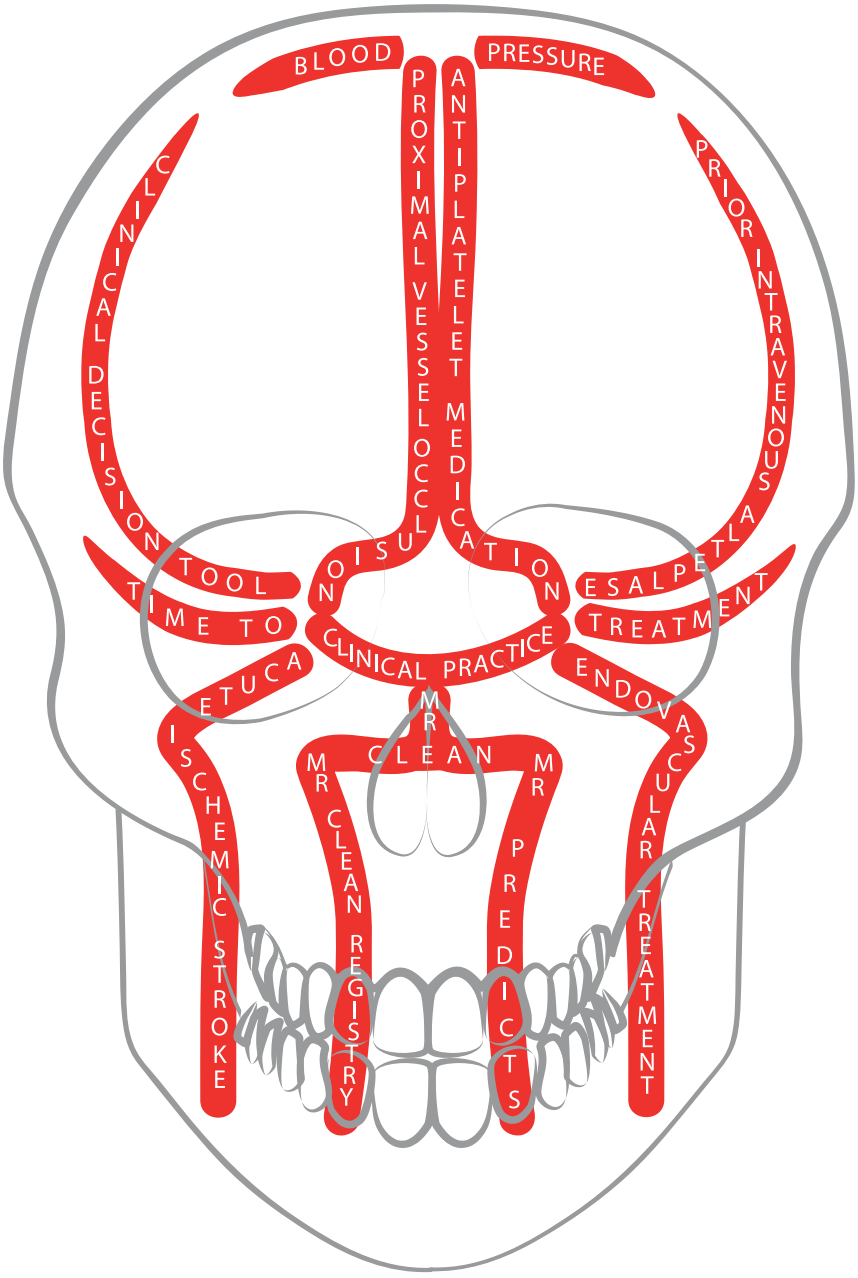
Endovascular Treatment for Acute Ischemic Stroke

Towards Personalized Treatment in Clinical Practice



Maxim J.H.L. Mulder

Endovascular Treatment for Acute Ischemic Stroke

Towards Personalized Treatment in Clinical Practice

Maxim J.H.L Mulder

The studies described in this thesis were performed at the Department of neurology and radiology, Erasmus MC, Rotterdam, the Netherlands

Financial support for the publication of this thesis was obtained from:
Hartstichting

ISBN/EAN: 978-94-028-0842-1

Design: Job Sanders & Evalyn Mulder

Endovascular Treatment for Acute Ischemic Stroke

Towards Personalized Treatment in Clinical Practice

Gepersonaliseerde intra-arteriële behandeling van het acute herseninfarct in de klinische praktijk

Proefschrift

ter verkrijging van de graad van doctor aan de
Erasmus Universiteit Rotterdam
op gezag van de rector magnificus

Prof.dr. H.A.P. Pols

en volgens besluit van het College voor Promoties.

De openbare verdediging zal plaatsvinden op
dinsdag 28 november 2017 om 15.30 uur

door

Maxim Johan Heymen Laurence Mulder

geboren te Delft

Promotiecommissie

Erasmus University Rotterdam

Promotoren:
Prof.dr. D.W.J. Dippel
Prof.dr. A. van der Lugt

Overige leden:
Prof.dr. M.G.M. Hunink
Prof.dr. C.J.M. Klijn
Prof.dr. F. Zijlstra

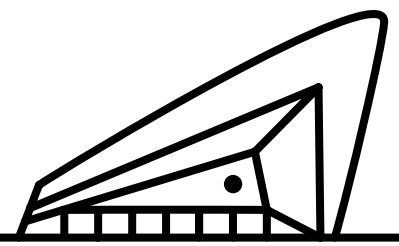
Copromotor:
Dr. H.F. Lingsma

Paranimfen:
Evalyn E.A.P. Mulder
Laus J.M.M. Mulder

Table of contents

1

Introduction



Brain

The human brain is the most complex organ of our body and it sets us humans apart from all other species. This magnificent organ consists of 86 billion neurons with terrific capabilities; controlling the whole body, processing the environment (e.g. feeling, seeing, hearing, touching), generating thoughts, storing valuable memories and communicating. The brain is a highly active organ, even while asleep. When at rest, it consumes about 20% of the cardiac output, although it weighs only 1.5 kg on average (2% of our body weight). Although our brain consumes lots of energy, it does not have an energy storage. Therefore, it is highly dependent on the supply of blood, enriched with oxygen and glucose. This blood is transported via the heart, through intracranial blood vessels, to the energy consuming neurons in the brain.

Acute ischemic stroke

Because of its high energy demand, any problem in the blood supply of our brain results in loss of brain function within just a few seconds.[1] A common cause of disrupted blood supply to the brain is an acute ischemic stroke. Stroke is the second most common cause of both death and disability.[2] In Western countries, 80% of all strokes are ischemic.[3]

Most ischemic strokes are caused by atherosclerosis or cardioembolism, resulting in a thrombus in one of the intracranial blood vessels.[3] When one of the intracranial blood vessels is blocked (i.e. occluded) with such a thrombus, focal 'neurological deficit' acutely occurs. Various deficits may occur alone or in combination, depending on both the location and extent of the arterial occlusion. Some commonly encountered deficits resulting from an ischemic stroke are: impaired speech, paresis of the arm, paresis of the leg, facial drop, loss of sensation, impaired vision, coma.

Time is brain

Every minute that a blood vessel of the brain is blocked, results in the loss of 1.9 million neurons, and 12 km of myelinated fibers. The rate of neuronal loss is comparable to rapid brain aging, 3.6 years for every hour of delayed opening of the blocked vessel.[4] Clinical deficits do not necessarily reflect irreversible damage, they may be (partially) reversible when the blocked vessel is opened timely. Therefore, early recanalization of the arterial occlusion, by removing the occluding thrombus is essential to limit or even reverse clinical deficits.[5]

Intravenous alteplase treatment

Intravenous alteplase treatment (IVT) aims to dissolve the thrombus that blocks the vessel. For over two decades IVT has been standard of care in all ischemic stroke patients that arrive early.[6] However, IVT has shown to be less effective in patients with proximal occlusions, that is, a thrombus in a large intracranial (brain) vessel. Proximal vessel occlusions represent 10-61% of acute ischemic strokes, proven with a CT/MR-angiography of the blood vessels towards and in the brain. Patients with such a proximal vessel occlusion are usually severely affected, because a large part of the brain is suddenly without oxygen and glucose supply.[7-9]Previous studies showed that in 68%-81% of these patients, IVT did not achieve acute recanalization (i.e. opening of the blood vessel).[10-12] Due to the limited response to IVT, 73% of these patients is dead or invalidated at three months after stroke.[13]

Endovascular treatment

In 1988, the first study was published that suggested endovascular treatment (EVT) to be potentially successful in achieving recanalization of proximal vessel occlusions.[14] Subsequently, multiple randomized controlled trials (RCTs) that showed that EVT was indeed more effective in achieving recanalization the brain arteries of these patients. However, these studies did not demonstrate any beneficial effect on functional outcome.[15-20] In 2015, there was a major breakthrough in EVT; MR CLEAN was the first trial to show a positive effect of EVT on functional outcome.[21] Four randomized controlled trials followed shortly, confirming that EVT is highly beneficial in these patients.[22-25] Several factors have contributed to the positive results of the latter trials: all studies required evidence of proximal vessel occlusions in the anterior circulation before randomization, newer improved devices were used, and reperfusion was achieved faster.[26]

With a number needed to treat of 2.6, EVT is considered highly effective.[13] This number needed to treat implies that almost forty patients will have improved functional outcome, when 100 patients are treated with EVT. This convincing evidence resulted in a quick update of the American Heart Association/American Stroke Association guidelines for the Early Management of Patients with Acute Ischemic Stroke. The guidelines now recommend EVT for patients with proximal anterior circulation occlusions.[27]

At the moment, efforts are being made to implement EVT in clinical practice. The treatment is performed under fluoroscopy and usually the femoral artery is punctured. Then a catheter is guided through the aorta, towards the cerebral arteries, in order to reach the thrombus which blocks the cerebral blood supply and elicits the acute neurological deficit. The objective is to restore the brain flow as soon as possible by removing the occluding thrombus, in order to achieve the highest probability that the patient's neurological status will improve. Thrombus removal is done with 'mechanical' devices (e.g. stent-retriever thrombectomy or aspiration), sometimes combined with locally used fibrinolytic medication.

Despite aforementioned evidence regarding EVT benefit, introduction of EVT in clinical practice reveals several remaining uncertainties, such as: the effectiveness of EVT in specific subgroups, optimal patient selection for EVT, and the safe implementation of EVT in clinical practice.

Endovascular treatment in specific subgroups

The inclusion and exclusion criteria of the RCTs showing benefit of EVT have resulted in underrepresentation of some specific subgroups that are encountered in clinical practice. Subgroups that are commonly encountered are patients with: old age, distal (M2) segment occlusion, no prior intravenous alteplase treatment, and high blood pressure. Extensive debate regarding the effectiveness of EVT in these subgroups remains and many centers withhold EVT in these patients. Furthermore, there is no consensus regarding additional treatments and management (in specific subgroups), such as the optimal antiplatelet regime, blood pressure lowering, and anesthesia.

Patient selection for endovascular treatment

The clear treatment benefit that was shown in the five trials can be seen as an average effect for the total treated trial population. However, it is likely that treatment benefit varies among individual patients.[28 29] It is important to consider the potential heterogeneity of treatment effects. Conventional subgroup analyses are mainly focused on differences in relative treatment effect and only assess one variable at a time. While in clinical practice, personalized treatment decisions are ideally based on absolute treatment effects, which depend on multiple patient characteristics. Using a multivariable regression modelling approach combining prognostic (differences in the absolute probability to achieve good outcome) and predictive effects (differences in the relative treatment effect), is considered to be able to assess clinically relevant heterogeneity in treatment benefit among patients.[29 30]

Endovascular treatment in clinical practice

In general, the question after positive randomized controlled trials is how to interpret the results and to what extent the results can be generalized when this treatment is used in clinical practice.[28 31] Clinical trials always use strict in- and exclusion criteria. For example, older patients are likely to be excluded. Four out of the five EVT trials, used additional imaging parameters (apart from proximal anterior circulation occlusion on CT angiography) to select eligible patients.

Overall, the stroke treatment landscape has changed since EVT is no longer an experimental treatment. We learned from the positive EVT trials, the importance of removing the thrombus as soon as possible, which emphasizes the importance of an efficient and fast workflow. Proximal anterior circulation occlusion patients are now going to the angiography suite in the comprehensive stroke center as soon as possible and the effect of intravenous alteplase is no longer awaited. Furthermore, formal written consent for EVT is no longer needed, experience is expanding, inter-hospital agreements for transfer of EVT patients are being implemented, and both EVT techniques and devices are being improved. At last, a broader patient population is treated with EVT, varying from children to patients that are 100 years old. Given all these changes, EVT in clinical practice will presumably be performed in a different population and may possibly result in different outcomes and complications compared to the recent (positive) trials.

Aims and outline of the thesis

Uncertainties regarding EVT in current clinical practice as described above have resulted in the following aim of this thesis: to improve personalized EVT for acute ischemic stroke in clinical practice.

Specific research questions are:

1. What is the effect of EVT in commonly encountered patient subgroups?
2. How can we improve EVT selection for individual patients?
3. What is the occurrence, outcome and safety of EVT in routine clinical practice?

Chapter 2 attempts to answer research question #1. The focus is on three different patient subgroups that are commonly encountered in clinical practice: patients without prior IVT (2.1), patients using prior antiplatelet medication (2.2) and the relation of baseline blood pressure with EVT (2.3). All these subgroups are studied in the MR CLEAN trial.

Chapter 3 aims to develop a clinical decision tool for EVT, in order to improve EVT selection for individual patients (research question #2). The tool is based on multiple variables, combining clinical and radiological patient characteristics. With this decision tool we aim to predict EVT benefit for individual patients.

In chapter 4, EVT in clinical practice is studied to answer research question #3. Part 4.1 focusses on the possible number of EVT candidates in clinical practice, based on the Erasmus stroke database. The subsequent parts (4.2 & 4.3), discuss the outcome and safety of EVT in current clinical practice and the association of time to treatment with EVT outcomes. This will be studied in the MR CLEAN Registry.

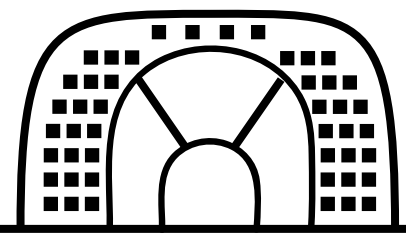
A general discussion of this thesis, including implications and future directions, are presented in Chapter 5, followed by a summary in both English and in Dutch (chapter 6).

References

1. van Putten MJ, et al. EEG Monitoring in Cerebral Ischemia: Basic Concepts and Clinical Applications. J Clin Neurophysiol 2016;33(3):203-10.
2. Lopez AD, et al. Global and regional burden of disease and risk factors, 2001: systematic analysis of population health data. Lancet 2006;367(9524):1747-57.
3. van der Worp HB, et al. Clinical practice. Acute ischemic stroke. N Engl J Med 2007;357(6):572-9.
4. Saver JL. Time is brain--quantified. Stroke 2006;37(1):263-6.
5. Rha JH, et al. The impact of recanalization on ischemic stroke outcome: a meta-analysis. Stroke 2007;38(3):967-73.
6. Adams HP, Jr., et al. Guidelines for Thrombolytic Therapy for Acute Stroke: a Supplement to the Guidelines for the Management of Patients with Acute Ischemic Stroke. A statement for healthcare professionals from a Special Writing Group of the Stroke Council, American Heart Association. Stroke 1996;27(9):1711-8.
7. Fischer U, et al. NIHSS score and arteriographic findings in acute ischemic stroke. Stroke 2005;36(10):2121-5.
8. Smith WS, et al. Significance of large vessel intracranial occlusion causing acute ischemic stroke and TIA. Stroke 2009;40(12):3834-40.
9. Lima FO, et al. Prognosis of untreated strokes due to anterior circulation proximal intracranial arterial occlusions detected by use of computed tomography angiography. JAMA Neurol 2014;71(2):151-7.
10. Christou I, et al. Arterial status after intravenous TPA therapy for ischaemic stroke. A need for further interventions. Int Angiol 2001;20(3):208-13.
11. del Zoppo GJ, et al. Recombinant tissue plasminogen activator in acute thrombotic and embolic stroke. Ann Neurol 1992;32(1):78-86.
12. Bhatia R, et al. Low rates of acute recanalization with intravenous recombinant tissue plasminogen activator in ischemic stroke: real-world experience and a call for action. Stroke 2010;41(10):2254-8.
13. Goyal M, et al. Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials. Lancet 2016;387(10029):1723-31.
14. del Zoppo GJ, et al. Local intra-arterial fibrinolytic therapy in acute carotid territory stroke. A pilot study. Stroke 1988;19(3):307-13.
15. del Zoppo GJ, et al. PROACT: a phase II randomized trial of recombinant pro-urokinase by direct arterial delivery in acute middle cerebral artery stroke. PROACT Investigators. Prolyse in Acute Cerebral Thromboembolism. Stroke 1998;29(1):4-11.
16. Furlan A, et al. Intra-arterial prourokinase for acute ischemic stroke. The PROACT II study: a randomized controlled trial. Prolyse in Acute Cerebral Thromboembolism. JAMA 1999;282(21):2003-11.
17. Ogawa A, et al. Randomized trial of intraarterial infusion of urokinase within 6 hours of middle cerebral artery stroke: the middle cerebral artery embolism local fibrinolytic intervention trial (MELT) Japan. Stroke 2007;38(10):2633-9.
18. Broderick JP, et al. Endovascular therapy after intravenous t-PA versus t-PA alone for stroke. N Engl J Med 2013;368(10):893-903.
19. Ciccone A, et al. Endovascular treatment for acute ischemic stroke. N Engl J Med 2013;368(10):904-13.
20. Kidwell CS, et al. A trial of imaging selection and endovascular treatment for ischemic stroke. N Engl J Med 2013;368(10):914-23.
21. Berkhemer OA, et al. A randomized trial of intraarterial treatment for acute ischemic stroke. N Engl J Med 2015;372(1):11-20.
22. Campbell BC, et al. Endovascular therapy for ischemic stroke with perfusion-imaging selection. N Engl J Med 2015;372(11):1009-18.
23. Goyal M, et al. Randomized assessment of rapid endovascular treatment of ischemic stroke. N Engl J Med 2015;372(11):1019-30.
24. Jovin TG, et al. Thrombectomy within 8 hours after symptom onset in ischemic stroke. N Engl J Med 2015;372(24):2296-306.
25. Saver JL, et al. Stent-retriever thrombectomy after intravenous t-PA vs. t-PA alone in stroke. N Engl J Med 2015;372(24):2285-95.
26. Hacke W. Interventional thrombectomy for major stroke--a step in the right direction. N Engl J Med 2015;372(1):76-7.
27. Powers WJ, et al. 2015 American Heart Association/American Stroke Association Focused Update of the 2013 Guidelines for the Early Management of Patients With Acute Ischemic Stroke Regarding Endovascular Treatment: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. Stroke 2015;46(10):3020-35.
28. Rothwell PM. Treating individuals 2. Subgroup analysis in randomised controlled trials: importance, indications, and interpretation. Lancet 2005;365(9454):176-86.
29. Kent DM, et al. Assessing and reporting heterogeneity in treatment effects in clinical trials: a proposal. Trials 2010;11:85.
30. Hayward RA, et al. Multivariable risk prediction can greatly enhance the statistical power of clinical trial subgroup analysis. BMC Med Res Methodol 2006;6:18.
31. Frieden TR. Evidence for Health Decision Making - Beyond Randomized, Controlled Trials. N Engl J Med 2017;377(5):465-75.

2

Uncertainties in Endovascular Treatment



2.1

Endovascular treatment in patients who are not eligible for intravenous alteplase

MR CLEAN subgroup analysis

Maxim J.H.L. Mulder, Olvert A. Berkhemer, Puck S.S. Fransen, Debbie Beumer,
Lucie A. van den Berg, MD; Hester F. Lingsma, Yvo B.W.E.M. Roos,
Robert J. van Oostenbrugge, Wim H. van Zwam, Charles B.L.M. Majoie,
Aad van der Lugt, Diederik W.J. Dippel
For the MR CLEAN investigators

August 2016
International Journal of Stroke

Abstract

Background and Purpose

Patients with acute ischemic stroke due to intracranial large vessel occlusion benefit from endovascular treatment. Uncertainty exists about the effect of endovascular treatment in patients with contraindications for treatment with intravenous alteplase treatment. Our aim was to describe the clinical characteristics of this subgroup of patients and whether endovascular treatment is as safe and effective as it is after intravenous alteplase treatment.

Methods

All 500 MR CLEAN patients were included and we distinguished between patients who were and were not treated with intravenous alteplase treatment. We estimated the effect of endovascular treatment on the shift on the modified Rankin Scale score with ordinal logistic regression analysis and tested for interaction of intravenous alteplase treatment with endovascular treatment on outcome. Furthermore, safety parameters and serious adverse events were analyzed.

Results

Fifty-five patients (11%) were not treated with intravenous alteplase treatment, mostly because of prolonged coagulation time tests or recent surgery. These patients were older and more often had atrial fibrillation or other vascular comorbidity. There was no interaction between intravenous alteplase treatment and intervention effect (p=0.927). Endovascular treatment effect size in patients without intravenous alteplase treatment was 2.06 [95% CI: 0.69–6.13] and in patients with intravenous alteplase treatment 1.71 [95% CI: 1.22–2.40]. There were no safety issues.

Conclusions

For patients with acute ischemic anterior circulation stroke caused by intracranial large vessel occlusion, who have contraindications for intravenous alteplase, intra-arterial treatment is not less effective or less safe than in patients who receive the treatment after intravenous alteplase.

Introduction

Endovascular treatment (EVT) with retrievable stents is safe and effective for patients with acute ischemic stroke (AIS) caused by a proximal intracranial occlusion in the anterior circulation.[1-5] In MR CLEAN, the intervention contrast was EVT versus no EVT against a background of best medical care, including intravenous alteplase treatment (IVT) if indicated.[5] However, whether EVT in patients with contraindications for IVT is effective and safe, is still a point of discussion.[6 7] MR CLEAN showed that intervention reached favorable outcome with and without IVT, without treatment interaction. Whether this intervention effect is supported by effect on secondary outcomes, safety of intervention, and what the reasons for no IVT, and clinical characteristics of this subgroup are, is still unknown. Therefore, this in-depth analysis of the no IVT subgroup is needed.

Reasons for not treating with IVT vary from arriving too late for IVT to be effective (beyond 4.5 h) to contraindications for treatment with thrombolytic medication because of increased risk of major bleeding or loss of efficacy.[8] Particular patients with contraindications for IVT could be included in the trial and be randomized to usual care or intervention (no IVT subgroup): late treatment between 4.5 and 6 h after onset and treatment in patients with possible elevated bleeding risk after thrombolytic medication.[9] The MR CLEAN trial was one of the three recent trials which allowed randomization despite contraindications for IVT.[2 3 5]

In this subgroup analysis, we describe the clinical characteristics of patients with contraindications for IVT, and the effectiveness and safety of EVT in this specific subgroup.

Methods

Patient eligibility and methods of the MR CLEAN trial have been reported previously.[5 9] In short, MR CLEAN was a randomized clinical trial of EVT versus
no EVT along with best medical care in patients with a proximal intracranial arterial occlusion in the anterior circulation demonstrated on vessel imaging, treatable within 6 h after symptom onset. Background medical management was delivered according to national standards and guidelines, and could include treatment with IVT within the first 4.5 h after onset of symptoms. Particular patients with contraindications for IVT could be included in the trial and be randomized to usual care or intervention: late treatment between 4.5 and 6 h after onset and treatment in patients with possible elevated bleeding risk after thrombolytic medication (an elevated increased international normalized ratio (INR) (1.7–3.0), a thrombocyte count of 40– 90x10^9/L, a history of intracerebral hemorrhage, severe head injury<four weeks, previous AIS in a different vascular distribution in the preceding six weeks, arterial puncture at a non-compressible site within the previous seven days, and major surgery, gastro-intestinal bleeding or urinary tract bleeding within the previous two weeks).[9]

All patients or their legal representatives provided written informed consent before randomization. The central medical ethics committee and the research board of each participating center approved the study protocol.[9] This is a post-hoc analysis.

Outcome and Safety Measures

The primary outcome measure was the modified Rankin Score (mRS) at 90 days. Secondary outcome measures included functional independence (mRS 0–2) at 90 days and neurological assessment with NIHSS at 24 h and five to seven days or discharge if earlier, and activities of daily living measured with the Barthel Index. Radiological outcome measures included arterial recanalization measured with Computed Tomography Angiography (CTA) or Magnetic Resonance Angiogram at 24 h, the modified Thrombolysis in Cerebral Infarction (TICI) score on Digital Subtraction Angiography (DSA), and final infarct volume on non-contrast CT (NCCT) at five to seven days. Safety parameters included hemorrhagic complications, hemicraniectomy, progression of ischemic stroke, recurrent ischemic stroke, and death. Symptomatic intracranial hemorrhage (SICH) was defined as neurological deterioration of four or more points on the NIHSS and neuroimaging confirmed intracranial hemorrhage. 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.[10] Progression of ischemic stroke was defined as neurological deterioration with an increase of two or more points on the NIHSS, follow-up CT or MRI brain compatible with diagnosis of ischemia, and no other obvious cause for neurological deterioration.

Statistical Analysis

Patients were analyzed according to the intention to treat principle. The primary effect parameter was the adjusted common odds ratio (acOR) for a shift in direction of a better outcome on the mRS, which was estimated with multivariable ordinal logistic regression analysis. We used multiplicative interaction terms to test for interaction of IVT with intervention on outcome.

The acOR and all secondary effect parameters were adjusted for potential imbalances in major prespecified prognostic variables adapted from the original trial protocol statistical analysis plan: age, time since onset to randomization, previous stroke, atrial fibrillation, diabetes mellitus, and presence of intracranial carotid artery terminus occlusion. The common odds ratios were reported with 95% confidence intervals (CI) to indicate statistical precision. Patients who died were not assigned NIHSS scores and were not included in analyses of such scores. Safety parameters and serious adverse events (SAEs) in IV subgroups were analyzed and divided according to treatment allocation. Interaction terms on these outcomes between IVT and EVT were calculated. Binary outcomes were analyzed with logistic regression and reported as odds ratios with 95% CIs. All p-values are two-sided. Statistical analyses were performed with Stata/SE 13.1 (StataCorp, Texas, USA).

Results

Patient and center characteristics

Of the 500 patients randomized in MR CLEAN, 445 (89%) received IVT (Figure 1). Of the 445 patients who were treated with IVT 203 (46%) were allocated to intervention (Table 1). Of the 55 patients who were not treated with IVT, 30 (55%) were allocated to intervention. In the IVT group, 416 (93%) patients were treated with IVT within 3 h from symptom onset, 27 (6%) within 3.0–4.5 h, and 2 (1%) after 4.5 h.

Of the 55 patients in the no IVT group, five patients (9%) were admitted outside the time window for IVT (0–4.5 hours) and 44 patients (80%) had possible elevated bleeding risk mostly with INR with a mean of 2.2 (1.7–2.7) or recent surgery (Table 1). In the remaining 6 (11%) patients, reasons for not treating with IVT were not formal contraindications. Patients not treated with IVT were on average 2.1 years older, more often had atrial fibrillation, had a higher pre-stroke mRS, less often used antiplatelet medication, and used more anticoagulant medication (Table 2). In their medical history, there was more ischemic stroke, more hypertension, and more peripheral arterial disease. In the no IVT subgroup, there were no differences in baseline characteristics for control vs. intervention except for occlusion side, with more strokes in the left hemisphere in the intervention arm.

Figure 1. Intravenous alteplase treatment and treatment allocation in the MR CLEAN trial. IVT: intravenous alteplase treatment.

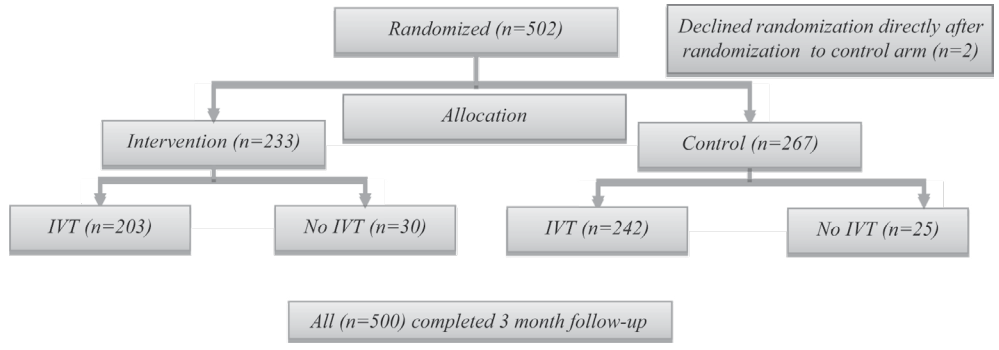


Table 1. Contraindications and other reasons for no treatment with intravenous alteplase.

	Total (n=55)	Intervention (n=30)	Control (n=25)
INR 1.7-3.0	18	12	6
Platelet count less than 90 x 10^9/L	2	1	1
Surgery or intervention within 2 weeks prior to event	15	7	8
Recent ischemic stroke within 6 weeks prior to event	4	3	1
Use of contraindicated anticoagulants	4	2	2
Time from onset to arrival exceeds 4.5 hours	5	3	2
Cerebral contusion within 4 weeks prior to event	1	1	0
Other reasons	6	2	4

Table 2. Clinical characteristics of IVT & no IVT subgroups.

	IVT (N=445)	No IVT (n=55)
Age - median (IQR)	65.4 (54.3-76.2)	67.5 (61.5-77.8)
Male sex – n. (%)	257 (58%)	35 (64%)
NIHSS - median (IQR)	18 (14-22)	19 (14-22)
Clinical localization: Left hemisphere – n. (%)	239 (54%)	30 (55%)
Atrial Fibrillation – n. (%)	105 (24%)	30 (55%)
History of Ischemic Stroke – n. (%)	43 (10%)	11 (20%)
History of Hypertension – n. (%)	194 (44%)	33 (60%)
History of Diabetes Mellitus – n. (%)	56 (13%)	12 (22%)
History of Myocardial Infarction – n. (%)	69 (16%)	6 (11%)
History of Peripheral Artery Disease – n. (%)	17 (4%)	7 (13%)
History of Hyperlipidemia – n. (%)	116 (26%)	13 (24%)
Current Smoking – n. (%)	129 (29%)	14 (25%)
Current Statin Use – n. (%)	124 (28%)	19 (35%)
Current Antiplatelet Use – n. (%)	135 (30%)	9 (16%)
Current Anticoagulant Use – n. (%)	16 (4%)	23 (42%)
Systolic blood pressure - mean mmHg (SD)	146 ± 25	144 ± 25
Pre-stroke modified Rankin Scale score – n. (%)		
0	368 (83%)	36 (65%)
1	43 (10%)	7 (13%)
2	18 (4%)	7 (13%)
3	10 (2%)	5 (9%)
4	4 (1%)	0
5	2 (0%)	0
Level of Occlusion – n. (%)		
ICA	3 (1%)	1 (2%)
ICA-T	120 (27%)	14 (25%)
M1	282 (64%)	37 (67%)
M2	37 (8%)	2 (4%)
A1	2 (0%)	1 (2%)
Onset to IV alteplase in min - median (IQR)	85 (65-110)	NA
Onset to randomization in min - median (IQR)	201 (153-262)	191 (134-253)
Onset to EVT in min - median (IQR)	265 (214-315)	242 (200-300)
Onset to reperfusion in min - median (IQR)	343 (283-394)	310 (242-404)
Duration of procedure in min – median (IQR)	72 (52-97)	67 (43-88)

Primary outcome

The effect size in patients not treated with IVT was similar to that in patients treated with IVT (Table 3). This was not different after adjustment for prognostic factors (no IVT: acOR=2.1 [95% CI: 0.7–6.1]; IVT: acOR=1.7[95% CI: 1.2-–2.4]). The overall effect of EVT was positive and significant (acOR=1.67 95% CI: 1.21–2.30) and there was no significant interaction between IVT and EVT (p=0.927). No patients were lost to follow-up.

Secondary outcomes and safety parameters

For secondary clinical and neuro-imaging outcomes, the effect of EVT was positive and significant, with no significant interaction between IVT and EVT for any secondary outcome (Table 3). After adjustment for prognostic factors, effect sizes were slightly attenuated, but again no significant interaction was found. All secondary outcomes suggest benefit of EVT in the no IVT group and were significant for NIHSS after one week and recanalization on follow-up imaging (Table 4).

Table 3. Primary and secondary outcomes and treatment effect of endovascular treatment in patients with and without intravenous alteplase treatment.

	IVT (n=445)	No IVT (n=55)		Unadjusted intervention effect in IVT group (95% CI)	Unadjusted effect of intervention in no IVT (95% CI)	Treatment interaction (p-value)
Primary						
mRS at 90 days – median (IQR)	2 (1-4)	2 (0-3)	cOR	1.7 (1.2 to 2.4)	1.5 (0.6 to 4.0)	0.927
Secondary – clinical						
mRS 0-2 at 90 days – n. (%)	117 (27%)	10 (18%)	OR	2.1 (1.3 to 3.2)	2.2 (0.5 to 9.7)	0.929
NIHSS at 5-7 days or discharge – mean (SD)*	12 (±8)	12 (±8)	β	-2.9 (-4.5 to -1.2)	-6.5 (-11.5 to -1.6)	0.116
Barthel Index of 19 or 20 at 90 day – n. (%)	161 (40%)	11 (21%)	OR	2.0 (1.4 to 3.1)	2.5 (0.6 to 11.0)	0.777
Secondary – radiological						
No intra-cranial occlusion on follow-up CTA – n. / total n. (%)	188/354 (53%)	21/40 (53%)	OR	5.9 (3.7 to 9.4)	11.9 (2.7 to 53.0)	0.380
Final infarct volume on follow-up NCCT - n. (% of total)†	278 (62%)	30 (55%)				
Volume in milliliters – mean (SD)	82 (±72)	94 (±87)	β	-25.0 (-42.0 to -8.1)	8.8 (-60.0 to 77.7)	0.245

Abbreviations: 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, 18 missing*
† Final infarct volume on NCCT after 5 days (range 3-9 days)

Table 4. Secondary outcomes in intervention and control of IVT subgroups.
** NIHSS was measured in survivors only, 18 missing*
† Final infarct volume on NCCT after 5 days (range 3-9 days)

	IVT		No IVT	
	Intervention (n=203)	Control (n=242)	Intervention (n=30)	Control (n=25)
mRS 0-2 at 90 days – n. (%)	69 (34%)	48 (20%)	7 (23%)	3 (12%)
NIHSS at 5-7 days or discharge - median (IQR)*	9 (2-17)	14 (7-18)	7 (2-14)	17 (10-22)
Barthel Index 19-20 at 90 days – n./total n. (%)	91/186 (49%)	70/219 (32%)	8/29 (28%)	3/23 (13%)
Recanalization during intervention (TICI score 2B/3) – n./ total n. (%)	98/168 (58%)	-	18/29 (62%)	-
No intra-cranial occlusion on follow-up CTA – n./ total n. (%)	124/165 (75%)	64/189 (34%)	17/22 (77%)	4/18 (22%)
Final infarct volume on follow-up NCCT total n. – median (IQR)†	126 47 (22-93)	152 80 (38-126)	19 56 (23-148)	11 66 (27-138)

Table 5. Safety parameters and serious adverse events.

	IVT		No IVT		
	Intervention (n=203)	Control (n=242)	Intervention (n=30)	Control (n=25)	Treatment interaction (p-value)
Safety parameters					
Death within 90 days - n (%)	39 (19%)	51 (21%)	10 (33%)	8 (32%)	0.778
Hemicraniectomy - n (%)	12 (6%)	11 (5%)	2 (7%)	2 (8%)	0.673
Serious Adverse Events*					
Patients with at least one SAE - n (%)	92 (45%)	100 (41%)	18 (60%)	13 (52%)	0.779
Symptomatic ICH - n (%)	16 (8%)	15 (6%)	2 (7%)	2 (8%)	0.680
- Parenchymal hematoma type 1	0	2 (1%)	0	0	-†
- Parenchymal hematoma type 2	12 (6%)	13 (5%)	2 (7%)	1 (4%)	-†
- Hemorrhagic infarction type 1	1 (0%)	0	0	0	-†
- Hemorrhagic infarction type 2	1 (0%)	0	0	1 (4%)	-†
- Subarachnoid hemorrhage	2 (1%)	0	0	0	-†
Recurrent ischemic stroke - n (%)	10 (5%)	0	3 (10%)	1 (4%)	-†
Progression of Ischemic stroke - n (%)	40 (20%)	42 (17%)	6 (20%)	6 (24%)	0.577
Pneumonia - n (%)	21 (10%)	37 (15%)	6 (20%)	6 (24%)	0.765
Other Infection - n (%)	14 (7%)	10 (4%)	2 (7%)	0	0.990
Cardiac Ischemia - n (%)	1 (0%)	4 (2%)	0	0	-†
Extracranial Hemorrhage - n (%)	0	2 (1%)	0	0	-†
Allergic Reaction - n (%)	0	0	1 (3%)	0	-†
Other Complication - n (%)	24 (12%)	32 (13%)	4 (13%)	5 (20%)	0.650

Abbreviation: ICH = Intra Cerebral Hemorrhage
** Only first events of one type are listed. Patients experiencing multiple events of one type have been counted once.*
† Too few events for interaction analysis

Recanalization rates were higher on CTA after 24 h than after intervention (17/22=77% vs. 18/29=62%) in the no IVT group allocated to EVT. In this subgroup patients who had both DSA and follow-up CTA, 13/22 (59%) had TICI 2B/3 on DSA and 17/22 (77%) had recanalization on CTA. Median final infarct volume was lower in the EVT (56 vs 66 mL) group of patients with contraindications for IVT despite higher mean values, because of outliers. Secondary clinical and radiological outcomes in our population cohort further support this effect size of EVT in patients with IVT contraindications. There were no differences in occurrence of death, hemicraniectomy, and SAE's between intervention and control both among the patients who were and who were not pretreated with IVT (Table 5).

Discussion

We compared outcomes, safety parameters, SAE's, and treatment effect between MR CLEAN patients who were and were not pretreated with IVT in a randomized clinical trial of EVT versus usual care for AIS. We found no interaction between IVT pretreatment and EVT for the primary or any of the secondary outcomes or for SAE's: outcomes and treatment effect in patients were similar for pretreated patients and not pretreated patients. Moreover, we observed no differences in the occurrence of death and SAE's between patients with and without EVT in those who were not pretreated with IVT.

Other studies

Patients with contraindications for IVT show similar effect size of EVT as patients treated with IVT. These data are corroborated by subgroup analysis in Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion With Emphasis on Minimizing CT to Recanalization Times (ESCAPE) and Randomized Trial of Revascularization With Solitaire FR Device Versus Best Medical Therapy in the Treatment of Acute Stroke Due to Anterior Circulation Large Vessel Occlusion Presenting Within Eight Hours of Symptom Onset (REVASCAT).[2 3] Moreover, when effects in these subgroups of the three trials are meta-analyzed, there is a significant effect (OR=1.7[95% CI: 1.2–2.4]).[6] The updated AHA/ASA guidelines for the early treatment of AIS state that: "Too few data are available from the small number of those who did not receive intravenous r-tPA, either for time-based or non-time-based exclusion criteria, to determine with certainty if there are characteristics that identify those who benefited from endovascular treatment."[7] Our analysis and the combined effect estimate from the three trial data support the benefit of EVT in these patients. We look forward to patient level-pooled analysis together with ESCAPE and REVASCAT, and expect similar effect sizes with significant odds ratios.

The difference in recanalization between CTA at 24h and DSA, which was also found in the main paper,[5] may be explained by further spontaneous recanalization, perhaps through facilitation of the endogenous thrombolytic pathway.

Safety

Patients with contraindications for IVT comprise a heterogeneous group. They are older, more often have atrial fibrillation, a history of ischemic stroke, hypertension, or peripheral arterial disease. The high prevalence of atrial fibrillation (AF) in the patients who are not treated with IVT can be explained by concomitant use of coumarines. Because these patients often have a complicated vascular history and 25% had recent surgery or interven-

tion (often cardiothoracic), this could very well explain the higher rate of mortality in this subgroup overall compared to the IVT pretreated patients. Similarly, the high frequency of recent cardiothoracic surgery or intervention and of atrial fibrillation likely explains the higher rate of recurrent ischemic stroke. Taken together, it is no surprise that functional outcomes are somewhat less favorable in this subgroup than in pretreated patients. Importantly, functional and radiological outcomes suggest effect of EVT in the no IVT subgroup. Furthermore mortality and occurrence of SAE's were not different between patients with and without EVT in those who were not pretreated with IVT. Therefore EVT appears safe in this population.

Limitations

A limitation of this study is the small number of patients who did not receive IVT (n=55). No effect was found on final infarct volume (n=30) after intervention in the no IVT group despite lower median value; this is likely caused by outliers in the intervention group. Since there were no differences in occurrence of SICH between pretreated and not pretreated patients, but our study size was such that the power to detect differences was limited. Moreover, since only five patients (9%) were admitted outside the time window for IVT (0–4.5 h), this subgroup is not informative of patients who present beyond the 4.5 h window.

However, as there is no sign of interaction with treatment and the observed effects are clinically plausible, and above that, effect sizes are similar, we propose that there is no reason to assume that the effect of EVT in patients with contraindications for IVT is different from the effect in patients without these contraindications. This conclusion is further supported by a meta-analysis of effect estimates of EVT in the no IVT subgroups from MR CLEAN, ESCAPE, and REVASCAT.[6] We look forward to the results of a pooled analysis of the individual patient data of all trials.

Conclusions

For patients with acute ischemic anterior circulation stroke caused by intracranial large vessel occlusion, who have contraindications for intravenous alteplase, intra-arterial treatment is not less effective or less safe than in patients who receive the treatment after intravenous alteplase.

References

1. Saver JL, et al. Stent-retriever thrombectomy after intravenous t-PA vs. t-PA alone in stroke. N Engl J Med 2015;372(24):2285-95.
2. Jovin TG, et al. Thrombectomy within 8 hours after symptom onset in ischemic stroke. N Engl J Med 2015;372(24):2296-306.
3. Goyal M, et al. Randomized assessment of rapid endovascular treatment of ischemic stroke. N Engl J Med 2015;372(11):1019-30.
4. Campbell BC, et al. Endovascular therapy for ischemic stroke with perfusion-imaging selection. N Engl J Med 2015;372(11):1009-18.
5. Berkhemer OA, et al. A randomized trial of intraarterial treatment for acute ischemic stroke. N Engl J Med 2015;372(1):11-20.
6. Mulder MJ, et al. Letter by Mulder et al Regarding Article, "2015 AHA/ASA Focused Update of the 2013 Guidelines for the Early Management of Patients With Acute Ischemic Stroke Regarding Endovascular Treatment: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association". Stroke 2015;46(11):e235.
7. Powers WJ, et al. 2015 American Heart Association/American Stroke Association Focused Update of the 2013 Guidelines for the Early Management of Patients With Acute Ischemic Stroke Regarding Endovascular Treatment: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. Stroke 2015;46(10):3020-35.
8. Jauch EC, et al. Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2013;44(3):870-947.
9. Fransen PS, et al. MR CLEAN, a multicenter randomized clinical trial of endovascular treatment for acute ischemic stroke in the Netherlands: study protocol for a randomized controlled trial. Trials 2014;15:343.
10. Fiorelli M, et al. Hemorrhagic transformation within 36 hours of a cerebral infarct: relationships with early clinical deterioration and 3-month outcome in the European Cooperative Acute Stroke Study I (ECASS I) cohort. Stroke 1999;30(11):2280-4.

2.2

Prior antiplatelet treatment and functional outcome after endovascular treatment

MR CLEAN subgroup analysis

Maxim J.H.L. Mulder, Olvert A. Berkhemer, Puck S.S. Fransen, Debbie Beumer, Lucie A. van den Berg, Hester F. Lingsma, Heleen M den Hertog, Julie Staals, Sjoerd F.M. Jenniskens, Robert J. van Oostenbrugge, Wim H. van Zwam, Charles B.L.M. Majoie, Aad van der Lugt, Diederik W.J. Dippel
For the MR CLEAN investigators

July 2017
International Journal of Stroke

Abstract

Background and Purpose

In patients with acute ischemic stroke who receive antiplatelet treatment, uncertainty exists about the effect and safety of endovascular treatment. Our aim was to study whether endovascular treatment in patients with prior antiplatelet treatment is safe and whether prior antiplatelet treatment modifies treatment effect.

Methods

All 500 MR CLEAN patients were included. We estimated the effect of endovascular treatment with ordinal logistic regression analysis, and tested for interaction of antiplatelet treatment with endovascular treatment on outcome. Furthermore, safety parameters and serious adverse events were analyzed.

Results

The 144 patients (29%) on antiplatelet treatment were older, more often male, and had more vascular comorbidity. Endovascular treatment effect size after adjustments in antiplatelet treatment patients was 1.7 (95% confidence interval 0.9–3.2), and in no antiplatelet treatment patients 1.8 (95% confidence interval: 1.2–2.6). There was no statistically or clinically significant interaction between prior antiplatelet treatment and the relative effect of endovascular treatment (p=0.78). However, in patients on antiplatelet treatment, the effect of successful reperfusion on functional outcome in the intervention arm of the trial was doubled: the absolute risk difference for favorable outcome after successful reperfusion in patients on prior antiplatelet treatment was 39% versus 18% in patients not on prior antiplatelet treatment ($P_{interaction}$=0.025). Patients on antiplatelet treatment more frequently had a symptomatic intracranial hemorrhage (15%) compared to patients without antiplatelet treatment (4%), without differences between the control and intervention arm.

Conclusions

Prior treatment with antiplatelet agents did not modify the effect of endovascular treatment in patients with acute ischemic stroke presenting with an intracranial large vessel occlusion. There were no safety concerns. In patients with reperfusion, antiplatelet agents may improve functional outcome.

Introduction

Although randomized controlled trials (RCTs) showed benefit of endovascular treatment (EVT) in patients with acute ischemic stroke (AIS) due to intracranial large vessel occlusion, a large proportion of patients still experiences poor outcome at three months.[1-6] Large ischemic core, but also incomplete microvascular reperfusion may be responsible for the high rate of poor outcome, even after acute endovascular reperfusion.[7]

International guidelines recommend that patients with acute myocardial infarction undergoing primary percutaneous coronary intervention receive a combination of multiple antiplatelet agents and anticoagulant medication ''as early as possible before angiography,'' for optimal outcome.[8] The use of antiplatelet medication in the acute phase of AIS in general has a small beneficial effect, and there is no net effect of anticoagulant treatment in AIS.[9] Early administration of intravenous aspirin in AIS patients treated with intravenous alteplase (IVT) is associated with increased risk of intracranial hemorrhage,[10] and this may also be the case for EVT. In the recently published trials that show benefit of EVT in patients with AIS with large vessel occlusion, and in recently updated guidelines, the role of antithrombotic medication in the acute phase is not addressed.[1-5 11 12]

Hence, we need an answer to the question whether treatment with antithrombotic or antiplatelet agents directly before EVT leads to better outcomes than the current strategy, which is to postpone this treatment to 24 hours after intervention, similar to what was recommended after IVT. The first step is to analyze the effect and safety of EVT in patients who were already on antiplatelet treatment (APT). In this MR CLEAN subgroup analysis, we describe the clinical characteristics of patients on APT, their functional outcome, and the effectiveness and safety of EVT in this specific subgroup.[10]

Methods

Patient eligibility and methods of the MR CLEAN trial have been reported previously.[1 13] In short, MR CLEAN was a randomized clinical trial of EVT versus no EVT along with best medical care in patients with a proximal intracranial arterial occlusion in the anterior circulation demonstrated on vessel imaging, treatable within 6 h after symptom onset. Background medical management was delivered according to national standards and guidelines, and could include treatment with IVT within the first 4.5 hours after onset of symptoms. We distinguished between patients who were on daily APT (e.g., any antiplatelet agent) and those who were not.

All patients or their legal representatives provided written informed consent before randomization. The central medical ethics committee and the research board of each participating center approved the study protocol.[13] This is a post-hoc analysis.

Outcome and Safety Measures

The primary outcome measure was the modified Rankin Score (mRS) at 90 days.[14] Secondary outcome measures included 90-day functional independence (mRS 0–2), favorable outcome (mRS 0–3), neurological assessment with the National Institute of Health Stroke Score (NIHSS) at five to seven days or discharge if earlier. Radiological outcome measures included the modified thrombolysis in cerebral infarction (mTICI) score on digital subtraction angiography (DSA), arterial recanalization measured with computed tomography angiography (CTA) or magnetic resonance angiogram (MRA) at 24 hours, and final infarct

volume on noncontrast CT (NCCT) at five to seven days.[15 16] An independent rater (A.J.Y.) assessed angiographic outcomes on DSA imaging, using the mTICI score, which ranges from 0 (no reperfusion) to 3 (complete reperfusion).[15]

Safety parameters included hemorrhagic complications, hemicraniectomy, progression of ischemic stroke, pneumonia, other infections, and death. Symptomatic intracranial hemorrhage (SICH) was defined as neurological deterioration of four or more points on the NIHSS and neuroimaging confirmed intracranial hemorrhage. We used the European Cooperative Acute Stroke Study (ECASS) classification of intracerebral hemorrhage.[17] Progression of ischemic stroke was defined as neurological deterioration with an increase of two or more points on the NIHSS, follow-up CT or MRI brain compatible with diagnosis of ischemia, and no other obvious cause for neurological deterioration.

Statistical Analysis

Data were analyzed according to the intention to treat principle. The primary effect parameter was the adjusted common odds ratio (acOR) for a shift in direction of a better outcome on the mRS, which was estimated with multivariable ordinal logistic regression analysis. The common odds ratios were reported with 95% confidence interval (CI) to indicate statistical precision. Binary outcomes were analyzed with logistic regression and reported as odds ratios with 95% CI. The acOR and all secondary effect parameters were adjusted in two steps, first for major prognostic factors: age, NIHSS at baseline, and collateral score. In the second step, we added baseline characteristics that significantly differed between patients with APT and without APT and could account for confounding by indication. We used multiplicative interaction terms to test for interaction of APT with intervention on outcome. Safety parameters in APT subgroups were analyzed and divided according to treatment allocation. All p-values are two-sided. Statistical analyses were performed with Stata/SE 13.1 (StataCorp, Texas, USA).

Results

Patient characteristics

Of the 500 patients randomized in MR CLEAN, 144 patients (29%) were on APT (Figure 1). Most patients on APT were on monotherapy only (>95% using aspirin), 33 patients (23%) were on dual antiplatelet treatment. Patients on dual antiplatelet treatment most often used a combination of aspirin and dipyridamole (70%) or aspirin and clopidogrel (27%).

Figure 1. Treatment allocation and prior antiplatelet use in the MR CLEAN trial.

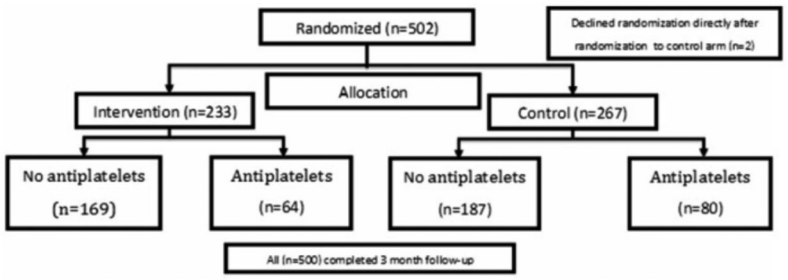


Table 1. Clinical characteristics of antiplatelet treatment (APT) subgroups.

	No APT (N=356)	APT (n=144)
Age - median (IQR)	63 (53-74)	71 (62-78)
Male sex – n. (%)	196 (55%)	96 (67%)
NIHSS - median (IQR) *	18 (14-22)	18 (15-22)
Clinical localization: left hemisphere – n. (%)	187 (53%)	82 (57%)
Baseline systolic blood pressure (mmHg) - mean(SD)	144 ± 25	148 ± 26
Medical history		
Atrial fibrillation – n. (%)	86 (24%)	49 (34%)
Ischemic stroke – n. (%)	14 (4%)	40 (28%)
Hypertension – n. (%)	129 (36%)	98 (68%)
Diabetes mellitus – n. (%)	42 (12%)	26 (18%)
Myocardial infarction – n. (%)	12 (3%)	63 (44%)
Peripheral artery disease – n. (%)	11 (3%)	13 (9%)
Intoxication & medication		
Current smoking – n. (%)	101 (28%)	42 (29%)
Statin use – n. (%)	55 (15%)	88 (61%)
Anticoagulant use – n. (%)	33 (9%)	6 (4%)
Pre-stroke modified Rankin Scale score – n. (%)		
0	299 (84%)	105 (73%)
1	29 (8%)	21 (15%)
2	15 (4%)	10 (7%)
>2	13 (4%)	8 (6%)
Imaging		
Level of occlusion on non-invasive vessel imaging– n. (%)‡		
ICA	3 (1%)	1 (1%)
ICA-T	101 (28%)	33 (23%)
M1	218 (61%)	101 (70%)
M2	30 (8%)	9 (6%)
A1	3 (1%)	0
ASPECTS on NCCT– median (IQR) †	9 (7-10)	9 (8-10)
Workflow		
Onset to ER in min - median (IQR)	99 (45-195)	82 (50-180)
Onset to IV alteplase in min - median (IQR)	83 (65-110)	91 (68-120)
Onset to randomization in min - median (IQR) §	202 (149-261)	199 (154-260)
Onset to IAT in min - median (IQR)	258 (210-305)	260 (214-315)
Onset to reperfusion in min - median (IQR)	339 (271-393)	342 (278-410)
Duration of procedure in min – median (IQR)	73 (52-101)	68 (47-93)

** Scores on the National Institutes of Health Stroke Scale (NIHSS) The NIHSS is a 15-item scale, and values for 30 of the 7500 items were missing (0.4%).*
† The Alberta Stroke Program Early Computed Tomography Score (ASPECTS). 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, so the level of occlusion was not known.
§ Data were missing for two patients

Table 2. Primary and secondary outcomes and effect of intra-arterial treatment (IAT) in patients with and without antiplatelet treatment (APT), adjusted for age, sex, NIHSS, collateral score and vascular comorbidity.†

	Outcome			IAT effect		
	No APT (n=356)	APT (n=144)		No APT (95% CI)	APT (95% CI)	*Treatment interaction (p-value)*
Primary						
mRS at 90 days – median (IQR)	2 (2-4)	2 (0-3)	cOR	1.8 (1.2 to 2.7)	1.7 (0.9 to 3.2)	0.78
Secondary – clinical						
mRS 0-2 at 90 days – n. (%)	97 (28%)	60 (20%)	OR	2.3 (1.4 to 3.9)	2.0 (0.7 to 5.3)	0.71
mRS 0-3 at 90 days – n. (%)	167 (47%)	47 (33%)	OR	2.2 (1.3 to 3.5)	1.8 (0.8 to 4.1)	0.75
NIHSS at 5-7 days or discharge – mean (SD)*	12 (±8)	11 (±8)	β	-3.1 (-4.7 to -1.5)	-3.0 (-5.8 to -0.3)	0.72
Barthel Index of 19 or 20 at 90 days - n.(%)	131 (41%)	41 (30%)	OR	2.3 (1.4 to 3.9)	2.1 (0.9 to 4.7)	0.79
Secondary – radiological						
No intra-cranial occlusion on follow – up imaging – n. / total n. (%)	151/289 (52%)	58/105 (55%)	OR	6.9 (4.0 to 11.8)	9.5 (3.3 to 27.8)	0.50
Final infarct volume on follow-up NCCT - n. (% of total) ‡	224 (63%)	84 (58%)				
Final infarct volume in millilitres – mean (SD)	82 (±73)	87 (±78)	β	-22.4 (-40.0 to -4.8)	-26.3(-60.7 to 8.1)	0.51

Abbreviations: 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

* *Scored in survivors only (56 died), 18 missing*

† *Chi-square test of the difference in log likelihood ratios of the undatjusted model vs. the model with adjustment for prognostic variables and significant different baseline variables showed significant improvement after adjustments (p<0.001).*

‡ *Final infarct volume on NCCT after 5 days (range 3-9 days)*

Patients in the APT subgroup were on average 8.1 years older, more often male, and more often had an increased prestrike mRS (Table 1). They more often had a history of ischemic stroke, hypertension, myocardial infarction, atrial fibrillation, and peripheral arterial disease, and more frequently used statins. In the APT subgroup nor in the no APT subgroup there were differences in baseline characteristics between the control and intervention arm.

Primary outcome

There was no interaction between APT and EVT (p=0.78). The effect estimate of EVT in the APT group without any adjustments was small (cOR=1.2 [95% CI: 0.7–2.2]), but increased after adjustment for prognostic factors (acOR=1.5 [95% CI: 0.8–2.8]). After adjustment for prognostic factors and baseline differences, effect sizes were similar in both subgroups (APT: acOR=1.7 [95% CI: 0.9–3.2]; no APT: acOR=1.8 [95% CI: 1.2–2.7]).

Secondary outcomes and safety parameters

EVT effect was comparable for secondary outcomes in both APT subgroups (Tables 2 & 3). There was no statistically or clinically significant interaction between APT and the relative effect of EVT (p=0.78). In EVT patients, there was interaction with APT and reperfusion on primary outcome (ordinal mRS). APT doubled the effect of successful reperfusion on functional outcome in the intervention arm of the trial ($P_{interaction}$=0.025, Figure 2). The absolute risk difference for favorable outcome (mRS 0–3) by successful reperfusion in APT patients was 39% versus 18% in patients without APT. In EVT patients with good reperfusion, recanalization on follow-up CTA at 24 hours was 96% in those with APT and 95% in those without APT.

There was no interaction of APT and EVT for safety parameters (Table 4). We observed no differences in occurrence of death, SICH, and other safety parameters between intervention and control among the APT subgroups. Compared to the no APT subgroup, the APT subgroup had higher mortality (9%), more SICHs (11%), more cardiac ischemia (3%), and less hemicraniectomy procedures (5%). SICH occurred in six patients (18%) of the dual antiplatelet treatment group versus 15/111 (14%) in the single antiplatelet users, which was not statistically different (p=0.51).

Table 3. Secondary outcomes in intervention and control of antiplatelet treatment (APT) subgroups.

	No APT (n=356)		APT (n=144)	
	Intervention (n=169)	Control (n=187)	Intervention (n=64)	Control (n=80)
mRS 0-2 at 90 days – n. (%)	61 (36%)	38 (20%)	15 (23%)	13 (16%)
NIHSS at 5-7 days or discharge – median (IQR)*	8 (3-16)	15 (6-19)	8 (1-17)	13 (9-18)
Barthel Index 19-20 at 90 days – n./total n. (%)	76/151 (51%)	55/168 (33%)	23/64 (36%)	24/74 (24%)
Successful reperfusion during intervention (mTICI score 2B/3) – n./ total n. (%)	84/143 (59%)	-	32/54 (59%)	-
No intra-cranial occlusion on follow-up CTA – n./ total n. (%)	105/141 (74%)	46/148 (31%)	36/46 (78%)	22/59 (37%)
Final infarct volume on follow-up NCCT total n.- median (IQR)†	110 49 (22-95)	114 75 (33-130)	35 47 (17-98)	49 88 (46-123)

Abbreviations: mRS = modified Rankin Scale; NIHSS = National Institutes of Health Stroke Scale; mTICI = modified Thrombolysis in Cerebral Infarction; CTA = Computed Tomography Angiography; NCCT = Non Contrast Computed Tomography

* *Scored in survivors only (56 died), 18 missing*

† *Final infarct volume on NCCT after 5 days (range 3-9 days)*

Table 4. Safety parameters* for intervention and control in patients with and without prior antiplatelet treatment (APT), and treatment interaction (adjusted for age, sex, NIHSS, collateral score and vascular comorbidity).

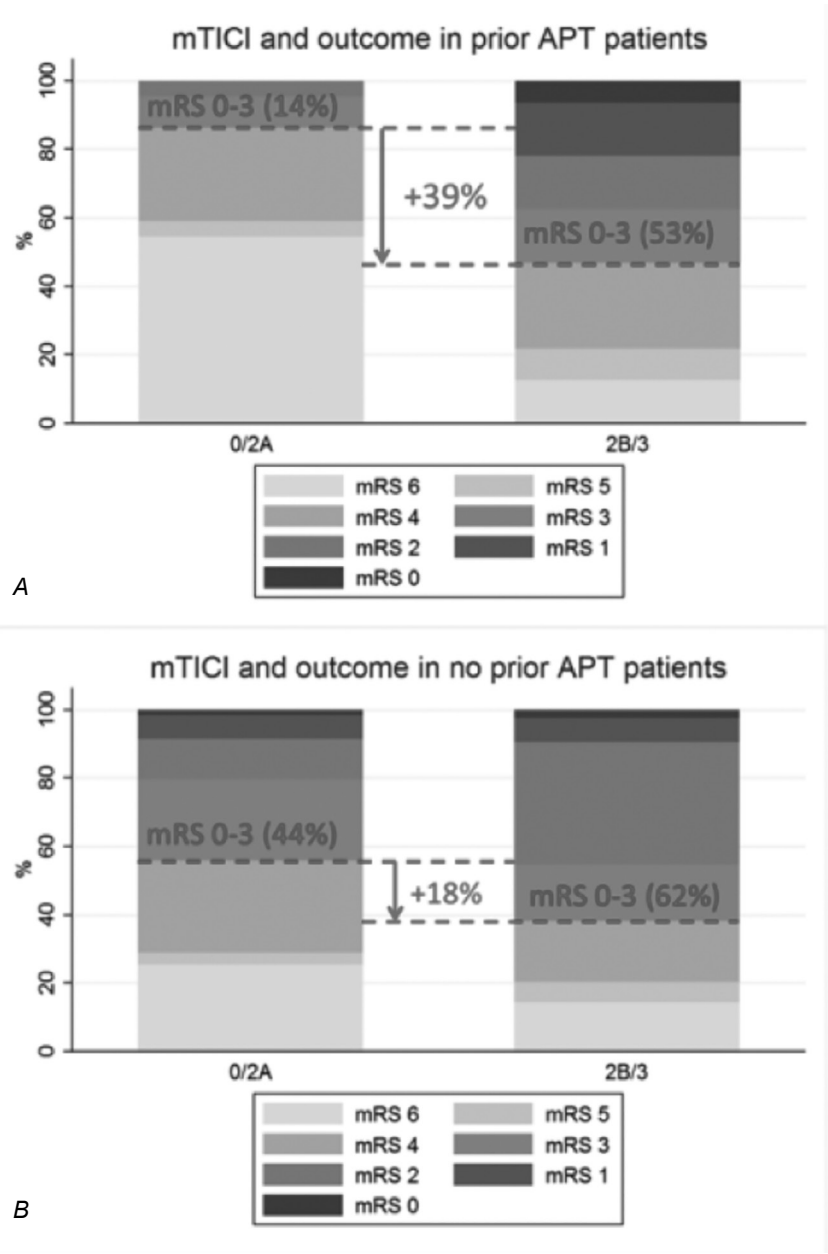
	No APT (n=356)		APT (n=144)		Treatment interaction
	Intervention (n=169)	Control (n=187)	Intervention (n=64)	Control (n=80)	(p-value)
Death within 90 days - n (%)	28 (17%)	39 (21%)	21 (33%)	20 (25%)	0.77
Hemicraniectomy - n (%)	13 (8%)	11 (6%)	1 (2%)	2 (3%)	0.28
Patients with at least one SAE - n (%)	72 (43%)	78 (42%)	38 (59%)	35 (44%)	0.87
Symptomatic ICH - n (%)	7 (4%)	7 (4%)	11 (17%)	10 (13%)	0.48
Parenchymal hematoma type 1	0	0	0	2 (3%)	-†
Parenchymal hematoma type 2	3 (2%)	6 (3%)	11 (17%)	8 (10%)	-†
Hemorrhagic infarction type 1	1 (1%)	0	0	0	-†
Hemorrhagic infarction type 2	1 (1%)	1 (1%)	0	0	-†
Subarachnoid hemorrhage	2 (1%)	0	0	0	-†
Progression of Ischemic stroke – n (%)	32 (19%)	39 (21%)	14 (22%)	9 (11%)	0.58
Pneumonia - n (%)	15 (9%)	29 (16%)	11 (17%)	14 (18%)	0.82
Other Infection - n (%)	12 (7%)	6 (3%)	4 (6%)	4 (5%)	0.27
Cardiac Ischemia - n (%)	0	1 (1%)	1 (2%)	3 (4%)	1.00
Extracranial Hemorrhage - n (%)	0	2 (1%)	0	0	-†
Allergic Reaction - n (%)	1 (1%)	0	0	0	-†
Other Complication - n (%)	22 (13%)	29 (16%)	6 (9%)	8 (10%)	0.68

Abbreviation: APT= antiplatelet treatment; ICH = Intra Cerebral Hemorrhage; SAE = serious adverse event

** Only first events of one type are listed. Patients experiencing multiple events of one type have been counted once.*

† Too few events for interaction analysis

Figure 2. Functional outcome by reperfusion (mTICI) in patients with (a) and without (b) prior antiplatelet treatment (APT). In prior APT patients, the effect of successful reperfusion on functional outcome in the intervention arm of the trial was doubled: the absolute risk difference for favorable outcome after successful reperfusion in antiplatelet treatment patients was 39% versus 18% in patients without antiplatelet treatment (Pinteraction¼0.025).



Discussion

The effect of EVT was similar for patients on APT and patients not on APT. We observed no differences in the occurrence of serious adverse events between patients. with and without EVT who were on APT, although APT in general was associated with increased risk of hemorrhagic events. We did find that in patients in the intervention arm of the trial on prior APT, the effect of successful reperfusion on functional outcome was doubled.

Other studies

One meta-analysis of prior APT use in AIS concerned all studies published until April 2013.[18] Patients had more vascular comorbidity at baseline and higher SICH occurrence, similar to our observations. Effect of EVT on SICH in APT patients was not reported. Furthermore, this meta-analysis showed that outcome was worse in the APT subgroup. No adjustments for prognostic factors were made, and the effect of EVT in the APT subgroup was not addressed.

APT was also not addressed in the recent positive [1 3-6 19] RCTs or pooled individual patient data. To our knowledge, this is the first study that explores the effect and safety of EVT in patients who are on APT. In the recently updated American Heart Association/ American Stroke Association guidelines, the role of antithrombotic treatment is not adressed.[11]

Antiplatelet medication and endovascular treatment

Although we did not observe statistically or clinically significant interaction of APT with EVT, our data suggest that APT may improve functional outcome after reperfusion. In the intervention arm of the trial, APT doubled the effect of successful reperfusion on functional outcome. This might suggest that in patients in whom reperfusion is achieved by EVT, peri-procedural APT may be beneficial, as it is in percutaneous interventions for acute myocardial infarctions.[8] Since there were no differences in (large vessel) recanalization on follow-up CTA between APT and no APT patients with reperfusion during intervention, their improved functional outcome may be explained by improved distal (small vessel) recanalization because of less distal microvascular obstruction by APT use.

However, it remains unknown whether de novo peri-procedural treatment with antiplatelet agents will improve distal revascularization and clinical outcome and outweighs a possible increased risk of hemorrhage. The only way to address this question is to perform an RCT and compare peri-procedural antiplatelet treatment with control in patients with AIS patients who undergo EVT for intracranial large vessel occlusion.

Limitations

Patients in the APT group were older, more often male, and had more vascular comorbidity. However, after adjustment for these baseline differences, EVT effect in the APT subgroup increased. Since we found no interaction of APT with EVT on outcome and safety, and effect sizes after adjustments were similar, EVT in these patients may be considered effective and safe. Since mTICI was used to indicate reperfusion after EVT, we had no score correlating with slow distal reperfusion. Slow distal reperfusion could indicate incomplete microvascular reperfusion. For studies focusing on microvascular reperfusion in AIS patients, another reperfusion score than mTICI could be suggested. Finally, our analysis concerns a small post-hoc sample of 144 patients on prior APT, and we look forward to a pooled subgroup analysis of the other recent thrombectomy trials, to see if our results will be confirmed,[3-5 19] and prospective controlled studies to test the effect of APT additional to intervention.

Conclusions

Prior treatment with antiplatelet agents did not modify the effect of EVT in patients with AIS presenting with an intracranial large vessel occlusion. There were no safety concerns. In patients with good reperfusion after EVT, antiplatelet agents may improve functional outcome.

References

1. Berkhemer OA, et al. A randomized trial of intraarterial treatment for acute ischemic stroke. N Engl J Med 2015;372(1):11-20.
2. Campbell BC, et al. Endovascular therapy for ischemic stroke with perfusion-imaging selection. N Engl J Med 2015;372(11):1009-18.
3. Goyal M, et al. Randomized assessment of rapid endovascular treatment of ischemic stroke. N Engl J Med 2015;372(11):1019-30.
4. Jovin TG, et al. Thrombectomy within 8 hours after symptom onset in ischemic stroke. N Engl J Med 2015;372(24):2296-306.
5. Saver JL, et al. Stent-retriever thrombectomy after intravenous t-PA vs. t-PA alone in stroke. N Engl J Med 2015;372(24):2285-95.
6. Goyal M, et al. Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials. Lancet 2016;387(10029):1723-31.
7. Bai J, et al. Revisiting cerebral postischemic reperfusion injury: new insights in understanding reperfusion failure, hemorrhage, and edema. Int J Stroke 2015;10(2):143-52.
8. Task Force on the management of STseamiotESoC, et al. ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. Eur Heart J 2012;33(20):2569-619.
9. The International Stroke Trial (IST): a randomised trial of aspirin, subcutaneous heparin, both, or neither among 19435 patients with acute ischaemic stroke. International Stroke Trial Collaborative Group. Lancet 1997;349(9065):1569-81.
10. Zinkstok SM, et al. Early administration of aspirin in patients treated with alteplase for acute ischaemic stroke: a randomised controlled trial. Lancet 2012;380(9843):731-7.
11. Powers WJ, et al. 2015 American Heart Association/American Stroke Association Focused Update of the 2013 Guidelines for the Early Management of Patients With Acute Ischemic Stroke Regarding Endovascular Treatment: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. Stroke 2015;46(10):3020-35.
12. Widimsky P. Periprocedural antithrombotic medication in acute ischemic stroke treated by catheter-based thrombectomy. A review. Cor et Vasa 2015;57:e139-e142.
13. Fransen PS, et al. MR CLEAN, a multicenter randomized clinical trial of endovascular treatment for acute ischemic stroke in the Netherlands: study protocol for a randomized controlled trial. Trials 2014;15:343.
14. van Swieten JC, et al. Interobserver agreement for the assessment of handicap in stroke patients. Stroke 1988;19(5):604-7.
15. Zaidat OO, et al. Recommendations on angiographic revascularization grading standards for acute ischemic stroke: a consensus statement. Stroke 2013;44(9):2650-63.
16. Boers AM, et al. Automated cerebral infarct volume measurement in follow-up noncontrast CT scans of patients with acute ischemic stroke. AJNR Am J Neuroradiol 2013;34(8):1522-7.
17. Fiorelli M, et al. Hemorrhagic transformation within 36 hours of a cerebral infarct: relationships with early clinical deterioration and 3-month outcome in the European Cooperative Acute Stroke Study I (ECASS I) cohort. Stroke 1999;30(11):2280-4.
18. Meseguer E, et al. Outcomes after stroke thrombolysis according to prior antiplatelet use. Int J Stroke 2015;10(2):163-9.
19. Campbell BC, et al. Endovascular stent thrombectomy: the new standard of care for large vessel ischaemic stroke. Lancet Neurol 2015;14(8):846-54.

2.3

Baseline blood pressure effect on the benefit and safety of endovascular treatment

MR CLEAN subgroup analysis

Maxim J.H.L. Mulder, Saliha Ergezen, Hester F. Lingsma, Olvert A. Berkhemer, Puck S.S. Fransen, Debbie Beumer, Lucie A. van den Berg, Geert Lycklama à Nijeholt, Bart J. Emmer, H. Bart van der Worp, Paul J. Nederkoorn, Yvo B.W.E.M. Roos, Robert J. van Oostenbrugge, Wim H. van Zwam, Charles B.L.M. Majoie, Aad van der Lugt, Diederik W.J. Dippel
For the MR CLEAN investigators

July 2017
Stroke

Abstract

Background and Purpose

High blood pressure (BP) is associated with poor outcome and the occurrence of symptomatic intracranial hemorrhage in acute ischemic stroke. Whether BP influences the benefit or safety of intra-arterial treatment (IAT) is not known. We aimed to assess the relation of BP with functional outcome, occurrence of symptomatic intracranial hemorrhage and effect of IAT.

Methods

This is a post hoc analysis of the MR CLEAN (Multicenter Randomized Clinical Trial of Endovascular Treatment of Acute Ischemic Stroke in the Netherlands). BP was measured at baseline, before IAT or stroke unit admission. We estimated the association of baseline BP with the score on the modified Rankin Scale at 90 days and safety parameters with ordinal and logistic regression analysis. Effect of BP on the effect of IAT was tested with multiplicative interaction terms.

Results

Systolic BP (SBP) had the best correlation with functional outcome. This correlation was U-shaped; both low and high baseline SBP were associated with poor functional outcome. Higher SBP was associated with symptomatic intracranial hemorrhage (adjusted odds ratio, 1.25 for every 10 mm Hg higher SBP [95% confidence interval, 1.09–1.44]). Between SBP and IAT, there was no interaction for functional outcome, symptomatic intracranial hemorrhage, or other safety parameters; the absolute benefit of IAT was evident for the whole SBP range. The same was found for diastolic BP.

Conclusions

BP does not affect the benefit or safety of IAT in patients with acute ischemic stroke caused by proximal intracranial vessel occlusion. Our data provide no arguments to withhold or delay IAT based on BP.

Introduction

Both low and high blood pressure (BP) are associated with poor functional outcome in acute ischemic.1 2 The combination of reperfusion therapy and high BP may increase the risk of symptomatic intracranial hemorrhage (SICH).3-7 The American Heart Association/American Stroke Association (AHA/ASA) acute ischemic stroke guidelines recommend a BP threshold of 185/110 mm Hg for intravenous thrombolysis (IVT) candidates.8-10 There is no consensus on how to proceed in patients with a BP above this IVT threshold: withhold IVT, delay IVT until BP spontaneously decreases or administer acute BP-lowering treatment.

Intra-arterial treatment (IAT) by means of stent thrombectomy for patients with acute ischemic stroke and a proximal arterial occlusion in the anterior circulation is highly effective.11-17 The average increase in likelihood of good functional outcome at 90 days after IAT is 19.5%.18 Three studies suggest that high BP is a risk factor for poor outcome and SICH in patients treated with IAT.19-21 It is currently unknown whether BP interacts with IAT effect. The recent focused AHA/ASA guideline update about IAT provide no guidance whether a specific BP should be considered a contraindication for IAT, or whether a certain BP should be treated before IAT.22

The aim of this study was to assess the relation between BP before IAT with functional outcome and safety parameters and to assess whether BP affects the benefit and safety of IAT.

Methods

This is a post hoc analysis of data of the MR CLEAN (Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands). The trial design and patient eligibility criteria have been reported previously.[11 23] In short, MR CLEAN was a randomized clinical trial of IAT versus no IAT along with usual medical care in patients with a proximal intracranial arterial occlusion in the anterior circulation, who could be treated within 6 hours after symptom onset. Background medical management was delivered according to national standards and guidelines, and could include treatment with IVT within the first 4.5 hours after onset of symptoms. Systolic BP (SBP) and diastolic BP (DBP) were measured at base- line, between emergency room admission and start of IAT (intervention arm) or stroke unit admission (control arm). Mean arterial pressure (MAP) was calculated using the following formula: (2×DBP+SBP)/3. Routine BP measurements were used. There were no detailed instructions for measurements, but all centers used automated BP measurement in the emergency room and stroke unit. BP >185/110 mm Hg was an exclusion criterion for entry into the study and this was registered prospectively. The MR CLEAN study protocol provided no recommendations on whether and how to treat BP exceeding 185/110 mm Hg in included patients, but treatment was allowed.

All patients or their legal representatives provided written informed consent before randomization. A central medical ethics committee and the research board of each participating center approved the study protocol.

Outcome and Safety Measures

The primary analysis was interaction assessment between BP and IAT effect on the primary outcome of the trial, the modified Rankin Scale (mRS) score at 90 days.[24] Furthermore, interaction was assessed between BP and IAT on secondary clinical and radiological outcome measures. Secondary clinical outcome measures were functional independence (mRS 0–2) at 90 days, stroke severity at 5 to 7 days or discharge, if earlier, assessed with the National Institutes of Health Stroke Score (NIHSS),[25] and the Barthel Index.[26] Radiological out- come measures included arterial recanalization measured with computed tomographic angiography or magnetic resonance angiogram at 24 hours, and infarct volume on non-contrast CT at 5 to 7 days. In patients with IAT, the modified thrombolysis in cerebral infarction (mTICI) score on digital subtraction angiography was used to assess reperfusion. The mTICI score is a 5-point scale, which ranges from 0 (no reperfusion) to 3 (complete antegrade reperfusion of the previously ischemic territory, with the absence of visualized occlusion in all distal branches).[27 28]

Interaction between BP and IAT on safety parameters was also tested. Safety parameters included death, hemicraniectomy, SICH, and progression of ischemic stroke. SICH was defined as neurological deterioration of 4 or more points on the NIHSS and neuroimaging confirming intracranial hemorrhage. We used the ECASS III (European Cooperative Acute Stroke Study) classification of intracranial hemorrhage.[29] Progression of ischemic stroke was defined as neurological deterioration with an increase of 2 or more points on the NIHSS, with follow-up brain CT or magnetic resonance imaging compatible with a diagnosis of ischemia and without other causes for neurological deterioration.

Statistical Analysis

Patients were analyzed according to the “intention to treat” principle. All interaction and logistic regression analyses were adjusted for potential imbalances in prognostic variables at baseline; age, NIHSS, and collateral score. Adjusted odds ratios (ORs) are reported with 95% confidence intervals (CIs). All P values are 2-sided. Statistical analyses were performed with Stata/SE 14.1 (Stata Corp, College Station, TX). All analyses were done in the total MR CLEAN patient group.

Statistical Analysis of BP and Outcome

To assess whether the relation between BP and outcome was non- linear, we used squared terms, restricted cubic spline, and fractional polynomials. We tested which model best fitted the data with the delta log likelihood ratio as the test statistic.[30-32] The model that best fit- ted the relation of BP with functional outcome was used for further analysis. The log likelihood ratios were further used to assess which BP measurement (SBP, DBP, or MAP) had the strongest correlation with functional outcome. The nadir identified by the nonlinear models was used to divide the population in 2 subgroups. The effect of BP on outcome was estimated separately in these 2 subgroups with regression models. The effect of BP on functional outcome in these subgroups was determined using logistic regression.

Statistical Analysis of Baseline BP and Effect of IAT The interaction between BP and IAT was tested with multivariable ordinal logistic regression analysis with an interaction term. We computed (common) ORs per 10 mm Hg SBP increase to assess the relation of SBP with the outcome on the mRS; full scale (ordinal regression analysis) and dichotomized (mRS 0–2 versus 3–6, logistic regression analysis). The absolute benefit of IAT for different BP values was computed using the estimated probability of good functional outcome (mRS 0–2) for the intervention and control arm.

Results

Patient Characteristics

For all 500 patients included in the trial, BP was measured and entered into the database. Mean baseline SBP (SD) was 145 mm Hg (±25), mean DBP was 82 mm Hg (±15), and mean MAP was 103 mm Hg (±16). Most SBP values were between 105 and 200 mm Hg (Figure 1). Four patients (1%) were included in the study, despite a BP of >185/110 mm Hg at randomization. In 29 additional patients, baseline BP was >185/110 mm Hg. In these 33 patients (7%), SBP alone exceeded the threshold value in 21 patients, DBP alone in 5 patients and both SBP and DBP in 7 patients. Of these 33 patients, 8 patients (24%) were acutely treated with antihypertensive therapy, 7 patients (21%) had a spontaneous reduction in BP to ≤185/110 mm Hg without treatment, and of the remaining 18 patients (55%), the BP course and possible BP-lowering treatment were not recorded.

Baseline BP and Outcome

The association between BP and functional outcome (ordinal mRS) was best fitted using fractional polynomial regression analysis. SBP had better correlation with functional outcome than MAP and DBP (P<0.01). We found a U-shaped relation between SBP and functional outcome with the nadir at 120 mm Hg; both low and high SBP were associated with poor functional outcome (Figure 2).

Figure 1. Distribution of systolic blood pressure in total MR CLEAN population. 95% of baseline blood pressures were within 105-200 mm Hg range (grey vertical lines).

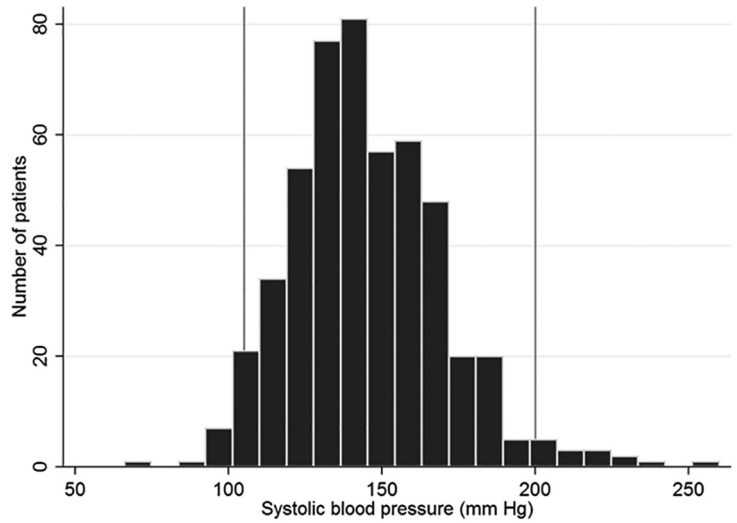


Figure 2. Relation of systolic blood pressure (SBP) with functional outcome (modified Rankin Scale [mRS] score after 90 days) in the total Multicenter Randomized Clinical Trial of Endovascular Treatment of Acute Ischemic Stroke in the Netherlands (MR CLEAN) population using ordered fractional polynomial regression. x axis: continuous SBP in mm Hg. y axis: log odds ratio (OR) for the estimated mRS. The nadir indicates that SBP of 120 mm Hg corresponds with best functional outcome; both low and high SBP were associated with poor functional outcome. CI indicates confidence interval.

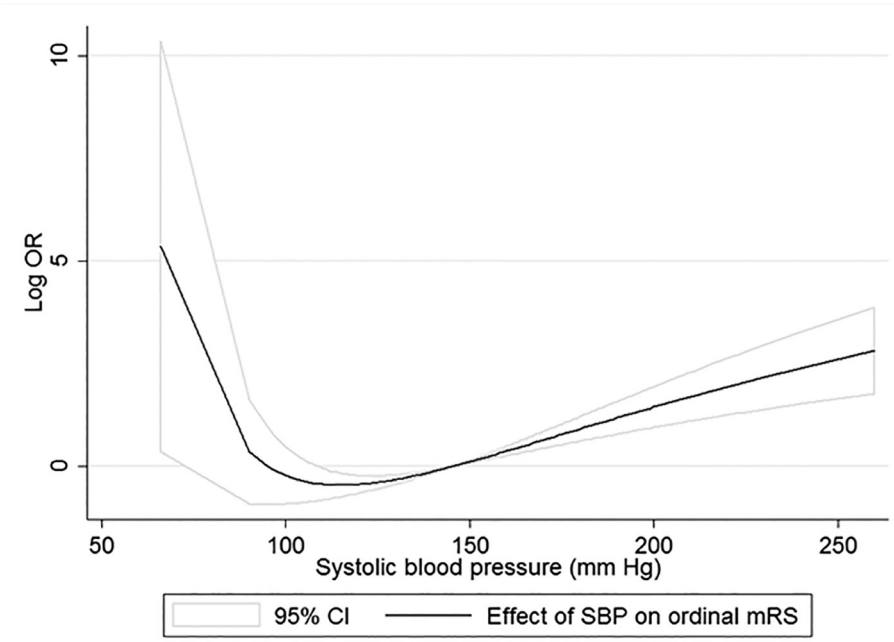


Table 1. Clinical characteristics of systolic blood pressure (SBP) subgroups with 120 mm Hg as reference point.

	SBP < 120 mm Hg	SBP ≥ 120 mm Hg	p-value
Age - median (IQR)	60 (45-69)	66 (56-77)	<0.01
Male sex – n. (%)	34 (49%)	258 (60%)	0.10
NIHSS - median (IQR)*	17 (13-21)	18 (14-22)	0.62
Clinical localization: Left hemisphere – n. (%)	41 (59%)	228 (53%)	0.31
SBP - mean mm Hg (SD)	110 ± 8	151 ± 22	<0.01
IV alteplase treatment- n. (%)	60 (87%)	385 (89%)	0.56
Medical history			
Atrial fibrillation – n. (%)	14 (20%)	121 (28%)	0.18
Ischemic stroke – n. (%)	5 (7%)	49 (11%)	0.31
Hypertension – n. (%)	20 (29%)	207 (48%)	<0.01
Diabetes mellitus – n. (%)	4 (6%)	64 (15%)	0.04
Myocardial infarction – n. (%)	10 (14%)	65 (15%)	0.90
Peripheral artery disease – n. (%)	3 (4%)	21 (5%)	0.85
Pre-stroke modified Rankin Scale score – n. (%)			0.58
0	55 (80%)	349 (81%)	
1	7 (10%)	43 (10%)	
2	6 (9%)	19 (4%)	
>2	1 (1%)	20 (5%)	
Medication and intoxications			
Statin use – n. (%)	22 (32%)	121 (28%)	0.52
Antiplatelet use – n. (%)	16 (23%)	128 (30%)	0.27
Anticoagulant use – n. (%)	6 (9%)	33 (8%)	0.77
Antihypertensive medication use – n. (%)	28 (41%)	214 (50%)	0.16
Current smoking – n. (%)	28 (41%)	115 (27%)	0.02
Imaging			
ASPECTS on NCCT– median (IQR)†	9 (8-10)	9 (8-10)	0.92
Level of occlusion on non-invasive vessel imaging– n. (%)‡			
ICA	1 (1%)	3 (1%)	
ICA-T	20 (29%)	114 (27%)	
M1	44 (64%)	275 (64%)	
M2	4 (6%)	35 (8%)	
A1	0	3 (1%)	
Collateral score on CTA- median (IQR) §	2 (2-3)	2 (1-3)	0.27
Workflow			
Onset to SEH (minutes)- median (IQR))	72 (45-175)	101 (49-200)	0.12
Onset to IV alteplase (minutes)- median (IQR)	79 (64-108)	86 (66-112)	0.35
Onset to randomization (minutes)- median (IQR)	179 (146-237)	202 (152-265)	0.09
Onset to IAT (minutes)- median (IQR)	245 (230-290)	265 (210-315)	0.85
Onset to reperfusion (minutes)- median (IQR)	316 (291-351)	342 (264-397)	0.93
Duration of procedure (minutes)– median (IQR)	69 (48-101)	71 (51-95)	0.88

** Scores on the National Institutes of Health Stroke Scale (NIHSS). The NIHSS is a 15-item scale. Values for 30 of the 7500 items were missing (0.4%).*
† The Alberta Stroke Program Early Computed Tomography Score (ASPECTS). 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
§ missing in 6 patients due to CTA not performed or of insufficient quality

The effect of SBP on functional outcome was comparable for IAT and control patients (Figure 3). There was a U-shaped relation of SBP with good functional outcome (mRS 0–2) and death at 90 days, with the nadir around 120 mm Hg (Figure 4). The associations of MAP and DBP with functional outcome were also concave, but for DBP, there was no evident relation of lower DBP with poor functional outcome (Figure 5).

On the basis of the nadir of the U-shape, 2 SBP subgroups were created (<120 and ≥120 mm Hg). In 69 patients (14%), SBP was lower than 120 mm Hg (Figure 6). Patients with SBP ≥120 mm Hg were on an average age of 6 years (P<0.001), smoked less often (14%; P=0.02), and more often had a history of hypertension (19%; P=0.01) or diabetes mellitus (9%; P=0.04) than patients having an SBP lower than 120 mm Hg (Table 1).
Baseline characteristics of IAT and control patients were similar for the 2 SBP subgroups except for previous use of anticoagulant medication (IAT: 19% versus control: 0%) in the SBP <120 mm Hg group and antihypertensive medication (IAT: 44% versus control: 54%) in the SBP ≥120 mm Hg group. In patients with SBP <120 mm Hg, lower SBP was associated with poor functional outcome (10 mm Hg lower SBP; adjusted common odds ratio [acOR]=0.63 [95% CI, 0.42–0.94]). In these patients, the likelihood of good functional

Table 2. Primary and secondary outcomes of intervention and control in patients with systolic blood pressure (SBP) under 120 mm Hg and of 120 mm Hg and above. Intra-arterial treatment interaction effects were computed with ordinal logistic regression using the total SBP range (adjusted for age, NIHSS and collateral score).

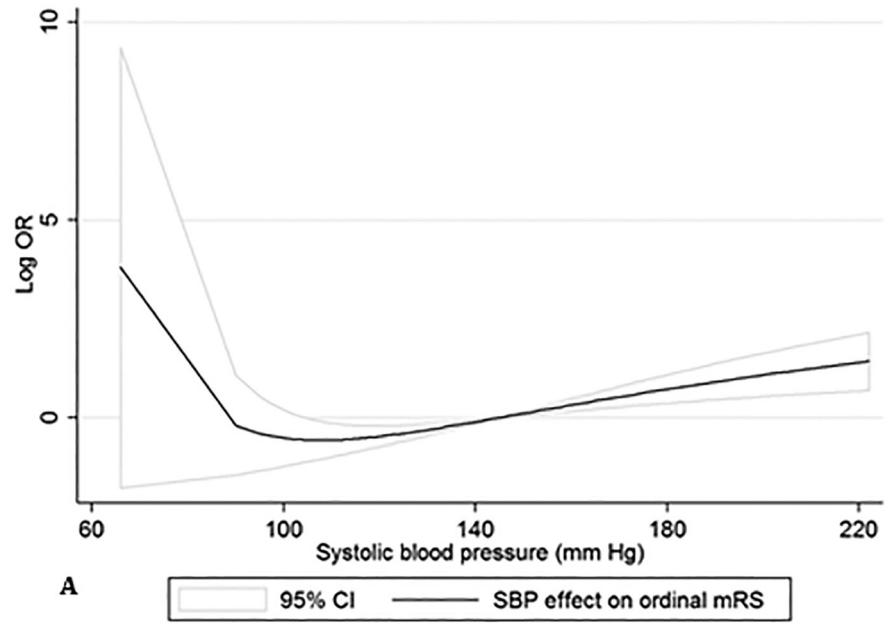
	SBP < 120 mm Hg (n=69)		SBP ≥ 120 mm Hg (n=431)		
	Intervention (n=32)	Control (n=37)	Intervention (n=201)	Control (n=230)	Treat-ment inter-action p-value
mRS at 90 days – median (IQR)	3 (2-4)	3 (2-5)	3 (2-5)	4 (3-5)	0.90
mRS 0-2 at 90 days – n. (%)	13 (41%)	10 (27%)	63 (31%)	41 (18%)	0.52
NIHSS at 5-7 days or discharge - median (IQR)*	6 (2-17)	11 (4-18)	9 (2-17)	15 (8-18)	0.16
Barthel Index 19-20 at 90 days – n./total n. (%)	17/30 (57%)	13/34 (38%)	82/185 (44%)	60/208 (29%)	0.64
Reperfusion during intervention (mTICI score 2B/3) – n./ total n. (%)	18/27 (67%)	-	98/170 (58%)	-	
No intracranial occlusion on follow-up CTA – n./ total n. (%)	20/26 (77%)	14/33 (42%)	121/161 (75%)	54/174 (31%)	0.55
Final infarct volume on follow-up NCCT total n. – median (IQR)†	17 66 (17-90)	29 83 (21-118)	128 73 (24-96)	134 96 (39-127)	0.52

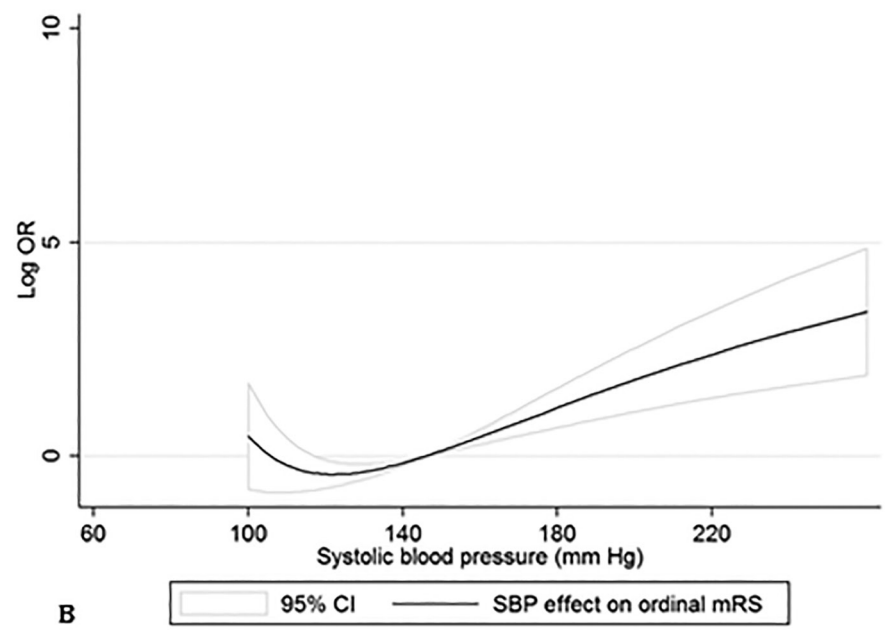
Abbreviations: mRS = modified Rankin Scale; NIHSS = National Institutes of Health Stroke Scale; mTICI = modified Thrombolysis in Cerebral Infarction; CTA = Computed Tomography Angiography; NCCT = Non Contrast Computed Tomography

* *Scored in survivors only (56 died), 18 missing*

† *Final infarct volume on NCCT after 5 days (range 3-9 days)*

Figure 3. Relationship of systolic blood pressure (SBP) with functional outcome (modified Rankin Scale (mRS) at 90 days); in the control group (A) and the intra-arterial treatment group (B).





outcome (mRS 0–2) decreased with 39% for each 10 mm Hg lower SBP. In patients with an SBP of ≥120 mm Hg, higher SBP was associated with poor functional outcome (acOR=0.83 [95% CI, 0.76–0.90] per 10 mm Hg SBP). In these patients, the likelihood of good functional outcome (mRS 0–2) decreased with 19% for each 10 mm Hg higher SBP. Death and other serious adverse events occurred more often in the SBP ≥120 mm Hg group. Higher SBP was associated with a higher probability of SICH (Figure 4). For every 10 mm Hg higher SBP, the acOR for SICH was 1.25 (95% CI, 1.09–1.44), resulting in a 21% increased SICH likelihood.

Baseline BP and Effect of IAT

We found no interaction between SBP and the effect of IAT on functional outcome (P=0.90). The effect of SBP on out- come was the same in the control group (acOR=0.88 [95% CI, 0.80–1.00] per 10 mm Hg SBP increase) as in the intervention group (acOR=0.88 [95% CI, 0.79–0.98] per 10 mm Hg SBP increase). The association of SBP with good functional outcome (mRS 0–2) was similar in the control group (aOR=0.84 [95% CI, 0.73–0.98] per 10 mm Hg SBP increase) as in the intervention group (aOR=0.90 [95% CI, 0.77–1.04] per 10 mm Hg SBP increase). There was also no interaction between SBP and IAT for secondary clinical and radiological outcomes (Table 2).

Figure 4. Relationship of systolic blood pressure with good functional outcome, defined as modified Rankin Scale (mRS) of 0-2 at 90 days (A), mortality at 90 days (B), and occurrence of symptomatic intracranial hemorrhage (SICH; C).

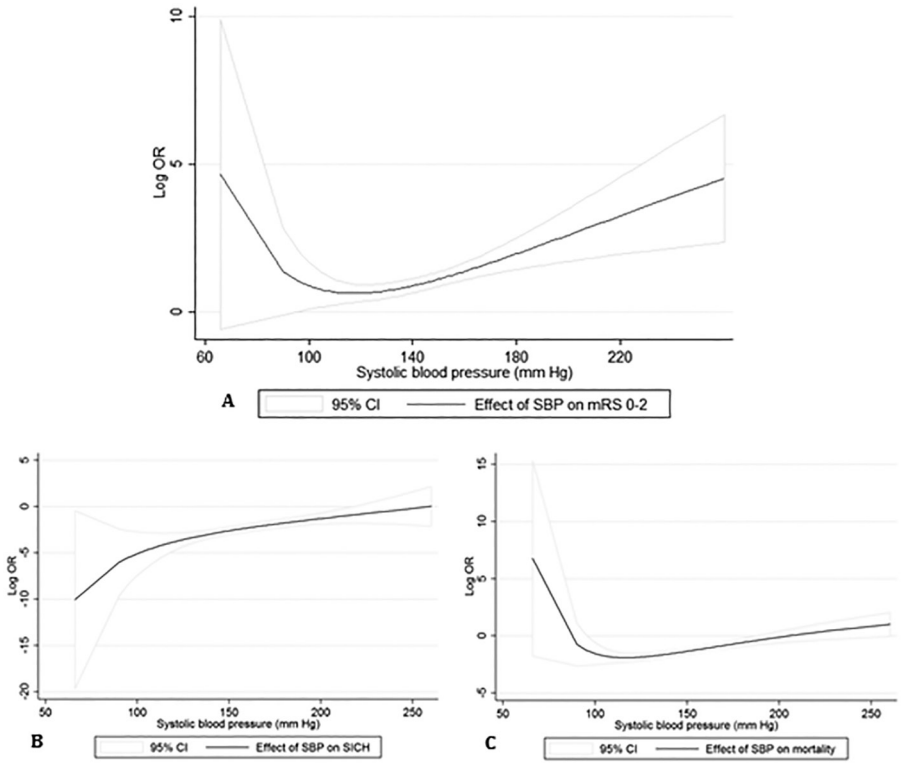


Figure 7 shows the association of high SBP with poor functional outcome for both treatment arms. The absolute effect of IAT is evident for every SBP quintile and there was no difference in the relative effect (P interaction=0.52). Furthermore, there was no association between SBP and reperfusion after intervention (P=0.56). In addition, SBP did not influence IAT effect on the occurrence of SICH (P=0.80) or any other safety parameter (Table 3). For DBP, there were comparable findings: no interaction between DBP and the effect of IAT on functional outcome (P=0.48), secondary outcomes or safety parameters (Tables 4 & 5).

Figure 5. Relationship of diastolic blood pressure (DBP; A) and mean arterial blood pressure (MAP; B) with functional outcome (modified Rankin Scale (mRS) at 90 days).

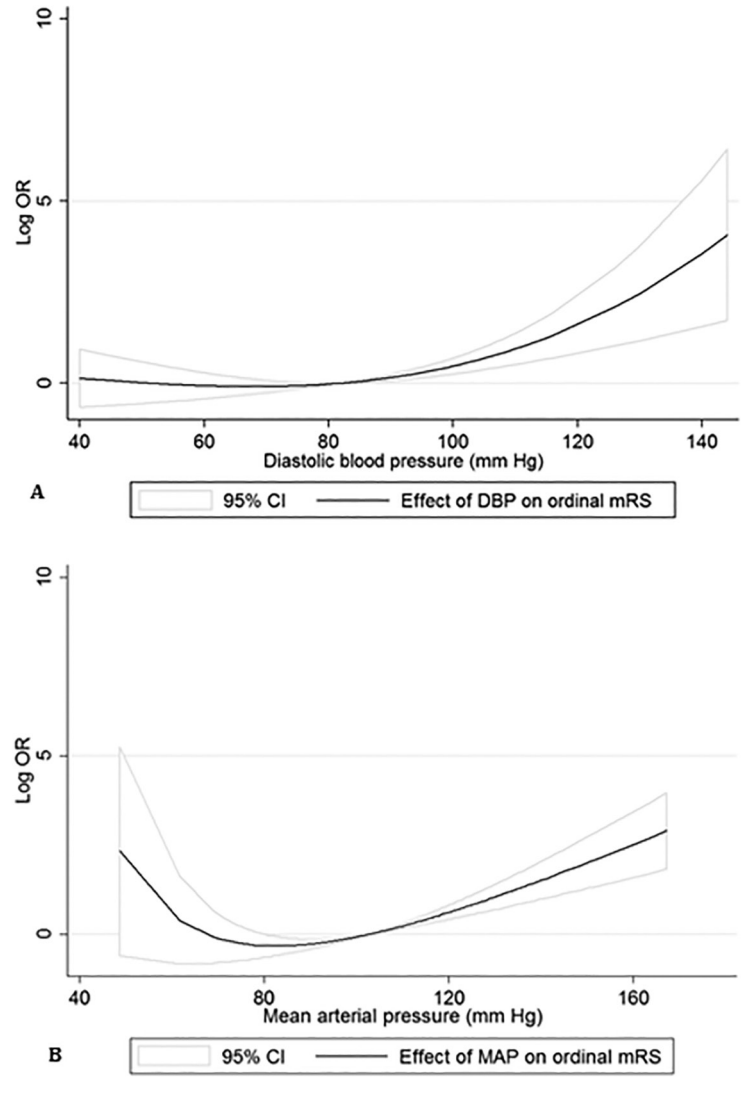


Table 3. Safety parameters* of intervention and control in patients with systolic blood pressure (SBP) under 120 mm Hg and of 120 mm Hg and above. Intra-arterial treatment interaction effects were computed with ordinal logistic regression using the total SBP range (adjusted for age, NIHSS and collateral score).

	SBP < 120 mm Hg (n=69)		SBP ≥ 120 mm Hg (n=431)		Treatment
	Intervention (n=32)	Control (n=37)	Intervention (n=201)	Control (n=230)	interaction (p-value)
Death within 90 days - n (%)	6 (19%)	6 (16%)	43 (21%)	53 (23%)	0.18
Hemicraniectomy – n (%)	3 (9%)	0	11 (5%)	13 (6%)	0.56
Symptomatic ICH - n (%)	0	0	18 (9%)	17 (7%)	0.80
Parenchymal hematoma type 1	0	0	0	2 (1%)	-†
Parenchymal hematoma type 2	0	0	14 (7%)	14 (6%)	0.42
Hemorrhagic infarction type 1	0	0	1 (0%)	0	-†
Hemorrhagic infarction type 2	0	0	1 (0%)	1 (0%)	0.63
Subarachnoid hemorrhage	0	0	2 (1%)	0	-†
Progression of Ischemic stroke - n (%)	7 (22%)	4 (11%)	39 (19%)	43 (19%)	0.46

Abbreviation: ICH = Intra Cerebral Hemorrhage, NA = not applicable
** Only first events of one type are listed. Patients experiencing multiple events of one type have been counted once.*
† Too few events for interaction analysis

Table 4. Interaction between diastolic blood pressure and intra-arterial treatment on primary and secondary outcomes. Intra-arterial treatment interaction effects were computed with ordinal logistic regression using the total systolic blood pressure range (adjusted for age, NIHSS and collateral score).

	Treatment interaction p-value
mRS at 90 days – median (IQR)	0.48
mRS 0-2 at 90 days – n. (%)	0.91
NIHSS at 5-7 days or discharge - median (IQR)*	0.48
Barthel Index 19-20 at 90 days – n./total n. (%)	0.84
No intracranial occlusion on follow-up CTA – n./ total n. (%)	0.88
Final infarct volume on follow-up NCCT total n. – median (IQR)†	0.69

Abbreviations: mRS = modified Rankin Scale; NIHSS = National Institutes of Health Stroke Scale; mTICI = modified Thrombolysis in Cerebral Infarction; CTA = Computed Tomography Angiography; NCCT = Non Contrast Computed Tomography
** Scored in survivors only (56 died), 18 missing*
† Final infarct volume on NCCT after 5 days (range 3-9 days)

Figure 6. Treatment allocation and systolic blood pressure (SBP) in the MR CLEAN trial.

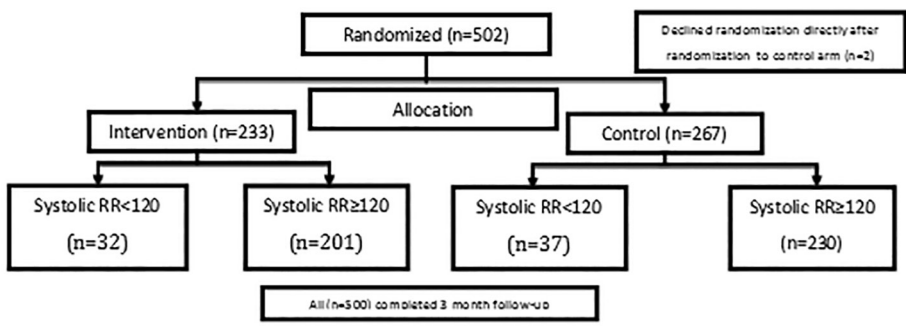
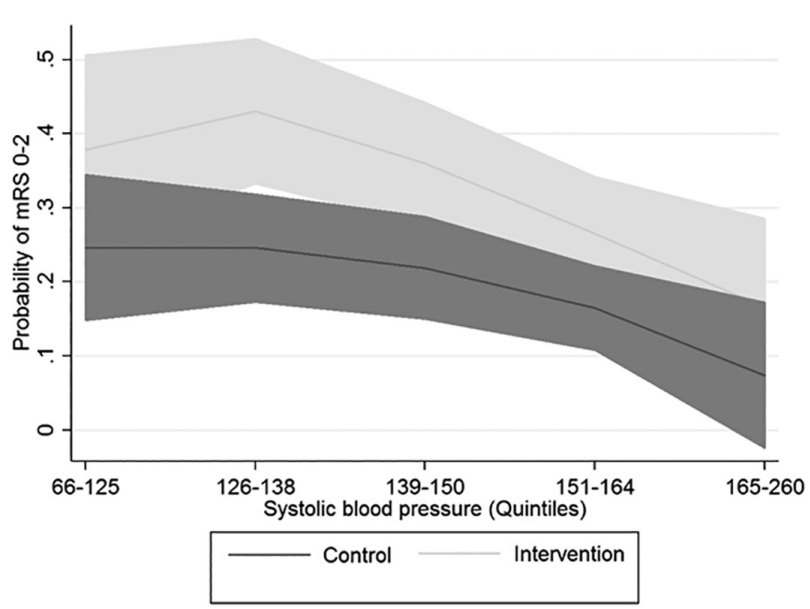


Table 5. Interaction between diastolic blood pressure and intra-arterial treatment on safety parameters. Intra-arterial treatment interaction effects were computed with ordinal logistic regression using the total systolic blood pressure range (adjusted for age, NIHSS and collateral score).

	Treatment interaction (p-value)
Death within 90 days - n (%)	0.60
Hemicraniectomy – n (%)	0.61
Symptomatic ICH - n (%)	0.92
Parenchymal hematoma type 1	-†
Parenchymal hematoma type 2	0.47
Hemorrhagic infarction type 1	-†
Hemorrhagic infarction type 2	0.60
Subarachnoid hemorrhage	-†
Progression of Ischemic stroke - n (%)	0.84

Abbreviation: ICH = Intra Cerebral Hemorrhage, NA = not applicable
**Only first events of one type are listed. Patients experiencing multiple events of one type have been counted once.*
† Too few events for interaction analysis

Figure 7. Probability of good functional outcome (modified Rankin Scale [mRS] score of 0–2) for the intervention (light) and the control group (dark), with 95% confidence intervals. x axis: systolic blood pressure (SBP) in quintiles. y axis: probability of good functional outcome at 90 days defined as mRS score of 0 to 2. The decreasing lines at higher SBP levels show that the probability of mRS score of 0 to 2 decreases with higher SBP in both treatment arms. The parallel course of both lines indicates that IAT benefit is equal for every SBP quintile (Pinteraction=0.52).



Discussion

To our knowledge, this is the first study to assess the relation between BP and the effect of IAT. Our most important finding was that baseline BP does not change IAT effectiveness and does not interact with IAT on functional outcome and safety parameters.

We confirmed the strong association between SBP and functional outcome in ischemic stroke. This association was U-shaped; both low and high baseline SBP were associated with poor functional outcome. Furthermore, higher SBP was associated with an increased risk of SICH. Despite these associations, baseline BP did not change IAT effectiveness or safety.

Baseline BP and Outcome

We found a U-shaped relation of BP with functional outcome, with the nadir around 120 mm Hg. There were comparable shapes and inflection points for SBP relation with mortality and good functional outcome. Previous studies investigating BP relation with outcome, specifically in acute ischemic stroke, also showed that both low and high BP were associated with poor functional outcome.[1 2]

Of the 3 previous studies on BP and outcome after IAT, one did not investigate the relation of BP with functional outcome,[19] the second study found that higher SBP was associated with poor functional outcome after IAT,[20]and the third study found SBP not to be a predictor of outcome after multivariable analysis.[21]The second and the third study did not test for nonlinearity. All studies were not designed to assess interaction of BP with treatment effect because there was no control group without IAT.

Our data provide no insight in the treatment of certain BP levels in the acute phase; an increased BP may be an effective response in patients with intracranial large vessel occlusion, and we cannot predict what will happen when we artificially lower BP. Randomized trials of BP lowering in these patients are clearly warranted, as it concerns a strong prognostic factor and the clinical context is different from previous, neutral trials of BP lowering.[33 34]

Our study showed that higher SBP increased the risk of SICH. There were no SICHs in the <120 mm Hg group. These data are in line with the studies of randomized IVT trials that found high BP to be associated with SICH.[3-7] We found no interaction of baseline BP with IAT on SICH or other safety parameters, so IAT may be considered safe, independently of BP.

Baseline BP and Effect of IAT

Our analysis emphasizes that the effect of IAT is evident for the whole BP range despite the strong relation of BP with functional outcome. In addition, BP did not influence IAT effect on the occurrence of SICH or any other safety parameter. Most SBP values were within a 105 to 200 mm Hg range. Our data provide no argument that within this range, the effect of IAT diminishes or IAT may even be harmful.

The BP threshold for IVT candidates was established during the pilot study preceding the NINDS trial.[35] Therefore, it was used in the NINDS trial.[36] Since then, AHA/ASA acute ischemic stroke guidelines recommend this BP threshold for IVT candidates.[8-10] There is overwhelming evidence of the association of high BP with poor outcome in acute ischemic stroke.[4 6 7 33 34 37 38] This is true for acute ischemic stroke patients treated with and without IVT. In only one of these studies, IST3 (International Stroke Trial), the interaction between BP and IVT on outcome was analyzed. The association between BP and functional outcome or occurrence of SICH was not affected by IVT in this study.[39] Further analyses in large IVT trials could shed more light on this subject and specifically on the appropriateness of this BP threshold.

The first guideline update on IAT does not state whether a certain BP threshold should be used in IAT candidates.22 Our data provide no evidence for a BP threshold in IAT candidates, at least within the range of 105 to 200 mm Hg. As this is the first study to investigate the relation of BP with IAT effect, we aim to do a similar analysis in the pooled individual patient data of the HERMES collaboration. This data set contains patient data of 7 trials with now more than 1700 patients in total.[11-17]

Limitations

There were only 69 patients with an SBP of <120 mm Hg, which has led to limited precision of our association estimates, especially at the lower end of the SBP range. However, it is clinically acceptable to assume that in acute ischemic stroke with low SBP (<80 mm Hg), functional outcome will be poor. Auto regulation at this low level may be disturbed, and required perfusion pressure will probably not be reached.39 Four patients in MR CLEAN had a BP exceeding 185/110 mm Hg at randomization. Consequently, they should be considered protocol violations. These patients were included in the main paper and in this study, according to the intention to treat principle. In total, 33 of the 500 patients (7%) had a baseline BP of >185/110 mm Hg. As few patients (5%) in MR CLEAN had an SBP <105 mm Hg or >200 mm Hg, uncertainty on IAT effect remains outside this SBP range.

Unfortunately, details about the course of BP during or after intervention are not available in our patients. Also, we had no data on the time interval between BP measurement and groin puncture. Nevertheless, even with one inherently inaccurate measurement, we found a strong association with outcome. Multiple measurements will probably result in precise estimates and provide more precise estimates. Further studies should provide more insight in: the interplay between BP rise and fall during intervention; the relation between BP, collaterals and ischemic core; and the risk of hemorrhage.

Conclusions

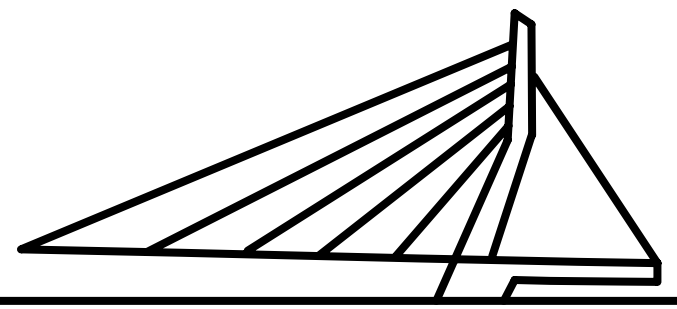
In patients with acute ischemic stroke due to proximal intra- cranial vessel occlusion, baseline BP does not affect the benefit or safety of IAT, although BP is an independent prognostic

References

1. Castillo J, et al. Blood pressure decrease during the acute phase of ischemic stroke is associated with brain injury and poor stroke outcome. Stroke 2004;35(2):520-6.
2. Leonardi-Bee J, et al. Blood pressure and clinical outcomes in the International Stroke Trial. Stroke 2002;33(5):1315-20.
3. The NINDS t-PA Stroke Study Group. Intracerebral hemorrhage after intravenous t-PA therapy for ischemic stroke. Stroke 1997;28(11):2109-18.
4. Ahmed N, et al. Relationship of blood pressure, antihypertensive therapy, and outcome in ischemic stroke treated with intravenous thrombolysis: retrospective analysis from Safe Implementation of Thrombolysis in Stroke-International Stroke Thrombolysis Register (SITS-ISTR). Stroke 2009;40(7):2442-9.
5. Brott T, et al. Hypertension and its treatment in the NINDS rt-PA Stroke Trial. Stroke 1998;29(8):1504-9.
6. Tsivgoulis G, et al. Pre-tissue plasminogen activator blood pressure levels and risk of symptomatic intracerebral hemorrhage. Stroke 2009;40(11):3631-4.
7. Tsivgoulis G, et al. Association of pretreatment blood pressure with tissue plasminogen activator-induced arterial recanalization in acute ischemic stroke. Stroke 2007;38(3):961-6.
8. Adams HP, Jr., et al. Guidelines for Thrombolytic Therapy for Acute Stroke: a Supplement to the Guidelines for the Management of Patients with Acute Ischemic Stroke. A statement for healthcare professionals from a Special Writing Group of the Stroke Council, American Heart Association. Stroke 1996;27(9):1711-8.
9. Adams HP, Jr., et al. Guidelines for the early management of adults with ischemic stroke: a guideline from the American Heart Association/American Stroke Association Stroke Council, Clinical Cardiology Council, Cardiovascular Radiology and Intervention Council, and the Atherosclerotic Peripheral Vascular Disease and Quality of Care Outcomes in Research Interdisciplinary Working Groups: the American Academy of Neurology affirms the value of this guideline as an educational tool for neurologists. Stroke 2007;38(5):1655-711.
10. Jauch EC, et al. Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2013;44(3):870-947.
11. Berkhemer OA, et al. A randomized trial of intraarterial treatment for acute ischemic stroke. N Engl J Med 2015;372(1):11-20.
12. Bracard S, et al. Mechanical thrombectomy after intravenous alteplase versus alteplase alone after stroke (THRACE): a randomised controlled trial. Lancet Neurol 2016;15(11):1138-47.
13. Campbell BC, et al. Endovascular therapy for ischemic stroke with perfusion-imaging selection. N Engl J Med 2015;372(11):1009-18.
14. Goyal M, et al. Randomized assessment of rapid endovascular treatment of ischemic stroke. N Engl J Med 2015;372(11):1019-30.
15. Jovin TG, et al. Thrombectomy within 8 hours after symptom onset in ischemic stroke. N Engl J Med 2015;372(24):2296-306.
16. Muir KW, et al. Endovascular therapy for acute ischaemic stroke: the Pragmatic Ischaemic Stroke Thrombectomy Evaluation (PISTE) randomised, controlled trial. J Neurol Neurosurg Psychiatry 2017;88(1):38-44.
17. Saver JL, et al. Stent-retriever thrombectomy after intravenous t-PA vs. t-PA alone in stroke. N Engl J Med 2015;372(24):2285-95.
18. Goyal M, et al. Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials. Lancet 2016;387(10029):1723-31.
19. Goyal N, et al. Admission systolic blood pressure and outcomes in large vessel occlusion strokes treated with endovascular treatment [published online ahead of print April 26, 2016]. J Neurointerv Surg 2016.doi: 10.1136/neurintsurg-2016-012386.
20. John S, et al. Lower Intraprocedural Systolic Blood Pressure Predicts Good Outcome in Patients Undergoing Endovascular Therapy for Acute Ischemic Stroke. Interv Neurol 2016;4(3-4):151-7.
21. Nogueira RG, et al. Predictors of good clinical outcomes, mortality, and successful revascularization in patients with acute ischemic stroke undergoing thrombectomy: pooled analysis of the Mechanical Embolus Removal in Cerebral Ischemia (MERCI) and Multi MERCI Trials. Stroke 2009;40(12):3777-83.
22. Powers WJ, et al. 2015 American Heart Association/American Stroke Association Focused Update of the 2013 Guidelines for the Early Management of Patients With Acute Ischemic Stroke Regarding Endovascular Treatment: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. Stroke 2015;46(10):3020-35.
23. Fransen PS, et al. MR CLEAN, a multicenter randomized clinical trial of endovascular treatment for acute ischemic stroke in the Netherlands: study protocol for a randomized controlled trial. Trials 2014;15:343.
24. van Swieten JC, et al. Interobserver agreement for the assessment of handicap in stroke patients. Stroke 1988;19(5):604-7.
25. Brott T, et al. Measurements of acute cerebral infarction: a clinical examination scale. Stroke 1989;20(7):864-70.
26. Mahoney FI, et al. Functional Evaluation: The Barthel Index. Md State Med J 1965;14:61-5.
27. Zaidat OO, et al. Recommendations on angiographic revascularization grading standards for acute ischemic stroke: a consensus statement. Stroke 2013;44(9):2650-63.
28. Boers AM, et al. Automated cerebral infarct volume measurement in follow-up noncontrast CT scans of patients with acute ischemic stroke. AJNR Am J Neuroradiol 2013;34(8):1522-7.
29. Hacke W, et al. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. N Engl J Med 2008;359(13):1317-29.
30. Collins GS, et al. Quantifying the impact of different approaches for handling continuous predictors on the performance of a prognostic model. Stat Med 2016;35(23):4124-35.
31. Royston P. A strategy for modelling the effect of a continuous covariate in medicine and epidemiology. Stat Med 2000;19(14):1831-47.
32. Royston P, et al. The use of fractional polynomials to model continuous risk variables in epidemiology. Int J Epidemiol 1999;28(5):964-74.
33. Investigators ET, et al. Efficacy of nitric oxide, with or without continuing antihypertensive treatment, for management of high blood pressure in acute stroke (ENOS): a partial-factorial randomised controlled trial. Lancet 2015;385(9968):617-28.
34. Berge E, et al. Effects of Blood Pressure and Blood Pressure-Lowering Treatment During the First 24 Hours Among Patients in the Third International Stroke Trial of Thrombolytic Treatment for Acute Ischemic Stroke. Stroke 2015;46(12):3362-9.
35. Brott TG, et al. Urgent therapy for stroke. Part I. Pilot study of tissue plasminogen activator administered within 90 minutes. Stroke 1992;23(5):632-40.
36. Tissue plasminogen activator for acute ischemic stroke. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. N Engl J Med 1995;333(24):1581-7.
37. Demchuk AM, et al. Predictors of good outcome after intravenous tPA for acute ischemic stroke. Neurology 2001;57(3):474-80.
38. Molina CA, et al. Improving the predictive accuracy of recanalization on stroke outcome in patients treated with tissue plasminogen activator. Stroke 2004;35(1):151-6.
39. The International Stroke Trial (IST): a randomised trial of aspirin, subcutaneous heparin, both, or neither among 19435 patients with acute ischaemic stroke. International Stroke Trial Collaborative Group. Lancet 1997;349(9065):1569-81.

3

Patient Selection for Endovascular Treatment



3.1

Towards personalized endovascular treatment for acute ischemic stroke patients

Study protocol

Maxim J.H.L. Mulder*, Esmee Venema*, Bob Roozenbeek, Joseph P. Broderick, Sharon D. Yeatts, Pooja Khatri, Olvert A. Berkhemer, Yvo B.W.E.M. Roos, Charles B.L.M. Majoie, Robert J. van Oostenbrugge, Wim H. van Zwam, Aad van der Lugt, Ewout W. Steyerberg, Diederik W.J. Dippel, Hester F. Lingsma

March 2017
British Medical Journal Open

**Equal contribution*

Abstract

Background and Purpose

Overall, endovascular treatment (EVT) proved to be beneficial in patients with acute ischemic stroke due to a proximal occlusion in the anterior circulation. However, heterogeneity in treatment benefit may be relevant for personalized clinical decision making. Our aim is to improve selection of patients for EVT by predicting individual treatment benefit or harm.

Methods & analysis

We will use data collected in the Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands (MR CLEAN) trial to analyses the effect of baseline characteristics on outcome and treatment effect. A multivariable proportional odds model with interaction terms will be developed to predict the outcome for each individual patient, both with and without EVT. Model performance will be expressed as discrimination and calibration, after bootstrap resampling and shrinkage of regression coefficients, to correct for optimism. External validation will be conducted on data of patients in the Interventional Management of Stroke III trial (IMS III). Primary outcome will be the modified Rankin Scale (mRS) at 90 days after stroke.

Ethics and dissemination

The proposed study will provide an internationally applicable clinical decision aid for EVT. Findings will be disseminated widely through peer-reviewed publications, conference presentations and in an online web application tool. Formal ethical approval was not required as primary data were already collected.

Introduction

In 2015, five consecutive randomized controlled trials (RCTs) showed that endovascular treatment (EVT) improves functional outcome in patients with a proximal occlusion in the anterior circulation.[1-6] This was a major breakthrough in the field, and EVT is now implemented in updated guidelines on acute ischemic stroke (AIS) management.[7] Ideally, EVT will be targeted at patients who are expected to have optimal benefit: personalized treatment. In this study protocol, we present seven steps for development and validation of a clinical decision aid to predict which individual patients with AIS will benefit most from EVT.[8 9]

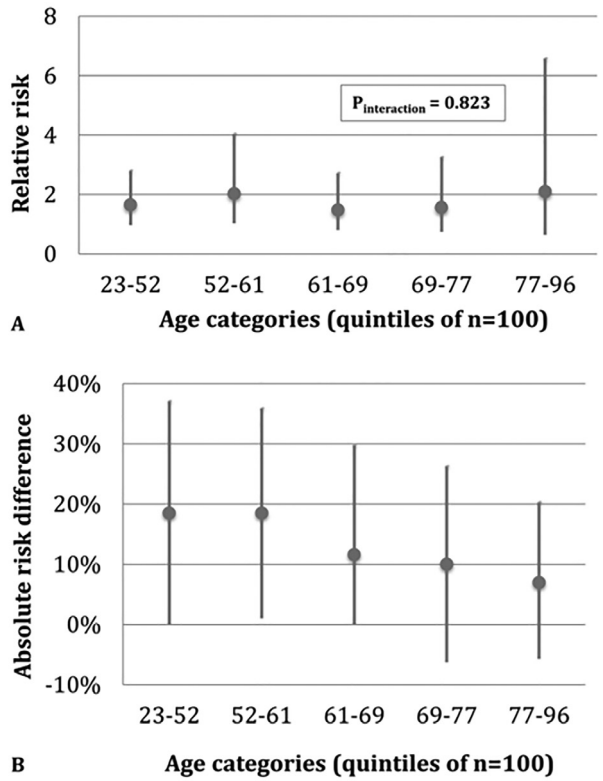
Methods and analysis

Step 1: problem definition and data inspection

Problem definition RCTs provide estimates of treatment effects for average patients. However, it is important to take potential heterogeneity of treatment effects into account. Clinically relevant differences in the absolute effect of a treatment can be caused by (1) differences in the relative treatment effect (predictive effects) and (2) differences in baseline risk on the outcome of interest (prognostic effects).[10 11] For example, in the Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands (MR CLEAN) trial, there is no predictive effect of age; the relative treatment effect is constant across age subgroups.[5] This is demonstrated by a non-significant test for interaction between age and treatment (figure 1A). However, variation in baseline risk on favorable outcome according to age results in a larger absolute treatment benefit in younger patients (figure 1B).

Conventional subgroup analyses are focused mainly on predictive effects and assess the effect of only one variable at a time. If predictive and prognostic effects of multiple characteristics are evaluated simultaneously in multivariable prediction modelling, it is likely that larger heterogeneity in treatment benefit between individual patients will be found. Our aim is to improve selection of patients for EVT by predicting treatment benefit or harm for individual patients with stroke.

Figure 1. Relative risk (A) and absolute risk difference (B) for good functional outcome (mRS 0–2) in MR CLEAN sort by age. MR CLEAN, Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands; mRS, modified Rankin Scale.



Development data

We will use data of the MR CLEAN trial (n=500), which was a phase 3 multicenter clinical trial with randomized treatment group assignment, open-label treatment and blinded end point evaluation. EVT plus usual care (which could include intravenous administration of alteplase) was compared with usual care alone. EVT consisted of arterial catheterization with a microcatheter to the level of occlusion and delivery of a thrombolytic agent, mechanical thrombectomy or both.[5]

Severity of stroke was assessed at baseline with the National Institutes of Health Stroke Scale (NIHSS; range 0–42). Baseline CT was evaluated with the Alberta Stroke Program Early CT Score (ASPECTS; range 0–10). Baseline imaging (CT angiography) was used to determine the location of occlusion and to grade the quality of collateral flow to the ischemic area with a four-point scale. Detailed information about the MR CLEAN trial can be found in the study protocol and the publication of the main results.[5 12]

End points of interest

The primary outcome will be the modified Rankin Scale (mRS), a seven-point scale ranging from 0 (no symptoms) to 6 (death) at 90 days after stroke.[13] We will provide estimates of treatment benefit as the absolute increase in probability on functional independence (defined as mRS 0–2) and survival (defined as mRS 0–5).

Step 2: coding of variables

As variables, we will use patient characteristics that are expected to predict outcome, or that are expected to interact with treatment, based on expert opinion and the recent literature (table 1). Non-linearity of continuous variables will be tested by comparing the two log likelihood of models with linear and restricted cubic spline functions.[14]

Timing of treatment is an essential predictor of outcome. Since time to randomization was not a reliable indicator for time to treatment in the MR CLEAN trial and will not be applicable in clinical practice, we will use time from stroke onset to groin puncture. Since time to groin puncture is not observable in the control group, we will explore imputation approaches based on the correlation with time to randomization. All other baseline variable values are more than 98% complete in the MR CLEAN data, so we choose simple imputation by the mean for continuous variables and simple imputation by the mode for categorical variables.

Table 1. Patient characteristics that are expected to predict outcome (prognostic), or that are expected to interact with treatment (predictive)

	% of data complete in MR CLEAN	Prognostic	Predictive
Clinical			
Age[15 16]	100%	x	
Baseline NIHSS[17 18]	100%	x	
History of diabetes mellitus[19]	100%	x	
History of previous stroke[20]	100%	x	
History of atrial fibrillation[21 22]	100%	x	
Pre-stroke mRS score[20]	100%	x	
Systolic blood pressure[23]	100%	x	
IV treatment with alteplase[24-26]	100%	x	
Time from onset stroke to groin puncture[27 28]	100%*	x	x
Radiological			
ASPECTS[16 29]	99.2%	x	
Location of intracranial occlusion on non-invasive vessel imaging[30 31]	99.8%	x	
Collateral score on CTA[31 32]	98.4%	x	x

**Of patients undergoing intra-arterial treatment.*
ASPECTS, Alberta Stroke Program Early CT score; CTA, CT angiography; IV, intravenous; NIHSS, National Institutes of Health Stroke Scale;
MR CLEAN, Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands; mRS, modified Rankin Scale.

Steps 3 and 4: model specification and estimation

We will test the effect of variables on functional outcome and treatment effect with proportional odds regression modelling. All variables from table 1 will be tested for effect on outcome and interaction with treatment effect. Prognostic variables (main effects) and predictive variables (interaction effects) with a p value of 0.15 in univariable and multivariable analyses will be included in our final model. A p value of 0.15 was chosen to make the predictor selection less data driven and prevent overfitting.[14 33] We will perform shrinkage of all regression coefficients with ridge regression to prevent overfitting of the model.[14] Predicted probabilities for each of the mRS categories, with and without treatment, will be derived from the ordinal model. All statistical analyses will be performed within the computing environment R V.3.2.2 (The R Foundation).

Step 5: model performance

Model performance will be expressed in discrimination and calibration. Discrimination will be quantified with the c-statistic. The c-statistic is similar to the area under the curve for binary outcomes and estimates the probability that out of two randomly chosen patients, the patient with the higher predicted probability of a good outcome will indeed have a better outcome. Calibration refers to the agreement between predicted and observed risks and will be assessed graphically with validation plots, and expressed as calibration slope and an intercept. The calibration slope describes the relative overall effect of the variables in the validation sample, and is ideally equal to 1. The intercept indicates whether predictions are systematically too high or too low, and should ideally be 0.[34] We will calculate a general c-statistic to express the performance of our ordinal model and additional calibration plots with specific c-statistics for the predictions of favorable functional outcome (mRS 0–2) and survival (mRS 0–5).

Step 6: model validity

The c-statistic will be internally validated with a bootstrap procedure (500 samples with replacement) to estimate the degree of optimism in parameter estimates.[8] After penalization of the regression coefficients, we will externally validate the model on data of patients in the Interventional Management of Stroke III trial (IMS III) with an occlusion in the anterior circulation on noninvasive vessel imaging.[35] Coefficients of the final model will be fitted on the combined development and validation data sets.

After validation, we will assess whether the model can be used to discriminate between patients with low and high expected benefit by making individual predictions of outcome for all patients included in the development and validation data.

Step 7: model presentation

The final model will be digitally available for use in clinical practice, both for mobile devices and as a web application. It will provide predictions of all mRS categories for each individual patient, both with and without EVT.

Ethics and dissemination

Findings will be disseminated widely through peer-reviewed publications, conference presentations and in an online web application tool. Formal ethical approval was not required for this study as primary data were already collected.

Discussion

Compared with the current subgroup analyses on the effect of EVT, our modelling approach has multiple advantages. First, it accounts for the fact that patients have multiple characteristics that simultaneously affect the likelihood of treatment benefit.[36] Thus, our model will show more clinically relevant heterogeneity in treatment benefit between patients. Second, a multivariable prediction model substantially increases statistical power to identify heterogeneity in treatment effects compared with other approaches.[37] These include neural network and decision trees. We use regression modelling since it is considered more robust, especially in relatively small data sets.[38 39]

There are some differences between patients included in the MR CLEAN trial and the IMS III trial that may influence the external validity of our model. IMS III had different inclusion criteria, used older devices and older treatment paradigms than MR CLEAN. In order to overcome these limitations, we will use only those patients in IMS III with an occlusion in the intracranial anterior circulation on non-invasive vessel imaging. We will compare the baseline characteristics of the derivation and validation cohort and describe relevant differences that might lead to an underestimation or overestimation of the model performance. Interestingly, substantial treatment effect in the IMS III patients with proven intracranial large vessel occlusion has been reported.[40]

Furthermore, even though the MR CLEAN trial has included most patients of the recent RCTs, the cohort remains relatively small for the development of a prediction model, especially for the selection of the main effect and interaction effects. We will reduce regression coefficients to prevent overfitting and also perform external validation. In the future, we will further validate and update our model in the pooled individual patient data of the Highly Effective Reperfusion evaluated in Multiple Endovascular Stroke Trials (HERMES) collaboration, harboring data of all patients from recent randomized trials regarding EVT (over 1700 patients in total). Moreover, we aim to investigate the validity of our model predicting outcome after treatment in clinical practice. Our model will therefore be tested by applying it to recently treated patients in all Dutch neurovascular centers participating in the MR CLEAN Registry (mrclean-trial.org).

We will use a proportional odds model to analyze the full mRS score as outcome. Formally, this model requires the assumption that the ORs are the same for each cut-off of the mRS. However, previous studies have shown that even if the proportionality assumption is violated, proportional odds analysis is still more efficient than dichotomization.[41] In addition, all recent RCTs on the effect of EVT used the full mRS and analyzed their results with proportional odds regression.

Conclusion

The proposed study will provide an internationally applicable clinical decision aid for the selection of patients for EVT. We consider this study an important next step towards personalized treatment of patients with AIS.

References

1. Saver JL, et al. Stent-retriever thrombectomy after intravenous t-PA vs. t-PA alone in stroke. N Engl J Med 2015;372(24):2285-95.
2. Jovin TG, et al. Thrombectomy within 8 hours after symptom onset in ischemic stroke. N Engl J Med 2015;372(24):2296-306.
3. Goyal M, et al. Randomized assessment of rapid endovascular treatment of ischemic stroke. N Engl J Med 2015;372(11):1019-30.
4. Campbell BC, et al. Endovascular stent thrombectomy: the new standard of care for large vessel ischaemic stroke. Lancet Neurol 2015;14(8):846-54.
5. Berkhemer OA, et al. A randomized trial of intraarterial treatment for acute ischemic stroke. N Engl J Med 2015;372(1):11-20.
6. Goyal M, et al. Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials. Lancet 2016;387(10029):1723-31.
7. Powers WJ, et al. 2015 American Heart Association/American Stroke Association Focused Update of the 2013 Guidelines for the Early Management of Patients With Acute Ischemic Stroke Regarding Endovascular Treatment: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. Stroke 2015;46(10):3020-35.
8. Steyerberg EW. Clinical prediction models: a practical approach to development, validation, and updating. New York: Springer, 2009.
9. Steyerberg EW, et al. Towards better clinical prediction models: seven steps for development and an ABCD for validation. Eur Heart J 2014;35(29):1925-31.
10. Rothwell PM. When should we expect clinically important differences in response to treatment? . Treating Individuals: from randomised trials to presonalised medicine The Lancet, Elsevier 2007.
11. van Klaveren D, et al. Estimates of absolute treatment benefit for individual patients required careful modeling of statistical interactions. J Clin Epidemiol 2015;68(11):1366-74.
12. Fransen PS, et al. MR CLEAN, a multicenter randomized clinical trial of endovascular treatment for acute ischemic stroke in the Netherlands: study protocol for a randomized controlled trial. Trials 2014;15:343.
13. van Swieten JC, et al. Interobserver agreement for the assessment of handicap in stroke patients. Stroke 1988;19(5):604-7.
14. Harrell FE. Regression modeling strategies: with applications to linear models, logistic regression, and survival analysis. New York: Springer-Verlag 2001.
15. Wardlaw JM, et al. Recombinant tissue plasminogen activator for acute ischaemic stroke: an updated systematic review and meta-analysis. Lancet 2012;379(9834):2364-72.
16. Goyal M, et al. Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials. Lancet 2016.
17. Broderick JP, et al. Endovascular Therapy Is Effective and Safe for Patients With Severe Ischemic Stroke: Pooled Analysis of Interventional Management of Stroke III and Multicenter Randomized Clinical Trial of Endovascular Therapy for Acute Ischemic Stroke in the Netherlands Data. Stroke 2015;46(12):3416-22.
18. Frankel MR, et al. Predicting prognosis after stroke - A placebo group analysis from the National Institute of Neurological Disorders and Stroke rt-PA Stroke Trial. Neurology 2000;55(7):952-59.
19. Luitse MJ, et al. Diabetes, hyperglycaemia, and acute ischaemic stroke. Lancet Neurol 2012;11(3):261-71.
20. Karlinski M, et al. Intravenous Thrombolysis for Stroke Recurring Within 3 Months From the Previous Event. Stroke 2015;46(11):3184-9.
21. Sanak D, et al. Is atrial fibrillation associated with poor outcome after thrombolysis? J Neurol 2010;257(6):999-1003.
22. Heshmatollah A, et al. The effect of intra-arterial treatment in patients with acute ischemic stroke and atrial fibrillation. A MR CLEAN substudy (unpublished data). 2015.
23. Jauch EC, et al. Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2013;44(3):870-947.
24. Tissue plasminogen activator for acute ischemic stroke. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. N Engl J Med 1995;333(24):1581-7.
25. Hacke W, et al. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. N Engl J Med 2008;359(13):1317-29.
26. Mulder MJ, et al. Treatment in patients who are not eligible for intravenous alteplase: MR CLEAN subgroup analysis. Int J Stroke 2016.
27. Emberson J, et al. Effect of treatment delay, age, and stroke severity on the effects of intravenous thrombolysis with alteplase for acute ischaemic stroke: a meta-analysis of individual patient data from randomised trials. Lancet 2014;384(9958):1929-35.
28. Fransen PS, et al. Time to Reperfusion and Treatment Effect for Acute Ischemic Stroke: A Randomized Clinical Trial. JAMA Neurol 2015:1-7.
29. Barber PA, et al. Validity and reliability of a quantitative computed tomography score in predicting outcome of hyperacute stroke before thrombolytic therapy. ASPECTS Study Group. Alberta Stroke Programme Early CT Score. Lancet 2000;355(9216):1670-4.
30. Puetz V, et al. Intracranial thrombus extent predicts clinical outcome, final infarct size and hemorrhagic transformation in ischemic stroke: the clot burden score. International Journal of Stroke 2008;3(4):230-36.
31. Tan IYL, et al. CT Angiography Clot Burden Score and Collateral Score: Correlation with Clinical and Radiologic Outcomes in Acute Middle Cerebral Artery Infarct. Am J Neuroradiol 2009;30(3):525-31.
32. Berkhemer OA, et al. Collateral Status on Baseline Computed Tomographic Angiography and Intra-Arterial Treatment Effect in Patients With Proximal Anterior Circulation Stroke. Stroke 2016;47(3):768-76.
33. Steyerberg EW, et al. Prognostic modelling with logistic regression analysis: a comparison of selection and estimation methods in small data sets. Stat Med 2000;19(8):1059-79.
34. Steyerberg EW, et al. Assessing the performance of prediction models: a framework for traditional and novel measures. Epidemiology 2010;21(1):128-38.
35. Broderick JP, et al. Endovascular therapy after intravenous t-PA versus t-PA alone for stroke. N Engl J Med 2013;368(10):893-903.
36. Kent DM, et al. Assessing and reporting heterogeneity in treatment effects in clinical trials: a proposal. Trials 2010;11:85.
37. Hayward RA, et al. Multivariable risk prediction can greatly enhance the statistical power of clinical trial subgroup analysis. BMC Med Res Methodol 2006;6:18.
38. van der Ploeg T, et al. Modern modelling techniques are data hungry: a simulation study for predicting dichotomous endpoints. BMC Med Res Methodol 2014;14:137.
39. van der Ploeg T, et al. Modern modeling techniques had limited external validity in predicting mortality from traumatic brain injury. J Clin Epidemiol 2016.
40. Demchuk AM, et al. Recanalization and clinical outcome of occlusion sites at baseline CT angiography in the Interventional Management of Stroke III trial. Radiology 2014;273(1):202-10.
41. McHugh GS, et al. A simulation study evaluating approaches to the analysis of ordinal outcome data in randomized controlled trials in traumatic brain injury: results from the IMPACT Project. Clin Trials 2010;7(1):44-57.

3.2

Selection of patients for endovascular treatment

Development and validation in MR CLEAN & IMS III

Maxim J.H.L. Mulder*, Esmee Venema*, Bob Roozenbeek, Joseph P. Broderick,
Sharon D. Yeatts, Pooja Khatri, Olvert A. Berkhemer, Bart J. Emmer, Yvo B.W.E.M. Roos,
Charles B.L.M. Majoie, Robert J. van Oostenbrugge, Wim H van Zwam,
Aad van der Lugt, Ewout W. Steyerberg, Diederik W.J. Dippel, Hester F. Lingsma

May 2017
British Medical Journal

**Equal contribution*

Abstract

Aim

To improve the selection of patients with acute ischemic stroke for endovascular treatment using a clinical decision tool to predict individual treatment benefit.

Methods

Multivariable regression modelling with data from two randomized controlled clinical trials. Setting 16 hospitals in the Netherlands (derivation cohort; n=500) and 58 hospitals in the United States, Canada, Australia, and Europe (validation cohort; n=260). The primary outcome was the modified Rankin Scale (mRS) score at 90 days after stroke. We constructed an ordinal logistic regression model to predict outcome and treatment benefit, defined as the difference between the predicted probability of good functional outcome (mRS score 0-2) with and without endovascular treatment.

Results

11 baseline clinical and radiological characteristics were included in the model. The externally validated C statistic was 0.69 (95% confidence interval 0.64 to 0.73) for the ordinal model and 0.73 (0.67 to 0.79) for the prediction of good functional outcome, indicating moderate discriminative ability. The mean predicted treatment benefit varied between patients in the combined derivation and validation cohort from −2.3% to 24.3%. There was benefit of endovascular treatment predicted for some individual patients from groups in which no treatment effect was found in previous subgroup analyses, such as those with no or poor collaterals.

Conclusions

The proposed clinical decision tool combines multiple baseline clinical and radiological characteristics and shows large variations in treatment benefit between patients. The tool is clinically useful as it aids in distinguishing between individual patients who may experience benefit from endovascular treatment for acute ischemic stroke and those who will not.

Introduction

Stroke is the second most common cause of mortality worldwide and the most common cause of disability in high income countries.[1] In Western countries, 80% of strokes are ischemic.[2] Ischemic strokes caused by a proximal occlusion in the intracranial cerebral arteries result in poor outcome.[3 4] Endovascular treatment improves functional outcome in patients with acute ischemic stroke caused by a proximal occlusion,[5-11] with a number needed to treat of 5 (odds ratio 2.35, 95% confidence interval 1.85 to 2.98).[12] However, this is an average treatment effect and it is likely that treatment benefit will vary for individual patients.[13 14] In current practice there is debate on the selection of candidates for endovascular treatment because of uncertainty of treatment benefit in specific subgroups and patients not included in the trials.[12 15]

Clinicians combine multiple characteristics in their clinical decision making when treating an individual patient. For example, consider a man aged 70 who is admitted 40 minutes after the onset of symptoms, with a severe left hemisphere ischemic stroke and a National Institutes of Health Stroke Scale (NIHSS) score of 22, an Alberta Stroke Program Early Computed Tomography Score (ASPECTS, see box 1) of 7, and an M1 occlusion but no collaterals on computed tomography (CT) angiography (see box 1). A previous subgroup analysis using data from the Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands (MR CLEAN) trial suggested no treatment effect for patients with no or poor collaterals.15 If this man can be treated soon after onset of stroke, will he benefit from endovascular treatment? Consider a woman aged 80 with diabetes and high systolic blood pressure, who arrived in a primary stroke center too late for treatment with intravenous tissue plasminogen activator, with a NIHSS score of 22, ASPECTS of 9, and a carotid T occlusion with good collaterals on CT angiography. Should she be transferred to an intervention center 40 miles away if endovascular treatment is just possible within the six hour time window?

We developed and validated a clinical decision tool to provide individualized predictions of the effect of endovascular treatment based on multiple characteristics. Such a tool may be helpful to support clinical judgment when making complicated decisions on endovascular treatment.

Methods

In short, we developed a multivariable prediction model in patients included in the MR CLEAN trial (Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands, n=500) and validated this model in a subgroup of patients with an occlusion on CT angiography in the IMS III trial (Interventional Management of Stroke III, n=260). The primary outcome was the modified Rankin Scale (mRS) score at 90 days after stroke. We constructed an ordinal logistic regression model to predict functional outcome and treatment benefit. This benefit was defined as the difference between the predicted probability of good functional outcome (mRS score 0-2) with and without endovascular treatment. Variables were selected using univariable and multivariable selection steps (P<0.15).

Derivation cohort

We used data from all 500 patients of MR CLEAN (derivation cohort) for the development of our model.[5] MR CLEAN was a phase III multicenter clinical trial with randomized treatment group assignment, open label treatment, and blinded outcome evaluation. Endovascular treatment plus usual care was compared with usual care alone (control group). Usual care could include intravenous tissue plasminogen activator if eligible. Enrolled patients were 18 years or older (no upper age limit), had a score of 2 or higher on the National Institutes of Health Stroke Scale (NIHSS) (range 0-42), an occlusion of the proximal internal carotid artery, middle cerebral artery (M1 or M2), or anterior cerebral artery (A1 or A2), established with CT angiography. The start of endovascular treatment had to be possible within six hours after stroke onset. The imaging committee evaluated the findings on baseline non-contrast CT for the ASPECTS and non-invasive baseline vessel imaging (CT angiography, magnetic resonance angiography, or digital subtraction angiography) for the location of the occlusion and collateral score. More detailed information about MR CLEAN can be found in the study protocol and the publication of the main results.[5 16]

Model development

Patient characteristics obtained before treatment that are expected to predict outcome or to interact with treatment, based on expert opinion or recent literature, were specified in advance in our statistical analysis plan.[17] We used ordinal logistic regression modelling, which assumes proportional odds, to test the effect of age, baseline NIHSS score, systolic blood pressure, treatment with intravenous tissue plasminogen activator, history of ischemic stroke, atrial fibrillation, diabetes mellitus, pre-stroke mRS score, ASPECTS, location of occlusion, collateral score, and time to treatment, as well as the corresponding interactions with treatment. The primary outcome was the mRS score, a 7 point scale ranging from 0 (no symptoms) to 6 (death), at 90 days after stroke.[18] For additional analyses, we derived the probabilities for good functional outcome (mRS score 0-2) from the ordinal model. Treatment benefit was defined as the difference between the predicted probability of good functional outcome with and without endovascular treatment.

In our final multivariable model we selected the main effects or interaction terms with a P value of <0.15 in univariable and multivariable analyses. Location of occlusion was analyzed categorically and ASPECTS and collateral score were analyzed continuously. Continuous variables were not dichotomized. Non-linearity of continuous variables was tested with restricted cubic spline functions.[19] In the final model we used restricted cubic spline functions for age and systolic blood pressure. As a measure of time to treatment we used the time from stroke onset to groin puncture. Since groin puncture was not performed in control participants, time to groin puncture was not observable in the control arm. Single imputation based on regression using age, NIHSS score, transfer between hospitals, hospital of first presentation, and time to randomization, was used to assign time to expected groin puncture (R2=0.89). Since all other variables were more than 98% complete within the derivation cohort, we used simple imputation by the mean for continuous variables and simple imputation by the mode for categorical variables.

Internal validation with bootstrapping was used to estimate the degree of optimism in the final model. To correct for this optimism we reduced the regression coefficients using penalized regression.[19 20] Coefficients of non-linear terms and interaction terms were reduced with a larger penalty than the main effects.[20]

External validation

External validation of our model was performed in the IMS III trial.[21] The IMS III trial (n=656) was a phase III multicenter clinical trial with randomized treatment group assignment, open label treatment, and blinded outcome evaluation. The trial tested the approach of intravenous tissue plasminogen activator followed by endovascular treatment compared with standard intravenous tissue plasminogen activator. Further details on the methods used in the trial have been reported extensively.[21 22]

We included patients with proved occlusion in the anterior circulation on non-invasive vessel imaging and an available mRS score at 90 days in the validation cohort (n=260). Missing collateral scores because of insufficient CT angiography imaging (n=68) were replaced by single imputation with regression using age, history of diabetes mellitus, and presence of internal carotid T occlusion. Single imputation for time to groin puncture (n=102, primarily control patients) was performed using age, NIHSS score, time to randomization, and transfer between hospitals. All other variables were more than 98% complete. Missing values were imputed with the mean for continuous variables or the mode for categorical variables.

Model performance in the validation cohort was expressed by discrimination and calibration. Discrimination was quantified with the concordance or C statistic, which varies between 0.5 for a non-informative model and 1 for a perfectly discriminating model.[23] We calculated the general C statistic of our ordinal model and an additional C statistic for the predictions of good functional outcome (mRS score 0-2).

Calibration refers to the level of agreement between predicted risks and observed outcome; this was assessed graphically with a validation plot for the prediction of good functional outcome (mRS score 0-2) expressed as calibration slope and intercept. The calibration slope describes the effect of the predictors in the validation sample versus the derivation sample, and is ideally equal to 1. The intercept indicates whether predictions are systematically too high or too low, and should ideally be zero.[24]

After external validation, the regression coefficients were fitted on a dataset combining all patients in the derivation and validation cohort. To assess if our model could be used to select individual patients for endovascular treatment, we estimated the individual predictions for all 760 patients included in this combined dataset. We created a scatter plot with the predicted probabilities of good functional outcome (mRS score 0-2) for these patients without endovascular treatment on the x axis and the predicted probabilities with endovascular treatment on the y axis. We made additional plots for the predictions of patients with no or poor collaterals and patients with low ASPECTS, since prespecified subgroup analyses showed that these groups had no or limited benefit of treatment.

All statistical analyses were performed with R statistical software (version 3.2.2) and the rms library (version 4.4-0). The web application was developed with the R Shiny package (shiny version 0.13.0).

Patient involvement

No patients were involved in setting the research question or the outcome measures, nor were they involved in developing plans for design or implementation of the study. No patients were asked to advise on interpretation or writing up of results. There are plans to disseminate the results of the research to the relevant patient community.

Figure 1. Illustration of univariable interaction effects in the derivation cohort (n=500). Interaction with treatment is expressed as the log odds for good functional outcome (modified Rankin Scale 0-2) with and without intra-arterial treatment (IAT) on the y-axis. Variables on the x-axis are expressed continuously (time to groin puncture) or categorically (previous stroke, atrial fibrillation and collateral score)

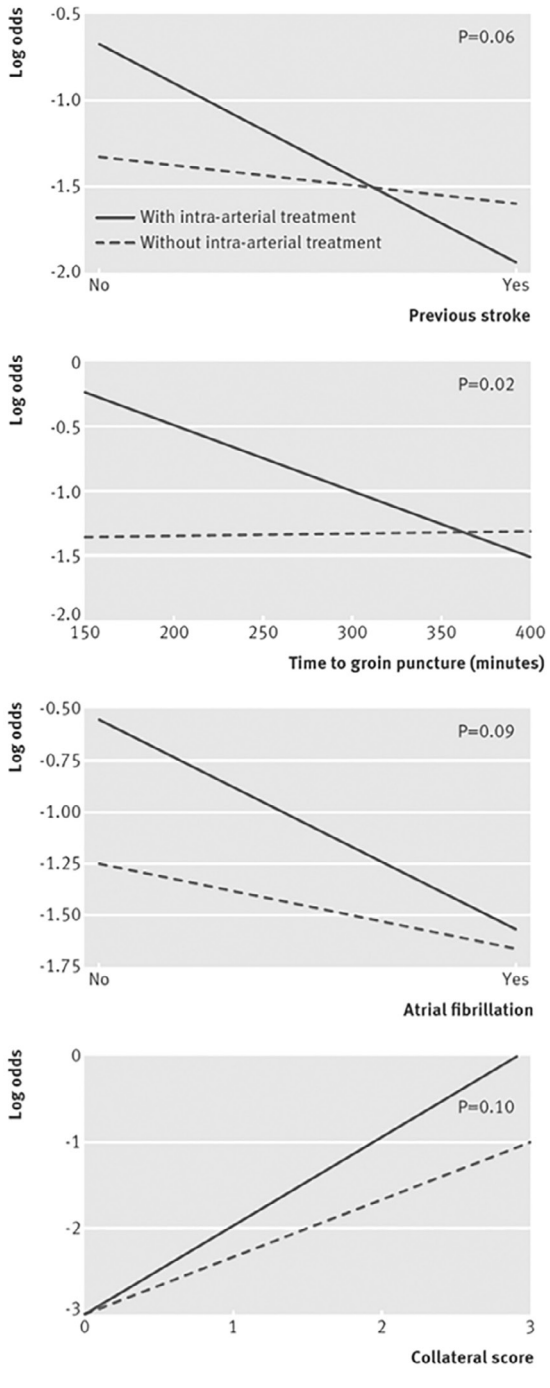


Table 1. Overview of the derivation and validation cohort.

	Derivation cohort	Validation cohort
Included patients – n	500	260
Age, years – mean (SD)	65 (14)	67 (12)
Male sex – n (%)	292 (58%)	135 (52%)
Baseline NIHSS – median (IQR)	18 (14-22)	17 (14-21)
Systolic blood pressure, mmHg – mean (SD)	145 (25)	149 (26)
Treatment with IV tPA, n (%)	445 (89%)	260 (100%)
Allocation to IAT, n (%)	233 (47%)	174 (67%)
Medical history		
Ischaemic stroke – n. (%)	54 (11%)	28 (11%)
Atrial fibrillation – n. (%)	135 (27%)	89 (35%)
Diabetes mellitus – n. (%)	68 (14%)	49 (19%)
Pre-stroke mRS – n. (%)		
0	404 (81%)	231 (89%)
1	50 (10%)	22 (8%)
2	25 (5%)	7 (3%)
≥3	21 (4%)	0
Imaging		
ASPECTS on NCCT – median (IQR)	9 (8-10)	8 (6-9)
Location of occlusion on non-invasive vessel imaging – n. (%)		
ICA-(T)	138 (28%)	66 (25%)
M1	319 (64%)	144 (55%)
M2	39 (8%)	50 (19%)
A1	3 (1%)	0
Workflow		
Onset to randomization, min – median (IQR)	200 (150-261)	143 (120-170)
Onset to groin puncture, min – median (IQR)	260 (210-311)	205 (168-235)
Onset to reperfusion, min – median (IQR)	340 (274-395)	275 (238-319)
Outcome		
Recanalization (mTICI 2B/3) – n. (%)	116 (59%)	69 (45%)
mRS at 90 days – n (%)		
0	7 (1%)	27 (10%)
1	36 (7%)	46 (18%)
2	84 (17%)	39 (15%)
3	87 (17%)	36 (14%)
4	133 (27%)	44 (17%)
5	45 (9%)	18 (7%)
6 (mortality)	108 (22%)	50 (19%)

Abbreviations; ASPECTS = Alberta Stroke Program Early CT score; IAT = intra-arterial treatment; ICA-(T) = internal carotid artery (with terminal segment); IQR = interquartile range; IV tPA = intravenous tissue plasminogen activator; mRS = modified Rankin Scale; mTICI = modified thrombolysis in cerebral infarction scale; NCCT = non-contrast computed tomography; NIHSS = National Institutes of Health Stroke Scale.

Results

Table 1 shows that the baseline patient characteristics and important characteristics of workflow and outcome were similar between the derivation cohort (n=500) and validation cohort (n=260). The validation cohort was somewhat more homogeneous, by not including patients with baseline disability (premorbid mRS score ≥3) or patients not treated with intravenous tissue plasminogen activator.

Most variables were predictors of outcome (table 2). The strongest predictors in multivariable analysis were age (P<0.001), baseline NIHSS score (P<0.001), systolic blood pressure (P<0.001), history of ischemic stroke (P=0.03), diabetes mellitus (P=0.02), pre-stroke mRS score (P=0.003), ASPECTS (P=0.001), location of occlusion (P=0.03), and collateral score (P<0.001). Interactions with relative treatment effect were found in univariable analysis for history of ischemic stroke, atrial fibrillation, time to groin puncture, and collateral score (all P≤0.10, figure 1). In the multivariable model, the effects of endovascular treatment were similar to the univariable analysis, with larger effects in patients without previous ischemic stroke (P=0.07), patients with better collateral scores (P=0.07), and patients with shorter times to groin puncture (P=0.13). Atrial fibrillation was not significant in multivariable analysis as either a main effect (P=0.67) or interaction effect (P=0.27), and was therefore excluded from the model.

The final multivariable model included age, baseline NIHSS score, systolic blood pressure, treatment with intravenous tissue plasminogen activator, history of ischemic stroke, diabetes mellitus, pre-stroke mRS score, ASPECTS, location of occlusion, collateral score, and time from stroke onset to groin puncture. We added terms representing the interaction between treatment and each of previous stroke, collateral score, and time to groin puncture. The internally validated C statistic for ordinal outcome was 0.74 without interaction terms and this increased to 0.75 by adding interaction with treatment. The C statistic for good functional outcome was 0.79.

Table 2. Main effects in the derivation cohort (n=500). Presented common odds ratios reflect the effect on the reversed modified Rankin Scale (odds ratio >1 corresponds with better functional outcome).

	Univariable model		Multivariable model	
	Common odds ratio (95% CI)	p-value	Common odds ratio (95% CI)	p-value
Intra-arterial treatment	1.66 (1.21 to 2.28)	0.002	1.86 (1.34 to 2.59)	<0.001
Age (per year)		<0.001		<0.001
<65 years	0.97 (0.95 to 0.99)		1.00 (0.97 to 1.02)	
>=65 years	0.92 (0.89 to 0.94)		0.92 (0.89 to 0.95)	
Baseline NIHSS (per point)	0.91 (0.88 to 0.94)	<0.001	0.93 (0.90 to 0.96)	<0.001
Systolic blood pressure (per 10 mmHg)		<0.001		<0.001
<130 mmHg	1.12 (0.88 to 1.41)		1.24 (0.97 to 1.59)	
>=130 mmHg	0.76 (0.70 to 0.83)		0.77 (0.70 to 0.85)	
Treatment with IV tPA	1.85 (1.12 to 3.08)	0.017	1.62 (0.94 to 2.79)	0.083
History of ischaemic stroke	0.48 (0.29 to 0.80)	0.005	0.53 (0.31 to 0.92)	0.028
Atrial fibrillation	0.52 (0.36 to 0.73)	<0.001	0.92 (0.62 to 1.36)	0.791
Diabetes mellitus	0.37 (0.23 to 0.59)	<0.001	0.54 (0.33 to 0.90)	0.023
Pre-stroke mRS	0.63 (0.52 to 0.77)	<0.001	0.72 (0.58 to 0.90)	0.003
ASPECTS (per point)	1.16 (1.07 to 1.26)	<0.001	1.16 (1.06 to 1.28)	0.001
Level of occlusion on non-invasive imaging		0.016		0.030
ICA-(T)	1.0 (reference)		1.0 (reference)	
M1	1.53 (1.08 to 2.17)		1.43 (0.98 to 2.07)	
M2	2.11 (1.15 to 3.88)		2.35 (1.20 to 4.60)	
Collateral score	1.95 (1.62 to 2.36)	<0.001	1.61 (1.31 to 1.96)	<0.001
Time from onset stroke to groin puncture (per 30 minutes)	0.94 (0.88 to 1.00)	0.069	0.93 (0.86 to 1.00)	0.039

Abbreviations; ASPECTS = Alberta Stroke Program Early CT score; CI = confidence interval; CTA = computed tomography angiography; IAT = intra-arterial treatment; ICA-(T) = internal carotid artery (with terminal segment); IQR = interquartile range; IV tPA = intravenous tissue plasminogen activator; mRS = modified Rankin Scale; NCCT = non-contrast computed tomography; NIHSS = National Institutes of Health Stroke Scale.

External validation

Similar effects were found for most variables in the validation cohort except for systolic blood pressure, diabetes mellitus, and the interaction between history of ischemic stroke and treatment effect. The externally validated C statistic was 0.69 (95% confidence interval 0.64 to 0.73) for the ordinal model and 0.73 (0.67 to 0.79) for the prediction of good functional outcome (figure 2).

Figure 2. Calibration plot for predicted good functional outcome, defined as modified Rankin Scale (mRS) 0-2, in the validation cohort (n=260). The calibration slope reflects the strength of the predictors. The calibration intercept reflects the calibration-in-the-large, indicating whether predicted probabilities are systematically too low or too high. The overall observed proportion of patients with mRS 0-2 in the validation cohort was higher as to be expected using our model. The linear bar chart shows the distribution of patients with (=1) or without (=0) an observed outcome of mRS 0-2. Discrimination between low and high likelihood of good functional outcome was moderate (c-statistic=0.72 [95% CI:0.65 to 0.77]).

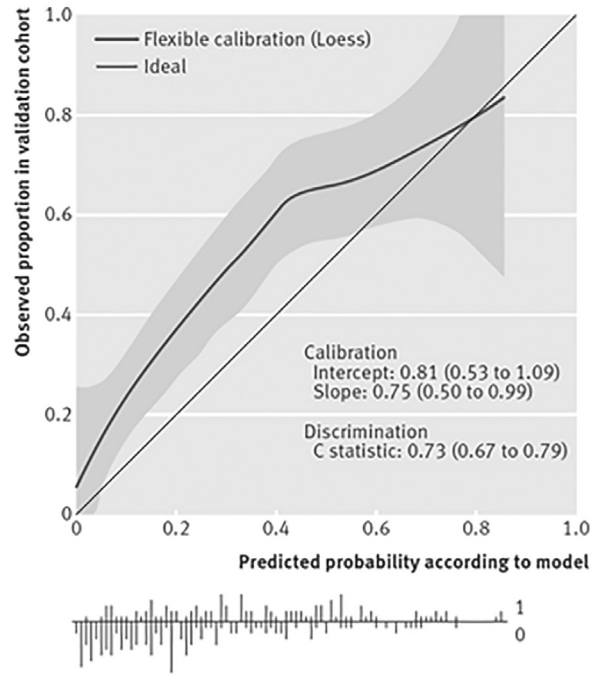


Figure 3. Predicted probabilities of good functional outcome (modified Rankin Scale (mRS) 0-2) for all individual patients in the combined derivation and validation cohort (n=760). Each dot represents one individual patient, with the probability of good functional outcome (mRS 0-2) without intra-arterial treatment (IAT) expressed on the x-axis, and the probability for good functional outcome with IAT on the y-axis. Above the diagonal line the predicted probability of good functional outcome with IAT is higher than that without IAT. The farther above this line, the larger the predicted effect of treatment. 3B. patients highlighted with no or poor collaterals (score 0-1); 3C. patients highlighted with low Alberta Stroke Program Early CT score (ASPECTS, score 0-5).

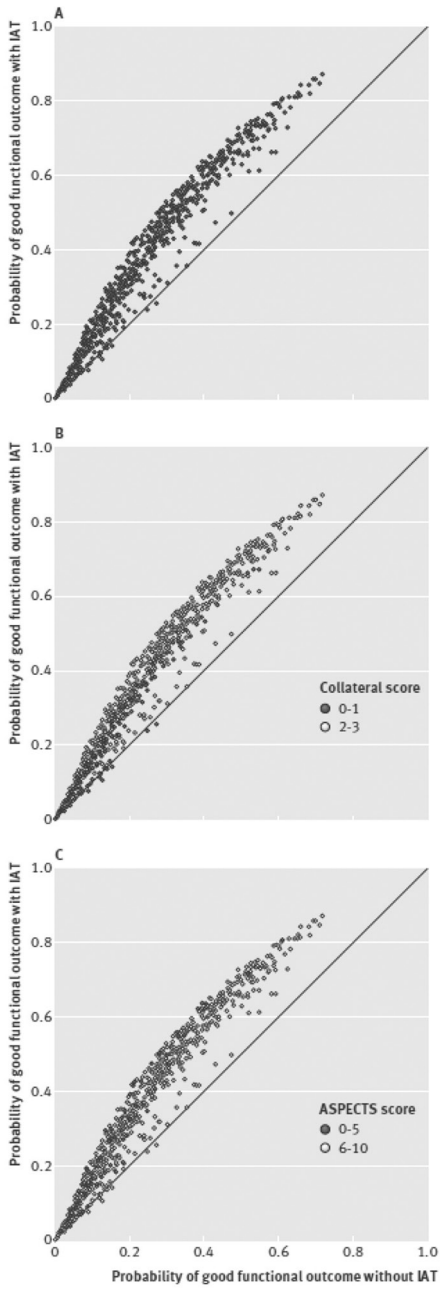
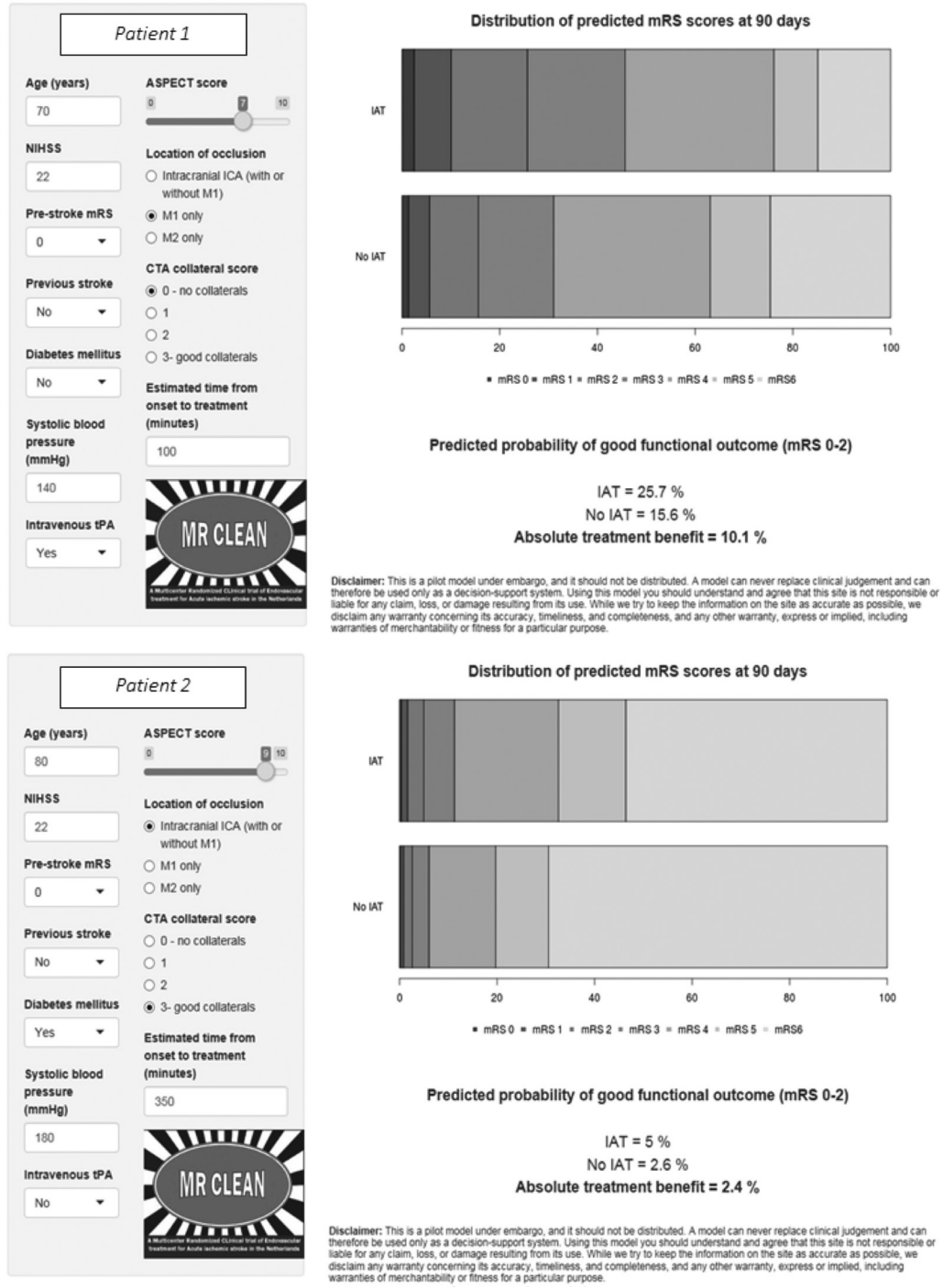


Figure 4. Screen shots of the web-application based on our model. Baseline characteristics and predicted probabilities of good functional outcome (modified Rankin Scale (mRS) 0-2) for two case-examples as discussed in the introduction.



The expected benefit of endovascular treatment varied largely between patients in the combined derivation and validation cohort (figure 3 top graph). Mean predicted absolute treatment benefit was an 11.8% higher probability of mRS score 0-2 compared with the probability without endovascular treatment, and varied from −2.3% to 24.3% between individual patients in the combined derivation and validation cohort. The individual predictions for patients with no or poor collaterals (score 0 or 1) or low ASPECTS (score 0-5) illustrate the substantial variation in outcome and treatment benefit in these groups (figure 3 middle and bottom graphs). For some patients, who have multiple characteristics that negatively affect treatment benefit, the model predicts no benefit or even harm.

We calculated the predicted probabilities of good functional outcome with and without endovascular treatment for the two patients described in the introduction (figure 4). The first patient is expected to benefit from endovascular treatment despite absent collaterals and moderate ASPECTS. The probability of achieving a good functional outcome increases by 11 percentage points, from 16% without endovascular treatment to 27% with endovascular treatment. The predictions for the second patient illustrate that a good collateral score does not guarantee a large treatment benefit. The 80 year old patient has a low probability of achieving a good functional outcome (3% without endovascular treatment and 5% with endovascular treatment), with some shift on the total mRS scale.

We implemented our model in a web application that provides predictions of outcome for individual patients with acute ischemic stroke based on baseline clinical and radiological characteristics for use in clinical practice. It shows bar charts with the expected distribution of mRS categories with and without endovascular treatment, the predicted probabilities of good functional outcome, and the predicted absolute treatment benefit (figure 4). This web application was made accessible online at www.mrpredicts.com.

Discussion

We developed and externally validated a clinical decision tool to predict the benefit of endovascular treatment for individual patients with acute ischemic stroke, based on multiple patient characteristics. The predicted treatment benefit varied substantially between individual patients with different risk profiles.

Strengths and weaknesses in relation to other studies

Two risk scores have been described previously for the prediction of functional outcome after endovascular treatment.[25 26] These scores are of limited value because they were developed on older cohorts of patients who were treated before the introduction of stent retrievers and contain only a small number of clinical variables. Furthermore, they do not provide individual predictions and most of the variables and outcome measures in these studies had been dichotomized, which is considered to be statistically inefficient and biologically implausible.[27] Our model combines 11 baseline clinical and radiological characteristics simultaneously to provide individualized predictions of the effect of endovascular treatment. In contrast, conventional subgroup analyses focus mainly on predictive effects and assess the effect of only one variable at a time. Previous subgroup analyses of trials on endovascular treatment have tested whether there are differences in effect of such treatment based on time to treatment,[28-32] stroke severity,[12 33] and collateral score.[15] Analyzing one variable at a time may provide mechanistic insights to inform future studies and shape clinical considerations. However, they are of limited value in individual patient care, because treatment benefit is influenced by multiple individual factors simultaneously.[13 14] Furthermore, even with similar relative treatment effects, individual patients may have different absolute treatment effects owing to different baseline risks. More targeted individual treatment decisions can be obtained by using a more complex multivariable modelling approach to identify individual patients with large or small expected treatment benefit.[13]

We found modest interaction with treatment for history of ischemic stroke, collateral score, and time from stroke onset to groin puncture. For collateral score and time to groin puncture, interaction with effect of endovascular treatment was already shown in previous subgroup analyses.[15 28] Both variables are clinically likely to cause an interaction with endovascular treatment. However, previous stroke has not been studied for interaction with treatment before, and was an unexpected finding in our study. It may be a chance finding, since it was not reproduced in the validation cohort and we have no clinical explanation. When the regression coefficients were fitted on data of the combined derivation and validation cohort and the coefficients of interaction terms were reduced to prevent overfitting, the interaction effect for previous stroke in the final model was small. Further validation should reveal whether the relative effect of endovascular treatment is modified by experience of a previous stroke. Our study has several limitations. The discriminative ability of the model in the external validation was modest. It should be emphasized that the C statistic for the ordinal outcome is a conservative measure. It assesses discrimination between exact categories of the mRS, instead of discrimination between two groups with different outcome (e.g. mRS score 0-2 v mRS score 3-6). Externally validated C statistics of all cutoffs were better than the ordinal C statistic (e.g. 0.73 for good functional outcome and 0.75 for mortality). Nevertheless, the relatively small sample size and inclusion of interaction terms in the model may have resulted in some optimism and overfitting, despite shrinkage of the regression coefficients. The calibration was also suboptimal; despite the fact that most patients were treated with first generation thrombectomy devices, patients in the Interventional Management of Stroke III trial (IMS III) had a better outcome than predicted by our model. This could be explained by the patient selection in IMS III (e.g. premorbid mRS score 0-2, age <82 years, treatment with intravenous tissue plasminogen activator),[34] which resulted in a better prognosis overall. Patients in the IMS III control group had better outcomes than patients in the control group in the Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands (MR CLEAN) trial (mRS score 0-2=39% (IMS III with occlusion on CT angiography) v 19% (MR CLEAN)), leading to inadequate calibration of our model.[5 34]

Implications for clinicians

Despite its limitations, the currently developed model is the first to predict the effect of endovascular treatment for individual patients on arrival at the emergency department. When compared with other models used in neurovascular practice, HAS-BLED (C-statistic 0.65) and CHA2DS2-VASc (0.61), it performs accurately.[35 36] The predictions made by our decision tool often agree with clinical intuition, which should not be surprising. However, estimates derived from large datasets are preferable to the subjective opinion of a doctor, whose experience, no matter how vast, can never match the information contained in large datasets.[37]

Currently, some centers withhold endovascular treatment in specific subgroups of patients (e.g., low ASPECTS, no collaterals, age >80 years, or M2 occlusion). Indeed, our

model predicts no benefit of endovascular treatment for some patients, especially when a patient has more than one characteristic that negatively affects the effect of endovascular treatment. The decision not to treat may be particularly relevant in patients who have to be transferred to an intervention center. The model may help to identify patients without expected benefit of endovascular treatment and topple the balance in favor of no treatment. More importantly, our study shows that treatment should not be withheld based on one characteristic. Some patients belonging to one of the subgroups that are considered as having no benefit of endovascular treatment, such as poor collaterals or low ASPECTS, may still benefit from endovascular treatment substantially if other characteristics are favorable. This emphasizes the importance of making personalized treatment decisions, instead of using average treatment effects, and shows the need for combining multiple clinical and radiological baseline characteristics instead of withholding treatment based on one characteristic.[38]

This is the first model for endovascular treatment decision making. The predictions of our model should be considered as a starting point for clinical decision making, and not as a final recommendation. Our model was developed using the MR CLEAN database, consisting of an unselected population with few selection criteria. Therefore, our model is likely applicable in centers that use few clinical and radiological selection criteria. Future analyses within larger studies may refine the current recommendations and improve the validity of the model.

Conclusion

The proposed clinical decision tool combines multiple baseline clinical and radiological characteristics and shows large variations in treatment benefit between patients. The tool is clinically useful as it aids in identifying individual patients who may benefit from endovascular treatment for acute ischemic stroke.

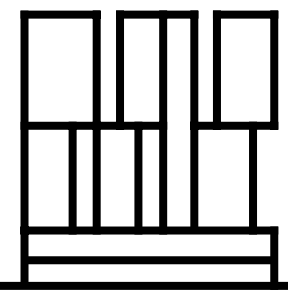
References

1. Lopez AD, et al. Global and regional burden of disease and risk factors, 2001: systematic analysis of population health data. Lancet 2006;367(9524):1747-57.
2. van der Worp HB, et al. Clinical practice. Acute ischemic stroke. N Engl J Med 2007;357(6):572-9.
3. Lima FO, et al. Prognosis of untreated strokes due to anterior circulation proximal intracranial arterial occlusions detected by use of computed tomography angiography. JAMA Neurol 2014;71(2):151-7.
4. Smith WS, et al. Significance of large vessel intracranial occlusion causing acute ischemic stroke and TIA. Stroke 2009;40(12):3834-40.
5. Berkhemer OA, et al. A randomized trial of intraarterial treatment for acute ischemic stroke. N Engl J Med 2015;372(1):11-20.
6. Campbell BC, et al. Endovascular stent thrombectomy: the new standard of care for large vessel ischaemic stroke. Lancet Neurol 2015;14(8):846-54.
7. Goyal M, et al. Randomized assessment of rapid endovascular treatment of ischemic stroke. N Engl J Med 2015;372(11):1019-30.
8. Jovin TG, et al. Thrombectomy within 8 hours after symptom onset in ischemic stroke. N Engl J Med 2015;372(24):2296-306.
9. Saver JL, et al. Stent-retriever thrombectomy after intravenous t-PA vs. t-PA alone in stroke. N Engl J Med 2015;372(24):2285-95.
10. Bracard S, et al. Mechanical thrombectomy after intravenous alteplase versus alteplase alone after stroke (THRACE): a randomised controlled trial. Lancet Neurol 2016;15(11):1138-47.
11. Muir KW, et al. Endovascular therapy for acute ischaemic stroke: the Pragmatic Ischaemic Stroke Thrombectomy Evaluation (PISTE) randomised, controlled trial. J Neurol Neurosurg Psychiatry 2017;88(1):38-44.
12. Goyal M, et al. Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials. Lancet 2016;387(10029):1723-31.
13. Kent DM, et al. Assessing and reporting heterogeneity in treatment effects in clinical trials: a proposal. Trials 2010;11:85.
14. Rothwell PM. Treating individuals 2. Subgroup analysis in randomised controlled trials: importance, indications, and interpretation. Lancet 2005;365(9454):176-86.
15. Berkhemer OA, et al. Collateral Status on Baseline Computed Tomographic Angiography and Intra-Arterial Treatment Effect in Patients With Proximal Anterior Circulation Stroke. Stroke 2016;47(3):768-76.
16. Fransen PS, et al. MR CLEAN, a multicenter randomized clinical trial of endovascular treatment for acute ischemic stroke in the Netherlands: study protocol for a randomized controlled trial. Trials 2014;15:343.
17. Mulder MJ, et al. Towards personalised intra-arterial treatment of patients with acute ischaemic stroke: a study protocol for development and validation of a clinical decision aid. BMJ Open 2017;7(3):e013699.
18. van Swieten JC, et al. Interobserver agreement for the assessment of handicap in stroke patients. Stroke 1988;19(5):604-7.
19. Harrell FE. Regression modeling strategies: with applications to linear models, logistic regression, and survival analysis. New York: Springer-Verlag 2001.
20. Steyerberg EW. Clinical prediction models: a practical approach to development, validation, and updating. New York: Springer, 2009.
21. Broderick JP, et al. Endovascular therapy after intravenous t-PA versus t-PA alone for stroke. N Engl J Med 2013;368(10):893-903.
22. Khatri P, et al. Methodology of the Interventional Management of Stroke III Trial. Int J Stroke 2008;3(2):130-7.
23. Steyerberg EW, et al. Assessing the performance of prediction models: a framework for traditional and novel measures. Epidemiology 2010;21(1):128-38.
24. Steyerberg EW, et al. Towards better clinical prediction models: seven steps for development and an ABCD for validation. Eur Heart J 2014;35(29):1925-31.

25. Flint AC, et al. Predicting long-term outcome after endovascular stroke treatment: the totaled health risks in vascular events score. AJNR Am J Neuroradiol 2010;31(7):1192-6.
26. Hallevi H, et al. Identifying patients at high risk for poor outcome after intra-arterial therapy for acute ischemic stroke. Stroke 2009;40(5):1780-5.
27. Scott SC, et al. Statistical assessment of ordinal outcomes in comparative studies. J Clin Epidemiol 1997;50(1):45-55.
28. Fransen PS, et al. Time to Reperfusion and Treatment Effect for Acute Ischemic Stroke: A Randomized Clinical Trial. JAMA Neurol 2015:1-7.
29. Goyal M, et al. Analysis of Workflow and Time to Treatment and the Effects on Outcome in Endovascular Treatment of Acute Ischemic Stroke: Results from the SWIFT PRIME Randomized Controlled Trial. Radiology 2016;279(3):888-97.
30. Menon BK, et al. Analysis of Workflow and Time to Treatment on Thrombectomy Outcome in the Endovascular Treatment for Small Core and Proximal Occlusion Ischemic Stroke (ESCAPE) Randomized, Controlled Trial. Circulation 2016;133(23):2279-86.
31. Ribo M, et al. Association Between Time to Reperfusion and Outcome Is Primarily Driven by the Time From Imaging to Reperfusion. Stroke 2016;47(4):999-1004.
32. Saver JL, et al. Time to Treatment With Endovascular Thrombectomy and Outcomes From Ischemic Stroke: A Meta-analysis. JAMA 2016;316(12):1279-88.
33. Broderick JP, et al. Endovascular Therapy Is Effective and Safe for Patients With Severe Ischemic Stroke: Pooled Analysis of Interventional Management of Stroke III and Multicenter Randomized Clinical Trial of Endovascular Therapy for Acute Ischemic Stroke in the Netherlands Data. Stroke 2015;46(12):3416-22.
34. Demchuk AM, et al. Recanalization and clinical outcome of occlusion sites at baseline CT angiography in the Interventional Management of Stroke III trial. Radiology 2014;273(1):202-10.
35. Lip GY, et al. Comparative validation of a novel risk score for predicting bleeding risk in anticoagulated patients with atrial fibrillation: the HAS-BLED (Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile INR, Elderly, Drugs/Alcohol Concomitantly) score. J Am Coll Cardiol 2011;57(2):173-80.
36. Lip GY, et al. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. Chest 2010;137(2):263-72.
37. Lingsma HF, et al. Early prognosis in traumatic brain injury: from prophecies to predictions. Lancet Neurol 2010;9(5):543-54.
38. Kent DM, et al. Risk and treatment effect heterogeneity: re-analysis of individual participant data from 32 large clinical trials [published online ahead of print July 3, 2016]. Int J Epidemiol 2016.

4

Endovascular Treatment in Clinical Practice



4.1

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

Maxim J.H.L. Mulder*, Debbie Beumer*, Ghesrouw Saiedie, Susanne Fonville,
Robert J. van Oostenbrugge, Wim H. van Zwam, Philip J. Homburg,
Aad van der Lugt, Diederik W J Dippel

September 2016
Neurovascular imaging

**Equal contribution*

Abstract

Background & purpose

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 (EVT) 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]).

Conclusions

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 endovascular treatment.

Introduction

Recently published randomized clinical trials showed that endovascular treatment (EVT) 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 EVT 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 EVT, 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

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 electronical 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 0.6x0.6 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.

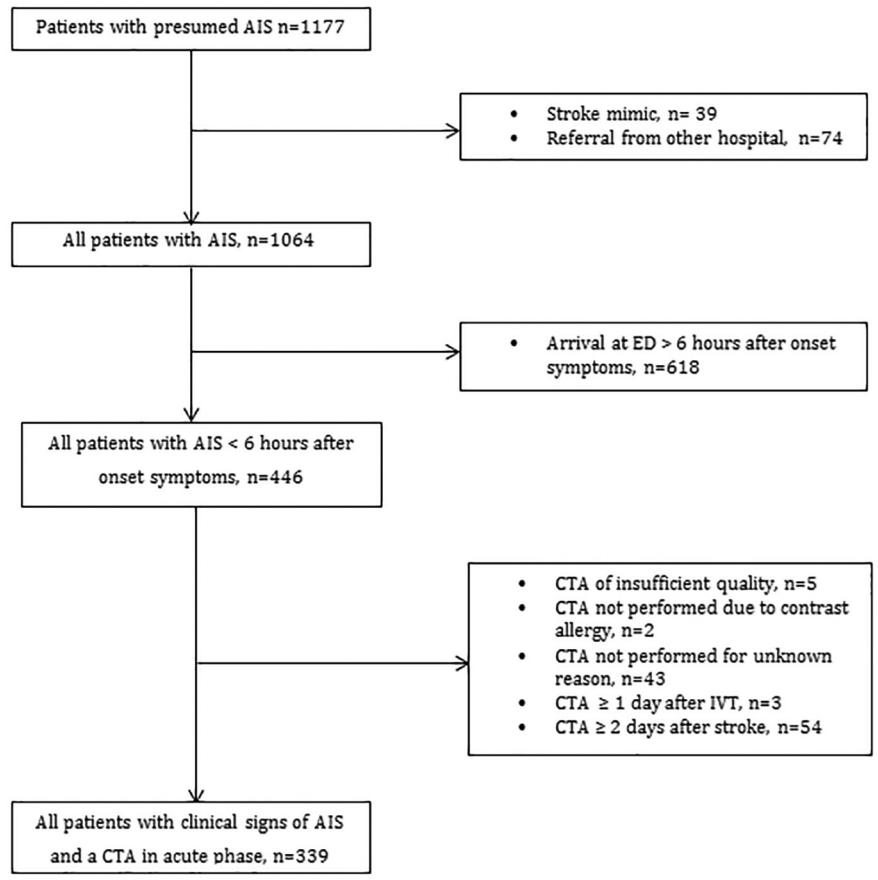
Statistical analysis

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 1). 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 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 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).

Figure 1. Inclusion chart of the patients. ED=emergency department, CTA=computer tomography angiography, AIS= acute ischemic stroke.



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 1). Patients with NIHSS of 1 or 2 had a 10 % likelihood of LVO (Figure 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 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 1).

Table 1. Baseline characteristics of the study population with and without acute intracranial large vessel occlusion (LVO). All patients arrived at the emergency department within 6 hours 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.

	LVO (n=104)	No LVO (n=235)	P-value
Age (years), mean (SD)	64 (15)	62 (16)	0.29
Male sex, n (%)	52 (50%)	118 (50%)	0.97
Caucasian ethnicity, n (%)	79 (76%)	187 (80%)	0.46
Systolic blood pressure, mean (SD)	160 (38)	167 (33)	0.10
Diastolic blood pressure, mean (SD)	85 (21)	89 (19)	0.09
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)	0.40
Previous ischemic stroke, n (%)	18 (17%)	52 (23%)	0.28
Previous heart disease, n (%)	14 (13%)	41 (18%)	0.34
Previous atrial fibrillation, n (%)	14 (14%)	19 (8%)	0.13
NIHSS on admission, median (IQR)	13 (6-18)	3 (2-7)	0.00

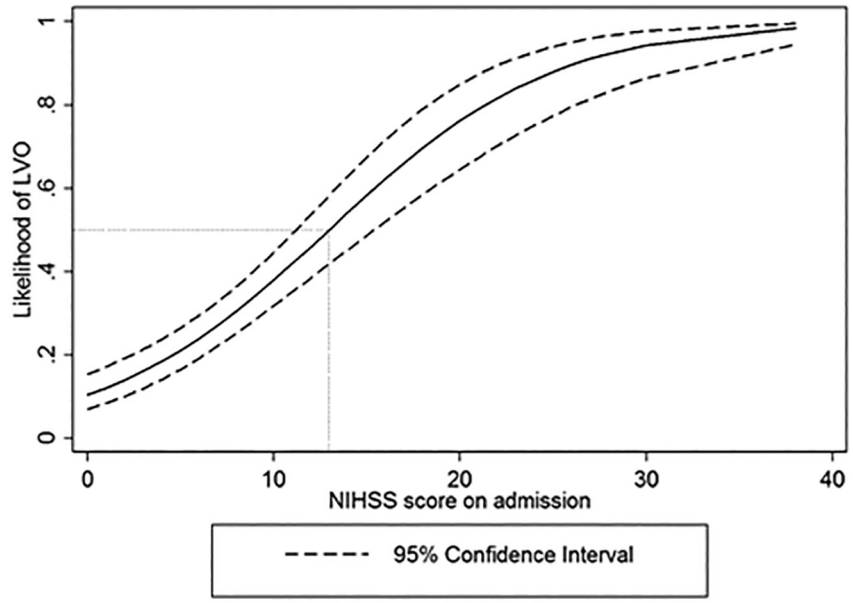
BMI= body mass index. NIHSS= National Institutes of health Stroke Scale. NIHSS on admission significantly differed between both groups.

Table 2. Distribution and location of acute intracranial large vessel occlusion (LVO)

Anatomical location LVO	Number and percentage of total symptomatic LVO (n=104)
Anterior circulation (n=76)	
Anterior cerebral artery, A1 segment, n (%)	0
Intracranial carotid artery, n (%)	23 (22%)
Middle cerebral artery, M1 segment, n (%)	37 (36%)
Middle cerebral artery, M2 segment, n (%)	16 (15%)
Posterior circulation (n=28)	
Intracranial vertebral artery, n (%)	9 (9%)
Posterior cerebral artery, P1 segment, n (%)	8 (8%)
Posterior cerebral artery, P2 segment, n (%)	2 (2%)
Basilar artery, n (%)	9 (9%)

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

Figure 2. The association between NIH Stroke Scale 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 hours of symptom onset. For each point increase in NIHSS aOR is 1.23 (95% Confidence Interval 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 EVT candidate.

Clinical practice

Our study suggests that almost one third of all patients with AIS may be candidates for EVT, 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 EVT 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.[11 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]

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

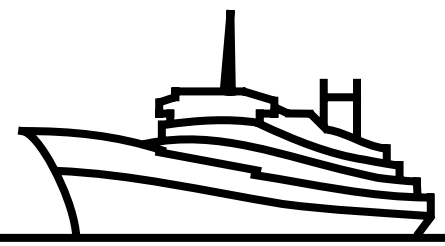
Of all patients with acute ischemic stroke who arrive within 6 h of symptom onset at the emergency department, almost one out of three will have an intracranial large vessel occlusion and may be eligible for endovascular treatment.

References

1. Berkhemer OA, et al. A randomized trial of intraarterial treatment for acute ischemic stroke. N Engl J Med 2015;372(1):11-20.
2. Campbell BC, et al. Endovascular stent thrombectomy: the new standard of care for large vessel ischaemic stroke. Lancet Neurol 2015;14(8):846-54.
3. Goyal M, et al. Randomized assessment of rapid endovascular treatment of ischemic stroke. N Engl J Med 2015;372(11):1019-30.
4. Jovin TG, et al. Thrombectomy within 8 hours after symptom onset in ischemic stroke. N Engl J Med 2015;372(24):2296-306.
5. Saver JL, et al. Stent-retriever thrombectomy after intravenous t-PA vs. t-PA alone in stroke. N Engl J Med 2015;372(24):2285-95.
6. Goyal M, et al. Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials. Lancet 2016;387(10029):1723-31.
7. Casaubon LK, et al. Canadian Stroke Best Practice Recommendations: Hyperacute Stroke Care Guidelines, Update 2015. Int J Stroke 2015;10(6):924-40.
8. Powers WJ, et al. 2015 American Heart Association/American Stroke Association Focused Update of the 2013 Guidelines for the Early Management of Patients With Acute Ischemic Stroke Regarding Endovascular Treatment: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. Stroke 2015;46(10):3020-35.
9. Smith WS, et al. Significance of large vessel intracranial occlusion causing acute ischemic stroke and TIA. Stroke 2009;40(12):3834-40.
10. Weimar C, et al. Distribution and outcome of symptomatic stenoses and occlusions in patients with acute cerebral ischemia. Arch Neurol 2006;63(9):1287-91.
11. Heldner MR, et al. Clinical prediction of large vessel occlusion in anterior circulation stroke: mission impossible? J Neurol 2016.
12. Heldner MR, et al. National Institutes of Health stroke scale score and vessel occlusion in 2152 patients with acute ischemic stroke. Stroke 2013;44(4):1153-7.
13. Hansen CK, et al. Stroke severity and incidence of acute large vessel occlusions in patients with hyper-acute cerebral ischemia: results from a prospective cohort study based on CT-angiography (CTA). Int J Stroke 2015;10(3):336-42.
14. de Monye C, et al. Sixteen-detector row CT angiography of carotid arteries: comparison of different volumes of contrast material with and without a bolus chaser. Radiology 2005;237(2):555-62.
15. de Monye C, et al. Optimization of CT angiography of the carotid artery with a 16-MDCT scanner: craniocaudal scan direction reduces contrast material-related perivenous artifacts. AJR Am J Roentgenol 2006;186(6):1737-45.
16. Fischer U, et al. NIHSS score and arteriographic findings in acute ischemic stroke. Stroke 2005;36(10):2121-5.

5

Discussion



Marking a new era

Ischemic stroke patients with a proximal occlusion in the anterior circulation, in general fared poor despite intravenous alteplase treatment (IVT).[1] Publication of the MR CLEAN trial (on 1 January 2015) led to a breakthrough in acute ischemic stroke treatment. The MR CLEAN was the first and largest (n=500) randomized controlled trial to show the benefit of endovascular treatment (EVT) for patients with proximal anterior circulation occlusions.[2] This great achievement was possible because of a well-established collaboration of all EVT centers in the Netherlands, that has continued after the final MR CLEAN trial inclusion by registering all EVT patients in the MR CLEAN Registry for more than three years already (n>3000).

After publication of the main MR CLEAN trial results, ongoing randomized controlled trials were stopped prematurely because of loss of equipoise or after formal interim analyses. These trials confirmed that EVT is indeed beneficial in acute ischemic stroke patients with proximal anterior circulation occlusions.[3-6] Shortly after these five positive trials were published, the American Heart Association/American Stroke Association guidelines were updated and now recommend EVT in acute ischemic stroke patients that have a proximal occlusion in the anterior circulation.[7] Subsequently, EVT is currently being implemented as standard of care for these patients in the Western world. However, there is still ongoing debate concerning EVT effectiveness in various subgroups, individual patient selection for EVT, and generalizability of the trial results towards clinical practice.

The main objective of this thesis was to improve personalized EVT for acute ischemic stroke in current clinical practice.

Review and interpretation of main findings

Subgroups

The updated American Heart Association/American Stroke Association guidelines of 2015 noted that EVT benefit was uncertain in patients who were not treated with prior IVT.[7] This thesis part 2.1 showed that EVT, in patients who were not treated with IVT in the MR CLEAN trial, was not less effective, nor less safe than in patients who were treated with IVT. We found this in spite of the fact that patients not treated with IVT were older, and had more vascular comorbidity. Therefore, we concluded that EVT is both safe and effective in patients that were not treated with prior IVT.

Combining data from MR CLEAN, REVASCAT, and ESCAPE showed the EVT effect estimate, in patients that were not treated with prior IVT, to be both clinically and statistically significant (OR=2.3 [95% CI: 1.5–3.7]).[8] In addition, the Highly Effective Reperfusion evaluated in Multiple Endovascular Stroke Trials (HERMES) collaboration published their first meta-analysis of patient data, showing a substantial EVT benefit in IVT ineligible patients and no interaction of IVT with EVT on functional outcome.[9] Altogether, these publications eliminated the doubt regarding EVT effect and safety in patients without prior IVT.

In primary percutaneous coronary interventions, peri-procedural antiplatelet and anticoagulant treatment improves outcome.[10] However, early administration of intravenous aspirin in acute ischemic stroke patients treated with IVT is associated with an increased risk of intracranial hemorrhage,[11] and this might also be the case for EVT.

Incomplete microvascular reperfusion may be responsible for poor outcome in EVT patients after successful reperfusion.[12] Therefore, it is hypothesized that acute administration of antiplatelet medication could improve microvascular reperfusion, and so facilitate better functional outcome after EVT. In the recently published EVT trials and in the updated guidelines, the role of antithrombotic medication in the acute phase was not addressed.[2-7 9 13 14]

In part 2.2, we presented the findings of the first study that investigated the effects of EVT in patients who had already been using antiplatelet medication. We showed that the effect of EVT was similar to patients who were not using this medication.

High blood pressure (BP) is associated with poor outcome and the occurrence of symptomatic intracerebral hemorrhage (SICH) after acute ischemic stroke. The current American Heart Association and American Stroke Association guidelines recommend not to use IVT in patients with a BP above 185/110 mm Hg.[15] This is based on the publication of the NINDS trial, were patients with a higher blood pressure were not eligible.[16] However, the updated guidelines do not contain recommendations regarding EVT and BP.

Part 2.3 described the first study to investigate possible interaction of BP with EVT. We confirmed the strong association between systolic BP and functional outcome in ischemic stroke. This association was U-shaped; both low and high baseline Systolic BP were associated with poor functional outcome. Furthermore, higher Systolic BP was associated with an increased risk of SICH. Our most important finding was that baseline BP does not change EVT effect, nor does it interact with EVT on safety parameters. Therefore, there seems to be no reason to withhold or delay EVT based on the BP value.

Patient selection

Since every patient has many characteristics that potentially influence treatment effect, conventional subgroup analysis are essentially valueless when it comes to individual treatment decision.[17] Based on the HERMES data, the number needed to treat for improving functional outcome was 2.6.[9] Since this is an average treatment effect, it is likely that treatment benefit will vary among individual patients.[17 18] In addition, as one of the British Medical Journal editors stated: 'Currently, clinicians make decisions about the suitability of endovascular thrombectomy using patient's clinical and imaging findings to provide a qualitative estimate of the probability of a given outcome. At some centers, individual features such as age or specific imaging findings are used to determine eligibility.'[19] This selection does not consider the large variation of treatment benefit and harm in individual patients, but places patients in a specific subgroup (i.e. old age or poor collaterals).

Chapter 3 presents the development (3.1) and results (3.2) of the first multivariable regression model that predicts EVT benefit for individual patients based on information available at the emergency department. Independent predictors of outcome were: age, baseline NIHSS score, systolic BP, history of ischemic stroke, diabetes mellitus, pre-stroke mRS score, ASPECTS, location of occlusion, treatment with IVT, collateral score, and time to groin puncture. There was large difference in EVT benefit between individual patients. Furthermore, in some patients within subgroups where no treatment effect was found in previous analyses (such as: patients with no collaterals or a poor ASPECTS score), the model still predicted EVT benefit. This emphasizes the importance of considering multiple clinical and imaging variables simultaneously when making treatment decisions, stressing

the fact that a single characteristic cannot dominate clinical decision making. Our clinical decision tool is now available online (www.mrpredicts.com). By combining multiple clinical and radiological characteristics, this decision tool predicts EVT benefit for individual patients upon emergency department arrival.

Clinical practice

After the first randomized trials reported the beneficial effect of EVT in early 2015, full implementation and integration of EVT in the Dutch health care system started. The MR CLEAN-Registry is a post-trial Registry of EVT in the Netherlands (www.mrclean-trial.org). The Registry started directly after the last patient was randomized for the MR CLEAN trial, on March 16, 2014. The purpose was to monitor the implementation, outcome and safety of EVT in the Netherlands after the MR CLEAN trial.

The first part of chapter 4 showed that 30% of the acute ischemic stroke patients had proximal circulation occlusion, when emergency department presentation was within 6 hours of symptom onset. Thus, almost one third of acute ischemic stroke patients could be EVT candidates, when arriving within the current EVT time window. This is in line with the data from Copenhagen, where 29% of the patients who received IVT, had proximal anterior circulation occlusion.[20] Studies that showed higher rates of proximal anterior circulation occlusion also included patients transferred from other hospitals.[21 22] Furthermore, this study confirmed the strong association between baseline National Institute of Health Stroke Scale (NIHSS) score and the occurrence of proximal anterior circulation occlusion.[20 22 23] When the NIHSS score was ≥12 points, the probability of proximal anterior circulation occlusion was 75%.

In part 4.2, we used the unique data gathered in the MR CLEAN Registry, showing the first outcomes and effects of EVT in routine clinical practice. Since the start of the MR CLEAN Registry there has been a steady increase of EVT patients. During the start of the Dutch MR CLEAN Registry, in March 2014, 5 to 20 patients were treated each month. This amount increased to 95 to 117 each month, at the first months of 2016. The treated population in routine clinical practice was older, had more frequently intravenous alteplase treatment contraindications, had a higher pre stroke mRS score and was treated faster. In this chapter we showed that in routine clinical practice, EVT is at least as effective and safe as in the trial setting.

The final part (4.3), showed time to EVT in current clinical practice is strongly associated with functional outcome, even stronger than in previous trials. These findings emphasize that functional outcome of EVT patients can be greatly improved by shortening onset to treatment times.

Thesis considerations

Specific limitations with regard to the studies presented in this thesis are discussed in the individual chapters. Some general limitations, regarding the subgroup analysis, prediction modelling and the MR CLEAN Registry are discussed below.

Chapter 2 is based on post-hoc subgroup analyses of the MR CLEAN trial. These analyses were considered necessary because of potential heterogeneity of treatment effect. However, only the subgroup analysis in patients without prior IVT was pre-specified. Published subgroup analysis should be considered with care, especially when they are post-hoc.[18] Since part 2.2 and 2.3 were the first analyses in these subgroups, we recommend analyzing prior antiplatelet medication and BP in other cohorts to see whether this findings hold.

In Chapter 3 we used trial data for developing and validating a clinical decision tool, so the applicability in clinical practice could be debated. However, we used the MR CLEAN trial (considered to have used the broadest inclusion criteria and most widely used imaging modalities) for the development. Therefore, this model should be quite representable for all patients enrolled in clinical practice when no additional imaging selection is used.

For the first part of chapter 4 (4.1), all patient data are from the Erasmus stroke database. Since all patients presented in our large interventional stroke center, there is the possibility that patients with severe deficits (with a higher probability of proximal circulation occlusion), were more likely to be primarily triaged to our center. This would result in lower occurrence of proximal vessel occlusion in stroke patients arriving at other Dutch hospitals. Unfortunately, the occurrence of proximal vessel occlusion in these hospitals is unknown. Therefore, the presented rate of proximal circulation occlusion could be above average, compared to other Dutch hospitals.

In the parts that used data from the MR CLEAN Registry (4.2 & 4.3), a broad Dutch population is registered; e.g. there is no age or comorbidity limit and no additional selection based on imaging parameters, apart from a proximal artery occlusion on CT angiography. This should be taken into consideration, when generalizing these findings towards other stroke communities/ countries.

Clinical implications

Subgroups

After combining findings from part 2.1 with the HERMES patient pooled analysis, EVT became generally accepted to be safe and effective, regardless prior IVT or not.

Part 2.2 is the first study that showed the effect and safety of EVT for patients that where already using antiplatelet medication prior to current acute ischemic stroke. In acute interventions for myocardial infarction multiple antiplatelet agents and anticoagulants should be given as soon as possible, since they improve outcome.[10] Our analysis is the first step towards more insight regarding optimal peri-procedural antiplatelet management in EVT patients. Our post-hoc analysis shows that EVT is effective and safe in patients that are already taking antiplatelet medication. However, both control and intervention patients had a 3 to 4 times increased risk of SICH. On the other hand, in patients with successful reperfusion, the absolute effect of EVT was more than doubled. Because of the increased risk of hemorrhage in stroke patients, the fact that this is a post-hoc subgroup analysis, and also that current findings are not confirmed by other studies, no firm conclusions should be drawn.

That BP does not interact with EVT effect, is encountering common assumptions in acute ischemic stroke (2.4). Since the implementation of IVT, there has always been a BP threshold of 185/110 mm Hg for IVT candidates.[24] It has been commonly known that high baseline BP results in poor outcome in acute ischemic stroke patients. We showed that high

baseline BP was also associated with poor functional outcome and increased SICH risk in EVT patients. However, BP did not alter EVT effect, there was no BP interaction with EVT on outcome. Therefore we stressed that despite that baseline blood pressure is associated with functional outcome, it is not associated with EVT effect. So, as compared to high age, high BP is associated with poor outcome, but there is clear from EVT benefit in these patients. Therefore, acute ischemic stroke patients should undergo reperfusion therapy as soon as possible, regardless their BP.

Patient selection

Here we developed and validated the first model that predicts EVT benefits for individual patients, combining eleven clinical and radiological characteristics available at the emergency department. When compared to other models that are currently used in neurovascular clinical practice, the HAS-BLED (C-statistic 0.65) and CHA_2DS_2-VASc (0.61), our decision tool performs accurately (C-statistic 0.73).[25 26] Our study shows that treatment should not be withheld based on one characteristic. Some patients that are now considered not to benefit from EVT (i.e. with poor collaterals or low ASPECTS), could still substantially benefit from EVT when other characteristics are favorable. This emphasizes the importance of making personalized treatment decisions, and the need for combining multiple patient characteristics simultaneously.

Since this model was developed using the MR CLEAN data, with an unselected population and only few selection criteria, it is likely applicable in centers that use few clinical and radiological selection criteria as well. As a model can never replace clinical judgement, it should only be used as a decision-support tool. We suggest the tool may be particularly relevant in patients who have to be transferred to an intervention center or when there is doubt whether EVT will be beneficial. Medpage that reported on the published tool, put it this way: 'When in Doubt, Tool May Help Predict Success of Stroke Thrombectomy'.[27]

Clinical practice

As stated in the considerations section, the presented rate of proximal circulation occlusions in part 4.1 may not be generalizable to all Dutch stroke centers. To compare the data from the Erasmus University Medical Center with other hospitals (both smaller intervention and primary stroke centers), data regarding the NIHSS score of presenting stroke patients of other centers are essential, since this is clearly associated with the occurrence of proximal vessel occlusions.

Unconfined of the exact occurrence of proximal vessel occlusion, it is important to identify all possible patients with large vessel occlusion who might benefit from EVT. Therefore, it is important to get more patients at the right hospital (within the right time window) and to detect all proximal vessel occlusions. The latter can be achieved by optimizing the CT-angiography assessment and performing CT angiography in all patients with sudden neurological deficit. As shown in this study, even patients with minimal neurological deficit (NIHSS 1 or 2), may have a proximal vessel occlusion.

In part 4.2, the MR CLEAN Registry showed that EVT in current clinical practice is highly effective and safe. The MR CLEAN Registry consist of EVT patients that were treated in Dutch routine clinical practice. Compared to patients treated during the MR CLEAN trial, in routine clinical practice patients were treated with a worse prognosis: higher age, higher pre-stroke mRS, and more IVT contraindications. EVT patients in the MR CLEAN Registry

had even better functional outcome compared to EVT patients in the MR CLEAN trial. This can partly be explained by the clear improvement in onset to EVT times.

The number of performed EVTs clearly increased in the two years after the MR CLEAN trial, emphasizing improvements in national awareness concerning these patients. Since the MR CLEAN Registry is still ongoing it will keep us up to date regarding the number of EVT patients in the Netherlands.

The final part (4.3) emphasizes that functional outcome of EVT patients can be greatly improved by being faster. Various factors contribute to shortening time to EVT; recognition of symptoms by the patient or bystanders, taking the right patient to the right hospital (prehospital triage), pre-notification of the stroke teams, and workflow optimization in the referring and intervention centers.. Until now the only proven therapy for acute proximal vessel occlusion patients is opening the vessel as quickly as possible. Therefore, workflow should be structured in order to reach this goal, whether it is during a busy day, the weekend, or in the middle of the night.

Altogether, this thesis shows that EVT is safe and effective in acute ischemic stroke patients without prior IVT (2.1) and regardless of the BP level (2.3). The effect of time delay on patients' outcome appears to be greater in clinical practice than in previous trials (4.3). Furthermore, as showed in chapter 3, EVT should not be withhold based on one single patient characteristics. The combined findings implicate the necessity to proceed with the EVT process also in patients with a blood pressure above 185/110 mm Hg. CTA should be performed as quickly as possible to determine whether the patient is an EVT candidate, regardless of the decision to delay or withhold IVT. EVT should be initiated as soon as possible to achieve the best possible outcome in these patients and when in doubt whether the patient will benefit, our online app (www.mrpredicts.com) may help in the decision making process.

Future research

Despite that EVT is highly beneficial, there is still a high percentage of unsuccessful reperfusion, mortality and complications. EVT in current clinical practice still results in dependency or mortality in more than half of the patients. This strongly emphasizes that acute ischemic stroke caused by proximal vessel occlusion is a serious disease and there is room for improvement. This thesis focused on a part of the entire stroke care: personalizing EVT in clinical practice.

Acute ischemic stroke, as a vascular disease, is often a consequence of systemic processes (e.g. systemic atherosclerosis, atrial fibrillation, hypertension), that were already present prior to the actual event. Preventing acute ischemic strokes (and other vascular events) in this group, and so reducing the worldwide vascular events and burden, is the driving factor behind the profuse blood pressure and cholesterol control. Targeted prevention of these risk factors after a stroke or other vascular event, to reduce the risk of a second event, is important as well. However, still a large proportion of proximal vessel occlusion patients display no clear cause of their stroke. One promising direction that is currently investigated, with use of the MR CLEAN Registry data, is whether thrombus histopathology may help to determine the cause. When histopathology could point out whether the stroke was

caused by a cardioembolism, carotid artery disease or another cause, this could improve targeted secondary prevention.

To improve the intervention and peri-procedural medical management, more information is needed on the role of incomplete microvascular reperfusion,[12] possible procedural vascular damage, the interplay of the coagulation system, and poor outcome despite successful reperfusion. This will provide insights regarding the necessary steps that have to be taken in order to achieve good functional outcome, apart from fast and successful reperfusion. To gain more insight into these topics, investigating aspirated blood and extracted thrombi could provide new insights in important factors relating to thrombus formation, thrombus extraction and the effect of used devices on the thrombus and vessel wall. These are all subjects that will be investigated in the MR CLEAN Registry and the new Dutch COnsortium for New TReatments of Acute STroke (CONTRAST). In one of the planned CONTRAST trials, the MR CLEAN Medication trial, EVT patients will be randomized for acute peri-procedural aspirin and/or heparin versus placebo. This is a promising trial and will certainly provide new insights.

Another era of added value could be gathering the data of procedures that failed, or where there was a successful reperfusion, but with poor outcome. Post-mortem will provide new insights into pathogenesis, thrombus characteristics, vessel wall damage, and incomplete distal reperfusion.

The BP analysis of these thesis, was the first performed in EVT patients. Similar studies in other/larger cohorts to confirm these findings are encouraged. We are currently working on analysis of the HERMES data, to gain more confidence in our findings.

The 'arbitrary' BP threshold for IVT patients of 185/110 mm Hg was established during the pilot study preceding the NINDS trial.[24] It is clear that a higher BP increases the risk of SICH. However, we do not know whether this is the case in all ischemic stroke patients, or only in those patients who were IVT treated. Therefore, it would be interesting to analyze whether BP interacts with IVT. Only when an interaction is proven, a IVT BP threshold could be justified, but may differ from the current 185/110 mm Hg. On the other hand, when no interaction is present, this long used BP threshold for IVT should be dismissed.

The data in this thesis have no implications for possible treatment of BP in the acute phase. Since we confirmed BP to be an independent predictor for outcome after EVT, treating BP could be of possible interest. In addition, details about the course of BP during or after intervention are not available in our patients. The effect of general anesthesia management on BP drops during EVT might be an explanation for the connection between general anesthesia use and poor outcome.[28] Further studies should provide more insight in the interplay between both the BP rise and fall during intervention, the relation between BP, collaterals, anesthetic management and ischemic core, and the risk of SICH.

The presented tool for predicting EVT benefit is the first step in predicting individual EVT benefits. Future analyses within larger studies may refine the current recommendations, and may help to improve the validity of the current model. Currently our model is being validated and updated in the pooled individual patient data of the HERMES collaboration. Moreover, we aim to investigate the validity of our model's predicted outcome, after treatment in clinical practice. Therefore, our model will be tested in the MR CLEAN Registry as well.

The presented tool predicts individual EVT benefit, based on the calculated functional outcome at 90 days, using patient variables before EVT is actually performed. The calculated functional outcome can be improved with a model using post EVT variables as well. Therefore we aim to develop and validate another multivariable model for functional outcome at 90 days, using patient characteristics pre- and post EVT. This tool can then be used by clinicians, to reliably estimate long term functional outcome after EVT to possibly guide patient management decisions and counsel the patients and family.

Final remarks

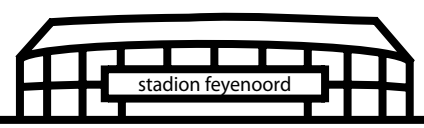
This thesis focused on personalized EVT for acute ischemic stroke patients, with proximal vessel occlusion in the anterior circulation, in clinical practice. Subgroup analysis of the MR CLEAN trial showed that EVT is effective and safe in patients without prior intravenous alteplase, patients that are already taking prior antiplatelet medication, and irrespective of patients' admission blood pressure. The developed and validated clinical decision tool that calculates the individual EVT benefit at the emergency department, is a first step towards personalized patient selection for EVT. Data of the MR CLEAN Registry showed that EVT is both safe and effective in routine clinical practice. Since the association of EVT times with outcome is even greater than in the previous trials, patients outcome after EVT can be greatly improved by shortening treatment delays. Despite the effectiveness and safety of EVT in current clinical practice, still more than half of all patients will be dependent or dead. This strongly emphasizes that acute ischemic stroke caused by proximal vessel occlusion still is a serious disease and there is much to in order to improve functional outcome of these patients.

References

1. Lima FO, et al. Prognosis of untreated strokes due to anterior circulation proximal intracranial arterial occlusions detected by use of computed tomography angiography. JAMA Neurol 2014;71(2):151-7.
2. Berkhemer OA, et al. A randomized trial of intraarterial treatment for acute ischemic stroke. N Engl J Med 2015;372(1):11-20.
3. Saver JL, et al. Stent-retriever thrombectomy after intravenous t-PA vs. t-PA alone in stroke. N Engl J Med 2015;372(24):2285-95.
4. Jovin TG, et al. Thrombectomy within 8 hours after symptom onset in ischemic stroke. N Engl J Med 2015;372(24):2296-306.
5. Goyal M, et al. Randomized assessment of rapid endovascular treatment of ischemic stroke. N Engl J Med 2015;372(11):1019-30.
6. Campbell BC, et al. Endovascular therapy for ischemic stroke with perfusion-imaging selection. N Engl J Med 2015;372(11):1009-18.
7. Powers WJ, et al. 2015 American Heart Association/American Stroke Association Focused Update of the 2013 Guidelines for the Early Management of Patients With Acute Ischemic Stroke Regarding Endovascular Treatment: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. Stroke 2015;46(10):3020-35.
8. Mulder MJ, et al. Letter by Mulder et al Regarding Article, "2015 AHA/ASA Focused Update of the 2013 Guidelines for the Early Management of Patients With Acute Ischemic Stroke Regarding Endovascular Treatment: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association". Stroke 2015;46(11):e235.
9. Goyal M, et al. Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials. Lancet 2016;387(10029):1723-31.
10. Task Force on the management of STseamiotESoC, et al. ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. Eur Heart J 2012;33(20):2569-619.
11. Zinkstok SM, et al. Early administration of aspirin in patients treated with alteplase for acute ischaemic stroke: a randomised controlled trial. Lancet 2012;380(9843):731-7.
12. Bai J, et al. Revisiting cerebral postischemic reperfusion injury: new insights in understanding reperfusion failure, hemorrhage, and edema. Int J Stroke 2015;10(2):143-52.
13. Muir KW, et al. Endovascular therapy for acute ischaemic stroke: the Pragmatic Ischaemic Stroke Thrombectomy Evaluation (PISTE) randomised, controlled trial. J Neurol Neurosurg Psychiatry 2017;88(1):38-44.
14. Bracard S, et al. Mechanical thrombectomy after intravenous alteplase versus alteplase alone after stroke (THRACE): a randomised controlled trial. Lancet Neurol 2016;15(11):1138-47.
15. Jauch EC, et al. Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2013;44(3):870-947.
16. Tissue plasminogen activator for acute ischemic stroke. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. N Engl J Med 1995;333(24):1581-7.
17. Kent DM, et al. Assessing and reporting heterogeneity in treatment effects in clinical trials: a proposal. Trials 2010;11:85.
18. Rothwell PM. Treating individuals 2. Subgroup analysis in randomised controlled trials: importance, indications, and interpretation. Lancet 2005;365(9454):176-86.
19. Merino JG. Selecting patients for endovascular treatment of acute stroke. BMJ 2017;357:j2059.
20. Hansen CK, et al. Stroke severity and incidence of acute large vessel occlusions in patients with hyper-acute cerebral ischemia: results from a prospective cohort study based on CT-angiography (CTA). Int J Stroke 2015;10(3):336-42.
21. Heldner MR, et al. Clinical prediction of large vessel occlusion in anterior circulation stroke: mission impossible? J Neurol 2016.
22. Heldner MR, et al. National Institutes of Health stroke scale score and vessel occlusion in 2152 patients with acute ischemic stroke. Stroke 2013;44(4):1153-7.
23. Fischer U, et al. NIHSS score and arteriographic findings in acute ischemic stroke. Stroke 2005;36(10):2121-5.
24. Brott TG, et al. Urgent therapy for stroke. Part I. Pilot study of tissue plasminogen activator administered within 90 minutes. Stroke 1992;23(5):632-40.
25. Lip GY, et al. Comparative validation of a novel risk score for predicting bleeding risk in anticoagulated patients with atrial fibrillation: the HAS-BLED (Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile INR, Elderly, Drugs/Alcohol Concomitantly) score. J Am Coll Cardiol 2011;57(2):173-80.
26. Lip GY, et al. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. Chest 2010;137(2):263-72.
27. Lou N. When in Doubt, Tool May Help Predict Success of Stroke Thrombectomy - Odds of benefit calculated with moderate power. https://www-medpagetodaycom/criticalcare/strokes/65060 2017 (May 5).
28. Treurniet KM, et al. A decrease in blood pressure is associated with unfavorable outcome in patients undergoing thrombectomy under general anesthesia [published online ahead of print April 12, 2017]. J Neurointerv Surg 2017.doi:10.1136/neurintsurg-2017-012988.

6

Summary & Samenvatting



Summary

Acute ischemic stroke patients with proximal vessel occlusion outcome had in general poor outcome, despite the use of intravenous alteplase treatment. Publication of the Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands (MR CLEAN; on January 1st, 2015), showed the great improvement in functional outcome of this severe ischemic stroke patients when treated with EVT. This has led to a breakthrough in acute ischemic stroke treatment. The MR CLEAN trial is the first and largest randomized controlled trial that showed the benefit of endovascular treatment (EVT) in patients with acute ischemic stroke caused by proximal vessel occlusion in the anterior circulation. This great achievement was possible due to a well-established collaboration of all EVT centers in the Netherlands. After the MR CLEAN trial, the cooperation continued by registering all the EVT patients in the MR CLEAN Registry (currently more than 3000 registered patients). With the data of the MR CLEAN Registry, we have been monitoring the implementation of EVT in Dutch clinical practice. The transition from an experimental intervention to routine clinical practice brings new questions and challenges.

The main objective of this thesis was to improve personalized EVT for acute ischemic stroke in clinical practice.

Chapter 2 focuses on the effect of EVT in certain patient subgroups. We used MR CLEAN trial data to perform three subgroup analyses. Part 2.1 shows that EVT is effective and safe in patients who had contraindications for intravenous alteplase treatment, in spite of the fact they were older and had more vascular comorbidities. For patients who already used antiplatelet medication, EVT was effective and safe as well (2.2). In the final part of this chapter (2.3), our most important finding was that baseline blood pressure does not interact with EVT on functional outcome or safety parameters. Therefore, our data provide no arguments to delay or withhold EVT based on blood pressure.

Chapter 3 focuses on improving patient selection for EVT. In this chapter a clinical decision that predicts EVT benefit for individual patients at the emergency department, was developed and validated. For the development, we used all MR CLEAN trial patients (n=500) and for the validation we used all proximal vessel occlusion patients from the Interventional Management of Stroke III Trial (n=260). This tool combines multiple clinical and radiological characteristics; age, baseline NIHSS score, systolic blood pressure, history of ischemic stroke, diabetes mellitus, pre-stroke mRS score, ASPECTS, occlusion segment, collateral score, and time from onset of symptoms to EVT start. The tool emphasizes the wide variety of treatment benefit in individual patients and the importance of combining multiple characteristics simultaneously. Our decision tool is the first step towards individualized selection of patients for EVT. The tool is now available online and may be used to support clinical judgment for making EVT decisions (www.mrpredicts.com).

Chapter 4 focuses on EVT in routine clinical practice. In part 4.1, the potential number of EVT candidates in clinical practice is investigated. Of all patients who presented with acute ischemic stroke (<6 hours of symptom onset) that were primarily admitted to the Erasmus University medical center, more than 30% had a proximal vessel occlusion.

In the MR CLEAN Registry we studied outcome and safety of EVT in current clinical practice (4.2). In routine clinical practice, EVT for patients with acute ischemic anterior circulation stroke due to intracranial proximal artery occlusion, is at least as effective and safe as in the trial setting. The treated population in routine clinical practice was older, had more frequently intravenous alteplase treatment contraindications, had a higher pre stroke mRS score and was treated faster. The final part (4.3) focuses on the association of EVT times with outcome in clinical practice. Time to EVT is strongly associated with functional outcome, even stronger than in previous trials. These findings emphasize that functional outcome of EVT patients can be greatly improved by shortening onset to treatment times.

Samenvatting

Patiënten met een acuut herseninfarct, wanneer veroorzaakt door een proximale afsluiting van een hersenbloedvat, hebben vaak een slechte uitkomst ondanks behandeling met intraveneuse alteplase. Publicatie van de Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands (MR CLEAN; 1 januari, 2015), leidde tot een doorbraak in de behandeling van het acute herseninfarct in deze ernstig aangedane groep met een proximale hersenbloedvat afsluiting. MR CLEAN was de eerste en grootste gerandomiseerde studie die de effectiviteit van intra-arteriële therapie (IAT) van het acute herseninfarct aantoonde voor deze patiënten groep. Deze doorbraak was mogelijk door de goede samenwerking tussen alle ziekenhuizen in Nederland die IAT uitvoerden. Na de laatste randomisatie in de MR CLEAN studie, werd deze goede samenwerking voortgezet in de MR CLEAN Registry. Hierin worden alle IAT patiënten van Nederland geregistreerd, om zo bij te houden hoe de invoering van IAT in de klinische praktijk gaat. Op dit moment zijn al meer dan 3000 patiënten ingevoerd in de MR CLEAN Registry. De implementatie van IAT in de praktijk bracht nieuwe vragen en onzekerheden aan het licht.

Het hoofddoel van deze thesis is om IAT in de klinische praktijk voor de individuele herseninfarct patiënt te verbeteren.

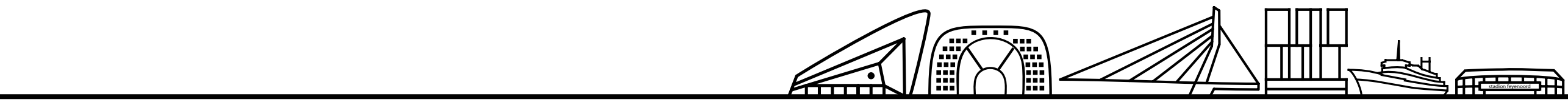
Hoofdstuk 2 richt zich op het effect van IAT in drie specifieke patiënt subgroepen. Hiervoor is data van de MR CLEAN studie gebruikt. Het eerste deel (2.1) laat zien dat IAT effectief en veilig is in patiënten met contra-indicaties voor intraveneuze alteplase, ondanks dat deze groep patiënten ouder is en vaker vasculaire belast. Deel 2.2 toont aan dat in patiënten die al plaatjes remmers gebruikten, IAT effectief en veilig is. Het laatste deel van dit hoofdstuk (2.3) laat zien dat voor elke bloeddrukwaarde IAT effectief en veilig is. Er zijn daarbij geen aanwijzingen gevonden om IAT uit te stellen of te onthouden in patiënten met een hoge bloeddruk.

Het verbeteren van individuele selectie van herseninfarct patiënten voor IAT is het doel van hoofdstuk 3. Hiervoor hebben we een klinisch beslismodel gemaakt en gevalideerd. Dit model voorspelt het voordeel van IAT voor individuele patiënten op het moment dat ze op de spoedeisende hulp komen en niet invasieve beeldvorming hebben ondergaan (blanco CT en CT angiografie). Na het maken (MR CLEAN studie; n=500) en valideren (IMS III studie; n=260) van dit model, bleken de volgende klinische en radiologische karakteristieken van belang: leeftijd, NIHSS, systolische bloeddruk, voorgeschiedenis (herseninfarct, diabetes en mRS), ASPECTS, occlusie segment, collateralen en de tijd van klachten tot IAT start. Het model benadrukt het grote verschil in behandelwinst tussen individuele patiënten en laat zien dat het essentieel is meerdere patiënt karakteristieken te combineren, om een goede behandelbeslissingen te kunnen maken. Dit is de eerste stap naar individuele patiënt selectie voor IAT. Het model kan gebruikt worden ter ondersteuning van klinische beslissingen en in gecompliceerde situaties (www.mrpredicts.com).

IAT in de klinische praktijk word besproken in hoofdstuk 4. Het eerste deel (4.1) bekijkt het aantal mogelijke IAT kandidaten. Van alle patiënten met een acuut herseninfarct die zich binnen 6 uur presenteerde op de spoedeisende hulp van het Erasmus MC, bleek meer dan 30% een proximale occlusie te hebben. De laatste twee delen zijn de eerste studies die gebruik maken van de MR CLEAN Registry data. Deel 4.2 bespreekt het aantal en type patiënten dat in de Nederlandse klinische praktijk behandeld is met IAT, na de MR CLEAN studie. IAT in de klinische praktijk blijkt minstens zo effectief en veilig als in de IAT groep van de MR CLEAN studie. In de klinische praktijk blijken IAT patiënte ouder te zijn, vaker intraveneuze alteplase contra-indicaties en een hogere 'pre-stroke' mRS score te hebben. Verder is de workflow duidelijk sneller dan in de MR CLEAN trial. Het effect van tijdverlies op de functionele uitkomst na IAT was in klinische praktijk duidelijk groter dan in de gepubliceerde gerandomiseerde studies (4.3). Dit onderstreept de noodzaak om patiënten met een acute herseninfarct en een proximale afsluiting van een hersenbloedvat, zo snel mogelijk te behandelen met IAT.

7

Dankwoord



Na- en Dankwoord

Als zoon van een neuroloog heb ik de indrukwekkende omslag in de zorg voor patiënten met een herseninfarct, in de volksmond beter bekend als beroerte, redelijk bewust meegemaakt. Er is een tijd geweest dat haast bij deze patiëntencategorie niet geboden was. Zo de patiënt al naar het ziekenhuis kwam, waren een bed en toewijding eigenlijk de enige behandeling. In navolging van de Verenigde Staten, waar in 1995 de eerste gunstige resultaten van het stolsel oplossende medicijn alteplase werden gemeld, werd in Nederland rond 1997 gestart met dit medicijn. De behandeling van herseninfarct patiënten met dit stolsel oplossende middel wordt ook wel intraveneuze-trombolyse, omdat het medicijn in een bloedvat wordt gespoten. Het ging daarbij om een sterk afgebakende groep herseninfarct-patiënten die mogelijk baat zouden kunnen hebben bij deze behandeling. Tegen het einde van de vorige eeuw druppelden langzaam maar zeker meer gunstige resultaten van deze behandeling binnen en aan het begin van het nieuwe millennium sloeg de beroertezorg een nieuw en hoopgevend pad in. IV-trombolyse werd de gouden standaard. Mijn vader vond het een magisch moment toen hij voor het eerst meemaakte dat een patiënt, nog tijdens de toediening van het stolsel oplossende medicijn, weer begon te spreken. Grote slagen werden gemaakt om de behandeling op steeds grotere schaal te kunnen toepassen, de neurologie werd een echt acuut vak. Het was niet langer zo dat louter bedachtzaam tot een diagnose werd gekomen, een daadwerkelijke behandeling behoorde nu tot de mogelijkheden, waarbij bovendien “FAST” handelen geboden was. En wat niemand voor mogelijk had gehouden werd bewaarheid, je zag zowaar met regelmaat een neuroloog door een ziekenhuisgang hollen.

De twee decennia sinds de introductie van IV-trombolyse heeft veel herseninfarct patiënten goeds gebracht. Dit gezegd hebbend is het effect van de behandeling niet voor elke patiënt even gunstig en komt niet iedere patiënt ervoor in aanmerking. Gelukkig voor (toekomstige) patiënten blijft de wetenschap op zoek naar vooruitgang. De volgende logische stap ten aanzien van behandeling van herseninfarcten was onderzoek doen naar interventies op de plaats delict, ofwel het stolsel uit de bloedvaten in de hersenen verwijderen (intra-arteriële trombectomie). Een dergelijke behandeling werd alom gezien als een hachelijke onderneming en onderzoeken ernaar leverden geen overtuigende resultaten op. Een aanzienlijk deel van de neurologen was dan ook sceptisch of ronduit pessimistisch over het potentieel van een dergelijke interventie. Tot daar was de Nederlandse MR CLEAN trial die in 2015 aantoonde dat openen van het afgesloten bloedvat, middels een via de lies ingebrachte katheter, aan een heel aantal patiënten met een ernstige herseninfarct soelaas kan bieden. De positieve onderzoeksresultaten waren dermate spectaculair, er werd zelfs gerept over een kleine revolutie, dat vrijwel direct besloten is de behandeling op een zo breed mogelijke schaal aan te bieden. Nu, ruim twee jaar later, is naar aanleiding van de MR CLEAN trial de acute herseninfarct-zorg in ons land opnieuw ingericht. De intra-arteriële trombectomie wordt zo snel en aan zo veel mogelijk patiënten die hier baat bij kunnen hebben, aangeboden en inmiddels zijn al meer dan 3000 patiënten in Nederland behandeld.

De slagzin van een wijs man (tevens mijn oom) “timing is everything” geldt niet alleen voor IV-thrombolyses en IA-thrombectomieën maar zeker voor ook mijn promotietraject. Kort voordat ik mijn artsenbul op mocht halen kwamen de positieve MR-CLEAN resultaten en kreeg ik de kans op de rijdende MR-CLEAN trein te springen. Dat was het begin van een fascinerende reis die zich in rap tempo heeft voltrokken.

Gedurende mijn promotieonderzoek heb ik samengewerkt met velen. Het proefschrift dat nu voor u ligt was er zonder hen niet gekomen. De talloze besprekingen, mails, track changes, be- en ontmoedigingen, conference calls, discussies ect. waren echt onmisbaar. Dank en waardering zijn dan ook op zijn plaats.

In de eerste plaats wil ik mijn beide promotoren, professor Dippel en professor Van der Lugt, en mijn copromotor dr. Lingsma, bedanken. Het was een eer en genoegen om in een altijd goede sfeer met zulke benaderbare, meedenkende en no-nonsense begeleiders te mogen werken aan het vervolg van de succesvolle MR CLEAN trial. Oprechte dank ook voor het vertrouwen dat jullie vanaf dag 1 in mij gesteld hebben.

Beste Diederik, in jou huist de bijzondere combinatie van een enerzijds internationaal vooraanstaand en zeer gedreven neurovasculair wetenschapper en anderzijds een toegankelijke en geduldige leermeester die letterlijk 24/7 bereikbaar is en altijd mee wil denken. Hoe vaak ik ook je kamer binnenstormde of iets onhandigs had uitgespookt, je bleef steeds geduldig en goed gehumeurd op zoek naar de volgende stap of oplossing. Ik heb ontzettend veel van je geleerd en niet alleen over het doen en opzetten van onderzoek. In de toekomst hoop ik nog vaak met je te mogen samenwerken en gebruik te mogen maken van je indrukwekkende kennis en kunde.

Beste Aad, scherpzinnig en met toekomstvisie, ben jij in staat complexe zaken tot de juiste proporties terug te brengen en te verhelderen, je hebt me laten zien dat onderzoek niet alleen maar om cijfertjes gaat. Daarbuiten was het ook echt leuk om van alles en nog wat met je te organiseren. Ook met jou hoop ik in de toekomst nog veel nieuwe onderzoeken te mogen opzetten en doen.

Beste Hester, onze wekelijkse meeting was altijd een feest en dat kwam niet alleen door de vaak aanwezige lekkernijen; naast je overweldigende statistische kennis wist je het altijd praktisch en overzichtelijk te houden voor een beginnende, klinisch onderzoeker.

Professor Hunink, professor Klijn en professor Zijlstra, leden van de kleine commissie. Hartelijk dank voor de tijd die jullie hebben willen vrijmaken voor het beoordelen van mijn proefschrift.

Voorts gaat mijn dank uit naar alle MR CLEAN trial investigators (p. 138). Jullie zijn niet alleen verantwoordelijk voor de aardverschuiving die heeft plaatsgevonden in de behandeling van acute herseninfarctpatiënten, maar ook voor de infrastructuur waarop de MR CLEAN Registry kon worden voortgebouwd.

Dan de MR CLEAN Registry executives; het was een waar genoegen om met jullie samen te werken. Als wijze heren hebben jullie mij wekelijks begeleid en zo de Registry tot een succes gemaakt, samen met alle ‘investigators’ (p. 136).

Ivo, dankzij jou stond het skelet van de studie als een huis. Daarmee heb jij de weg geplaveid waarop ik vlot door kon reizen. Het was ‘meui’ om samen te werken. Als de lach op onze gezichten dreigde te verdwijnen zetten we even wat drum & bass op.

Robert-Jan, de derde van onze 'Bosses of the Registry'. Ik ben ervan overtuigd dat je de Registry op een goede manier verder zal leiden, samen met Kars en Manon.

Bob, Esmee en Vicky, onze wekelijke research meetings waren niet alleen zeer nuttig maar ook gezellig. Bob, pragmatisch en altijd oog voor het klinische aspect. Vicky, meedenkend en scherpzinnig met een vrolijke noot. Esmee, statistisch wonder en topmens. Samen hebben we niet alleen de mooie app maar ook vele goede 'werk' tripjes gemaakt.

Neuro-interventieradiologen Bart Emmer en Adriaan van Es, hartelijk dank voor de immer prettige samenwerking.

Inger, steeds een helpende hand in de aanslag. Naziha en Martin, ook jullie stonden paraat ter ondersteuning. Eric (de site-) B(r)ouwer, de sites zijn dankzij jouw hulp strak en goed toegankelijk.

Geneeskunde studenten uit het Erasmus MC Saliha, Roger, Anouk en Daan, dank voor jullie bijdrage.

Daarnaast wil ik mijn collega's uit het AMC bedanken. Olvert, je hebt me het leven als Registry coördinator een stuk aangenamer gemaakt door je efficiency tips & tricks van het data formatten en checken, en het belang van kupjes koffie. Kilian "future of stroke changer" Treurniet, we hebben gelachen.

Buiten diegenen met wie ik direct heb samengewerkt om te komen tot dit proefschrift zijn er velen die mij mede professioneel en persoonlijk (soms een mix van die twee) gevormd en bijgestaan hebben en zonder wie ik überhaupt nooit aan een promotietraject zou zijn begonnen.

Tijdens mijn studie heb ik het voorrecht gehad om in de keuken van een aantal bijzondere artsen te mogen kijken, door hen is mijn enthousiasme voor de geneeskunde alleen maar groter geworden. Dank hiervoor, Dr.Arendse (KNO arts Ikazia), Dr. Brouwer (specialist ouderen geneeskunde, Hannie Dekhuizen), dr. Dik (kinderuroloog Juliana kinderziekenhuis), Dr. Slagboom (interventiecardioloog OLVG) dr. Vincent (neurochirurg,Erasmus MC) en last but not least Dr. Zuidgeest (neuroloog Ikazia).

Co-groep 13.21 (jaja, jullie staan erin), dank voor de leerzame SCOPE discussies, de alsmaar terugkerende witte jassen foto en bovenal de goede tijden.

Dank vrienden voor het leven:

De Corpsrecte heren, we hebben ons vanaf jaar 1 (iets met een gloeilamp) aardig omhoog gebrast! Ondanks dat we al ver buiten Rotterdam zijn uitgewaaid hebben we gelukkig altijd nog ons jaarlijkse kerstdiner (al is het in de zomer).

Sirwan (legend!), eindeloos genoten van je pizzabak specialiteiten. Onze danslessen in club BED waren onnavolgbaar. Op onderzoeksgebied ging je me voor en dat inspireerde. Mijn eerste paper is door jou opgezet en begeleid en nog altijd kan ik met je sparren. Ook dank dat je me hebt voorgesteld aan 'Johny' Jansen.

'Mother of God' Joeri (hoeveel colleges heb je slapend naast me doorgebracht?) en Winesh (hoeveel FIFA competities heb je tijdens college gespeeld?), mijn collegematen met wie ik koffiewolken toverde en de oude habboe lachte en op wie ik altijd terug kan vallen.

Waar zou ik zijn zonder mijn wereldse wolfjes? Als bijeengeraapt zooitje al zo'n 8750 burgers gegeten. Jammer toch dat onze vaste tenten steeds failliet gaan. Gelukkig hebben Erwin, Armin en ik de Wolfvaert opgericht zodat we wat dichter bij volle maan onze burgers kunnen eten.

Giel en Malina Spierings het waren geweldige tijden in Boston, hoe gastvrij kunnen mensen zijn! Giel, van jou heb ik geleerd dat een top-onderzoeker ook een topdokter en topneuroloog kan zijn, het heeft me geïnspireerd. Malina, thanks for your care, sense of humor, cooking and English lessons and your super ultra-quick spelling and grammar check of this thesis, you're the best!

Alice en later ook Robert, in mijn jeugd een tweede thuis. Dank ook voor Marius, mijn enige 'echte' neef. @Marius, als ik geen neuroloog zou willen worden werd ik graag de drummer van jouw band.

Mijn oom ("timing is everything") Ronald, scherp, stabiel, prettig, optimist, ongekend gevat humorist. Tante Renée, altijd betrokken en gezellig, altijd leuke gesprekken, altijd een welkom en geliefd gevoel. Felix en Max, helden! En uiteraard Feyenoord 1! Ik kijk uit naar nog vele mooie avonturen met jullie. Samen R&R, onderdeel van een ijzersterk elftal. Jullie zijn als de G&T's laatst in de bar, always a ball!

En dan, het bijzondere en super gezin waartoe ik mag behoren (tevens de magische 7 van het ijzersterke elftal). Eigenlijk zijn jullie alle 6 mijn paranimfen, want jullie staan altijd aan mijn zijde. Het is onmogelijk om in een paar woorden wat over jullie te zeggen, maar ik ga een poging wagen.

Het is een voorrecht de grote broer te zijn van de 'bende van Vijf', ik neem deze taak dan ook zeer 'serieus'.

Victoria (Tokkie), je danst door het leven, schrander en ambitieus. Een echt dametje dat zich graag met mij bemoeit, bovenal met mijn kapsel.

Alexia (Aloeloe), cadeau tijdens mijn eindexamens. Slim en sociaal, bizar sportief en ondanks je naam verre van een prinses…. gelukkig. Je bouwt alles wat je maar kan bedenken, echt awesome, 'synaps!'

(De) Storm, mijn steun en toeverlaat tussen al die meiden. Komiek én intellectueel van ons gezin, wandelende encyclopedie en vraagbaak. Ik blijf me verbazen hoe snel je nieuwe dingen oppikt . chhh ahhhh!

Evalyn (Iefkes, ohnee, Lyn), mijn maatje door dik en dun. Waar ik vroeger bij het zien van bloed wit wegtrok kneep jij er nog even extra in om het goed te laten ‘uitbloeden’. Vaardig, creatief (credits voor het ontwerpen van m’n boekje gaan naar jou en Job) en sportief (hoeveel medailles hebben we inmiddels?). You always got my back, nu ook weer als paranimf. De witte jas staat je trouwens top!

Mijn ouders, lieve P&F; dankzij jullie hebben we een gezellig top gezin. Jullie zijn er altijd geweest voor me en ook tijdens dit traject meer dan geïnteresseerd en meedenkend.

Fleur, wie had dat gedacht? Van de 10 geboden naar 10(+1) stellingen. Van jongs af aan heb je mij geleerd om een ambitieus doel te stellen en de weg ernaartoe te bepalen, met positieve energie, een warm hart en respect voor het belang van een ieder.

Pap, mijn grote voorbeeld (ook al helpen je Nike’s niet meer), inspiratiebron en nu mijn paranimf. Van kleins af aan mocht ik met je mee op visite, je tas vasthouden, onderonsjes in de lift. Met name door jou ken ik geen twijfel meer (ober of vrachtwagenchauffeur) ik wil echt neuroloog worden. Je enthousiasme voor de neurologie en ons gezin is groots en aanstekelijk.

Appendix

List of publications

PhD portfolio

Acknowledgements

About the author

List of Publications

This thesis

Chapter 2

Mulder MJ, Berkhemer OA, Fransen PS, Beumer D, van den Berg LA, Lingsma HF, Roos YB, van Oostenbrugge RJ, van Zwam WH, Majoie CB, van der Lugt A, Dippel DW. Effectiveness of Intra-arterial Treatment in Patients who are not Eligible for IV Alteplase. MR CLEAN subgroup analysis, International Journal of Stroke. 2016 Aug;11(6):637-45.

Mulder MJ, Berkhemer OA, Fransen PS, Beumer D, van den Berg LA, Lingsma HF, den Hertog HM, Staals J, Jenniskens SF, van Oostenbrugge RJ, van Zwam WH, Majoie CB, van der Lugt A, Dippel DW. Does prior antiplatelet treatment improve functional outcome after intra-arterial treatment for acute ischemic stroke? International Journal of Stroke. 2017 Jun;12(4):368-37

Mulder MJ, Ergezen S, Lingsma HF, Berkhemer OA, Fransen PS, Beumer D, van den Berg LA, Lingsma HF, Lycklama à Nijeholt GJ, Emmer BJ, van der Worp HB, Nederkoorn PJ, Roos YB, van Oostenbrugge RJ, van Zwam WH, Majoie CB, van der Lugt A, Dippel DW. The effect of baseline blood pressure on the benefit and safety of intra-arterial treatment in MR CLEAN. Stroke. 2017 Jul;48(7):1869-1876

Chapter 3

Mulder MJ*, Venema E*, Roozenbeek B, Broderick JP, Yeatts SD, Khatri P, Berkhemer OA, Roos YB, Majoie CB, van Oostenbrugge RJ, van Zwam WH, van der Lugt A, Steyerberg EW, Dippel DW, Lingsma HF. Towards personaliszed intra-arterial treatment of patients with acute ischaemic stroke: study protocol for development and validation of a clinical decision aid. BMJ Open 2017 Mar; doi: 10.1136/bmjopen-2016-013699.

Mulder MJ*, Venema E*, Roozenbeek B, Broderick JP, Yeatts SD, Khatri P, Berkhemer OA, Emmer BJ, Roos YB, Majoie CB, van Oostenbrugge RJ, van Zwam WH, van der Lugt A, Steyerberg EW, Dippel DW, Lingsma HF. Selection of patients for intra-arterial treatment for acute ischaemic stroke: development and validation of a clinical decision tool. BMJ. 2017 May 3;357

Chapter 4

Mulder MJ*, Beumer D*, Saiedie G, Saiedie G, Fonville S, van Oostenbrugge RJ, van Zwam WH, Homburg PJ, van der Lugt A, Dippel DW. Occurrence of intracranial large vessel occlusion in consecutive, non-referred patients with acute ischemic stroke. Neurovascular Imaging. 2016 Sep, 2:11 doi: 10.1186.

Mulder MJ*, Jansen IG*, Goldhoorn RJ*, Emmer BJ, van Es AC, Roozenbeek B, Schonewille WJ, van den Berg R, Coutinho JM, Staals J, Postma AA, Lycklama à Nijeholt GJ, Hofmeijer J, Martens JM, den Hertog HM, Sturm EJ, van der Worp HB, Lo RH, Schreuder TH, Heijboer RJ, Keizer K, Uyttenboogaart M, Eshghi O, Wermer MJ, van Walderveen MA, van Dijk EJ, Boogaarts HD, de Bruijn SF, van Dijk LC, van den Berg JS, van Hasselt BA, de Kort PL, Peluso JJ, Aerden LA, Dallinga RJ, Sprengers ME, Yo L, Jenniskens SF, Roosendaal SD, van der Kallen B, Van den Wijngaard IR, Bot JC, Van Doormaal PJ, Flach HZ, Venema E, Beenen LF,Lingsma HF, Yoo AJ, Vos JA*, Boiten J*, Roos YB*, van Oostenbrugge RJ*, van der Lugt A*, van Zwam WH*, Dippel DW*, Majoie CB*. Endovascular Treatment for acute ischaemic stroke in clinical practice: Data from the MR CLEAN Registry. *Submitted*

Mulder MJ, Jansen IG, Goldhoorn RJ, Venema E, Vhalos C, Roozenbeek B, Lingsma HF, Schonewille WJ, van den Wijngaard IR, Boiten J, Vos JA, Roos YB, van Oostenbrugge RJ, van Zwam WH, Majoie CB, van der Lugt A, Dippel DW. Time to treatment in endovascular treatment for acute ischemic stroke in clinical practice: MR CLEAN Registry. *Submitted*

Other publications

Darweesh SK, Polinder S, **Mulder MJ**, Baena CP, van Leeuwen N, Franco OH, Jacobs BC, van Doorn PA. Health-related quality of life in Guillain-Barré syndrome patients: a systematic review. J Peripher Nerv Syst. 2014 Mar;19(1) 24-35.

Mulder MJ, Lycklama À Nijeholt GJ, Dinkelaar W, de Rooij T, van Es AC, van der Kallen B, Emmer BJ, Thrombectomy in posterior circulation stroke through persistent primitive trigeminal artery: A case report. Interv Neuroradiol. 2015 Dec;21(6) 715–718.

Spierings ELH, **Mulder MJ**. Persistent orofacial muscle pain: its synonymous terminology and presentation. Cranio 2017 Sep; 35(5):304-307

Mulder MJ, Spierings ELH. Treatments of Orofacial Muscle Pain: A Review of Current Literature. Journal of Dentistry & Oral Disorders (accepted for publication)

Letters to the editor

Mulder MJ, van Oostenbrugge RJ, Dippel DW; MR CLEAN Investigators, Letter by Mulder et al Regarding Article, "2015 AHA/ASA Focused Update of the 2013 Guidelines for the Early Management of Patients With Acute Ischemic Stroke Regarding Endovascular Treatment: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association"; Stroke. 2015 Oct; doi: 0.1161/ STROKEAHA.115.010913.

Mulder MJ, Lingsma HF, Dippel DW. Response by Mulder et al to Letter Regarding Article, "Baseline Blood Pressure Effect on the Benefit and Safety of Intra-Arterial Treatment in MR CLEAN (Multicenter Randomized Clinical Trial of Endovascular Treatment of Acute Ischemic Stroke in the Netherlands)". Stroke. 2017 June; doi: 10.1161/ STROKEAHA.117.017996

Venema E, **Mulder MJ**, Lingsma HF. Letter by Venema et al Regarding Article, "Validating a Predictive Model of Acute Advanced Imaging Biomarkers in Ischemic Stroke". Stroke. 2017 Aug; doi: 10.1161/STROKEAHA.117.017505

**equal contribution*

Group publication

Berkhemer OA, Fransen PS, Beumer D, van den Berg LA, Lingsma HF, Yoo AJ, Schonewille WJ, Vos JA, Nederkoorn PJ, Wermer MJ, van Walderveen MA, Staals J, Hofmeijer J, van Oostayen JA, Lycklama à Nijeholt GJ, Boiten J, Brouwer PA, Emmer BJ, de Bruijn SF, van Dijk LC, Kappelle LJ, Lo RH, van Dijk EJ, de Vries J, de Kort PL, van Rooij WJ, van den Berg JS, van Hasselt BA, Aerden LA, Dallinga RJ, Visser MC, Bot JC, Vroomen PC, Eshghi O, Schreuder TH, Heijboer RJ, Keizer K, Tielbeek AV, den Hertog HM, Gerrits DG, van den Berg-Vos RM, Karas GB, Steyerberg EW, Flach HZ, Marquering HA, Sprengers ME, Jenniskens SF, Beenen LF, van den Berg R, Koudstaal PJ, van Zwam WH, Roos YB, van der Lugt A, van Oostenbrugge RJ, Majoie CB, Dippel DW; **MR CLEAN Investigators**. A randomized trial of intraarterial treatment for acute ischemic stroke; N Engl J Med 2015 (372), 11-20

Borst J, Berkhemer OA, Roos YB, van Bavel E, van Zwam WH, van Oostenbrugge RJ, van Walderveen MA, Lingsma HF, van der Lugt A, Dippel DW, Yoo AJ, Marquering HA, Majoie CB; **MR CLEAN investigators**. Value of Computed Tomographic Perfusion-Based Patient Selection for Intra-Arterial Acute Ischemic Stroke Treatment. Stroke. 2015;46(12):3375-82.

Santos EM, Marquering HA, den Blanken MD, Berkhemer OA, Boers AM, Yoo AJ, Beenen LF, Treurniet KM, Wismans C, van Noort K, Lingsma HF, Dippel DW, van der Lugt A, van Zwam WH, Roos YB, van Oostenbrugge RJ, Niessen WJ, Majoie CB; **MR CLEAN Investigators**. Thrombus Permeability Is Associated With Improved Functional Outcome and Recanalization in Patients With Ischemic Stroke. Stroke. 2016;47(3):732-41.

Fransen PS, Berkhemer OA, Lingsma HF, Beumer D, van den Berg LA, Yoo AJ, Schonewille WJ, Vos JA, Nederkoorn PJ, Wermer MJ, van Walderveen MA, Staals J, Hofmeijer J, van Oostayen JA, Lycklama À Nijeholt GJ, Boiten J, Brouwer PA, Emmer BJ, de Bruijn SF, van Dijk LC, Kappelle LJ, Lo RH, van Dijk EJ, de Vries J, de Kort PL, van den Berg JS, van Hasselt BA, Aerden LA, Dallinga RJ, Visser MC, Bot JC, Vroomen PC, Eshghi O, Schreuder TH, Heijboer RJ, Keizer K, Tielbeek AV, den Hertog HM, Gerrits DG, van den Berg-Vos RM, Karas GB, Steyerberg EW, Flach HZ, Marquering HA, Sprengers ME, Jenniskens SF, Beenen LF, van den Berg R, Koudstaal PJ, van Zwam WH, Roos YB, van Oostenbrugge RJ, Majoie CB, van der Lugt A, Dippel DW; **Multicenter Randomized Clinical Trial of Endovascular Treatment of Acute Ischemic Stroke in the Netherlands Investigators**. Time to Reperfusion and Treatment Effect for Acute Ischemic Stroke: A Randomized Clinical Trial. JAMA Neurol. 2016;73(2):190-6.

PhD portfolio

Research school:	COEUR
Erasmus MC Departments:	Neurology & Radiology
PhD period:	September 2015 – August 2017
Promotors:	prof.dr. D.W.J. Dippel & prof.dr. A. van der Lugt
Copromotor:	dr. H.F. Lingsma

PhD training	*Year*	*ECTS*
BROK	2015	0.3
Applied regression analysis (prof. Lemeshow)	2016	0.8
Research integrity course	2016	0.3
English writing course	2016	3.0
NIHES courses Advanced topics in decision (prof. Hunink) Advanced analysis of prognosis studies (prof. Steyerberg) Scientific speedreading Principles of Epidemiologic Data-analysis (prof. Rothman) Scientific writing (prof. Greenland)	2016	4.1
International conferences		
European Stroke Organisation Conference (Barcelona, Spain)	2016	1.1
American Acedemy of Neurology 2017 (Boston, USA)	2017	3.0
European Stroke Organisation Conference (Prague, Czech)	2017	1.2
Presentations		
Nederlandse Neurovasculaire Werkgroep, Amsterdam (oral)	2015	0.8
Rotterdamse Stroke Service symposium; Ridderkerk (oral)	2015	0.8
MR CLEAN Workshop; Rotterdam (oral)	2015	1.0
European Stroke Organisation Conference; Barcelona, Spanje (oral & 2 posters)	2016	2.2
MR CLEAN workshop; Amsterdam (oral)	2016	0.7
NVN wetenschapsdagen; Nunspeet (oral)	2016	0.5
MR CLEAN workshop; Maastricht (oral)	2017	0.5
American Academy of Neurology; Boston, MA, USA (oral)	2017	0.5
European Stroke Organisation Conference; Prague, Czech (oral)	2017	1.0
Teaching		
Saliha Ergezen; MR CLEAN Registry and supervising 2 manuscripts	2015-2017	1.0
COEUR cardiovasculair keuzeonderzoek, Erasmus MC	2016	0.5
Master thesis Roger Harmsma	2016	1.0
Anouk de Jong; MR CLEAN Registry and supervising 1 manuscript	2016	0.5
Daan Muijres; MR CLEAN Registry	2016-2017	0.4
Workshops, meetings and symposia		
Dutch neurovascular network scientific meeting (Amsterdam)	2015	0.2
Regionale neurologen bijeenkomst (Lantaarn Venster, Rotterdam)	2015	0.1
Arts assistenten vereniging wetenschapsmiddag (Erasmus MC)	2015	0.2
Rotterdamse Stroke Service bijeenkomst (Ridderkerk)	2015	0.2
Symposium on Quantitative Methods for Medical Research (Erasmus MC)	2015	0.1
The scientific basis for the evaluation of quality of hospital care (Erasmus MC)	2015	0.1
Regionale neurologen bijeenkomst (Erasmus MC)	2015	0.1
Two-weekly lectures, neurology department (Erasmus MC)	2015-2017	3.0
COEUR PhD day (Het nieuwe instituut, Rotterdam)	2016	0.2
European Stroke Organization Summer School (Hospital Universitario La Paz, Madrid, Spain)	2016	1.6
Clinical research and Ruysch lecture (prof. Demchuk, AMC)	2016	0.1
NVN wetenschapsdagen (Nunspeet)	2016	0.3
Clinical research & Spinoza lecture (prof. Goyal, AMC)	2016	0.1
Masterclass RCTs, imaging and workflow (prof. Goyal, AMC)	2016	0.2
Minisymposium: 'Advances in Intra-arterial Treatment of Acute Ischemic Stroke' (AMC)	2016	0.1
COEUR aneurysms (Erasmus MC)	2016	0.4
MR CLEAN workshop (MUMC)	2017	0.1
Regionale neurologen bijeenkomst (Erasmus MC)	2017	0.1
Biemond cursus (NVN)	2017	0.4
COEUR lecture 'Endovascular thrombectomy in acute ischemic stroke lecture' (Erasmus MC)	2017	0.3
Other activities		
Organization; MR CLEAN Workshop (Erasmus MC)	2015	1.2
Organization; MR CLEAN Workshop (AMC)	2016	1.2
Coordinating local NIMO study (Erasmus MC)	2016	1.0
Organizing committee; 1st Erasmus MC conference on acute stroke treatment	2016	4.0
Organization; MR CLEAN Workshop (MUMC)	2017	0.5
Organization; meet the expert prof. Goyal (Erasmus MC)	2017	0.3
Reviewing international literature for diverse journals	2015-2017	0.4
Total ECTS (European Credit Transfer System) is equal to a workload of 28 hours		**41.7**

Acknowledgements

MR CLEAN Registry investigators

Executive committee

Diederik W.J. Dippel[1];Aad van der Lugt[2];Charles B.L.M. Majoie[3];Yvo B.W.E.M. Roos[4];Robert J. van Oostenbrugge[5];Wim H. van Zwam[6];Jelis Boiten[14];Jan Albert Vos[8]

Study coordinators

Ivo G.H. Jansen[3];Maxim J.H.L. Mulder[1,2];Robert- Jan B. Goldhoorn[5,6]

Local principal **investigators**

Wouter J. Schonewille[7];Jan Albert Vos[8];Charles B.L.M. Majoie[3];Jonathan Coutinho[4];Marieke J.H. Wermer[9];Marianne A.A. van Walderveen[10];Julie Staals[5];Wim H. van Zwam[6];Jeannette Hofmeijer[11];Jasper Martens[12];Geert J. Lycklama à Nijeholt[13];Jelis Boiten[14];Bob Roozenbeek[1];Bart J. Emmer[2];Sebastiaan F. de Bruijn[15];Lukas C. van Dijk[16];H. Bart van der Worp[17] ;Rob H. Lo[18];Ewoud J. van Dijk[19];Jeroen Boogaarts[20];Paul L.M. de Kort[21];Jo Peluso[26];Jan S.P. van den Berg[22];Boudewijn A.A.M. van Hasselt[23];Leo A.M. Aerden[24];René J. Dallinga[25];Maarten Uyttenboogaart[28];Omid Eshghi[29];Tobien H.C.M.L. Schreuder[30];Roel J.J. Heijboer[31];Koos Keizer[32];Lonneke Yo[33];Heleen M. den Hertog[34];Emiel J.C. Sturm[35]

Imaging assessment committee

Charles B.L.M. Majoie[3](chair);Wim H. van Zwam[6];Aad van der Lugt[2];Geert J. Lycklama à Nijeholt[13];Marianne A.A. van Walderveen[10];Marieke E.S. Sprengers[3];Sjoerd F.M. Jenniskens[27];René van den Berg[3];Albert J. Yoo[37];Ludo F.M. Beenen[3];Stefan Roosendaal[3];Bas van der Kallen[13];Ido van den Wijngaard[13];Ad van Es[2];Bart Emmer[2,3];Jasper Martens[12]; Lonneke Yo[33];Jan Albert Vos[8]; Joost Bot[36], Pieter-Jan van Doormaal[2].

Writing committee

Diederik W.J. Dippel[1](chair);Aad van der Lugt[2];Charles B.L.M. Majoie[3];Yvo B.W.E.M. Roos[4];Robert J. van Oostenbrugge[5];Wim H. van Zwam[6];Geert J. Lycklama à Nijeholt[13];Jelis Boiten[14];Jan Albert Vos[8];Wouter J. Schonewille[7];Jeannette Hofmeijer[11];Jasper M. Martens[12];H. Bart van der Worp[17];Rob H. Lo[18]

Adverse event committee

Robert J. van Oostenbrugge[5](chair);Jeannette Hofmeijer[11];H. Zwenneke Flach[23]

Trial methodologist

Hester F. Lingsma[38]

Research nurses / local trial coordinators

Naziha el Ghannouti[1];Martin Sterrenberg[1];Corina Puppels[7];Wilma Pellikaan[7];Rita Sprengers[3];Marjan Elfrink[11];Joke de Meris[14];Tamara Vermeulen[14];Annet Geerlings[19];Gina van Vemde[22];Tiny Simons[30];Cathelijn van Rijswijk[21];Gert Messchendorp[28];Hester Bongenaar[32];Karin Bodde[24];Sandra Kleijn[34];Jasmijn Lodico[34]; Hanneke Droste[34];M. Wollaert[5];D. Jeurrissen[5];Ernas Bos[9];Yvonne Drabbe[15];Marjan Elfrink[11];Berber Zweedijk[17] ; Mostafa Khalilzada[15].

PhD / Medical students:

Esmee Venema[38]; Vicky Chalos[1,38];Kars J. Compagne[2]; Ralph R. Geuskens[3]; Tim van Straaten[19]; Saliha Ergezen[1]; Roger R.M. Harmsma[1]; Daan Muijres[1]; Anouk de Jong[1]; Wouter Hinseveld[7];Olvert A. Berkhemer[1,3,6];Anna M.M. Boers[3,39]; J. Huguet[3];P.F.C. Groot[3];Marieke A. Mens[3];Katinka R. van Kranendonk[3];Kilian M. Treurniet[3];Manon Kappelhof[3];Manon L. Tolhuijsen[3];Heitor Alves[3].

List of affiliations

Department of Neurology[1], Radiology[2], Public Health[38], Erasmus MC University Medical Center;
Department of Radiology[3], Neurology[4], Biomedical Engineering & Physics[39], Academic Medical Center, Amsterdam;
Department of Neurology[5], Radiology[6], Maastricht University Medical Center and Cardiovascular Research Institute Maastricht (CARIM);
Department of Neurology[7], Radiology[8], Sint Antonius Hospital, Nieuwegein;
Department of Neurology[9], Radiology[10], Leiden University Medical Center;
Department of Neurology[11], Radiology[12], Rijnstate Hospital, Arnhem;
Department of Radiology[13], Neurology[14], Haaglanden Medical Center, the Hague;
Department of Neurology[15], Radiology[16], HAGA Hospital, the Hague;
Department of Neurology[17], Radiology[18], University Medical Center Utrecht;
Department of Neurology[19], Neurosurgery[20], Radiology[27], Radboud University Medical Center, Nijmegen;
Department of Neurology[21], Radiology[26], Sint Elisabeth Hospital, Tilburg;
Department of Neurology[22], Radiology[23], Isala Klinieken, Zwolle;
Department of Neurology[24], Radiology[25], Reinier de Graaf Gasthuis, Delft;
Department of Neurology[28], Radiology[29], University Medical Center Groningen;
Department of Neurology[30], Radiology[31], Atrium Medical Center, Heerlen;
Department of Neurology[32], Radiology[33], Catharina Hospital, Eindhoven;
Department of Neurology[34], Radiology[35], Medical Spectrum Twente, Enschede;
Department of Radiology[36], VUMC, Amsterdam;
Department of Radiology[37], Texas Stroke Institute, Texas, United States of America;

MR CLEAN trial investigators

Funding
The MR CLEAN trial was funded by the Dutch Heart Foundation and through unrestricted grants from AngioCare BV, Covidien/EV3®, MEDAC Gmbh/LAMEPRO and Penumbra Inc.

Executive committee
Diederik W.J. Dippel[1];Aad van der Lugt[2];Charles B.L.M. Majoie[3];Yvo B.W.E.M. Roos[4];Robert J. van Oostenbrugge[5];Wim H. van Zwam[6];Olvert A. Berkhemer[1,3]; Puck S.S. Fransen[1,2];Debbie Beumer[1,5];Lucie A. van den Berg[4]

Local principal investigators
Wouter J. Schonewille[7];Jan Albert Vos[8];Charles B.L.M. Majoie[3];Yvo B.W.E.M. Roos[4];Paul J. Nederkoorn[4];Marieke J.H. Wermer[9];Marianne A.A. van Walderveen[10];Robert J. van Oostenbrugge[5];Wim H. van Zwam[6];Julie Staals[5];Jeannette Hofmeijer[11];Jacques A. van Oostayen[12];Geert J. Lycklama à Nijeholt[13];Jelis Boiten[14];Diederik W.J. Dippel[1];Patrick A. Brouwer[2];Bart J. Emmer[2];Sebastiaan F. de Bruijn[15];Lukas C. van Dijk[16];L. Jaap Kappelle[17];Rob H. Lo[18];Ewoud J. van Dijk[19];Joost de Vries[20];Paul L.M. de Kort[21];Jan S.P. van den Berg[22]; Willem Jan J. van Rooij[22]; Boudewijn A.A.M. van Hasselt[23];Leo A.M. Aerden[24];René J. Dallinga[25];Marieke C. Visser[26];Joseph C.J. Bot[27];Patrick C. Vroomen[28];Omid Eshghi[29];Tobien H.C.M.L. Schreuder[30];Roel J.J. Heijboer[31];Koos Keizer[32];Alexander V. Tielbeek[33];Heleen M. den Hertog[34];Dick G. Gerrits[35];Renske M. van den Berg-Vos[36];Giorgos B. Karas[37]

Imaging assessment committee
Charles B.L.M. Majoie[3] (chair);Wim H. van Zwam[6];Aad van der Lugt[2];Geert J. Lycklama à Nijeholt[13];Marianne A.A. van Walderveen[10], Joseph C.J. Bot[27];Henk A. Marquering[38];Ludo F. Beenen[3];Marieke E.S. Sprengers[3];Sjoerd F.M. Jenniskens[39], René van den Berg[3];Olvert A. Berkhemer[1,3];Albert J. Yoo[40]

Outcome assessment committee
Yvo B.W.E.M. Roos[4] (chair);Peter J. Koudstaal[1];Jelis Boiten;Ewoud J. van Dijk[19]

Adverse event committee
Robert J. van Oostenbrugge[5] (chair);Marieke J.H. Wermer[9];H. Zwenneke Flach[23]

Trial statisticians
Ewout W. Steyerberg[41];Hester F. Lingsma[41]

Data monitoring committee
Martin M. Brown[42] (Chair);Thomas Liebig[43];Theo Stijnen[44];Hester F. Lingsma[41]

Advisory board:
Tommy Andersson[45];Heinrich P. Mattle[46];Nils Wahlgren[47];Peter J. Koudstaal[1]

Research nurses / local trial coordinators
Esther van der Heijden[1];Naziha Ghannouti[1];Nadine Fleitour[4];Imke Hooijenga[4];Annemieke Lindl-Velema[5];Corina Puppels[7];Wilma Pellikaan[7];Kirsten Janssen[9];Nicole Aaldering[11];Marjan Elfrink[11];Joke de Meris[14];Annet Geerlings[19];Gina van Vemde[22];Ans de Ridder[17];Paut Greebe[17];José de Bont-Stikkelbroeck[21];Willy Struijk[15];Tiny Simons[30] ;Gert Messchendorp[28];Friedus van der Minne[28];Hester Bongenaar[32];Karin Bodde[26];

PhD / Medical students:
Silvan Licher[1];Nikki Boodt;Adriaan Ros[1];Esmee Venema[1];Ilse Slokkers[1];Raymie-Jayce Ganpat[1];Maxim Mulder[1];Nawid Saiedie[1];Alis Heshmatollah[1];Stefanie Schipperen[1]; Stefan Vinken[1];Tiemen van Boxtel[1];Jeroen Koets[1];Merel Boers[38];Emilie Santos[2;38];Jordi Borst[3];Ivo Jansen[3];Manon Kappelhof[3];Marit Lucas[38];Ralph Geuskens[38];Renan Sales Barros[38];Roeland Dobbe[38];Marloes Csizmadia[38]

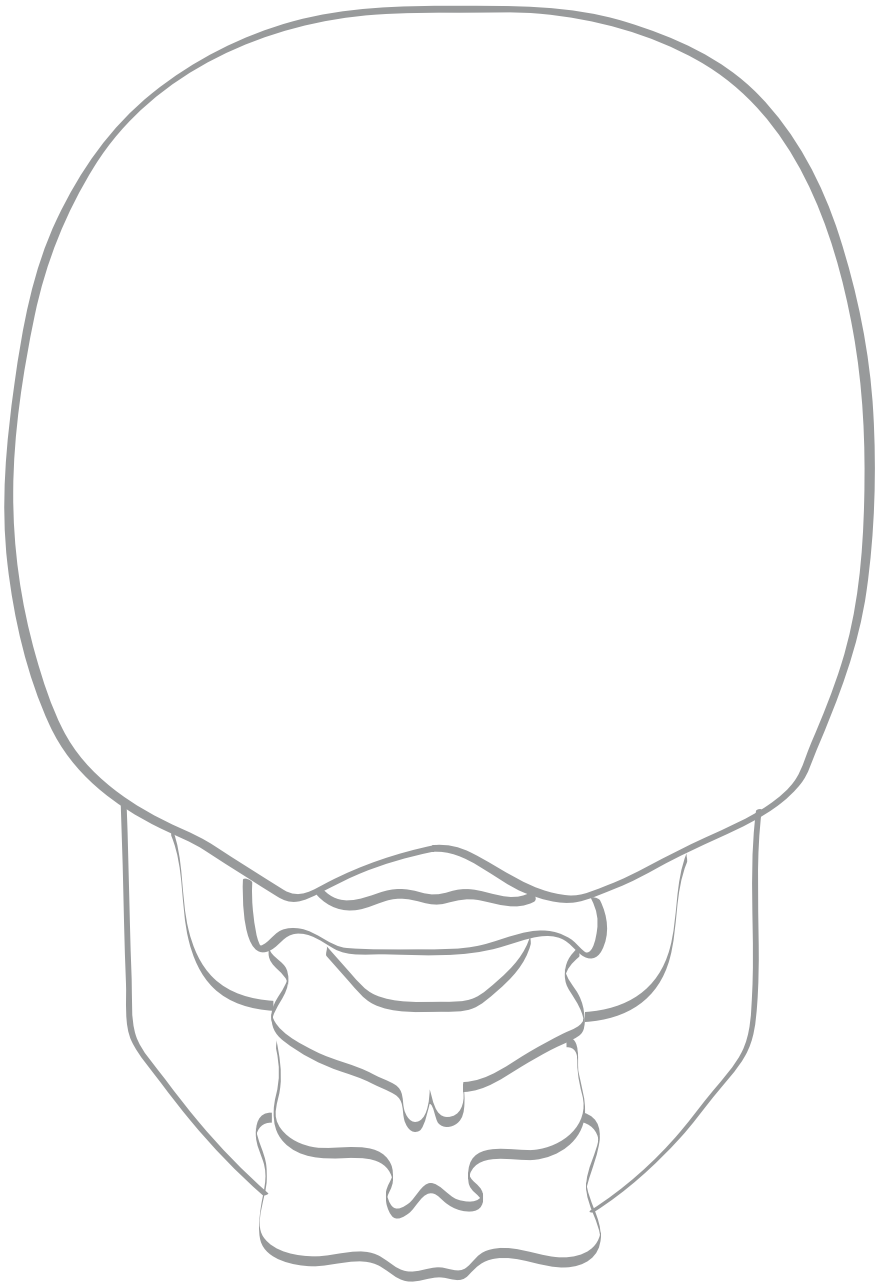
List of affiliations
Department of Neurology[1], Radiology[2], Public Health[41], Erasmus MC University Medical Center;Department of Radiology[3], Neurology[4], Biomedical Engineering and Physics[38], Academic Medical Center, Amsterdam; Department of Neurology[5], Radiology[6], Maastricht University Medical Center and Cardiovascular Research Institute Maastricht (CARIM); Department of Neurology[7], Radiology[8], Sint Antonius Hospital, Nieuwegein; Department of Neurology[9], Radiology[10], Medical Statistics and Bioinformatics[44], Leiden University Medical Center; Department of Neurology[11], Radiology[12], Rijnstate Hospital, Arnhem; Department of Radiology[13], Neurology[14], MC Haaglanden, the Hague; Department of Neurology[15], Radiology[16], HAGA Hospital, the Hague; Department of Neurology[17], Radiology[18], University Medical Center Utrecht; Department of Neurology[19], Neurosurgery[20], Radiology[39], Radboud University Medical Center, Nijmegen; Department of Neurology[21], Sint Elisabeth Hospital, Tilburg; Department of Neurology[22], Radiology[23], Isala Klinieken, Zwolle; Department of Neurology[24], Radiology[25], Reinier de Graaf Gasthuis, Delft; Department of Neurology[26], Radiology[27], VU Medical Center, Amsterdam; Department of Neurology[28], Radiology[29], University Medical Center Groningen, the Netherlands; Department of Neurology[30], Radiology[31], Atrium Medical Center, Heerlen; Department of Neurology[32], Radiology[33], Catharina Hospital, Eindhoven; Department of Neurology[34], Radiology35, Medical Spectrum Twente, Enschede; Department of Neurology[36], Radiology[37], Sint Lucas Andreas Hospital, Amsterdam; *all in the Netherlands*

Department of Radiology[40], Texas Stroke Institute, Texas, United States of America; UCL Institute of Neurology[42], National Hospital for Neurology and Neurosurgery, London, United Kingdom; Med. Fakultät[43], Uniklinik Köln, Germany; Department of Radiology[45], Neurology[47], Karolinska Univeristy Hospital, Stockholm, Sweden; Department of Neurology[46], University Hospital of Bern, Switzerland

About the author

Born, in accidental circumstances, in Delft, of all places, from day one Maxim was raised in Rotterdam and eventually became the oldest brother of four rascals, one boy and three girls. At elementary school he was a champion of building sand castle sculptures, when sand was available, and of hiding in the restroom to avoid class. At high school he exhibited memorable drawing and singing talents and qualified for the national finals of the Biologie Olympiade. After finishing high school at the Erasmus College in Rotterdam he directly started studying medicine at the Erasmus University MC. While a medical student, he led the Skillplaza Students Team, participated in the Advanced Student Anesthesiology Project, Erasmus Medical School Anatomy Research Project (head and neck), and Mastercursus Klinische Propedeuse. Apart from all that he greatly enjoyed dancing classes at the now regretfully closed BED (every Tuesday night), as well as weekly discussion group meetings that were further facilitated by eating delicious hamburgers.

In 2012 he commenced his research master project with Professor Dippel and also participated in gathering data for the MRCLEAN pre-trial and trial. Before starting his rotations he did investigational studies of headache and facial pain under supervision of Professor Spierings at Tufts Medical School in Boston, USA. After graduating from medical school he started working on his PhD thesis and helped coordinating the MR.CLEAN registry. During the same time he co-founded a shady boy band which delivered some performances of questionable quality (see photo below; Prague 2017). As of September, 2017, Maxim has been working at the Department of Neurology of Erasmus University Medical Center in Rotterdam.



ROTTERDAM
2017