Casper.