

Endovascular treatment for acute ischemic stroke

ON THE ROAD TO NATIONWIDE IMPLEMENTATION

Lucie Anne van den Berg



**ENDOVASCULAR TREATMENT FOR ACUTE ISCHEMIC STROKE:
On the road to nationwide implementation**

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Colofon

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Endovascular treatment for acute ischemic stroke: On the road to nationwide
implementation

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CONTENTS

Chapter 1	General introduction and Outline	7
Chapter 2	Two-year clinical follow-up of the multicenter randomized clinical trial of endovascular treatment for acute ischemic stroke in The Netherlands (MR CLEAN): design and statistical analysis plan of the extended follow-up study (Trials 2016; 17:555)	17
Chapter 3	Two-year outcome after endovascular treatment for acute ischemic stroke (N Eng J Med 2017; 376:1341-9)	29
Chapter 4	Economic evaluation of endovascular treatment for acute ischemic stroke (Stroke 2022; 53:968-975)	53
Chapter 5	Budget impact analysis of endovascular treatment for acute ischemic stroke patients in the Netherlands 2015-2021(submitted)	77
Chapter 6	Type of anesthesia and differences in clinical outcome after intra-arterial treatment for ischemic stroke (Stroke 2015;46:1257-62)	91
Chapter 7	The effect of anesthetic management during intra-arterial therapy for acute stroke in MR CLEAN (Neurology 2016;87:656-64)	107
Chapter 8	Improving workflow in endovascular treatment for acute ischemic stroke; experience in de Greater Amsterdam Area (in progress)	125
Chapter 9	General discussion	143
Appendices	Summary	162
	Nederlandse samenvatting	165
	Acknowledgements	169
	Portfolio	171
	Dankwoord	174
	List of publications	178
	About the author	182





CHAPTER 1

| General introduction and Outline

Acute ischemic stroke (AIS) is a disease which poses a heavy burden for both the patient as well as society. It is an important cause of long-term disability and a leading cause of death worldwide.¹ In the Netherlands every year over 25.000 patients are admitted with AIS, of which around 20% die and almost half of them is not able to return home.² Consequently, the economic impact of stroke is high; in the Netherlands the annual costs in 2011 associated with stroke patients estimated 1,84 billion euros.³ These numbers will only increase with the expected ageing in the years to come. Fortunately, during the past decade major improvements in the acute treatment strategies for AIS patients were achieved, resulting in positive effects on functional outcome.

PATHOPHYSIOLOGY OF ACUTE ISCHEMIC STROKE

An ischemic stroke may be the result of blockage of the large vessels of the proximal intracranial circulation, i.e., occlusions of the distal intracranial carotid artery, the proximal segment of the middle cerebral artery and the anterior cerebral artery, also called large vessel occlusions (LVO). Another important cause of ischemic stroke is cerebral small vessel disease, which is the result of chronic vascular changes that affect the arterioles, capillaries and small vessels supplying the white matter and deep structures of the brain. This thesis focusses on AIS caused by LVO's only, which account approximately one-third of AIS patients.^{4,5} An LVO AIS is mostly caused by an embolism or thrombotic occlusion, which obstructs cerebral blood flow. As a result, the patient suffers from acute focal neurological deficits. Depending on the involved vascular territory there may be for example impairment of language, vision or focal weakness of the arm or leg. In most patients, the thrombo-embolus originates from the heart or an atherosclerotic plaque in the internal carotid artery.⁶

After occlusion of the cerebral vessel, brain tissue in the vascular territory becomes hypoxic, followed by a cascade of events caused by ischemia, resulting in neuronal cell death. This ischemic cascade occurs within minutes after symptom onset and loss of neurons has been quantified on average to be approximately 2 million per minute.⁷ When reperfusion, and thereby oxygen, remains absent, cell death expands over time, resulting in irreversible damage and formation of a cerebral infarct, referred to as the infarct core. Around the infarct core is a zone called the penumbra.⁸ In the penumbra oxygen levels are a bit higher because of blood flow from a so-called collateral circulation. In the penumbra cell death occurs relatively slow, and this tissue is potentially salvageable. Acute reperfusion therapies aim to restore blood flow in the penumbra before irreversible damage takes place.

ACUTE REPERFUSION THERAPY

For 20 years AIS patients are treated with intravenous thrombolysis (IVT), the first proven reperfusion therapy.⁹ It consists of dissolution of the cerebral artery occlusion by a pharmacological agent, mostly recombinant tissue plasminogen activator (rt-PA). Until recently this therapy was proven effective when given within 4,5 hours of symptom onset

with increasing numbers needed to treat over time.^{10,11} During the past years this restricted time window could be extended. In a selected group of patients with unknown time of onset of symptoms, or onset up to 24 hours after presentation, and who show favorable imaging characteristics (small infarct core and large penumbra on neuroimaging e.g., diffusion-weighted magnetic resonance imaging (MRI-DWI) or computed tomographic perfusion imaging (CTP)) IVT has been shown to still be effective.^{12,13}

Besides this restricted time window, IVT has other important disadvantages. Firstly, rt-PA induces loss of microvascular integrity, which may precede an intracranial hemorrhage. As a result, IVT has significant contra-indications such as recent surgery, coagulation abnormalities, use of anticoagulants, and a history of intracranial hemorrhage. Secondly, it has been shown that the effect of IVT, i.e., dissolving the obstructing clot, in LVO AIS patients is limited.^{14,15}

Like percutaneous coronary intervention (PCI) in coronary artery disease, an alternative acute reperfusion treatment, intra-arterial treatment, or endovascular treatment (EVT), was explored from the nineties. During EVT a (neuro)interventionist performs intra-arterial catheterization to the level of the intracranial occlusion, mostly by access through the femoral artery. After introduction of the sheath, a guide wire is used to place a micro-catheter at the level of the intracranial occlusion to perform mechanical thrombectomy, deliver a thrombolytic agent, or both.

At the start of the current PhD project in early 2013, there was no proof of clinical effectiveness of either form of this therapy. First, trials explored the administration of intra-arterial thrombolytic agents only. These trials showed a trend toward better outcomes in favor of EVT, but there were important differences in design between these trials and there was no consistent comparison to up-to-date standard stroke care.¹⁶⁻²⁰ In the following years new techniques including innovative thrombectomy devices to mechanically remove the intracranial clot were studied. The most effective device in safely re-opening the occluded vessel, which resulted in better functional outcomes, appeared to be the so-called stent retriever. However, results on the use of stent retrievers came from small, mostly industry driven studies, in which there was only a head-to-head comparison with other thrombectomy devices.²¹⁻²⁷ The field still waited for larger independent randomized trials, which reflected best every day clinical practice, to adopt EVT in stroke guidelines.

In 2013 the results of three randomized clinical trials (IMS-III, SYNTHESIS expansion and MR RESCUE), in which EVT was compared to standard acute stroke therapy, were published. They all failed to show clinical benefit of EVT.²⁸⁻³⁰ Possible causes of these negative trials were the use of older generation thrombectomy devices, lack of confirmation of the presence of a LVO by vascular imaging and long time to treatment delays. In the meanwhile, in the Netherlands the Multicenter Randomized Clinical trial of Endovascular treatment for Acute ischemic stroke trial (MR CLEAN) started including patients in 18 Dutch stroke centers from 2010. This pragmatic trial compared EVT plus usual care (intervention group) to usual care alone (control group)

in patients with acute ischemic stroke caused by an imaging confirmed proximal intracranial arterial occlusion of the anterior circulation. This was the first trial to show clinical benefit of EVT over standard care in the world.³¹ After publication of this landmark trial in the *New England Journal of Medicine* (NEJM) in January 2015, several other positive trials followed, which indicated consistent results. A meta-analysis of pooled individual patient data from these trials showed that AIS patients treated with EVT had almost a two times higher chance of functional independency compared to patients treated with standard care, including IVT.³² Furthermore, results showed that EVT should not be withheld based on advanced age, early ischemic changes on neuro-imaging and moderate to severe neurological deficit, and that it does not lead to higher mortality or the occurrence of symptomatic intracerebral hemorrhage.^{31,32} The convincing evidence led to incorporation of EVT in international guidelines and it has been added to standard acute stroke care in the Western world. A new era for acute stroke treatment began.

In the period thereafter, EVT was extensively studied. For instance, improvement of imaging techniques led to better patient selection resulting in effectiveness of EVT up to 24 hours after stroke onset.^{33,34} However, the chance of a favorable outcome was still very time-dependent, and a significant number of AIS patients remains functional dependent after reperfusion therapy. Therefore, national, and international collaborations made efforts to widely implement EVT in clinical practice and further optimize treatment to maximize clinical outcome. For example, some controversy still existed about the optimal anesthetic management during EVT. During intervention, patients receive either general anesthesia, or local anesthesia at groin puncture site with or without conscious sedation. This is mainly based on the preference of the interventionist and/or the 24/7 availability of anesthesia for EVT at the neuro-intervention center.³⁵ Both strategies have advantages and disadvantages, and comprehensive studies were needed to provide clinical evidence on the best strategy.

Another important issue was the availability of data on the long-term clinical outcome after EVT. Most trials reported clinical outcome at a maximum of three months. However, the benefit of EVT on short-term disability might very well translate into longer-term improvements in survival and functional status, which could influence treatment decisions and estimates of cost-effectiveness.

ECONOMIC EVALUATIONS AND ACUTE STROKE THERAPIES

As mentioned before, healthcare costs associated with stroke are high and pose a heavy economic burden. Any treatment strategy that might reduce this burden is crucial. Moreover, in most countries governmental agencies and insurance companies require additional economic evidence before reimbursement of a novel treatment is granted.

To answer the question whether new therapies are good value for money in relation to their clinical effects, economic evaluations like cost-effectiveness studies need to be performed. The basic calculation in cost-effectiveness studies involves dividing the difference in costs in monetary units between alternative interventions by the associated difference in health in natural units of benefit like patients alive or, more disease-specific, like millimeters of mercuries of blood pressure. The results of the calculation are presented as additional costs per additional health benefit: the incremental cost-effectiveness ratio (ICER). If, more generally, quality adjusted life years (QALYs) are used to measure the impact of interventions on duration as well as quality of life, then cost-effectiveness analysis turns into cost-utility analysis and the ICER may then also be referred to as incremental cost-utility ratio (ICUR). Although variably reported in the literature,³⁶ threshold criteria for health care efficiency ('the new intervention offers good value for money') are most widely elaborated and accepted for QALYs as the general health outcome measure; the thresholds are in the range of \$50,000 to \$100,000 per QALY in the USA, or £20,000 to £30,000 per QALY in the UK and 20,000 to 80,000 euros in the Netherlands (depending on the burden of disease).

Another essential part of a comprehensive economic assessment is a budget impact analysis (BIA). The purpose of a BIA is to estimate the financial consequences of adoption and diffusion of a new health-care intervention within a specific healthcare setting or system context given inevitable resource constraints.³⁷ The tool can be used for budget planning, forecasting and for computing the impact of health technology changes on premiums in health insurance schemes.

Regarding acute stroke interventions, evidence on cost-effectiveness for IVT is quite extensively studied in several Western world countries. However, no specific studies were conducted in the Netherlands. There is a wide variability among studies in relation to for example time horizons and reported outcomes. Nevertheless, the point-estimates are relatively consistent across studies and show that IVT is a cost-effective treatment: it is either more effective and less costly (when given within 3 hours of onset), resulting in a cost saving situation, or the ICER is below the commonly applied threshold (when given within 4.5 hours).³⁸

Evidence on cost-effectiveness of EVT is currently growing and shows that it is indeed a cost-effective treatment in line with the large clinical effect.³⁹⁻⁴¹ However, most of these studies are model based, meaning input data is often retrieved from different resources and long-term outcomes are based on assumptions. To reflect real-life practice, studies based on empirical data with longer-term data are needed.

AIM AND OUTLINE OF THIS THESIS

The focus of this thesis is to provide evidence for the long-term clinical benefit and safety of EVT for acute ischemic stroke patients. Simultaneously an economic evaluation was conducted to assess cost-effectiveness and analyze the budget impact of EVT in addition to standard care in comparison to standard care alone in the Netherlands. To study this, we extended the follow-up duration from three months to two years in the MR CLEAN trial, during which clinical and economic outcome parameters were collected. In **Chapter 3** we describe the results of clinical outcomes, including functional outcome, quality of life, and mortality at two years in the MR CLEAN study. An economic evaluation is presented consisting of cost-effectiveness and cost-utility analyses (**Chapter 4**) and a Budget Impact Analysis (**Chapter 5**).

Besides data on long-term clinical outcomes and cost-effectiveness of EVT to guide reimbursement decisions, other challenges to further optimize treatment to improve clinical outcome of AIS patients after EVT are still present. An important aspect of the treatment itself is the question on optimal anesthetic management during EVT. From 2002 until the start of the MR CLEAN trial in 2010 all EVT patients in the Netherlands were registered in the so-called MR CLEAN pre-trial registry. Information concerning EVT procedures and treated AIS patients was gathered to assess pretrial experience in centers that were committed to participate in the MR CLEAN trial. Before the end of inclusion of the MR CLEAN trial we were able to study the association between type of anesthesia and clinical outcome in the MR CLEAN pre-trial cohort. In the MR CLEAN itself no recommendations were given regarding the type of anesthetic management during EVT. This provided the opportunity to perform a post-hoc analysis of the type of anesthetic management during EVT in relation to clinical outcome. Results of these studies are described in **Chapter 6 and 7** respectively.

One of the most important challenges to is to reduce time to treatment, as it one of the most prognostic factors for outcome after EVT for AIS patients. Since the implementation of EVT in 2015, the clinical and radiological work-up has evolved rapidly and logistics became more complex. Large differences between countries concerning population and hospital density require tailored solutions. Within the Greater Amsterdam Area we set out workflow improvements to optimize the logistic procedure to decrease time-to-treatment. To study the effect of these improvements we performed a prospective sequential comparison study, of which the results are described in **Chapter 8**.

The final part presents a general discussion of this thesis and (future) implications (**Chapter 9**). It is followed by a summary in English and Dutch.

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CHAPTER 1

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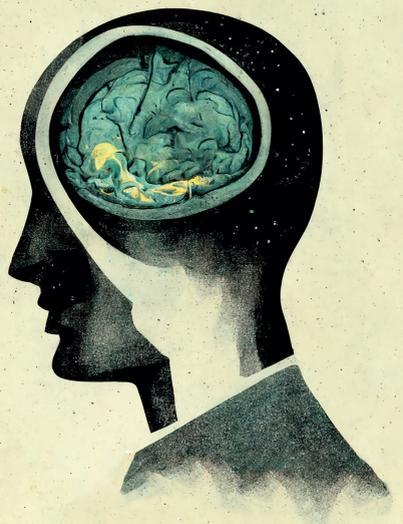
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CHAPTER 2

Two-year clinical follow-up in the multicenter randomized clinical trial of endovascular treatment for acute ischemic stroke in The Netherlands (MR CLEAN): design and statistical analysis plan of the extended follow-up study

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ABSTRACT

Background

MR CLEAN was the first randomized trial to demonstrate short-term clinical effectiveness of endovascular treatment in patients with acute ischemic stroke caused by large vessel occlusion in the anterior circulation. Several other trials confirmed that endovascular treatment improves clinical outcome at three months. However, limited data is available on long-term clinical outcome. We aimed to estimate the effect of endovascular treatment on functional outcome at two-year follow-up in patients with acute ischemic stroke. Secondly, we aimed to assess the effect of endovascular treatment on major vascular events and mortality during two years of follow-up.

Methods

MR CLEAN is a multicenter clinical trial with randomized treatment allocation, open label treatment and blinded endpoint evaluation. Patients included were 18 years or older with acute ischemic stroke caused by a proven anterior proximal artery occlusion who could be treated within 6 hours after stroke onset. The intervention contrast was endovascular treatment and usual care versus no endovascular treatment and usual care. The current study extended the follow-up duration from three months to two years. The primary outcome is the score on the modified Rankin scale at two years. Secondary outcomes include all-cause mortality and the occurrence of major vascular events within two years of follow-up.

Discussion

The results of our study provide information on the long-term clinical effectiveness of endovascular treatment, which may have implications for individual treatment decisions and estimates of cost-effectiveness.

INTRODUCTION

Stroke is one of the leading causes of disability and death worldwide.¹ Until recently the only proven effective therapy for acute ischemic stroke was intravenous (IV) thrombolysis with recombinant tissue plasminogen activator (rt-PA).² In January 2015 the results of the Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands (MR CLEAN) were published and demonstrated clinical effectiveness of endovascular treatment with respect to functional recovery at three months.³ In the subsequent months several other trials confirmed these results.⁴⁻⁸ However, results on long-term clinical outcome are still lacking. In the current paper we present the design and statistical analysis plan (SAP) of the extended, two-year clinical follow-up study of the MR CLEAN trial. The primary objective of our study is to estimate the effect of endovascular treatment in comparison to standard treatment on functional outcome at two-year follow-up in patients with acute ischemic stroke caused by a proximal occlusion in the anterior cerebral circulation. Secondary objectives include the effect of endovascular treatment on major vascular events, mortality, and quality of life during two years of follow-up.

METHODS

Study design and overall study plan

MR CLEAN was a multicenter clinical trial with randomized treatment allocation, open label treatment and blinded endpoint evaluation. The intervention contrast was endovascular treatment (mechanical thrombectomy with stent retriever in 97% of patients) versus no endovascular treatment. The treatment was provided in addition to usual care, which included IV rt-PA (in approximately 90% of patients). Patients were randomized in a 1:1 ratio. The randomization procedure was web-based, with the use of permuted blocks, stratified for center, dichotomized score on the National Institutes of Health Stroke Scale (NIHSS), treatment with IV rt-PA and intended mechanical treatment.⁹ Data were collected at baseline, 24 hours, one week and three months for the main trial. Detailed information of the main trial, treatment, blinding, statistical analysis and determination of sample size are described in the protocol and SAP of the MR CLEAN trial.¹⁰

Because of funding issues, the extended follow-up study came only into effect in May 2013. At that moment the inclusion of the MR CLEAN trial was well halfway the projected 500 patients to be included. As a result, many patients had already completed their three-month follow-up. Some patients had even passed the two-year follow-up point. After checking the Dutch Death Certificate Register, alive patients were re-invited to take part in the extended follow-up study. If patients did not wish to participate, a reply was to be sent back to the trial office. Approximately two weeks after sending the invitation letter, all willing participants were contacted by telephone to confirm their participation and to explain additional study goals and activities. For the remaining MR CLEAN trial inclusions and their legal representatives, the new follow-up duration with additional study activities were explained in an adjusted MR

CLEAN informed consent letter. All participating patients or his/her primary caregiver, in case the patient was unable to respond, were contacted by telephone at six months, one year, 18 months and two years of follow-up. One experienced research nurse, blinded for treatment allocation, assessed functional outcome using the modified Rankin scale (mRS) and noted the occurrence of medical events in-between follow-ups by a telephone interview.¹¹ The patient or his or her primary caregiver was also invited to complete the EuroQol EQ-5D-3L questionnaire to assess quality of life.¹²

Study population

Patients of 18 years or older with acute ischemic stroke caused by an anterior proximal artery occlusion who could be treated within 6 hours after stroke onset were eligible for inclusion in MR CLEAN. Detailed inclusion and exclusion criteria are described in the protocol of the MR CLEAN trial.¹⁰

Because the current extended follow-up study started more than two years later than the main MR CLEAN trial, many patients already completed their participation in the main trial at start of the extended follow-up study. As a result, different groups of patients emerge:

- a. Patients randomized before May 2011 (Group 1);
- b. Patients randomized between May 2011 and May 2013 who:
 - i. Had died by May 2013 (Group 2)
 - ii. Were untraceable or were living abroad in May 2013 (Group 3);
 - iii. Did not provide consent for extended follow-up or who withdrew consent during follow-up (Group 4);
 - iv. Provided consent for extended follow-up study with subsequently a different number of measurements during follow-up (Group 5).
- c. Patients randomized after May 2013 (Group 6).

As a consequence of the above, the population for the two-year follow-up analysis will be somewhat smaller than the one for the three-month follow-up analysis, with a varying number of available measurements over time. All patients with an available two-year follow-up visit will be included in the main long-term follow-up analyses. These include patients from group a, group i, group iv and group c. One major concern regarding the estimation of treatment effect in this selected patient population, might be an unbalanced distribution in treatment arms at two years. A possible threat for the treatment effect estimation at two years could be bias created by patients who decided not to consent for the long-term follow-up study (group iii). One reason for not participating in the long-term follow-up study might be that these patients had worse outcomes after three months and therefore felt they were not capable of participating in the follow-up visits. They may also be dissatisfied with being allocated to standard treatment as a reason for refusal for further participation. Both motivations may lead to relatively more patients available for the long-term follow-up who received intervention and had a good outcome at three months. This may cause serious selection bias, resulting in overestimation of the treatment effect.

To assess whether indeed the patient selection resulted in an unbalanced distribution, and thus unrepresentative 2-year trial population, we will compare main prognostic variables, three-month functional outcome and treatment allocation between patients who did not consent (group iii) to patients who consented for the extended follow-up study (group iv and c) and perform additional sensitivity analyses.¹³⁻¹⁵ In addition we will compare treatment effect on functional outcome at three months in patients who did not consent for the extended follow-up to patients with available 2-year follow-up.

Subgroup populations

The effect of intervention on the main endpoint, the mRS score at two years of follow-up, will be analyzed in the same pre-defined subgroups as in the main trial, including the following:

- Age 80 or over at time of randomization versus age less than 80 at time of randomization
- NIHSS at randomization in tertiles (2-15, 16-19 and 20 or higher)
- Terminal internal carotid artery occlusion present versus no terminal internal carotid artery occlusion
- Time since stroke onset to randomization 120 minutes or less versus more than 120 minutes.
- Extracranial >50% carotid stenosis or occlusion versus no >50% carotid stenosis or occlusion
- Alberta Stroke Program Early Computed Tomography Score (ASPECTS) 0-4 / 5-7 / 8-10

Study endpoints

Primary outcome measure

The primary outcome is the clinical outcome on the mRS at two years. The mRS is an ordinal scale ranging from 0 (no disability) to 6 (death).¹¹

Secondary outcome measures

Secondary outcome measures include:

- All-cause mortality within two years of follow-up. In addition, we will assess mortality in the period between three months and two years after inclusion in patients who were alive at three months of follow-up;
- Improvement according to the classical dichotomizations of the mRS at two years including: mRS 0-1 (excellent outcome) versus 2-6; mRS 0-2 (independency) versus 3-6 and mRS 0-3 (moderate good outcome) versus 4-6;
- First new major vascular events between 3 months and 2 years of follow-up;
- The quality of life using the EuroQol EQ-5D-3L questionnaire

Definitions and assessment of major vascular events

Definition of major vascular event

Major vascular events include fatal or nonfatal cardiac events, fatal or nonfatal stroke, or fatal or non-fatal major peripheral arterial or thrombo-embolic events. Cardiac events include myocardial infarction, resuscitation after cardiac arrest, and hospitalization for

unstable angina or cardiac insufficiency. Major peripheral events include all events related to non-coronary arterial disease leading to hospitalization or revascularization (e.g., new or worsening of claudication leading to revascularization). Major thrombo-embolic events include pulmonary embolism or cerebral venous thrombosis.

Recurrent stroke was defined according to the World Health Organization criteria as “rapidly developing symptoms and/or signs of focal, and at times global, loss of cerebral function, with symptoms lasting more than 24 hours or leading to death with no apparent cause other than that of vascular origin.”¹⁶ We defined a recurrent stroke as a stroke, using the above definition, in which (1) there was clinical evidence of the sudden onset of a new focal neurological deficit with no apparent cause other than that of vascular origin (ie, the deficit could not be ascribed to an intercurrent acute illness, epileptic seizure, or toxic effect) occurring at any time after the index stroke; or (2) there was clinical evidence of the sudden onset of an exacerbation of a previous focal neurological deficit with no apparent cause other than that of vascular origin.^{17,18}

Assessment of major vascular events

Reported events were checked by contacting the treating physicians, hospitals and/or general practitioners. Events had to be confirmed by available reports of events or otherwise orally confirmed by the treating physician or general practitioner. All events were centrally reviewed by two investigators (LAB and YR), who were blinded for treatment allocation.

Statistical Analysis

General considerations

LAB, MD and YR will perform all analyses. Estimates of treatment effects will be presented with 95% confidence intervals, unless specified otherwise. A two-tailed P value of ≤ 0.05 will be considered significant for all measures. All analyses will be based on the intention-to-treat principle. Analyses of the efficacy parameters will be adjusted according to the SAP of the main trial and results of the unadjusted analysis will be provided. The analysis will be performed after the last randomized patient has reached the two-year follow-up, after all data have been validated and the database is cleaned and after approval of the SAP by the executive committee.

As of March 30th 2016, follow-up was completed. The database for the long-term clinical follow-up was frozen as of April 6th 2016. The same day the data were extracted from the Online database. The first of May 2016 the SAP was finalized and agreed by the executive committee for the unblinded analyses of the two-year results by LAB, MD and YR. Preliminary results were presented at the 2016 European Stroke Organization Conference, May 12th, 2016, Barcelona.

Analysis of demographics and baseline characteristics

The baseline characteristics of all subjects listed per treatment sequence will be outlined in a table and summarized with descriptive statistics.

Analyses of efficacy parameters

Primary Endpoint

The long-term follow-up data will be analyzed at two years using the same methods as the three-month follow-up in MR CLEAN. The primary effect parameter takes the whole range of the mRS into account and will be estimated as an odds ratio for improvement on the mRS by ordinal logistic regression (shift analysis).¹⁹

Multivariable regression analysis will be used to adjust for chance imbalances in main prognostic variables between intervention and control group in the primary effect analysis, but also in all secondary analyses and subgroup analyses.²⁰ These main prognostic variables are: age, stroke severity (NIHSS) at baseline, time to randomization, previous stroke, atrial fibrillation, diabetes mellitus and terminal internal carotid artery occlusion versus no terminal internal carotid artery occlusion.

Secondary Endpoints

All-cause mortality for both time periods (inclusion until two years, and three months until two years) will be analyzed using the log-rank test with Kaplan-Meier plots. To adjust for the pre-specified factors a Cox regression model will be applied with risk ratio expressed as Hazard Ratio.

Major vascular events between three months and two years of follow-up will be analyzed by using person-years at risk to calculate the event rate in both treatment arms. This way events reported by patients who were lost to follow-up during the extended follow-up will be taken into account. Between group difference will be expressed as relative risk reduction.

The dichotomizations of the mRS at two years including: mRS 0-1 versus 2-6; mRS 0-2 versus 3-6 will be estimated with a multiple logistic regression with the odds ratio as effect parameter.

Quality of life will be displayed graphically per treatment group and for each dimension of the EQ-5D: mobility, self-care, usual activities, pain/complaints, and mood (anxiety/depression). Furthermore a composite health utility value will be derived for each completed 5-dimensional EQ-5D questionnaire with readily available scoring algorithms, reflecting societal preferences for different health states, elicited by time trade-off techniques applied to the general population.²¹ The effect parameter will be a regression parameter beta, estimated with a multiple linear regression model.

Additional procedures and sensitivity analyses for missing data

As stated earlier, patients who did not consent for the extended follow-up may introduce important selection bias. To gain as much as (legally) possible information on the clinical status of these patients, a waiver from the Institutional Review Board was attained to assess

CHAPTER 2

vital status of these patients at two years of follow-up. This information will be used for the survival analysis as well as for the sensitivity analyses of the primary outcome.

First, we will compare patients who did not consent to patients who consented for the extended follow-up, including the following variables: main prognostic variables, treatment allocation and functional outcome at three months (dichotomized mRS 0-3 versus 4-6). To test for any statistically significant differences between groups, categorical variables will be compared by the Chi-square test and continuous variables by Student's t-test or, in case of a non-normal distribution, the Mann-Whitney U test. Finally, we will develop alternative modelling scenarios to assess the robustness of the base case results (complete case analyses) of the primary outcome. Based on clinically plausible scenarios, the analyses will consist of two different scenarios created by single imputation for the mRS at two years in patients who did not consent:

1. Last observation carried forward: patients of whom we have information on vital status at two years and who died will be scored as an mRS 6 (death) and for all other patients the mRS score will be imputed with the available three-month mRS score.
2. Worst case scenario: patients of whom we have information on vital status at two years and who died, will be scored as an mRS 6, for patients with an mRS score of 5 (=severe disability) at three months, the mRS score will be imputed with an mRS 5 and for patients with an mRS < 5 at three months, the mRS score will be imputed with mRS 5.

Finally, we will compare treatment effect on functional outcome at three months in patients who did not consent for the extended follow-up to patients with available 2-year follow-up.

Subgroup analyses

Subgroups will be analyzed with an interaction term for each subgroup by treatment allocation and reported as subgroup specific estimates with 95% confidence intervals, displayed in a forest plot.

DISCUSSION

The MR CLEAN trial aimed to evaluate the effect of endovascular treatment on functional outcome after three months in patients with acute ischemic stroke. Additionally, it assessed safety and effect on recanalization of endovascular therapy. Limited evidence is available for the long-term outcome after endovascular treatment for acute ischemic stroke. In current study we extend the follow-up duration to two years after randomization to estimate the effect of endovascular treatment on functional outcome over the longer term. Secondary objectives include the effect of endovascular treatment on major vascular events and mortality during two years. This paper allows for peer-review of the proposed methods and provides a transparent statement of the planned analyses.

Limitations and concerns

The sample size of the main trial was not powered for an extended follow-up. During longer term follow-up studies loss to follow-up is a well-known phenomenon, resulting in smaller sample sizes. Furthermore, loss to follow may cause serious attrition bias. Both these problems may play an important role in our study, mainly because of the late start of the extended follow-up study. We therefore will provide clear information on the flow of patients through the study, differences in baseline and measured variables according to provision of consent for the long-term follow-up and perform additional sensitivity analyses for different scenarios. The results of our study will provide information on the long-term clinical effectiveness of endovascular treatment for patients with acute ischemic stroke. The benefit of endovascular treatment on short-term disability might translate into longer term improvements in survival and functional status, which could influence individual treatment decisions and estimates of cost-effectiveness. Subsequently it will have important additional value concerning implementation of endovascular treatment all over the world.

ABBREVIATIONS

ASPECTS	Alberta Stroke Program Early CT Score
EQ-5D	EuroQol 5D measurement tool for health-related quality of life.
IV	Intra Venous
MR CLEAN	Multicenter Randomized Clinical trial of Endovascular treatment for Acute ischemic stroke in the Netherlands.
mRS	Modified Rankin Scale.
NIHSS	National Institutes of Health stroke scale.
rt-PA	recombinant tissue plasminogen activator
SAP	Statistical Analysis Plan

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CHAPTER 3

Two-year outcome after endovascular treatment for acute ischemic stroke

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ABSTRACT

Background

Several trials of endovascular treatment for acute ischemic stroke showed better functional outcomes compared to conventional treatment at 90 days. We assessed the outcomes of endovascular treatment at 2 years in the MR CLEAN study.

Methods

The primary outcome was comparison of modified Rankin Scale (range 0 to 6, signifying no deficit to 6, signifying death) between patients who were randomized to endovascular treatment and patients treated with conventional therapy. Secondary outcomes included all-cause mortality and quality of life measured by a health utility index based on the European Quality of Life Scale Group 5 (range -0.329 to 1, indicating the worst and best health status respectively).

Results

Of the 500 patients randomized in the original trial, 391 (78.2%) had follow-up at 2 years and information on mortality was available in 459 (91.8%). The adjusted common odds ratio was 1.68 (95 % confidence interval [CI] 1.15 to 2.45, $p=0.007$) for a shift toward better outcomes on the modified Rankin Scale in favor of endovascular treatment. The quality-of-life measure was higher in patients randomized to endovascular treatment compared to patients in the conventional treatment group (0.48 versus 0.38, mean difference 0.10 [95% CI 0.03 to 0.16,] $p=0.006$). Cumulative 2-year mortality rates in the intervention and control group were 26.0% and 31.0% respectively (adjusted hazard ratio 0.9 [95% CI: 0.6 to 1.2] $p=0.460$).

Conclusions

The beneficial effect on functional outcome of endovascular treatment in acute ischemic stroke patients was similar at 2 years as was reported at 90 days.

INTRODUCTION

We reported the outcomes at 90 days of a trial of endovascular treatment within 6 hours of acute ischemic stroke due to intracranial arterial occlusion in the anterior circulation (Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands (MR CLEAN)).¹ Most patients in the intervention group were treated with mechanical thrombectomy by retrievable stents. The trial showed better functional recovery at 90 days with the intervention compared to standard treatment. Subsequently, the beneficial effect of mechanical thrombectomy on 90-day outcome was demonstrated by several other trials, as well as in a meta-analysis of individual patient data from these trials.²⁻⁶ Information regarding long-term outcome may be useful for clinical practice and for healthcare policy. We present the results of 2-year clinical follow-up of patients randomized in MR CLEAN.

METHODS

Study design and oversight

MR CLEAN was a randomized multicenter trial with open-label treatment and blinded end-point evaluation. Endovascular treatment plus usual care (which could include intravenous administration of recombinant tissue plasminogen activator (rt-PA)) was compared to usual care alone (control group) in patients with acute ischemic stroke caused by a proximal intracranial arterial occlusion of the anterior circulation.^{1,7} The protocol was amended during the study to include follow-up assessments up to two years after randomization. An economic evaluation was part of the amended protocol and is being conducted and reported separately. Study investigators at the coordinating center performed the collection of the data of the extended follow-up study. Members of the MR CLEAN executive committee designed the extended follow-up study, analyzed the data, wrote the manuscript, and made the decision to submit the manuscript for publication. The authors vouch for the accuracy of the data and analyses reported. The first author wrote the first draft of the manuscript. The study sponsor was not involved in the study design, study conduct, protocol review, or manuscript preparation or review. The study protocol is available with the full text of the paper reporting the original trial¹ at NEJM.org.

Patients and study activities

Eligible patients had a score of 2 or higher on the National Institutes of Health Stroke Scale (NIHSS; range 0 to 42, with higher scores indicating more severe neurological deficits) and could be treated within 6 hours after stroke onset.⁸ Intracranial artery occlusion had to be established with computed tomographic (CT) angiography (CTA), magnetic resonance angiography (MRA), or digital-subtraction angiography (DSA).

Funding for the extended follow-up study became available in May 2013, when the inclusion of the MR CLEAN trial was approximately halfway to the projected number of patients to be included. Consequently, many patients had completed their 90-day follow-up and some

patients were beyond the 2-year time point. After checking the Dutch Death Certificate register, patients who were alive were re-invited to take part in the extended follow-up study. After sending the invitation letter, they were contacted by telephone to confirm their participation and to explain additional study goals and activities. For patients who declined consent for the long-term follow-up, permission of the Institutional Review Board was obtained to use information on their vital status from the Dutch Death Certificate register.

For the remaining patients who were included in MR CLEAN after May 2013, the longer follow-up duration with additional study activities was part of the consent process. All patients - or their primary caregiver if they were unable to respond - who consented for the extended follow-up, were contacted by telephone at 6 months, one year, 18 months and two years. One study investigator (RS), who was blinded to treatment allocation, assessed functional outcome by means of a modified Rankin Scale (mRS) structured questionnaire validated for assessment by telephone.⁹ Medical events between follow up contacts were recorded from this interview. Furthermore, the patient or his/her primary caregiver was invited to complete the EuroQol EQ-5D-3L questionnaire to assess quality of life.¹⁰ Consensus about final functional outcome on the mRS was reached among the outcome assessors (LAB, YR and RS), based on the mRS structured questionnaire and additional information available in the detailed reports of the telephone interviews.

Outcome measures

The primary outcome was the modified Rankin Scale at 2 years. The mRS is an ordinal scale ranging from 0 (no disability) to 6 (death).^{11,12} Secondary outcomes included dichotomized scores of the mRS at 2 years (0-1 (excellent outcome), 0-2 (good outcome, indicating functional independence) and 0-3 (favorable outcome), all-cause mortality within 2 years of follow-up; first major vascular event after the index stroke between 90 days and two years of follow-up, and quality of life at two years using the EuroQol Group 5 dimension Self-Report Questionnaire (EQ-5D-3L).¹⁰ The EQ-5D-3L consists of a descriptive system with five items: mobility, self-care, usual activities, pain/discomfort and anxiety/ depression. Each dimension has three levels: 1, no problems; 2, some problems; 3, extreme problems. Major vascular events included fatal or nonfatal cardiac events, fatal or nonfatal recurrent stroke, and fatal or nonfatal major peripheral arterial or thromboembolic events (Supplemental Appendix). All major vascular events were confirmed by clinical reports, or by the treating physician or general practitioner. Two study members (LAB and YR), who were unaware of the treatment group assignments, reviewed all events. In case of disagreement, classification was based on consensus.

Statistical analysis

Analyses were based on the modified intention-to-treat principle. The effect on the primary endpoint at two years was calculated as adjusted common odds ratio for a shift in the direction of a better outcome on the mRS, estimated with ordinal logistic regression. Furthermore, dichotomized scores of the mRS at 2 years (0-1 versus 2-6, 0-2 versus 3-6 and 0-3 versus 4-6) were analyzed with logistic regression with the odds ratio as effect parameter. All-cause

mortality was assessed with a Kaplan–Meier survival curve and a Cox proportional-hazard model, with the hazard ratio as effect parameter. For this analysis all 500 trial patients were included. Additional information on vital status at two years from the Dutch Death Certificate register was used for the outcome information and patients with a remaining missing outcome were censored at time of their dropout. For the quality of life analysis, a utility value for each observed EQ-5D-3L health status profile was calculated with an existing algorithm based on valuations elicited by time trade-off techniques applied to the general Dutch population, with scores between -0.329 and 1, indicating the worst (serious problems in all domains) and best (no problems at all) health status respectively, with death being assigned a value of zero.¹³ An unstandardized regression parameter beta was estimated with a multivariable linear regression model, indicating the difference in health utility between the treatment arms. As in the main trial, all effect parameters were adjusted for potential imbalances in the following prognostic variables: age; stroke severity (NIHSS) at baseline; time from stroke onset to randomization; previous stroke, atrial fibrillation, diabetes mellitus; and occlusion of the internal carotid-artery terminus. To assess the difference in the occurrence of long-term major vascular events between the treatment arms, a rate ratio was calculated using person-years at risk.

Treatment effect modification was explored for the same prespecified subgroups as in the main trial (Supplemental Appendix).

To explore potential (selection) bias, patients with missing 2-year outcome were compared to patients with available 2-year outcome with the use of conventional statistics with respect to the following variables: main prognostic variables, treatment allocation and 90-day functional outcome. Additionally, a regression based multiple imputation was used to account for missing functional outcome data at two years as sensitivity analysis. A more detailed description of the multiple imputation method is described in the Supplemental Appendix.

A two-tailed P value of ≤ 0.05 was considered significant for all statistical tests. As we had a single primary outcome, we did not correct for multiple testing. All analyses were performed with the use of SPSS software (version 24.0).

RESULTS

Study Population

A total of 502 patients were randomized in 16 Dutch hospitals between December 2010 and March 2014 (Table S1 in the Supplemental Appendix). Two patients could not be included in the analysis, because their representatives withdrew consent. Two hundred thirty-three patients were assigned to the intervention group (46.6%) and 267 (53.4%) to the control group. Baseline characteristics were described previously.¹ Risk factors for poor outcome and risk factors for stroke, as well as pre-treatment with intravenous rt-PA were evenly distributed between

the two groups. The mean age of the study patients was 65 years and 58.4% were men, with a median NIHSS of 18 (IQR 14 to 22). In 17 patients (7.3%) assigned to the intervention group, endovascular treatment was never initiated, whereas one patient received endovascular treatment after being assigned to the control group.¹

At the time of the inception of the extension study, 332 patients were already included in the main trial and 168 patients were prospectively followed for up to two years after randomization. Fourteen of the 332 (4.2%) included patients had already passed the two years of follow-up and 87 died before they could be re-invited for the extended follow-up period (40 in the intervention arm versus (vs.) 47 in the control arm). The other 231 patients who were included in the original trial but who were not consented for extended follow-up initially were re-invited: 61 patients declined and patients withdrew consent during follow-up (total of 69 patients who declined consent; 18 in the intervention arm vs. 51 in the control arm). Twenty-six patients were lost to follow-up. In total 391 of the 500 patients (78.2%) had a 2-year follow-up and were included in the primary analysis for functional outcome (194 in the intervention arm and 197 in the control arm) (Figure S1 in the Supplemental Appendix). Baseline characteristics were evenly distributed between the groups and comparable with the main trial population (Table 1).

Table 1. Clinical characteristics at baseline of the 391 patients included in the primary outcome analysis of the MR CLEAN extended follow-up study, by treatment allocation: intervention (endovascular treatment) or control (no endovascular treatment).

Characteristic	Intervention (N=194)	Control (N=197)
Age in years - median (IQR)	65.9 (55.8-76.2)	65.5 (56.6-76.6)
Male sex - n (%)	111 (57.2%)	118 (59.9%)
NIHSS score - median (IQR; range)	17 (14-21)	18 (14-22)
Clinical localization: Left hemisphere - n (%)	96 (49.5%)	116 (58.9%)
History of ischemic stroke - n (%)	24 (12.4%)	23 (11.7%)
Atrial fibrillation - n (%)	53 (27.3%)	44 (22.3%)
Diabetes mellitus - n (%)	29 (14.9%)	25 (12.7%)
Pre-stroke modified Rankin Scale score - n (%)		
0	155 (79.9%)	156 (79.2%)
1	19 (9.8%)	24 (12.2%)
2	10 (5.1%)	8 (4.1%)
> 2	10 (5.1%)	9 (4.6%)
Systolic blood pressure - mean mmHg (SD)	147.5 (27.0)	144.8 (23.7)
Treatment with iv rt-PA - n (%)	168 (86.6%)	182 (92.4%)
Time from onset to start of IV alteplase - minutes median (IQR)	85 (68-110)	85 (65-112)

Table 1. Clinical characteristics at baseline of the 391 patients included in the primary outcome analysis of the MR CLEAN extended follow-up study, by treatment allocation: intervention (endovascular treatment) or control (no endovascular treatment). (continued)

Characteristic	Intervention (N=194)	Control (N=197)
Extent of infarct on CT as measured by NCCT ASPECTS – median (IQR) *	9 (8-10)	9 (8-10)
Intracranial arterial occlusion		
Intracranial ICA – n (%)	1 (0.5%)	1 (0.5%)
ICA-T – n (%)	49 (25.3%)	54 (27.4%)
M1 segment – n (%)	130 (67.0%)	124 (62.9%)
M2 segment – n (%)	13 (6.7%)	16 (8.1%)
A1/2 segment – n (%)	1 (0.5%)	2 (1.0%)
Extracranial ICA occlusion#	60 (30.9%)	51 (25.9%)
Time from onset to randomization – minutes median (IQR)	205 (152-249)	190 (148-248)
Time from onset to groin puncture – minutes median (IQR)	263 (210-307)	NA

Abbreviations: IQR = interquartile range; NIHSS = National Institutes of Health Stroke Scale range 0 to 42, higher scores indication more severe neurological deficits; SD = standard deviation; IV = intravenous; NCCT= non-contrast computerized tomography; ASPECTS = Alberta Stroke Program Early CT Score, range 0 to 10, higher scores indicate less early ischemic changes; ICA = Internal Carotid Artery (intracranial segment); ICA-T = Internal Carotid Artery with involvement of the M1 segment; M1/2 = Middle cerebral artery segments; A1/A2 = Anterior cerebral artery segments. ASPECTS was not available in 4 patients: NCCT was not performed in 1 patient; 3 patients had ACA territory strokes. # Extracranial ICA occlusions as reported by local investigators.

Primary end point

Of the 391 patients with available information on the mRS at two years follow-up, the adjusted common odds ratio was 1.68 [95% confidence interval [CI] 1.15 to 2.45, p=0.007] for a shift toward better outcomes on the mRS in favor of the intervention compared to conventional treatment. The median and interquartile range of the mRS for both groups and the effect size favoring intervention are shown in Table 2.

Secondary end points

Dichotomized modified Rankin Scale scores

Patients in the intervention arm were more likely to achieve good outcome (mRS 0-2) (37.1% vs. 23.9%, adjusted odd ratio 2.2 [95% CI: 1.30 to 3.73], p=0.003) and to have a favorable outcome (mRS 0-3) (55.2% vs. 40.6%, adjusted odd ratio 2.1 [95% CI: 1.30 to 3.43], p=0.003). There was no statistically significant difference between the treatment groups concerning patients with excellent outcome (mRS 0-1) (7.2% (intervention) vs. 6.1% (control), adjusted odd ratio 1.2 [95% CI: 0.54 to 2.6], p=0.641). (Table 2 and Figure 1).

■ **Table 2.** Primary and secondary outcomes and treatment effect.

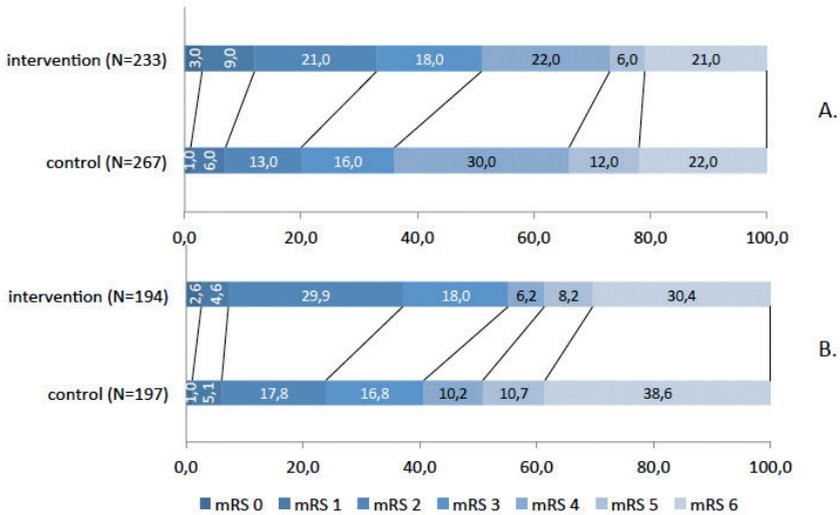
Outcome	Intervention (N=194)	Control (N=197)	Effect parameter	Unadjusted effect (95% CI)	Adjusted effect (95% CI)
Primary outcome					
mRS at 2 years – median (IQR)	3 (2-6)	4 (3-6)	cOR	1.63 (1.14-2.32)	1.68 (1.15-2.45)
Secondary outcomes					
mRS 0-1 at 2 years – n. (%) [*]	14 (7.2%)	12 (6.1%)	OR	1.2 (0.54-2.66)	1.2 (0.53-2.84)
mRS 0-2 at 2 years – n. (%) [^]	72 (37.1%)	47 (23.9%)	OR	1.9 (1.22-2.92)	2.2 (1.30-3.73)
mRS 0-3 at 2 years – n. (%) [#]	107 (55.2%)	80 (40.6%)	OR	1.8 (1.20-2.69)	2.1 (1.30-3.43)
EQ-5D at 2 years- mean (SD) [§]	0.48 (0.40)	0.38 (0.39)	Beta	0.10 (0.02-0.18)	0.10 (0.03-0.16)

The table lists numbers of patients and percentages in each treatment group, type of effect parameter (OR or linear regression coefficient), unadjusted and adjusted for age, NIHSS at baseline, time to randomization, previous stroke, atrial fibrillation, diabetes mellitus and presence of ICA terminus occlusion. Abbreviations: cOR = common Odds Ratio; OR = Odds Ratio; mRS = modified Rankin Scale; EQ-5D = EuroQol-5D.

^{*}mRS 0-1 indicates excellent outcome, [^] mRS 0-2 indicates good outcome (indicating functional independence); [#]mRS 0-3 favorable outcome.

[§]EQ-5D-3L is a standardized instrument for use as a measure of health status. The health status profile on 5 domains (mobility, self-care, daily activities, pain/complaints, and mood), each differentiating 3 levels of severity (no, some or serious problems/complaints) are converted to a score between -0.329 and 1, indicating the appreciation by the Dutch population of the worst (serious problems in all domains) and best (no problems at all) health status respectively, with death being assigned a value of zero. The EQ-5D-3L was missing in 2 patients.

■ **Figure 1.** Modified Rankin Scale at 90 days (A) and 2 years (B) by treatment allocation.

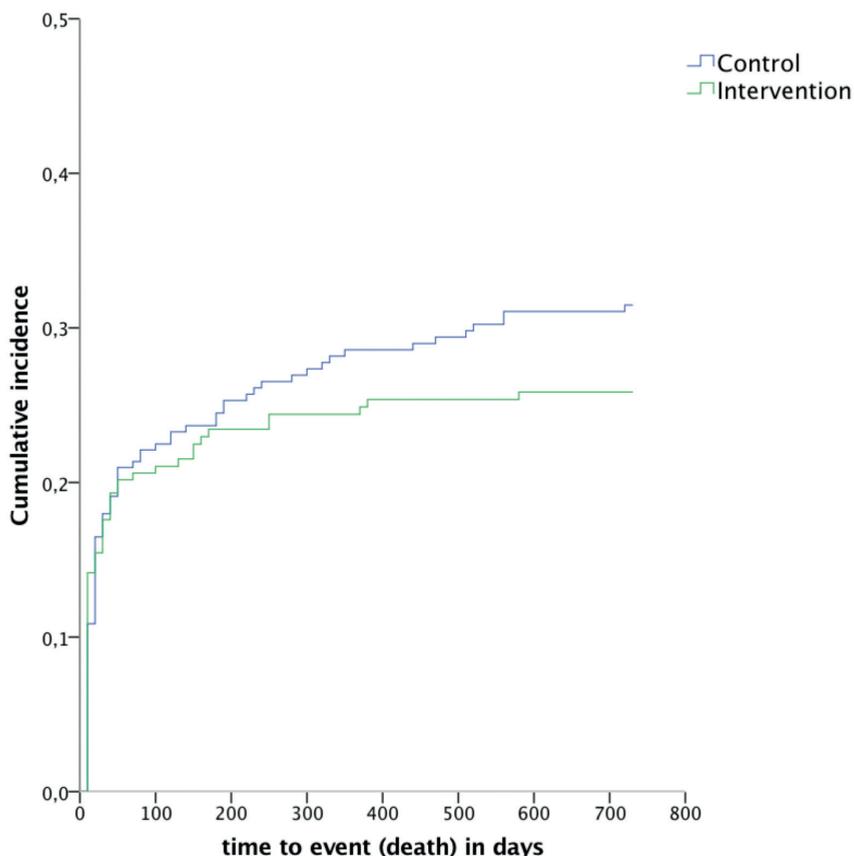


The percentages of patients are shown in each cell according to distribution of the modified Rankin Scale (range 0 to 6, with 0 indicating no symptoms, 1 no clinically significant disability, 2 slight disability (able to look after own affairs without assistance but unable to carry out all previous activities), 3 moderate disability (requires some help but able to walk unassisted), 4 moderately severe disability (unable to attend to bodily needs without assistance and unable to walk unassisted), 5 severe disability (requires constant nursing care and attention), and 6 death).

All-cause mortality

Information regarding vital status at two years was available in 459 patients of the original 500 patients (91.8%). The cumulative 2-year risk for mortality was 26.0 % and 31.0 % in the intervention and control group respectively (Figure 2, adjusted hazard ratio 0.9 [95% CI: 0.6 to 1.2], $p=0.460$).

■ **Figure 2.** Kaplan-Meier estimate of all-cause mortality rate over the two years after randomization.



Patients at risk

Intervention	233	175	159	157	155	155	153	153	153
Control	267	200	183	177	174	171	166	166	165

The x-axis shows the time in days, the y-axis shows the proportion of patients who died according to treatment allocation (intervention (green line) and control (blue line)). The adjusted hazard ratio for mortality was 0.9 (95% CI: 0.6 to 1.2, $p=0.460$) for the intervention compared to control.

Major vascular events

Eight major vascular events were recorded between 90 days and two years of follow-up (maximum follow-up per patient 1.75 years): five occurred during 239 person-years of follow-up in the intervention arm (incidence rate 0.02 per year) and three during 235 person-years of follow-up in the control arm of the study (incidence rate 0.01 per year) (rate ratio 1.64 [95%CI 0.40 to 6.78], $p=0.495$) (Table S3 in the Supplemental Appendix).

Quality of Life

Patients in the intervention arm had a higher quality of life as gauged by the EQ-5D-3L instrument at two years (mean health utility: 0.48) as compared to the control arm (mean health utility: 0.38). The treatment effect size estimated with multiple linear regression was 0.10 (95% CI 0.03 to 0.16, $p=0.006$) in favor of the intervention (Table 2). The difference in treatment effect was mainly attributable to the EQ-5D-3L dimensions of “mobility”, “self-care”, and “usual activities” (Figure S3 in the Supplemental Appendix).

Sensitivity analysis

Of the 109 patients whose outcomes were missing at two years, six patients died between 90 days and two years of follow-up and were scored mRS 6 at two years before multiple imputation. The remainder of 103 missing outcomes was imputed with multiple imputation. Patients with missing outcomes more often had atrial fibrillation at baseline (35.9% vs. 26.4%, $p=0.02$), were more often randomized to the control arm of the study (62% vs. 48.9%, $p=0.05$), had a longer median time from onset to randomization (218 minutes vs. 195 minutes, $p=0.003$) and had worse functional outcomes (mRS 4-5, indicating moderately severe or severe disability) at 90-day of follow-up (57.3% vs. 30%, $p=0.005$) as compared to patients with available 2-year follow-up (Table S2 in the Supplemental Appendix). The pooled effect on the primary outcome after multiple imputation (acOR 1.59 [95% CI: 1.08 to 2.35], $p=0.02$) was similar to the result of the available case analysis.

Subgroup analyses

There was no significant interaction (effect modification) between the pre-defined baseline variables and treatment at 2 years. The treatment effect remained consistent in all predefined subgroups (Figure S5). However, some subgroups were small resulting in wide confidence intervals.

DISCUSSION

The extended follow-up of the MR CLEAN trial indicates that endovascular treatment in patients with acute ischemic stroke results in similar functional recovery, as measured on the mRS, to the originally reported results at 90 days of an odds ratio for a shift towards better outcomes of 1.67 at 90 days compared to an odds ratio of 1.68 at 2 years. The proportion of patients who were functionally independent (mRS 0-2) at 2 years in the intervention group (37.1%) was also comparable to the 90-day results (32.6%). Although all these results are similar, there are notable differences between the 2 time points. First, during the extended follow-up period the difference in mortality increased in favor of the intervention, although not statistically significant. Second, the proportions of patients with mRS scores of 0 and 1 at 2 years were smaller than at 90 days, with no statistically significant difference between treatment arms. A possible explanation might be that stroke patients often undergo a period of (clinical) rehabilitation in the first months, during which they may not exactly realize the impact of the stroke on their daily activities. In the period thereafter, being at home with less

CHAPTER 3

care, subtle changes could be experienced that move patients from score 0 (no symptoms) to 1 (no significant disability) or even a score 1 to 2 (slight disability).

Studies of reperfusion therapy for ischemic stroke have suggested that the effects of intervention, intravenous rt-PA or endovascular treatment, do not diminish over time.¹⁴⁻¹⁸ The National Institute of Neurological Disorders and Stroke Recombinant Tissue Plasminogen Activator Stroke Study showed that patients treated with intravenous rt-PA were 30% more likely to have excellent outcome (mRS 0-1) at one year compared to the placebo-treated patients, which was similar to the 90-day results.¹⁵ Furthermore, the Interventional Management of Stroke Phase III Trial, found a greater proportion of patients with a good outcome (mRS 0-2) at one year in favor of endovascular treatment (32.5% versus 18.6%, $p=0.04$) in a subgroup of severely affected patients (NIHSS ≥ 20).^{16,17} Finally, in the Endovascular Revascularization With Solitaire Device Versus Best Medical Therapy in Anterior Circulation Stroke Within 8 Hours trial the distribution of the mRS expressed as common odds ratio was 1.80 (95%CI 1.10 to 2.99) at one year, which was comparable to the finding at 90 days (cOR 1.71 [95%CI 1.05 to 2.81]).¹⁸ Although all these studies were smaller and had shorter follow up period, their results regarding longer-term functional outcome are consistent with ours.

We observed few major vascular events during the 2-year follow-up after 90 days (1.6 % of 474 person years at risk). A possible explanation for this low rate could be that patients with large vessel occlusion, as included in MR CLEAN, may either have embolic disease (artery-to-artery or cardiogenic) or extra- or intracranial atherosclerosis and these conditions can nowadays be treated more effectively than other causes of ischemic stroke.¹⁹⁻²¹

Our study has several limitations. The trial was powered to detect an effect at 90 days and did not take into account loss to follow-up during the 2-year follow-up period. Furthermore, patients with missing outcome at two years had worse clinical characteristics, worse functional outcome at 90 days, and were more often allocated to the control arm and may thus have introduced important selection bias. However, sensitivity analysis in which missing outcomes were imputed by model based multiple imputation showed similar results compared to the available case analysis suggesting a limited effect of bias.

In conclusion, the beneficial effect of endovascular treatment in patients with acute ischemic stroke caused by a proximal intracranial occlusion of the anterior circulation was sustained during at least two years.

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SUPPLEMENT TO 'TWO-YEAR OUTCOME AFTER ENDOVASCULAR TREATMENT FOR ACUTE ISCHEMIC STROKE'

Additional methods and results

Treatment and study procedures

Patients were randomly assigned in a 1:1 ratio to receive endovascular treatment plus usual care or to usual care alone. The randomization procedure was web-based, with the use of permuted blocks, stratified for center, dichotomized score on the National Institutes of Health Stroke Scale (NIHSS; range 0 to 42, with higher scores indicating more severe neurological deficits), treatment with iv rt-PA and intended mechanical treatment.¹ Details of the intervention are published previously.² All patients underwent clinical and radiological assessment at baseline, after 24 hours, and at 5 to 7 days or at discharge if earlier. The follow-up interview for the original trial was scheduled at 90 days after randomization. One experienced trial investigator, who was blinded for treatment allocation, conducted a telephone interview with the patient, proxy or health care provider to assess functional outcome. Reports of these interviews were centrally reviewed by the outcome assessment committee, whose members were unaware of treatment-group assignment.

Classification of major vascular events

Cardiac events included myocardial infarction, resuscitation after cardiac arrest, and hospitalization for unstable angina or cardiac insufficiency. Stroke was defined according to the World Health Organization criteria as "rapidly developing symptoms and/or signs of focal, and at times global, loss of cerebral function, with symptoms lasting more than 24 hours or leading to death with no apparent cause other than that of vascular origin."³ Like other studies, we defined a recurrent stroke as a stroke, using the above definition, in which (1) there was clinical evidence of the sudden onset of a new focal neurological deficit with no apparent cause other than that of vascular origin (i.e., the deficit could not be ascribed to an inter-current acute illness, epileptic seizure, or toxic effect) occurring at any time after the index stroke; or (2) there was clinical evidence of the sudden onset of an exacerbation of a previous focal neurological deficit with no apparent cause other than that of vascular origin.⁴⁻⁶ Major peripheral events included all events related to non-coronary arterial disease leading to hospitalization or revascularization (e.g., new or worsening of claudication leading to revascularization). Major thromboembolic events included pulmonary embolism or cerebral venous thrombosis.

Subgroup analysis

Treatment effect modification was explored for the same prespecified baseline characteristics as in the main trial: NIHSS score (2 to 15, 16 to 19, or ≥ 20), age (≥ 80 years or < 80 years), occlusion of the internal carotid-artery terminus (yes or no), additional extracranial internal-carotid-

artery obstruction (yes or no), time from stroke onset to randomization (≤ 120 minutes or ≥ 120 minutes) and the Alberta Stroke Program Early CT score (ASPECTS) (0 to 4, 5 to 7 and 8 to 10, with lower scores indicating more extensive early signs of ischemic changes).⁷ Possible differences in treatment effect between subgroups were tested with interaction terms.

Missing values and sensitivity analysis

Because the current extended follow-up study started more than 2 years later than the main MR CLEAN trial, many patients already completed their participation in the main trial at start of the extended follow-up study. As a result different groups of patients emerged:

- a. Patients randomized before May 2011 (Group 1);
- b. Patients randomized between May 2011 and May 2013 who:
 - i. Had died by May 2013 (Group 2)
 - ii. Were untraceable or were living abroad in May 2013 (Group 3);
 - iii. Did not provide consent for extended follow-up or who withdrew consent during follow-up (Group 4);
 - iv. Provided consent for extended follow-up study with subsequently a different number of measurements during follow-up (Group 5).
- c. Patients randomized after May 2013 (Group 6).

As a consequence of the above, the population for the 2-year follow-up analysis is smaller than the one for the 90-day follow-up analysis, with a varying number of available measurements over time. All patients with an available 2-year follow-up visit were included in the main long-term follow-up analyses. These included patients from group 2, 5 and 6. However, the patients with missing outcomes might be different from the included patients, introducing selection bias. Patients who decided not to consent for the long-term follow-up study (group 4), may have had worse outcomes after 90 days and therefore felt they were not capable of participating in the follow-up visits. They may also be dissatisfied with being allocated to standard treatment as a reason for refusal for further participation. Both motivations may lead to relatively more patients available for the long-term follow-up who received intervention and had a good outcome at 90 days, resulting in overestimation of the treatment effect. To verify these assumptions we compared main prognostic variables, 90-day functional outcome on the modified Rankin Scale (mRS) and treatment allocation between patients with a missing 2-year outcome to patients with available outcomes at 2 years. Indeed, patients without follow-up more often had atrial fibrillation at baseline (35.9% versus 26.4%, $p=0.02$), were more often randomized to the control arm of the study (62% versus 48.9%, $p=0.05$), had a longer median time from onset to randomization (218 minutes versus 195 minutes, $p=0.003$) and had worse functional outcomes (mRS 4-5, indicating moderately severe or severe disability) at 90-day of follow-up (57.3% versus 30%, $p=0.005$) as compared to patients with available 2-year follow-up ($n=397$ (Table S3)). Thus, missing outcomes were considered missing at random, which justifies imputation using multiple regression. As a sensitivity analysis we imputed the missing outcomes with multiple imputation ($n=5$ imputation sets) using SPSS version 24.0. The NIHSS; baseline history of stroke, diabetes mellitus, atrial fibrillation; time from onset of stroke to

randomization; occlusion of the internal carotid artery terminus; treatment allocation and age were included as predictors in the imputation model. Because we assumed different effects in the predictor variables on the imputed outcome in the different 90-day mRS categories, the imputation model was fitted stratified for 90-day mRS. The pooled effect on the primary outcome after multiple imputation (acOR 1.59 [95% CI: 1.08 to 2.35], $p=0.02$) was similar to the result of the available case analysis.

Figure S1. CONSORT flow diagram: allocation and loss to follow-up in the MR CLEAN extended follow-up study. Group numbers refer to patients' groups as described in section "Missing values and sensitivity analyses".

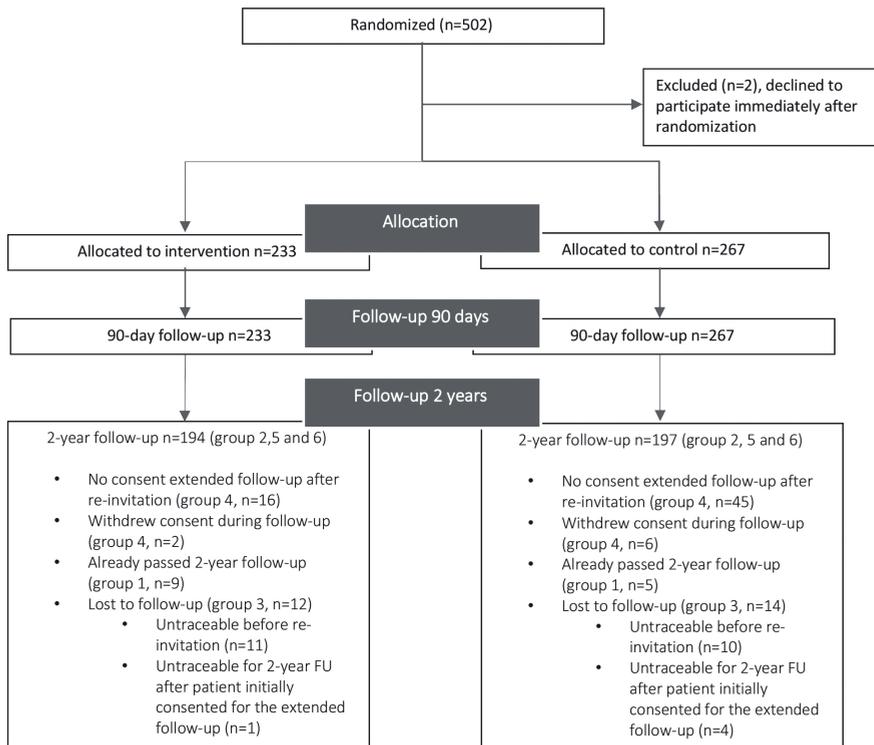
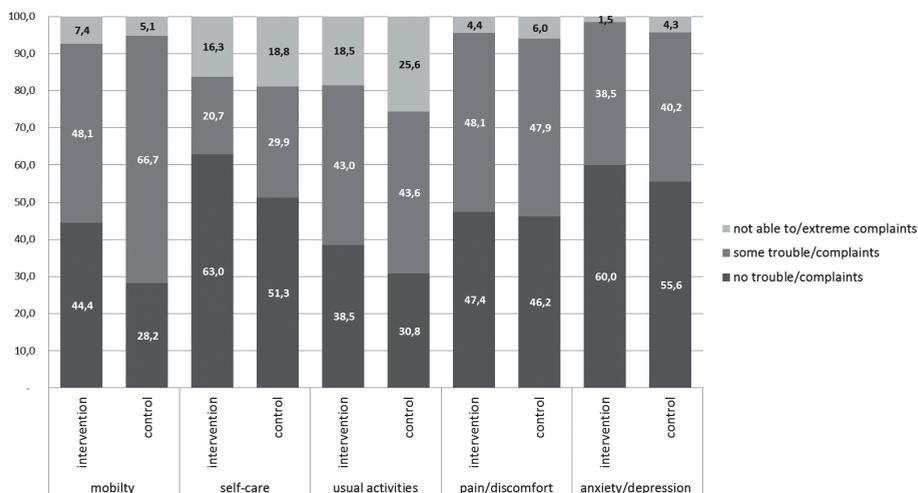
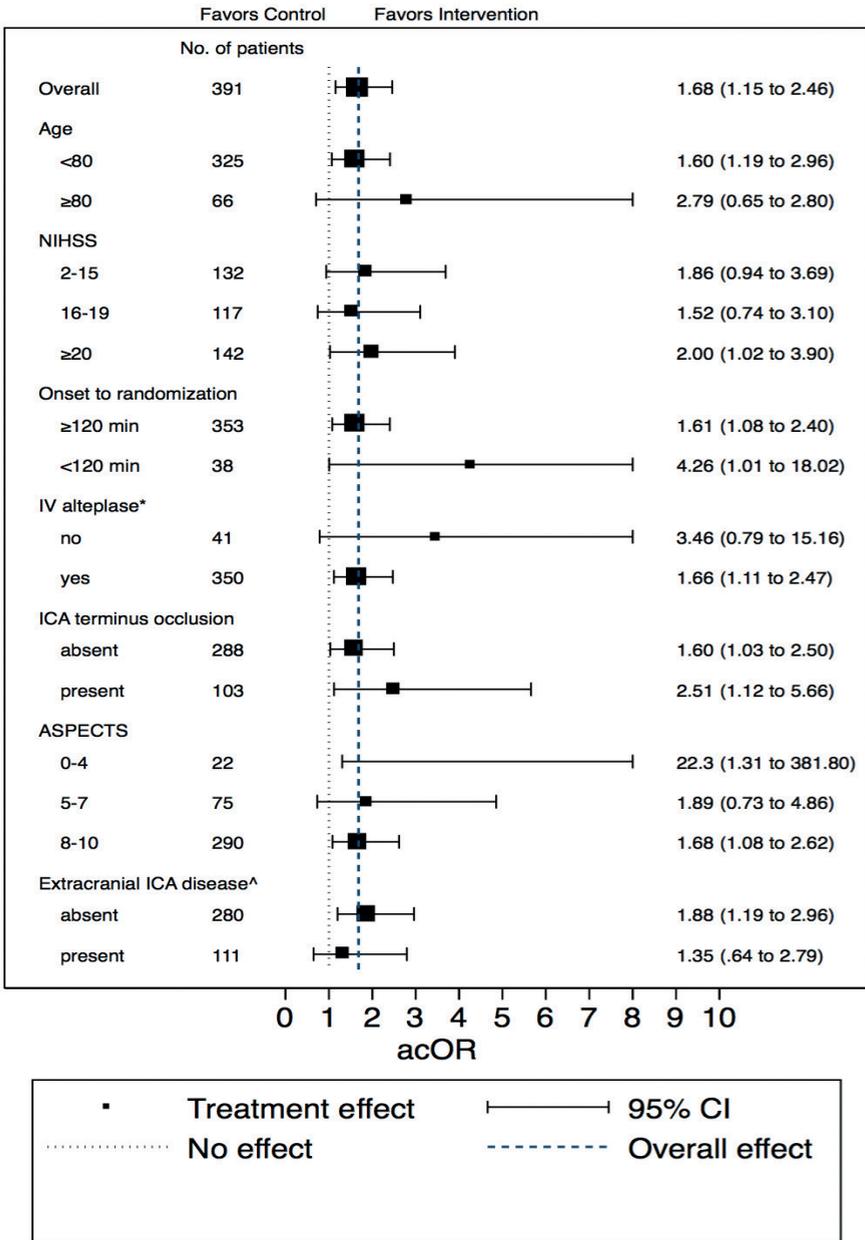


Figure S2. Distribution of scores in percentages in the EQ-5D-3L dimensions by treatment allocation at two years in patients with completed EQ-5D-3L scores (n=252).



The percentages of patients are shown in each cell according to the distribution in the different levels (not able to /extreme complaints, some trouble/complaints, no trouble / complaints) of the five EQ-5D domains (mobility, self-care, usual activities, pain/discomfort and anxiety/depression).⁸

■ Figure S3.



Adjusted effects of treatment on the overall distribution of the mRS in prespecified subgroups. Adjustments were made for age, NIHSS at baseline, time to randomization, previous stroke, atrial fibrillation, diabetes mellitus and presence of carotid T occlusion.

■ **Table S1.** Number of patients allocated and treated by center.

Center	Included	Allocated to intervention
Academic Medical Center / VU Medical Center, Amsterdam	74	34
Sint Antonius Hospital, Nieuwegein	80	40
Atrium MC, Heerlen	1	0
Maastricht University Medical Center	58	30
Erasmus University Medical Center, Rotterdam	26	15
Elisabeth Hospital, Tilburg	16	7
HAGA, the Hague	25	11
Isala Klinieken, Zwolle	10	6
Leiden University Medical Center	60	25
MC Haaglanden, the Hague	50	24
St. Radboud University Medical Center, Nijmegen	18	7
Reinier de Graaff Groep, Delft	7	3
Rijnstate Hospital, Arnhem	53	21
University Medical Center Groningen	3	1
University Medical Center Utrecht	19	9
Total	500	233

Table S2. Main prognostic variables and treatment allocation in patients with available functional outcome versus patients with missing functional outcome at two years.

Variable	Available outcome (N=397)	Missing outcome (N=103)
Age in years- median (IQR)	65.8 (56.0-76.4)	65.5 (52.1-75.8)
Male sex - n (%)	231 (58.2%)	61 (59.2%)
NIHSS - median (IQR)	17 (14-22)	18 (15-21)
Previous ischemic stroke- n (%)	47 (11.8%)	7 (6.8%)
Diabetes mellitus- n (%)	56 (14.1%)	12 (11.7%)
Atrial fibrillation- n (%)*	105 (26.4%)	37 (35.9%)
Carotid terminus occlusion on CTA - n (%)	105 (26.4%)	29 (28.2%)
Time since onset to randomization - median (IQR) (min)*	195 (150-248)	218 (171-292)
Treatment allocation: control - n (%)*	203 (48.9%)	64 (62.1%)
Severe disability at 90 days (mRS 4-5)-n (%)*	119 (30%)	59 (57.3%)

Abbreviations: CTA= Computed Tomography Angiography; IQR = interquartile range; NIHSS = National Institutes of Health Stroke Scale range 0 to 42, higher scores indication more severe neurological deficits; SD = standard deviation; * P value <0.05 after statistical testing: Chi-square test for categorical variables and Mann-Whitney-U test for continues variables.

Table S3. Absolute numbers of major vascular events between 90 days and two years after randomization according to treatment allocation.

	Intervention	Control
Any major vascular event	5	3
Ischemic stroke	2	3
Decompensated heartfailure	2	0
Revascularization surgery for PAD	1	0

Abbreviations: PAD=peripheral artery disease

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CHAPTER 4

Economic evaluation of endovascular treatment for acute ischemic stroke

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ABSTRACT

Background and Purpose

Endovascular treatment for acute ischemic stroke has been proven clinically effective, but evidence of the cost-effectiveness based on real world data is scarce. The aim of this study was to assess whether endovascular therapy plus usual care is cost-effective in comparison to usual care alone in acute ischemic stroke patients.

Methods

An economic evaluation was performed from a societal perspective with a two-year time horizon. Empirical data on health outcomes and the use of resources following endovascular treatment were gathered parallel to the MR CLEAN trial and its two-year follow-up study. Incremental cost-effectiveness ratios were calculated as the extra costs per additional patient with functional independence (modified Rankin Scale score 0-2) and the extra cost per quality adjusted life year (QALY) gained.

Results

The mean costs per patient in the intervention group were \$126,494 vs. \$143,331 in the control group (mean difference \$16,839, 95% confidence interval [CI]: \$38,113 to \$5456). Compared to patients in the control group, more patients in the intervention group achieved functional independence, 37.2% vs. 23.9%, (absolute difference 13.3 %, 95% CI: 4.0% to 22.0%) and they generated more QALYs, 0.99 vs. 0.83 (mean difference of 0.16 (95% CI: 0.04 to 0.29). Endovascular treatment dominated standard treatment with \$18,233 saved per extra patient with a good outcome and \$105,869 saved per additional QALY.

Conclusions

Endovascular treatment added to usual care is clinically effective, and cost saving in comparison to usual care alone in patients with acute ischemic stroke.

Abbreviations and Acronyms

ICER- Incremental cost-effectiveness ratios

ICU- intensive care unit

IVT- intravenous thrombolysis

MR CLEAN - Multicenter Randomized CLinical trial of Endovascular treatment for Acute ischemic stroke in the Netherlands

mRS- modified Rankin Scale score

QALY-quality adjusted life year

THRACE- The Thrombectomy des Artères Cérébrales trial

INTRODUCTION

Stroke is the third major cause of death and the most important cause of disability worldwide.¹ The disease poses a heavy burden for both the affected patient as well as society. In the Netherlands, annual health care costs in 2011 for patients with a stroke were approximately 1.84 billion euros.² In comparison, in the United Kingdom the treatment and productivity loss arising from stroke results in total societal costs of 8.9 billion pounds a year, whereas in the United States of America the estimated direct and indirect costs related to stroke patients in 2010 were 73.7 billion US dollars.^{3,4}

Treatment of acute ischemic stroke is aiming at early vessel recanalization to restore blood-flow. Early vessel recanalization strongly correlates with improved clinical outcome and reduced mortality.^{5,6} Endovascular treatment has been proven more effective to achieve early vessel recanalization, which resulted in better short and long-term clinical outcomes compared to standard treatment strategies, including intravenous thrombolysis (IVT) with recombinant tissue plasminogen activator.^{7,8} Hence, endovascular treatment is now regarded standard care for stroke patient and has been adopted in international guidelines. Despite its convincing clinical efficacy, large-scale implementation is often hampered by the relatively high costs involved with this treatment. Regulatory offices and health care insurance organizations in several countries demand cost-effectiveness studies to be done and to show a beneficial effect within certain cost limits before reimbursement is granted. Although endovascular treatment is an expensive treatment modality, it may well be cost-effective in comparison to the standard treatment by improving longer-term survival and quality of life, and by reducing demands for rehabilitation and nursing home stay after hospital discharge.⁹⁻¹² To date, evidence of the cost-effectiveness of endovascular treatment for acute ischemic stroke based on real world data is scarce.¹³⁻¹⁶ The aim of the current study is to assess whether endovascular therapy plus usual care is cost-effective in comparison to usual care alone in patients with acute ischemic stroke.

METHODS

Study design and patient population

This economic evaluation was conducted parallel to the Multicenter Randomized Clinical trial of Endovascular treatment for Acute ischemic stroke in the Netherlands (MR CLEAN) and the two- year follow-up study of the original trial. The study design, methods and results of MR CLEAN and its two-year follow-up study have been published previously.^{8,17-19}

The study is reported according to the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) guideline.²⁰ A completed checklist is presented as Supplemental Material. The clinical and economic data of this study are available from the corresponding author upon reasonable request.

CHAPTER 4

In brief, MR CLEAN was a randomized, multicenter trial comparing endovascular treatment plus usual care (intervention group) to usual care alone (control group) in patients with acute ischemic stroke caused by a proximal intracranial arterial occlusion of the anterior circulation. Usual care included best medical management according to national and international guidelines, including IVT. Trial treatment was open-label, and the evaluation of outcomes was blinded. Endovascular treatment consisted of intra-arterial catheterization with a microcatheter to the level of occlusion and delivery of a thrombolytic agent, mechanical thrombectomy, or both.

In total, 500 patients from 16 medical centers in the Netherlands were randomly assigned between December 2010 and April 2014, of which 233 to intervention plus usual care and 267 patients to usual care alone. The mean age was 65 years (range 23-96 years), and 445 patients (89.0%) were treated with IVT before randomization. Actual endovascular treatment was performed in 196 of the 233 patients in the intervention group, and 190 (81.5%) of these were treated with retrievable stents.¹⁸ At two-year follow-up, primary outcome (modified Rankin Scale score (mRS)) was available in 391 of the 500 patients.⁸

Perspective and time horizon

Endovascular treatment of acute ischemic stroke was evaluated economically from a societal perspective, including the costs of health care as well as non-reimbursed out-of-pocket expenses by patients. The time horizon was two years, in accordance with the length of the long-term clinical follow-up.

Measurements and valuation of costs and effects

Four information sources were used to gather data on health care resources: case report forms, medical files, hospital information systems, and the Erasmus University / institute of Medical Technology Assessment Medical Consumption Questionnaire - adapted to the study setting - during follow-up at three months, six months, one year, 18 months and two years following randomization. Unit costing of health care resources was done in adherence to the most recent Dutch manual for costing in health care research by the Erasmus institute of Medical Technology Assessment in collaboration with the National Health Care Institute.²¹

The original study was conducted in euros with the base year 2014. If unit costs originated from another year, we applied general consumer price indexing (Table I in the Supplemental Data). For conversion to US dollars, we used the average exchange rate EUR/USD of January first, 2014 (1.3764). Unit costs of endovascular treatment were determined by detailed calculation of personnel, materials and overhead. See the Supplemental Data for a detailed description of the gathered resources, unit costing and calculation of costs during the follow-up period.

Health effects were assessed with the use of the mRS score for the patient's functional outcome and EuroQol EQ-5D-3L questionnaire for the patient's quality of life at three months, six months, one year, 18 months and two years. The mRS score is an ordinal scale, ranging from 0 (no disability) to 6 (death). Scores of 0 to 2 represent functional independence (good

outcome) and scores 3-6 represent functional dependence or death (poor outcome).^{22,23} The EQ-5D-3L is a descriptive system existing of five domains: mobility, self-care, usual activities, and pain/discomfort and anxiety/ depression. Each dimension has three levels: 1, no problems; 2, some problems; 3, extreme problems. We transposed each EQ-5D-3L health status profile during follow-up into a health utility score by applying an existing scoring algorithm for the Netherlands, based on preferences from the general public, that were elicited with the time trade-off valuation technique.²⁴ Health utilities scores range from -0.329 for worst conditions to 1.0 for the best health status, with the health utility of death set to zero. The mRS score was assessed by telephone by two experienced study investigators; one assessed the three-month mRS score, and one assessed the mRS score during the rest of the follow-up. In addition, the patient or his/her primary caregiver was invited to complete the EuroQol EQ-5D-3L questionnaire.

Quality-adjusted life years (QALY) were calculated by taking the sumproduct of the derived health utilities and the lengths of the preceding periods between measurements or measurement and baseline.

To account for time preference, discounting was done for the second year of follow-up, at a rate of 4% for costs, and a rate of 1.5% for QALYs, both in agreement with the abovementioned Dutch manual for costing in health care research.²⁵

Primary outcomes were the difference in costs between the treatment arms per patient reaching functional independence (mRS 0-2) and per QALY.

Standard Protocol Approvals, Registrations, and Patient Consents

All patients or their legal representatives provided written informed consent before randomization in the trial. A central medical ethics committee and the research board of each participating center approved the study protocol. The study sponsors were not involved in the study design, study conduct, protocol review, or manuscript preparation or review. The MR CLEAN is registered under number 1804 in the Dutch trial register and under ISRCTN10888758 in the ISRCTN register.

Statistical analyses

Differences between the intervention and control groups concerning the use of resources, costs and QALYs were calculated along with their 95% (bias-corrected and accelerated) confidence intervals (detailed description of the calculated confidence intervals is provided in the Supplemental Data). Incremental cost-effectiveness ratios (ICERs) were calculated as the extra costs per additional patient with good functional outcome (mRS 0-2) and the extra cost per QALY gained. Results for the ICER of the extra costs per QALY gained are graphically displayed by planes with cost differences on the Y-axis and QALY differences on the X-axis (Cost/Effectiveness-plane) after non-parametric bootstrapping by drawing 1,000 samples of the same size as the original samples with replacement.

All analyses were performed with the use of SPSS software (version 24.0).

Missing data

We handled missing patient data during the two years of follow-up by making use of last observation carried forward and backward, and model based multiple imputation. A detailed description of the methods and analyses of missing data can be found in the Supplemental Data. The ICER of the extra costs per additional patient with a good functional outcome (mRS 0-2) was calculated only for patients who completed the follow-up at two years (n=391) without multiple imputation for missing data; under this restriction the cost effectiveness analysis closely mimics the clinical analysis of the dichotomized primary outcome.⁸

Sensitivity analyses

Both undiscounted and discounted results are reported. Furthermore, two alternatives for the multiple imputation approach of missing data were explored, applied to regular inpatient hospital days and Intensive Care Unit-days analyses. First, missing data were ignored by only using the available data. Second, a Kaplan-Meier survival analysis approach to the cost domain rather than the time domain was done with censoring of patients known to have missing data. Results of the different approaches can be found in Table IV of the Supplemental Data.

RESULTS

Used resources and costs

Table 1 shows the mean difference between the intervention and control group regarding the use of resources during the two years of follow-up. The numbers of inpatient days and day care treatments in a rehabilitation center and the number of consultations of a physiotherapist were lower in the intervention group.

Table 2 shows the mean difference between the intervention and control group in health care costs and out-of-pocket expenses during the two years of follow-up. The undiscounted mean costs of the intervention (mean difference \$12,612 (95 % CI: \$12,199 to \$13,074) and other diagnostic and therapeutic procedures (\$314 (95% CI: \$15 to \$614) were higher in the intervention group. However, the lower use of resources for inpatient (- \$10,958 (95% CI: \$19,753 to \$2164)) and day care treatment (- \$4802 (95% CI: \$8024 to \$1580) in a rehabilitation center and for consultations of the physiotherapist (- \$818 (95% CI \$1455 to \$180) resulted in undiscounted mean costs savings in favor of the intervention group.

From a societal perspective, endovascular treatment generated mean costs of \$126,494 (95% CI: \$113,962 to \$140,320) versus \$143,331 (95% CI: \$130,509 to \$155,558) in the control group, with a mean difference of \$16,839 (95% CI: \$38,113 to \$5456, P=0.073) per patient.

In the group of 391 patients who completed the two years of follow-up, the undiscounted mean societal costs per patient were \$102,198 (95% CI: \$90,563 to \$114,994) in the intervention group and \$104,616 (95% CI: \$91,474 to \$117,904) in the control group, with a mean difference of \$2417 (95% CI: \$21,956 to \$18,408 P=0.812) per patient.

Results of the discounted costs are presented in the Supplemental Data and were similar to the undiscounted costs (Table III).

Table 1. Mean difference between treatment groups in resource use during two years of follow-up, including lower and upper limits of the 95% confidence interval.

	Intervention (n=233)	Control (n=267)	Mean difference	Lower 95%	Upper 95%
Acute interventions					
Endovascular procedure (total,%)*	216 (92.7%)	1 (0.4%)			
IVT (total,%)	203 (87.1%)	242 (90.6%)			
Hospital admission (days)					
Regular admission	15.30	16.65	-1.39	-3.64	0.87
ICU admission	1.03	1.60	-0.56	-1.25	0.12
Institutional care (days)					
Rehabilitation center	61.04	78.35	-17.31	-31.20	-3.42
Day care rehabilitation center	13.78	25.18	-11.40	-19.05	-3.75
Nursing home	100.53	124.24	-23.70	-56.84	9.44
Home care (hours)					
Help	90.65	128.27	-37.62	-79.02	3.78
Care	151.14	173.28	-22.14	-83.38	39.09
Nursing	76.33	95.26	-18.93	-55.06	17.20
Consultations (visits)					
General practitioner	7.78	6.61	1.18	-0.55	2.91
Neurologist	2.60	2.72	-0.12	-0.94	0.70
Physiotherapist	48.78	66.78	-18.00	-32.02	-3.97
Ergo therapist	15.83	20.25	-4.42	-11.69	2.86
Speech therapist	19.19	27.92	-8.73	-18.15	0.69

Abbreviations: IVT is intravenous thrombolysis; ICU is intensive care unit; OTC is over the counter medication. *In the intervention arm 17 patients eventually did not receive endovascular treatment. These patients were not charged with procedural costs of the endovascular treatment. Furthermore in 3 patients in the intervention arm, endovascular therapy was initiated, however the procedure was terminated before actual thrombectomy could have taken place. In the control arm one patient crossed over to the intervention arm and received endovascular treatment. These patients were charged with procedural costs of endovascular treatment.

Table 2. Mean difference between treatment groups in undiscounted costs during two years of follow-up, including lower and upper limits of the 95% confidence intervals (in US dollars)

	Intervention (n=233)	Control (n=267)	Mean difference	Lower 95%	Upper 95%
Acute interventions					
Endovascular procedure	12663	51	12612	12199	13074
IVT #	1140	1186	-45	-26	118
Hospital admission					
Regular admission	10004	10912	-895	-2385	568
ICU admission	1683	2604	-921	-2045	204
Other procedures (diagnostic and interventions)	2241	1924	314	15	614
Institutional care					
Rehabilitation center	38649	49607	-10958	-19753	-2164
Day care rehabilitation center [^]	5804	10607	-4802	-8024	-1580
Nursing home	23246	28727	-5481	-13145	2182
Home care					
Help	2495	3530	-1035	-2175	105
Care	10401	11925	-1524	-5738	2691
Nursing	7669	9571	-1902	-5532	1729
Consultations					
General practitioner	445	377	67	-32	167
Neurologist	354	370	-17	-128	95
Physiotherapist	2216	3034	-818	-1455	-180
Ergo therapist	720	919	-201	-531	129
Speech therapist	793	1153	-361	-750	29
Out-of-pocket expenses					
Transport	1997	2138	-140	-779	497
Informal care/private help	1862	1664	198	-483	880
OTC	1331	1226	105	-390	599

Abbreviations: OTC is over-the-counter medication.

#The costs of IVT with alteplase are based on the costs of alteplase per 50 mg; Alteplase comes in flacons of 50 mg. As most patients need more than 50 mg with a maximum of 90 mg, each patient receiving intravenous alteplase was assigned as receiving 2 flacons, for a total of \$1309.

[^]According to the Dutch cost manual for health care research-2015 one hour of treatment in a rehabilitation center in day-care setting costs \$ 211, based on paragraph 4.16 of the cost manual we assume 1 visit lasts 2 hours (mean) for adults.

Health effects

During the two-years of follow-up, patients in the intervention group generated 0.99 (95% CI: 0.89 to 1.09) QALYs against 0.83 (95% CI: 0.75 to 0.91) in the control group, with a mean difference of 0.16 QALYs (95% CI: 0.04 to 0.29, P=0.01).

In the group of 391 patients with available mRS scores at two years, there was an absolute difference of 13.3 % (95% CI 4.0 to 22.0) in the proportion of patients who were functionally independent (mRS score 0-2) in favour of the intervention; patients in the intervention group generated on average 0.92 QALYs (95% CI: 0.82 to 1.04) during the two years of follow-up, patients in the control group 0.73 QALYs (95% CI: 0.62 to 0.82), with a mean difference of 0.2 QALYs (95% CI: 0.06 to 0.36, P=0.01) in favor of the intervention group, which well coincided with the difference in good outcome.

Results of the discounted QALYs are presented in the Supplemental Data and were similar to the undiscounted results.

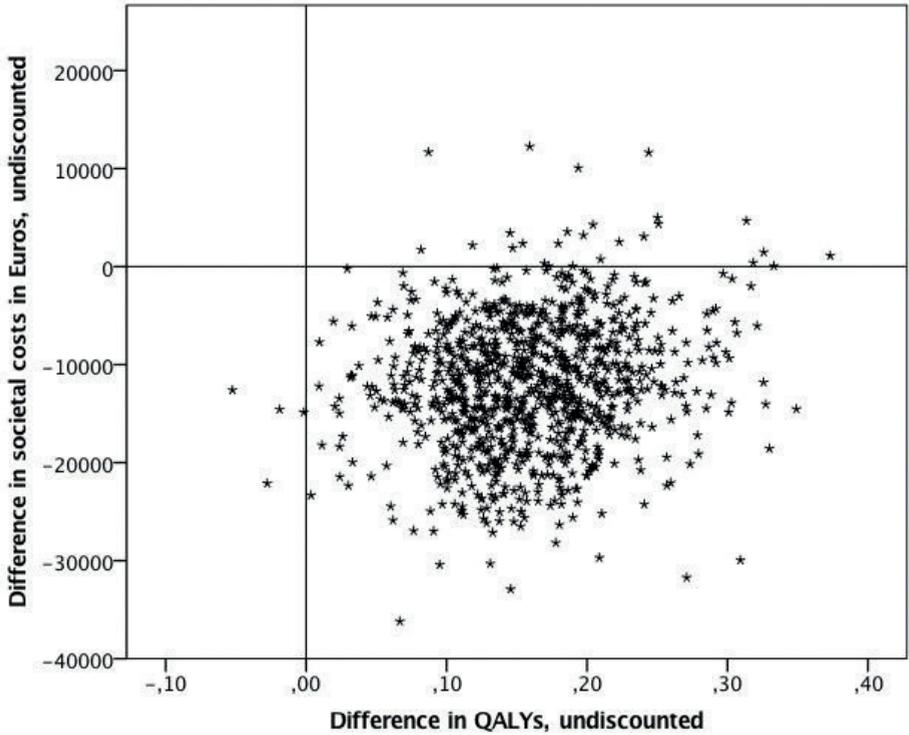
Extra costs per patient with good functional outcome

In the group of 391 patients, one extra patient recovered from the index stroke and became functionally independent for every seven to eight patients treated with endovascular treatment. The associated point-estimate for the incremental societal costs per patient with a good outcome was \$18,233, favoring the intervention.

Extra costs per additional QALY

The incremental costs per QALY gained were \$105,869, suggesting dominance - lower costs and better health outcomes - of the intervention over the control treatment. Figure 1 shows the Cost/Effectiveness-plane for the undiscounted mean differences between the intervention and control groups in societal costs and QALYs after 1,000 bootstrap replications. Most replications, 97%, generated cost savings and QALY gains (the lower right quadrant), indicating that endovascular treatment has a probability of being cost-effective of at least 0.97.

■ Figure 1.



Undiscounted mean differences between intervention and control groups in societal costs (Y-axis) by QALYs (X-axis) after 1,000 bootstrap replications, costs are expressed in 2014 euro's (equivalent of - 55,056 USD to 27,528 USD on the Y-axis).

DISCUSSION

This economic evaluation shows that endovascular treatment is cost-effective after two years in comparison to the current standard treatment in patients with acute ischemic stroke of the anterior circulation. Functional health improvements on the modified Rankin Scale following endovascular treatment positively affect patients' quality of life. The initial investment of a rather expensive add-on treatment of almost \$14,000 rapidly pays off in reduced costs of rehabilitation (both inpatient stays as well as day care treatment), reduced costs of physiotherapy and, to a lesser extent, reduced costs of nursing home stay. In the total study population, we observed that the number of QALYs per patient in the first two years following stroke added up to about one single QALY on average; moreover, most patients in the group with complete follow-up were functionally dependent or died at the end of the two years (69.6% (272/391)). This signifies stroke as a disease with a heavy burden and the societal willingness to pay per QALY should be at the higher end of around \$30,000 to \$100,000

range of the European political benchmark. If so, the probability of endovascular treatment for stroke being cost-effective is almost one, with a net monetary benefit (as \$100,000 times the QALY difference and minus the cost difference) of \$32,466 (95% CI: \$12,114 to \$52,399; undiscounted).

Strengths and weaknesses

The current study is not directly comparable to any of the previous studies on this topic for several reasons. Most previously published studies were model-based for the longer-term follow-up, with the use of Markov modeling.^{26–28} Input data in these studies were retrieved from different sources including available data from the literature, or even expert opinion. Due to the different input data and methodology of the model-based studies, and subsequently the major uncertainty in the models and outcomes, it seems valid to compare our results to economic studies using empirical data alongside a randomized clinical trial.¹³

The “Thrombectomie des Artères Cérébrales” (THRACE) study group conducted such an economic evaluation alongside their THRACE trial. THRACE compared clinical outcomes at three months for patients with moderate to severe strokes who received either IVT alone or IVT and endovascular treatment, within four and five hours respectively.¹³ In total 414 patients were included. Individual-level cost and health-utility data were collected from the perspective of the National Health Insurance system in France, which included only costs associated with the initial hospital stay. Their primary health related outcomes were rate of functional independence at three months, and the EQ5D at one year. The ICER, corresponding to the cost of one additional averted disability case, was estimated at \$19,379 (90% CI: \$10,576–\$79,822), whereas the ICER per one QALY gained was \$14 881 (90% CI, \$8595–\$47,007).¹³

There are several important differences comparing the THRACE trial to our study, all related to the clinical trial design as well as to the economic evaluation itself. THRACE compared the combination of endovascular treatment and IVT to IVT alone, THRACE included only a selected population based on stroke severity and THRACE had a limited duration of follow-up. In MR CLEAN in- and exclusion criteria were broad, reflecting every day clinical practice, and follow-up was available over a longer, two-year period. The THRACE economic sub-study included the initial procedural and hospitalization stay costs only. Thereby the high costs associated with rehabilitation and nursing home stay were not taking into account. As seen in our study, costs saved in these areas play an important part in the difference in costs between the treatment strategies, and subsequently in endovascular treatment showing near-dominance over control. Therefore, results from THRACE will mainly inform negotiations between insurer and health care provider, whereas the societal perspective in our study has wider implications related to priority setting across health care settings.

Our economic evaluation has several limitations and particularities. First, the delayed start of the present study compared to the original trial starting date posed a methodological challenge with regard to the handling of missing data. We have chosen to use a multiple imputation

approach as our main analysis. It resulted in intermediate estimates and differences, which presented the best, unbiased estimate available (See the illustration with the costs of inpatient hospital stay at the regular ward and ICU in the Supplemental Data, Table IV).

Second, we did not include costs associated with productivity loss by absenteeism from work or impaired productivity while at work in our study, also known as indirect costs, although usually included in economic evaluations from a societal perspective. In our study design we did plan to perform a subgroup analysis of patients who would be an active member on the workforce. Because of its potential redundancy, the costs of productivity loss have not yet been addressed. Due to the delayed start of the long-term extension study with its multiple missing data together with an a priori limited size of this subgroup sincerely limits the information value of such an exercise. The convincing evidence of endovascular therapy as an efficient treatment modality emerging from the present economic evaluation, suggests that extending the current scope to the employer perspective would only further underpin the necessity of implementing this therapy as soon as possible.

Conclusions and policy implications

In many Western countries stroke patients depend on and have access to institutional care by the hospital, rehabilitation center and nursing home, and to non-institutional care by physiotherapists and speech therapists. Therefore, the near dominance economically of the endovascular treatment over standard treatment with a high probability of cost savings per additional patient whose health has been improved, as demonstrated in our study, is highly relevant to other countries in the Western hemisphere that have at least a (roughly) comparable organization and financing of institutional and non-institutional health care.

In conclusion, our study demonstrates that endovascular treatment in patients with acute ischemic stroke caused by a proximal intracranial occlusion of the anterior circulation is cost-effective over two years from a societal perspective. Its proven clinical effectiveness and the cost savings in rehabilitation that fully compensate for the higher intervention costs in the hospital should simplify decision making on reimbursement and implementation of endovascular treatment for ischemic stroke worldwide.

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CHAPTER 4

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SUPPLEMENTAL APPENDIX

Additional methods

Gathered data on resource use, unit costing and calculation of costs

Whether a patient actually did or did not receive endovascular treatment and/or intravenous thrombolysis (IVT) was gathered from the case report forms and medical files. Inpatient hospital stay at the regular wards or intensive care units, as well as stays in a nursing home or rehabilitation center in the first three months were retrieved from medical files and case report forms. Transfer from primary stroke centers to intervention centers and screening prior to randomization of patients was not included. For the remainder of the follow-up data on inpatient stays and on (day care) rehabilitation treatment were gathered with the patient questionnaires.

Data on outpatient hospital consultations of the neurologist or out-of-hospital consultations of general practitioners, physiotherapists, speech therapists, or ergo therapists were gathered with the patient questionnaires.

The frequencies of diagnostic procedures and of therapeutic procedures other than the index intervention in the intervention group were extracted from hospital information systems of four hospitals that contributed the second to fifth highest numbers of inclusions to the study population. Except for eight patients with their follow-up period extending beyond the introduction date (October 25th, 2015) of a major information system change in one of these hospitals, complete index hospital data during two years of follow-up at maximum could be retrieved for the remaining 231 patients (46.2%; $N_{\text{intervention}}=105$ (45.1% of all 233 patients in the intervention group) $N_{\text{control}}=126$ (47.2% of all 267 patients in the control group)). Therapeutic procedures that were part of the index intervention in the intervention group were excluded during the analyses to prevent double counting.

Formal home care data were collected with the patient questionnaires, as were the data on out-of-pocket expenses.

For diagnostic and therapeutic procedures published tariffs of the four hospitals were used, which were in effect during the calendar period June 2014 until December 2014. In case of diagnostic and therapeutic procedures in the index hospitals a sentinel approach was applied: only procedures representing at least 0.1% of the total number of procedures were assigned a unit cost. The sentinel approach incorporated 89% of all procedures.

The unit costs of endovascular treatment were based on the use of personnel, material and overheads. The unit costs covered (a) the computed tomography (CT) angiography, (b) the time investment of the (neuro) interventionist, two radiology assistants, one anesthesiologist,

and two anesthesia assistants, (c) thrombectomy materials (e.g. (micro)guide wire, (balloon) guiding catheter, stent retriever, aspiration systems) (d) the basic angiography materials including contrast, syringes, vascular closure device, and heparin, (e) the depreciation of apparatus, (f) the maintenance of intervention room, and (g) the overhead costs (Table II in the Supplemental Appendix).

Costs were calculated as the sumproduct of the volume of used resources and their respective unit costs. Out-of-pocket expenses were calculated as reported by the patients. If patient questionnaires were the source of the counts of resources used, volumes were estimated by multiplying the reported number with the ratio of the length of time in-between measurements (three or six months) to the length of the recall period (one week, one month or three months).

Statistical analysis

Dealing with missing data

The presence of missing data of patients during follow-up was dealt with as follows.

Initially, a patient's use of resources or health utility was derived from available measurements during follow-up by carrying the last observation forward in case of unavailable measurements towards the end of follow-up, followed by carrying the first observation backward in case of unavailable measurements in-between the available ones. Because the first three months after randomization in this patient population may be quite different from the subsequent period of follow-up, available measurements at three months were never used in the last observation carried forward approach; in addition, available measurements at six months after randomization were only used in the first observation carried backward approach if considered plausible by at least two research team members without a contrasting opinion by a third (MD, YR and LvdB). Subsequently, we accounted for patients who died during follow-up, as the previous step may result in unrealistic posthumous values. Use of resources was (re) set to zero volume starting at the originally planned second measurement after a patient's death. Hence, if a patient died in the fourth month, his planned measurement of resource volume at six months was not set to zero, but the planned measurements at one year, 18 months and two years were, thereby accounting for resources used prior to a patient's death just after his last measurement at three months. A patient's health utility was (re) assigned zero values starting at the originally planned first measurement following death. Patients, who died before the two-year follow-up, were counted as patients with a 'poor outcome' on the dichotomized modified Rankin Scale score (mRS) (0-2: good outcome, 3-6: poor outcome).

Finally, the remaining missing measurements for alive or deceased patients without any measurement after the measurement at three months for the remainder of their life or the end-of-study, whichever came first, were considered missing (completely) at random and dealt with by multiple imputations (n=5). The multiple imputations were based on the variable set used in the main article of the Multicenter Randomized Clinical trial of Endovascular treatment

for Acute ischemic stroke in the Netherlands trial (MR CLEAN) trial that reported the short-term clinical outcomes: the National Institute of Health Stroke Scale score; baseline history of stroke, diabetes mellitus, or atrial fibrillation; time from onset of stroke to randomization; occlusion of the internal carotid artery terminus. In addition, gender and treatment allocation were included as predictors. Each dependent parameter (use of resources, health utility) was included as predictor and parameter to be imputed. The prediction of outcome data was constrained to the minimal and maximal values among the available observations of the dependent parameter during follow-up.

Multiple imputations of used resources were mostly performed for volume data. In case of missing out-of-pocket expenses or diagnostic and therapeutic procedures, costs were directly imputed. In case of the diagnostic and therapeutic procedures, we multiply imputed the yearly costs (in order to be able to account for discounting) and we included the number (or pooled estimate from multiple imputation) of regular hospital inpatient days as additional predictor.

Confidence intervals

For distinct volumes and costs of used resources 95% confidence intervals (CI) were calculated after averaging data per patient from the five multiple imputation sets. However, for significance testing of the differences between groups at the aggregated level of societal and health care costs as well as for significance testing of differences in QALYs we calculated 96% bias-corrected and accelerated (BCa) CIs (after stratification for treatment allocation and time to randomization subgroups). These “wider” 96% BCa CIs were calculated for programming convenience to represent the 95% CI as reported in order to compensate for the use of mean estimates from the multiply imputed datasets without directly accounting for the variance between those datasets. The resulting 95% CIs at the aggregate level slightly overcompensate, meaning that significant differences are somewhat less likely to emerge.

Additional results

Discounted difference in costs

The discounted cost savings for inpatient and day care treatment in a rehabilitation center and for consultations of the physiotherapist were 10816 USD, 4724 USD and 801 USD in favor of the intervention (Table III in the Supplemental Appendix).

The discounted mean societal costs were 123,294 USD (95% CI: 112,980 USD to 138,879 USD) in the intervention group and 141,666 USD (95% CI: 129,022 USD to 153,671 USD) in the control group, mean difference of - 16,374 USD (95% CI: - 37,307 USD to 5,629 USD, P=0.074).

In the group of 391 patients who completed the two years of follow-up, discounted mean costs were 101,430 USD (95% CI: 89,986 USD to 114,095 USD) in the intervention group and 103,624

USD (95% BI: 90,765 USD to 116,767 USD) in the control group, mean difference of – 2,193 USD, (95% BI: - 21,481 USD to 18,331 USD, P=0.833) .

Discounted difference in health effects

The discounted mean number of QALYs in the intervention group was 0.985 (95% CI: 0.886 to 1.081) and in the control group 0.828 (95% CI: 0.744 to 0.902) during the two years of follow-up, with the mean difference of 0.157 (95% CI: 0.043 to 0.284, P=0.011) being significantly in favor of the intervention group.

In the group of 391 patients, the discounted mean number of QALYs in the intervention group was 0.917 (95% CI: 0.809 to 1.036) and in the control group 0.719 (95% CI: 0.616 to 0.813) during the two years of follow-up, with the mean difference of 0.198 (95% CI: 0.06 to 0.355, P=0.009) being significantly in favor of the intervention group.

Extra costs per additional QALY

Similar results compared to the undiscounted extra costs per additional QALY were obtained for the societal perspective after discounting (probability > 0.97 and rising).

■ **Table I.** Unit costs

Resources		Unit	Costs*	Source
Acute interventions index admission	Endovascular procedure [#]	procedure	13,660	Top-down cost calculation
	Alteplase	50 mg	655	Medicijnkosten.nl 2016
Hospital admission	Regular admission	day	655	DCM-2015
	ICU admission	day	1,632	DCM-2015
Procedures	type of procedure	procedure	as supplied	Published tariffs
Institutional care	Nursing home	day	231	DCM-2015
	Rehabilitation center	day	633	DCM-2015
	Day care rehabilitation center [^]	hour	211	DCM-2015
Home care	Help	hour	28	DCM-2015
	Care	hour	69	DCM-2015
	Nursing	hour	100	DCM-2015
Consultations	Neurologist	visit	136	DCM-2015
	General practitioner [^]	visit	57	DCM-2015
	Physiotherapist	visit	45	DCM-2015
	Ergo therapist	visit	45	DCM-2011

■ **Table I.** Unit costs (continued)

Resources		Unit	Costs*	Source
	Speech therapist	visit	41	DCM-2015
Out-of-pocket expenses	Transport	monthly costs	as supplied	Patient self report
	Informal care/private help	monthly costs	as supplied	Patient self report
	OTC	monthly costs	as supplied	Patient self report

Abbreviations: DCM is Dutch costing manual for health care research; ICU is intensive care unit; OTC is over the counter medication.

* US dollars for the base year 2014

For an endovascular procedure an amount of 13,669 USD was charged, these are the mean of costs of the intervention with and without anesthesia. In MR CLEAN the mode of anesthesia was left to the discretion of the neuro-interventionist. Furthermore, during intervention the anesthesiologist is always stand-by, and additional material costs of general anesthesia appeared to be low. (see Table II).

^ For costs of a general practitioner visit, the mean (57 USD) of an outpatient visit (45 USD) and a home visit (69 USD) was used.

■ **Table II.** Unit costs of the endovascular procedure

	USD
Diagnostics-CTA [§]	194
Material*	8,060
Personnel [^]	1292
General anesthesia	103
Local anesthesia	43
Total costs #	
with general anesthesia	13,703
with local anesthesia	13,617

[§] Computed Tomography Angiography

*Material includes mean costs of e.g. mostly used catheters, sheaths, vascular closure device and stent retrievers.

[^]Personnel includes 1 (neuro-) interventionist, 1 anesthesiologist, 2 radiology assistants, 2 anesthesia assistants for a mean time of 1.5 hour per procedure, including administrative activities

#Total costs include an overhead rate of 42%

Table III. Mean difference between treatment groups in discounted costs during two years of follow-up, including lower and upper limits of the 95% confidence intervals (in 2014 US dollars). For units see Table I.

	Intervention (n=233)	Control (n=267)	Mean difference	Lower 95%	Upper 95%
Acute interventions					
Endovascular procedure*	12663	51	12612	12199	13074
IVT #	1140	1186	-45	-26	118
Hospital admission					
Regular admission					
Discounted	9973	10868	-895	-2361	573
ICU admission					
Discounted	1664	2570	-907	-2019	206
Other procedures (diagnostic and interventions)					
Discounted	2212	1899	314	15	611
Institutional care					
Rehabilitation center					
Discounted	38494	49310	-10816	-19519	-2114
Day care rehabilitation center^					
Discounted	5729	10451	-4724	-7898	-1548
Nursing home					
Discounted	22891	28306	-5415	-12933	2103
Home care					
Help					
Discounted	2450	3463	-1012	-2131	106
Care					
Discounted	10212	11691	-1480	-5614	2655
Nursing					
Discounted	7529	9387	-1858	-5416	1701
Consultations					
General practitioner					
Discounted	436	370	67	-30	164
Neurologist					
Discounted	350	365	-15	-125	95
Physiotherapist					

Table III. Mean difference between treatment groups in discounted costs during two years of follow-up, including lower and upper limits of the 95% confidence intervals (in 2014 US dollars). For units see Table I. (continued)

	Intervention (n=233)	Control (n=267)	Mean difference	Lower 95%	Upper 95%
Discounted	2176	2977	-801	-1426	-175
Ergo therapist					
Discounted	710	906	-195	-520	129
Speech therapist					
Discounted	778	1131	-354	-735	29
Out-of-pocket expenses					
Transport					
Discounted	1959	2098	-138	-765	489
Informal care/private help					
Discounted	1825	1630	195	-472	862
OTC					
Discounted	1305	1202	103	-381	588

Abbreviations: IVT is intravenous thrombolysis; ICU is intensive care unit; OTC is over-the-counter medication.

*In the intervention arm 17 patients eventually did not receive endovascular treatment, these patients were not charged with costs of endovascular treatment. In the control arm one patient crossed over to the intervention arm and received endovascular treatment, this patient was charged with procedural costs of the endovascular treatment.

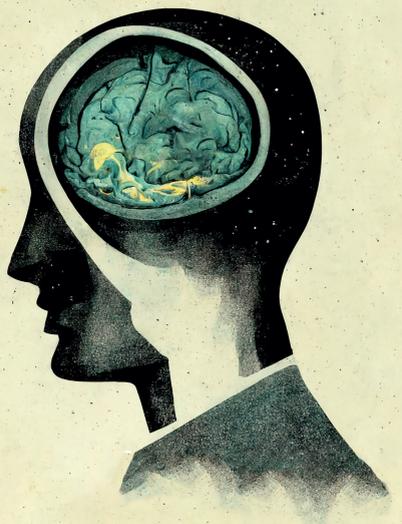
#The costs of IVT with alteplase are based on the costs of alteplase per 50 mg; Alteplase comes in flacons of 50 mg. As most patients need more than 50 mg with a maximum of 90 mg, each patient receiving intravenous alteplase was assigned as receiving 2 flacons, for a total of 1309 USD

^According to the Dutch cost manual for health care research-2015 one hour of treatment in a rehabilitation center in day-care setting costs 211 USD (2014), based on paragraph 4.16 of the cost manual we assume 1 visit lasts 2 hours (mean) for adults.

Table IV. Outcomes of different analytical approaches (available data, Kaplan Meier (KM) and Multiple imputation (MI) applied to regular inpatient hospital days and Intensive Care Unit days analyses.

Method		intervention	control	difference	Lower 95% CI	Upper 95 % CI
Available data						
Regular admission						
	days	13,7	14,4	-0,7	-2,9	1,3
	undiscounted costs	8953	9439	-486	-1891	863
	discounted costs	8942	9424	-482	-1880	863
IC admission						
	days	0,62	0,97	-0,35	-1,05	0,25
	undiscounted costs	1016	1583	-567	-1711	4,00
	discounted costs	1012	1572	-560	-1687	412
Regular admission	days	16,5	20,1	-3,6		
	undiscounted costs	10821	13140	-2319		
	discounted costs	10799	13057	-2257		
IC admission	days	1,39	4,41	-3,02		
	undiscounted costs	2268	7194	-4926		
	discounted costs	2253	7133	-4879		
MI approach						
Regular admission	days	15,27	16,65	-1,39	-3,64	0,87
	undiscounted costs	10004	10912	-908	-2385	568
	discounted costs	9973	10868	-895	-2361	573
IC admission	days	1,03	1,6	-0,56	-1,25	0,12
	undiscounted costs	1683	2604	-921	-2045	204
	discounted costs	1664	2570	-907	-2019	206

Abbreviations: CI is confidence interval; IC is intensive care; KM is Kaplan Meier; MI is multiple imputation.





CHAPTER 5

Budget impact analysis of endovascular treatment for acute ischemic stroke patients in the Netherlands 2015-2021

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Submitted ■

ABSTRACT

Objective

Endovascular treatment has been proven (cost-)effective for acute ischemic stroke patients. In this study we investigate the budget impact of large-scale implementation of endovascular treatment for acute ischemic stroke patients in the Netherlands during 2015-2021.

Methods

The budget impact analysis was done as part of the Multicenter Randomized Clinical trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands (MR CLEAN). It was performed from a health care perspective. Estimated yearly costs during follow-up after stroke for patients with or without receiving endovascular treatment as add-on to usual care were linked to numbers of new patients retrieved from two Dutch registries of endovascular treatment that started after the last inclusion in MR CLEAN (2014). Aggregated costs and costs per care sector were calculated prevalence-based with a population dynamic tool.

Results

From 2015, the yearly number of new acute ischemic stroke patients receiving endovascular therapy increased almost three times (812 (2015); 2370 (2021)). The introduction of endovascular treatment plus usual care would increase hospital care costs around €16 million yearly. However, in almost all other sectors it resulted in budget savings (rehabilitation mostly affected with minus €143 million in total).

Conclusion

Based on the yearly numbers of acute ischemic stroke patients who received endovascular treatment in the Netherlands from 2015 to 2021, introduction of endovascular treatment as add-on to usual care will continue to lead to net yearly budget savings of over €50 million.

INTRODUCTION

Stroke is a major contributor to the total burden of disease worldwide.¹ In the Netherlands the yearly incidence of stroke is approximately 46,000.² Over 25,000 patients are admitted with a stroke in Dutch hospitals yearly and more than 175,000 individuals live with the consequences of stroke, of whom almost half is seriously disabled.² As a result, health care costs associated with stroke are high, mostly due to rehabilitation and nursing home care after the initial hospitalization. In 2011, the annual costs in the Netherlands for patients with stroke were approximately 1.84 billion euros, which is about 3% of the total health care expenditures that year.²

To date, two acute treatment strategies for acute ischemic stroke patients are available: intravenous thrombolysis (IVT) and endovascular treatment.^{3,4} Both therapies aim at early opening of the occluded vessel to restore blood flow to the salvageable ischemic brain tissue that is not already infarcted, thereby improving clinical outcome. IVT has well-recognized contra-indications and is less effective in opening large vessel occlusions compared to endovascular treatment.^{5,6} However, for quite long trials failed to show clinical effectiveness of endovascular treatment compared to standard care, including IVT. In 2015, the Multicenter Randomized Clinical trial of Endovascular treatment for Acute ischemic stroke in the Netherlands trial (MR CLEAN) was the first trial to show clinical effectiveness of endovascular treatment, followed by eight other positive trials, further supporting clinical evidence.⁷ The clinical benefit of endovascular treatment has been proven substantial with a number needed to treat of less than 3 for improved functional outcome.⁴ As such, endovascular treatment has been adopted in international guidelines as standard acute stroke care.⁸ Subsequently the next challenge is to implement endovascular treatment for acute ischemic stroke safely on a large scale. To do so, evidence of cost-effectiveness is crucial to guide reimbursement decisions. Recently we have performed an economic evaluation from a societal perspective with a two-year time horizon alongside the MR CLEAN trial, which shows that endovascular treatment improved health and saved costs, thus dominating standard treatment, including IVT.⁹ To further inform health care policy makers we aimed to investigate the impact of large-scale implementation on the health care budget. In current study we have conducted a budget impact analysis (BIA) of endovascular treatment in the Netherlands from a health care perspective for the years 2015-2021. The results may guide reimbursement decisions and may influence price and volume negotiations between insurer and health care provider.

METHODS

Setting and time horizon

The BIA was performed as part of the economic evaluation of MR CLEAN and its extended follow-up study. The study design, methods and results of MR CLEAN, its long-term extension as well as a cost-effectiveness and cost-utility analysis have been described and published elsewhere.^{10,11} (Appendix I). The current analysis addresses the impact on the health care

budget of introducing endovascular treatment as add-on to usual care for acute ischemic stroke patients in the Netherlands as an add-on to usual care alone (including IVT). The budget impact was assessed for the first seven calendar years 2015-2021 following completion of the MR CLEAN patient inclusion and publication of the positive clinical results, which stimulated nationwide diffusion.⁷

Perspective, comparison, numbers of patients, prevalence-based

The BIA was performed from a Dutch health care perspective. We distinguished two major health care settings: *institutional care* by hospitals, rehabilitation centers or nursing homes, and *non-institutional care* by general practitioners (GP), paramedics or home care organizations.

The budget impact was assessed by comparing the estimated yearly costs of institutional and non-institutional care for Dutch patients who received endovascular treatment on top of usual care in the 2015-2021 period (Figure 1, Alternative scenario), with the health care costs they would have generated, if they only had received usual care (see Figure 1, Standard care scenario).

The MR CLEAN Registry study was set up to register all patients in the Netherlands who underwent endovascular treatment after the last MR CLEAN inclusion in 2014.¹² The registry stopped at the end of 2018. From 2019 until 2021 we retrieved data from the Dutch Acute Stroke Audit (DASA). The DASA is a clinical audit concerning stroke care for patients with acute ischemic stroke in the Netherlands and in which all consecutive stroke patients are registered, including data on endovascular treatment.¹³

From both registries yearly patient counts for the 2015-2021 period were available. In 2015 endovascular treatment was provided to 812 patients; the numbers of patients increased to 1138 (2016), 1478 (2017), 1712 (2018), 2233 (2019), 2322 (2020) and 2370 (2021).

The budget impact was assessed per calendar year and the analysis was prevalence-based without a half-year correction, meaning that estimated health care costs during the first and subsequent years of follow-up of distinct patients were assigned to the calendar year in which each patient's follow-up year started.

Cost components, costs and costs per follow-up year of patients

The costs of institutional care included the costs of care in the hospital, rehabilitation centers and nursing home. Hospital costs included the costs of acute interventions (endovascular procedure, IVT) other interventional and diagnostic procedures, inpatient stay (regular admission days and days at the intensive care unit) and consultations with the medical specialist. Endovascular treatment as evaluated in the MR CLEAN trial was a new treatment modality in the Netherlands and its unit costs were determined by detailed precalculation of mean use of personnel, materials and overhead (nearly €10,000) and reported as part of

the MR CLEAN economic evaluation.⁹ The costs of rehabilitation centers included the costs of inpatient stay as well as day care. Costs of nursing homes reflected the costs of inpatient stay.

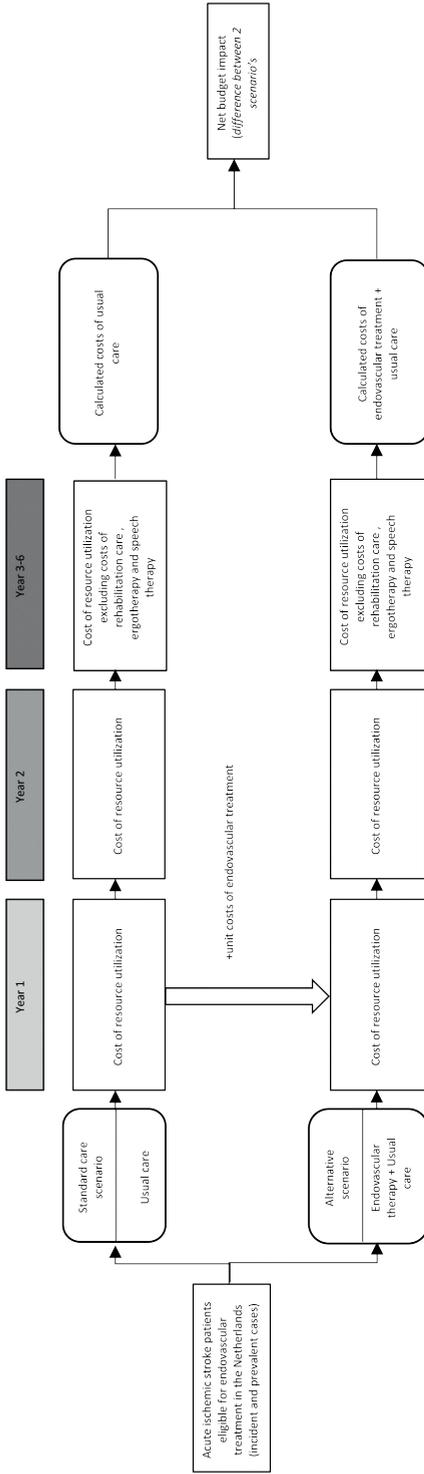
The costs of non-institutional care included the costs of GP, paramedics and formal home care. GP costs reflected the costs of GP visits. The costs of paramedical care included the costs of consultations provided by physiotherapists, ergo therapists and speech therapists. The costs of formal home care included the costs of hours of regular help, personal care and nursing care at home.

A full account of the measurements and valuation of health care resource utilization, respectively costs can be found in the method section of the MR CLEAN cost-effectiveness and cost-utility analysis.⁹ From that economic evaluation with a two-year time horizon the estimated mean health care costs during the first two years of patient follow-up were derived. Undiscounted costs during follow-up in Euros were used for the BIA with calendar year 2018, midway the 2015-2021 period, as the base year for costing after general consumer price-indexing (*cumulative multiplier 2014-2018: 1.04054*).¹⁴ The incident patients during 2015-2021 were assumed to have generated the mean health care costs during the first and second years of follow-up of the patients in the intervention group of the MR CLEAN extension study (Figure 1). If they would not have received endovascular treatment, we assumed that they would have generated the mean health care costs during the first and second years of follow-up for the patient in the control group (Figure 1).

For non-observed mean health care costs per patient in follow-up years 3-6 (Figure 1), we assumed after expert consultation with other stroke neurologists, and with specialized neuro-rehabilitation physicians and paramedics, that a patient's health status would gradually stabilize during the first or second year following stroke, and that rehabilitation efforts and paramedical care by ergo therapists or speech therapists would stop before the end of the second year because of goal achievement or expected lack of further improvement of health status. Contrarily, physiotherapy might still be continued as a maintenance therapy for muscle strength and mobility. It was therefore assumed that health care costs in the second year of follow-up without the costs of rehabilitation, ergotherapy and speech therapy would reasonably reflect the yearly costs in subsequent follow-up years 3-6.

All the mean costs per year of follow-up derived from the economic evaluation were calculated by dividing the total health care costs per year of follow-up by the original number of patients in the study arms, thus including deceased patients.⁹ Because most deceased patients after treatment for stroke died within the first year of follow-up followed by a gradual diminishing mortality risk and as long as the extrapolation of mean costs during the second year of follow-up to subsequent years is limited to the sixth year of follow-up, explicit modeling of mortality rates over time to improve precision of the budget impact can be ignored.¹⁵

Figure 1. Overall budget impact structure. The budget impact model estimates the nationwide impact on the costs of health care of endovascular treatment as add-on to usual care for eligible acute ischemic stroke patients in the years 2015-2021.



Assessment tool

A simple population dynamic model was developed in Microsoft Excel linking the derived mean health care costs by observed numbers of new patients during their years of individual follow-up under the standard care scenario or under the alternative endovascular treatment scenario to the calendar years of the budget impact period 2015-2021. We report the budget impact at the aggregated levels of (non) institutional care based on the national yearly patient numbers and mean costs estimates. However, the budget model is available upon request to allow assessments of budget impact at more local levels relevant to a specific market share or to explore the influence of uncertainty in the costs estimates. To the latter end, 95% confidence intervals for the mean costs were generated after bias correction by accelerated non-parametric bootstrapping, drawing 1000 samples of the same sizes as the original samples of the MR CLEAN study groups, with replacement.

RESULTS

Costs during years of follow-up

The estimated mean yearly costs of institutional care for patients who received endovascular treatment in the MR CLEAN intervention group were €60,146 in the first and €12,856 in the second year of follow-up. For the third to sixth year of follow-up the mean yearly costs were assumed to level at €8,226 (costs of the second year minus expenditures for rehabilitation). The estimated mean yearly costs of non-institutional care in the intervention group equaled €9,962 in the first, €8,740 in the second and €8,288 in subsequent follow-up years. (Table 1).

The mean yearly costs of institutional care for patients receiving usual care in the MR CLEAN control group were €62,214 in the first, €19,276 in the second year of follow-up, and an assumed yearly €10,040 in subsequent years. For non-institutional care the mean yearly costs were €11,546 in the first and €11,510 in the second years and assumed to level at €10,822 in subsequent years.

Table 1 reports further details by treatment scenario, care sector and follow-up year.

Table 1. Mean per patient costs of health care by treatment scenario, sector and follow-up year after stroke†

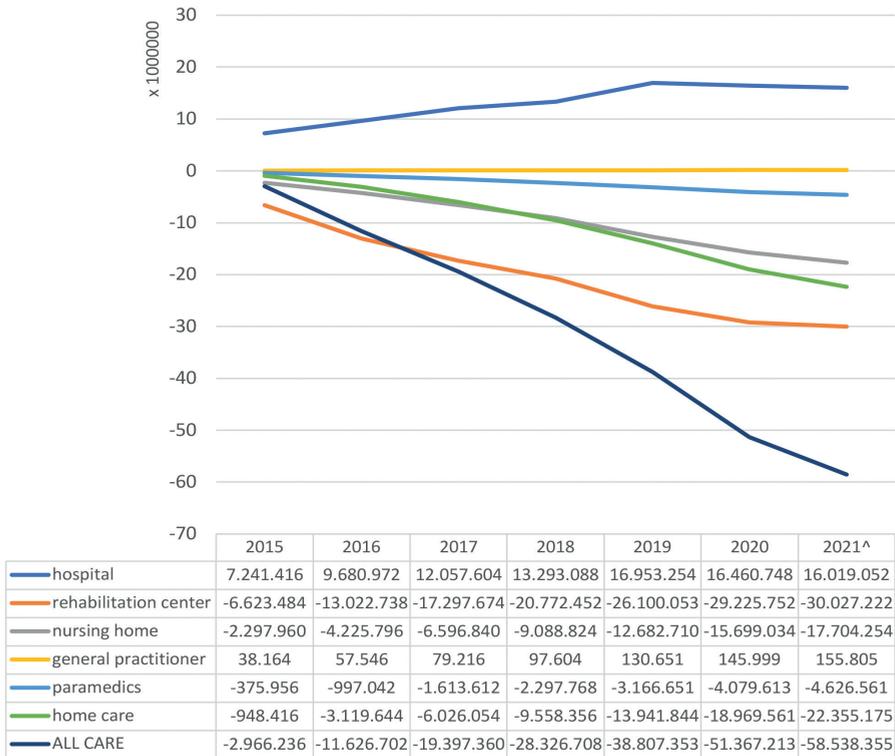
Alternative scenario: endovascular treatment plus usual care			
Care sector	Follow-up year at patient level		
	1st	2nd	3rd-6th
Institutional care	60146 (55317-64863)	12856 (10487-15473)	8226 (6268-10640)
Hospital	19922 (18983-20780)	1297 (1017-1572)	1297 (1017-1572)
Rehabilitation center	29363 (25985-32635)	4630 (3466-5873)	-
Nursing home	10860 (8890-13177)	6929 (5042-9238)	6929 (5042-9238)
Non-institutional care	9962 (82230-11871)	8740 (7238-10345)	8288 (6873-9803)
GP	185 (154-221)	152 (126-180)	152 (126-180)
Paramedics	1599 (1338-1886)	1219 (1027-1452)	767 (629-928)
physiotherapy	908 (757-1083)	767 (629-928)	767 (629-928)
ergotherapy	368 (284-458)	176 (135-223)	-
speechtherapy	322 (249-409)	276 (206-364)	-
Home care	8178 (6578-9910)	7370 (6099-8835)	7370 (6099-8835)
Total	70107 (64436-76076)	21597 (18428-25206)	16514 (13896-19625)
Standard care scenario: usual care			
Care sector	Follow-up year at patient level		
	1st	2nd	3rd-6th
Institutional care	62214 (57010-67209)	19276 (15825-22999)	10040 (8223-12170)
Hospital	11004 (10110-11979)	1873 (1450-2354)	1873 (1450-2354)
Rehabilitation center	37520 (33849-41432)	9236 (6885-12055)	-
Nursing home	13690 (11827-15635)	8167 (6391-10205)	8167 (6391-10205)
Non-institutional care	11546 (9891-13186)	11520 (9726-13211)	10822 (9146-12411)
GP	138 (114-162)	147 (124-173)	147 (124-173)
Paramedics	2062 (1748-2388)	1798 (1514-2076)	1100 (938-1251)
physiotherapy	1193 (1026-1382)	1100 (938-1251)	1100 (938-1251)
ergotherapy	415 (314-534)	280 (207-376)	-
speechtherapy	454 (356-568)	418 (320-520)	-
Home care	9346 (7811-10881)	9575 (7949-11140)	9575 (7949-11140)
Total	73760 (67796-79391)	30796 (26573-35398)	20862 (18140-23688)

† Costs are undiscounted, in Euros, and reported as mean (lower-upper 95% confidence limits). The costing base-year was 2018.

Budget impacts

The almost tripling increase - from 812 in 2015 to over 2300 in 2020-2021 - of new yearly patients, who received add-on endovascular treatment instead of just usual care increased pressure on hospital care budget up to €16 million yearly, or almost €92 million during 2015-2021. General practitioners experienced a more limited pressure with an increase of demand for care up to an extra €156,000 in 2021. Budget savings were noted in all other relevant care sectors. In descending order, the budgets for rehabilitation were mostly affected (-€143 million in total), followed by formal home care (-€75 million), nursing home care (-€68 million), and care by paramedics (-€17 million).

■ **Figure 2.** Budget impact 2015-2021 of endovascular treatment as add-on treatment to usual care



[^] Unknown mean costs of the 7th follow-year of new patients in 2015 have not been included in calendar year 2021

Figure 2 shows the budget impact per care sector for the successive calendar years 2015-2021. The yearly net reduction in budget across all care sectors first exceeded the €50 million mark in 2020 and further continued to increase.

DISCUSSION

We estimated the budget impact of having provided endovascular treatment for acute ischemic stroke patients in the Netherlands between 2015 and 2021, following the initially and later on confirmed positive results of the MR CLEAN study. Our analysis showed that the introduction of endovascular treatment as an add-on to usual care already has started to pay off by net budget savings of well over €50 million yearly. These results leave room for facing financial challenges or for additional expenditures in other areas of medicine where these are needed most.

We did not identify any other budget impact analyses of endovascular treatment of acute ischemic stroke in the literature to compare our results with. One previous study also conducted in the Netherlands estimated the future health care costs by considering the expected increase of stroke patients and a nationwide implementation of acute stroke services. The investigators estimated that the total costs of stroke based on, at the time, current practice increased from 1.62 billion euros in 2000 to 2.08 billion euros in 2020, taking into account the effect of demographic changes and trends in major risk factors for stroke. Implementing stroke services in 2020 would result in reduction of stroke costs by 13 %, to a total of 1.81 billion euros.¹⁶ Although these results are not directly comparable to our study, it too showed that stroke is a disease with a heavy burden for the total healthcare costs, and that implementing effective treatment strategies significantly result in cost reduction of the healthcare budget. Our findings further expand on these results, as endovascular treatment will be part of optimizing and implementation of acute stroke services.

Our BIA has several strengths and limitations. The input data for this BIA were retrieved from our economic evaluation that gathered empirical data on the use of resources following either endovascular treatment or usual care during two years of follow-up, alongside a pragmatic randomized clinical trial. Hence, results are based on real-life scenarios derived from a single source, instead of data based on extrapolation of assumptions from multiple sources, often used in economic studies. We did however made assumptions on the patient's health status and related costs after the two years of follow-up to estimate the costs in the subsequent years, without performing sensitivity analysis for different scenarios. The latter may have resulted in considerable changes in the estimated outcomes. Given the large amount of the net savings though, together with low rate of recurrent strokes or major complications observed during clinical follow-up, it is to be expected that such additional analysis will not change the results substantially.¹⁵ In addition, our model was based on observed rather than expected stroke patients, who proved eligible for endovascular treatment by having received treatment and being included in a nationwide Dutch registries. Hence, epidemiological uncertainty was absent.

The current BIA has not addressed the implementation costs of endovascular treatment to attain a geographically optimal spread across the nation beyond the cooperation of study centers already in place. Currently, the debate about how far centralization of endovascular treatment is needed or preferred is ongoing. As the positive results of the trials were only relatively recently known and Dutch hospitals are still in the process of improving their logistics

for endovascular treatment, it seems certain that patient numbers may continue to rise in the years to come.

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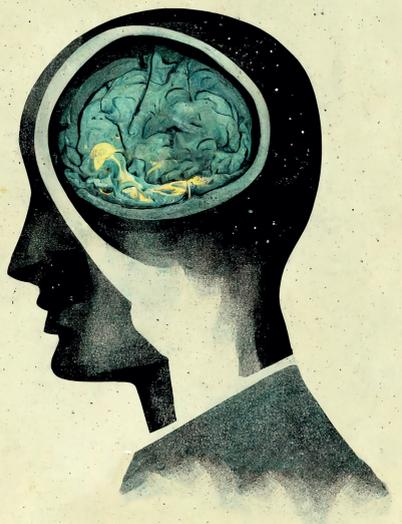
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APPENDIX I: STUDY DESIGN, METHODS AND RESULTS OF MR CLEAN AND ITS LONG-TERM EXTENSION

MR CLEAN was a randomized, multicenter trial in which endovascular treatment plus usual care (intervention group) was compared to usual care alone (control group) in patients with acute ischemic stroke caused by a proximal intracranial arterial occlusion of the anterior circulation.⁷ Usual care included best medical management according to national and international guidelines, including intravenous thrombolysis (IVT) with recombinant tissue plasminogen activator. Endovascular treatment consisted of intra-arterial catheterization with a microcatheter to the level of occlusion and delivery of a thrombolytic agent, mechanical thrombectomy, or both. Primary outcome of the trial was functional outcome, assessed by the modified Rankin Scale (mRS) score at 90 days. The mRS is a 7-point scale ranging from 0 (no symptoms) to 6 (dead).¹⁷ A score of 2 points or less indicates functional independence. In total, 500 patients from 16 medical centers in the Netherlands were randomly assigned in MR CLEAN between December 2010 and April 2014, of which 233 in the intervention group and 267 patients to the control group. The absolute difference in the rate of functional independence was 13,5 % (32,6% vs. 19,1%; 95% CI interval, 5,9 to 21,2) in favor of the intervention group, without significant differences in mortality or the occurrence of serious adverse events. At two-year follow-up the distribution of outcomes on the modified Rankin scale (mRS) favored endovascular treatment over usual treatment similar to the outcome at three months (difference 13.2%, (37,1% vs. 23,9%, 95% CI interval, 4 to 22).¹⁵ At two years, the mean health utility score was 0,48 among patients randomly assigned to endovascular treatment as compared with 0,38 among patients randomly assigned to usual treatment (mean difference, 0,10; 95% CI, 0,03 to 0,16; P=0,006). The cumulative 2-year mortality rate was 26,0% in the intervention group and 31,0% in the control group (adjusted hazard ratio, 0,9; 95% CI, 0,6 to 1,2; P=0,46). For the economic evaluation empirical data on the use of resources were gathered parallel to the MR CLEAN trial up to two years of follow-up.⁹ Incremental cost-effectiveness ratios as the extra costs per additional patient with functional independence (mRS 0-2) and the extra cost per quality adjusted life year (QALY) gained were calculated. The mean costs per patient in the intervention group were €91,902 vs. €104,135 in the control group (mean difference €12,234, 95% confidence interval [CI]: €27,690 to €3,964 (base year for unit costing 2014)). Endovascular treatment dominated standard treatment with €13,247 saved per extra patient with a good outcome and €76,937 saved per additional quality adjusted life year (QALY).





CHAPTER 6

Type of anesthesia and differences in clinical outcome after intra-arterial treatment for ischemic stroke

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ABSTRACT

Background and Purpose

Intra-arterial treatment (IAT) in patients with acute ischemic stroke (AIS) can be performed with or without general anesthesia (GA). Previous studies suggested that IAT without the use of GA (non-GA) is associated with better clinical outcome. Nevertheless, no consensus exists about the anesthetic management during IAT of AIS patients. This study investigates the association between type of anesthesia and clinical outcome in a large cohort of patients with AIS treated with IAT.

Methods

All consecutive patients with AIS of the anterior circulation who received IAT between 2002 and 2013 in 16 Dutch hospitals were included in the study. Primary outcome was functional outcome on the modified Rankin Scale at discharge. Difference in primary outcome between GA and non-GA was estimated using multiple ordinal regression analysis, adjusting for age, stroke severity, occlusion of the internal carotid artery terminus, previous stroke, atrial fibrillation, and diabetes mellitus.

Results

348 patients were included in the analysis; 70 patients received GA and 278 patients did not receive GA. Non-GA was significantly associated with good clinical outcome (OR: 2.1, 95% CI 1.02-4.31). After adjusting for pre-specified prognostic factors, the point estimate remained similar, statistical significance however was lost (OR: 1.9, 95 % CI: 0.89-4.24).

Conclusions

Our study suggests that patients with AIS of the anterior circulation undergoing IAT without general anesthesia have a higher probability of good clinical outcome compared to patients treated with general anesthesia.

INTRODUCTION

Intra-arterial treatment (IAT) has been proven effective and safe for patients with acute ischemic stroke (AIS).¹⁻³ Numerous studies have evaluated the effect of different thrombolytic agents and devices.^{4,5} However, less is known about the effect of anesthesia during IAT. During intervention, patients receive either general anesthesia (GA) or no GA (non-GA), referring to local anesthesia (LA) at groin puncture site with or without conscious sedation (CS). Recent retrospective studies suggest that non-GA is as feasible as GA and that GA may be associated with a lower rate of successful recanalization and worse clinical outcome.⁶⁻¹⁰ Several factors could contribute to these findings. Induction and recovery phases in GA are stressful and could lead to cardiac arrhythmias and cardiac ischemia. Furthermore inhaled and intravenous (IV) anesthetic agents are known to alter blood carbon dioxide (CO₂) and can cause blood pressure shifts that could lead to changes in cerebral autoregulation with decreased cerebral perfusion.¹¹

Currently, no consensus exists about the optimal anesthetic management of AIS patients during IAT. Previous studies suffered from several methodological limitations that prevent to draw definite conclusions.¹² Most important was the imbalance in stroke severity at baseline in most studies, resulting in more severe strokes in the GA group as compared to the non-GA group. Furthermore, the majority of studies had small numbers of patients. In the absence of definite evidence, current practice is largely based on local protocols and preferences of the neurointerventionalists.¹³ Possible advantages of GA are; (1) immobilization of the patient to prevent wire induced vessel injury and to facilitate navigation with a quicker recanalization; (2) adequate ventilation and airway protection; and (3) limiting patient discomfort. On the other hand, a non-GA approach (1) may reduce time to treatment initiation; (2) allow neurologic assessments during and after the procedure, (3) does not induce blood pressure lowering and (4) does not require intubation. Nonetheless, when using a non-GA approach there is a chance of a need to convert acutely to GA accompanied by emergency intubation, which is associated with a higher rate of aspiration pneumonia and poor outcome.¹⁴

In this retrospective study among 16 Dutch hospitals, we aimed to evaluate the relation between anesthetic management during IAT and clinical outcome. In most intervention centers in the Netherlands, a standard strategy regarding anesthetic management for acute stroke interventions is applied, thereby limiting bias through patient selection by baseline stroke severity in this study. We hypothesized that a non-GA approach during IAT in patients with AIS of the anterior circulation is associated with a better clinical outcome compared to GA based on a potentially shorter time from onset to treatment initiation, avoidance of potentially harmful blood pressure changes and quicker recovery without the use of GA.

METHODS

We conducted a retrospective cohort study in patients from the pre-trial cohort of the Multicenter Randomized Clinical Trial of Endovascular treatment for acute ischemic stroke in

the Netherlands (MR CLEAN), which consists of all consecutive patients with AIS treated with IAT in 16 stroke centers in The Netherlands. Information concerning procedures and treated patients was gathered in order to assess pretrial experience in centers that were committed to participate in the MR CLEAN trial.¹⁵ The registry started in October 2002 and continued until a center started participation in the trial. The institutional review board from the coordinating institution approved registration and use of the data. We only included patients with an anterior circulation stroke in our analysis. Patients were treated intra-arterially with a thrombolytic agent, a dedicated clot retriever or a retrievable stent. The method of intra-arterial treatment was left to the discretion of the treating neurointerventionalists.

Study procedures

All centers kept a prospective registry of patients who received IAT. Data collection itself was largely retrospective. Demographic variables, pre-morbid stroke risk factors, National Institutes of Health Stroke Scale (NIHSS) score at baseline, use of intravenous tissue type plasminogen activator (iv-rtPA), timing of baseline and treatment procedures, treatment type (intra-arterial thrombolytics, mechanical treatment or both) and type of anesthesia (GA or non-GA) were obtained from medical charts and intervention reports by trained medical researchers. When necessary and possible, NIHSS at baseline was reconstructed from clinical data with a modified algorithm.¹⁶ When missing, IAT time points were reconstructed using angiogram times. For start of IAT: time of first scan minus 5 minutes, for end of IAT: time of last scan plus 5 minutes.

Outcomes

The modified Rankin Scale score (mRS) for functional outcome at discharge was assessed by a certified neurologist or neurology fellow.¹⁷ Good clinical outcome was defined as mRS of ≤ 2 . Grade of recanalization was assessed with the modified Thrombolysis in Cerebral Infarction score (mTICI).¹⁸ Recanalization was defined as mTICI score 2b or 3 on Digital Subtraction Angiography (DSA) imaging at the end of the procedure. Three experienced observers from a center that was not involved in the treatment assessed all DSA runs. Observers were blinded for baseline data of the patient and for intervention center. All periprocedural and postprocedural complications, including conversion from local to general anesthesia, were recorded from intervention -and imaging reports and patient records. Symptomatic intracranial hemorrhage (SICH) was defined as parenchymal hemorrhage at any site in the brain on the CT-scan, being compatible with documented neurological deterioration. Asymptomatic intracranial hemorrhage (AICH) was defined as parenchymal hemorrhage at any site of the brain found on follow-up CT-scan without neurological deterioration.

Statistical analysis

Analyses were based on the intention to treat principle. Conversions from non-GA to GA were therefore counted in the non-GA arm of the study. Descriptive statistics were expressed as means with standard deviation (SD) or medians with interquartile range (IQR). Groups (non-GA versus GA) were compared by the Chi-square test for categorical variables and the Student-t

test or, in case of a non-normal distribution, the Mann-Whitney U test for continuous variables. Univariable logistic analysis was performed to determine an association between type of anesthesia and good clinical outcome. Multivariable logistic regression was performed to adjust for pre-defined prognostic variables: age, stroke severity (NIHSS) at baseline, occlusion of the internal carotid artery terminus (ICA-T), history of previous stroke, atrial fibrillation and diabetes mellitus. Additionally, we performed multivariable ordinal logistic regression analysis to assess the adjusted common odds ratio (acOR) for a shift in direction of a better outcome on the mRS, adjusted for the aforementioned variables. Statistical analyses were performed using SPSS version 22.0.

RESULTS

We identified 369 patients with an anterior circulation stroke and available information on anesthetic management during IAT and functional outcome at discharge. Of these 369 patients, we excluded 21 patients for multiple reasons, e.g. patients already under GA for other procedures, lack of information on timing of procedures or cross over to no intra-arterial treatment (see online supplemental material for patient flow-chart). 348 patients were used for the analysis; 278 patients were treated without GA and 70 patients with GA. Information on the use of CS and specific agents was not available in most of the cases. Patients received non-GA based on standard strategy in 274 cases. In four cases, procedure was started without GA despite the local standard strategy indicating GA. The majority of patients (N=63) received GA as initial treatment modality, based on the local standard strategy. Seven patients received GA because of agitation, respiratory insufficiency or decreased level of consciousness before start of the treatment, whereas they would normally be treated without GA.

Ten patients (10/278 (4%)) in the non-GA group converted to GA during treatment. In nine patients reason for conversion was agitation and patient movement. One patient suffered from respiratory insufficiency during treatment initiation. These converted cases were included in the non-GA group, based on the intention to treat principle.

Baseline characteristics

Patients treated under GA were significantly younger (57 years vs. 62 years) and less often had atrial fibrillation (9/70 (29%) vs. 40/278 (16%)). Furthermore, patients in the GA group had a longer time from onset of symptoms to start of IAT of 00:20 hours (median 04:01; IQR 01:53 hrs. vs. 03:40; IQR 01:41) and were more frequently treated with mechanical thrombectomy only (32/70 (46%) vs. 61/278 (22%)). The distribution of baseline stroke severity (NIHSS), pre-treatment with iv-rtPA and occlusion site was similar in both groups. (Table 1.)

■ **Table 1.** Baseline characteristics

	No general anesthesia (n=278)	General anesthesia (n=70)	P Value
Demographics			
Men -n (%)	149 (53.6)	35 (50.0)	0.59
Age in years - mean (SD)	62 (14.0)	57 (17.7)	0.03
Medical history and risk factors			
Diabetes mellitus -n (%)	40 (14.8)	9 (13.4)	0.77
Hypertension -n (%)	130 (51.7)	37 (44.8)	0.31
Atrial fibrillation -n (%)	79 (29.3)	11 (16.4)	0.03
Hypercholesterolemia or statin use -n (%)	63 (23.4)	22 (32.8)	0.07
Prior stroke or TIA -n (%)	38 (14.1)	8 (11.9)	0.65
Ischemic heart disease -n (%)	43 (15.9)	16 (23.9)	0.13
Clinical			
Baseline NIHSS -median, (IQR)	15 (7)	16 (5)	0.76
Time from symptom onset to start IAT (hours). median,(IQR)	03:40 (01:41)	04:01 (01:53)	0.02
Intravenous thrombolysis with rt-PA -n (%)	211 (75.9)	45 (65.2)	0.07
Most proximal site of occlusion as assessed on angiography			
M1 MCA (total -n (%))	184 (66.2)	49(70.0)	0.54
M2 MCA (total -n (%))	62 (22.3)	9 (12.9)	0.08
M3 MCA (total -n (%))	1 (0.4)	0	0.62
ICA (total -n (%))	8 (2.9)	3 (4.3)	0.55
ICA-T (total -n (%))	23 (8.3)	9 (12.9)	0.24
Procedure			
Mechanical IA therapy only -n (%)	61 (21.9)	32 (45.7)	<0.001
IA thrombolysis only -n (%)	81 (29.1)	9 (12.9)	0.01
Combination of IA thrombolysis and mechanical IA therapy -n (%)	136 (48.9)	29 (41.4)	0.26
Conversion from non-GA to GA -n (%)	10 (3.7)	NA	

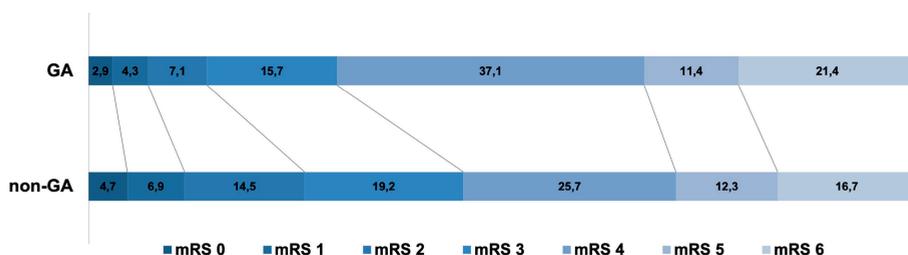
SD indicates standard deviation; IQR, interquartile range; ICA, internal carotid artery; MCA, middle cerebral artery; IA, intra-arterial; GA, general anesthesia

Clinical outcome

A total of 82 (82/348(24%)) patients were functionally independent (mRS 0-2) at discharge. Good clinical outcome was seen in 26% (72 /278) of patients in the non-GA group and in 14% (10/70) of patients in the GA group. A higher mortality rate was seen in the GA group (15/70(21%)) as compared to the non-GA group (46/278 (17%)), however this difference was not statistically significant (Table 2). The distribution of the mRS in both treatment groups is presented in Figure 1.

In unadjusted logistic regression analysis, non-GA was significantly associated with good clinical outcome (OR: 2.1, 95% CI 1.02-4.31). After adjusting for pre-specified prognostic factors, the point estimate remained positive, however did not reach statistical significance (OR: 1.9, 95 % CI: 0.89-4.24). The additional multivariable ordinal regression analysis showed a shift in distribution on the mRS in favor of the non-GA group (acOR 1.6, 95% CI: 0.98-2.54). This also was not statistically significant.

■ **Figure 1.**



Distribution of outcomes on the modified Rankin Scale (mRS) in percentages in patients who received general anesthesia (GA)(n =70) or no GA (non-GA) (n=278). mRS 0-1 indicate excellent outcome; mRS 2-3, moderate disability; mRS 4-5, severe disability; mRS 6, dead.

■ **Table 2.** Clinical, radiographic and safety outcomes

	No general anesthesia (n=278)	General anesthesia (n=70)	P Value
Clinical outcome			
mRS 0-2-n(%)	72 (25.9)	10 (14.3)	0.04
Mortality-n(%)	46 (16.5)	15 (21.4)	0.34
mTICI score post treatment*			
0- n (%)	36 (13.6)	11 (15.7)	0.55
1- n (%)	19 (7.2)	6 (8.6)	0.62
2a-n (%)	97 (36.6)	19 (27.1)	0.22

■ **Table 2.** Clinical, radiographic and safety outcomes (continued)

	No general anesthesia (n=278)	General anesthesia (n=70)	P Value
2b-n (%)	35 (13.2)	14 (20.0)	0.11
3- n (%)	78 (29.5)	20 (28.6)	0.93
Full recanalization (TICI 2b/3)	113 (42.6)	34 (48.6)	0.37
Procedural complications			
Total complications – n (%)	50 (18)	9 (12.9)	0.31
Vessel perforation – n (%)	4 (1.4)	0 (0)	0.31
Dissection – n (%)	12 (4.3)	2 (2.9)	0.58
Device related complications- n (%)	6 (2.2)	3 (4.3)	0.32
Hemodynamic and airway complications- n (%)	2 (0.7)	0 (0)	0.48
Reperfusion syndrome – n (%)	1 (0.4)	0 (0)	0.62
Migration of thrombus, microthrombi or restenosis – n (%)	10 (3.6)	4 (5.7)	0.42
Seizures during treatment – n (%)	3 (1.1)	0 (0)	0.38
Groin hematoma – n (%)	12 (4.3)	0 (0)	0.08
Postprocedural complications			
SICH- n (%)	33 (11.9)	8 (11.4)	0.92
AICH- n (%)	32 (11.5)	9 (12.9)	0.76
Progression of stroke† -n (%)	28 (10.1)	12 (17.1)	0.15
Pneumonia-n (%)	41 (14.7)	9 (12.9)	0.69
Other infection- n (%)	23 (8.3)	3 (4.3)	0.26
Cardiac arrhythmias‡- n (%)	6 (2.2)	0 (0)	0.38
Myocardial infarction-n (%)	1 (0.4)	0 (0)	0.62
Decompensated heartfailure-n (%)	2 (0.7)	1 (1.4)	0.57
Major extracranial hemorrhage-n (%)	4 (1.4)	2 (2.9)	0.42
PE/DVT-n (%)	2 (0.7)	1 (1.4)	0.57
Seizures-n (%)	10 (3.6)	5 (7.1)	0.19

NA indicates not applicable; TIA, transient ischemic attack; SICH, symptomatic intracranial hemorrhage; AICH, asymptomatic intracranial hemorrhage; PE, pulmonary embolism; DVT, deep venous thrombosis.

*mTICI scores were not available for 13 patients in the non-GA group.

†Progression of stroke was defined as symptomatic (malignant) brain edema seen on non-contrast CT that could have required hemicraniectomy

‡Cardiac arrhythmias did not include atrial fibrillation; atrial fibrillation seen on electrocardiography during admission was considered present before admission for stroke.

Periprocedural complications

Vessel perforation was seen in four patients (4/278 (1%)) treated without GA and did not occur in patients treated under GA. Two of these four patients had an accompanying SICH with an outcome of respectively four and five on the mRS at discharge. From one patient no SICH nor AICH was reported and had an mRS of three at discharge and one patient had an AICH with mRS four at discharge. Dissection of the internal carotid artery during treatment was seen in both groups (non-GA: 12/278 (4%) vs. GA: 2/70 (3%)) as well as device related complications (non-GA: 6/278 (2%) vs. GA: 3/70 (4%)). These included failure to deploy the retrievable stent, a broken guidewire, a broken stent and/or a part of device unable to retrieve.

Postprocedural complications

Postprocedural complications are summarized in Table 2. There was no difference in occurrence of symptomatic or asymptomatic intracranial hemorrhages between the two treatment groups. Progression of ischemic stroke and seizures was seen more often in the GA group. Pneumonia and other infections were more frequent in the non-GA group. However, these differences were not statistically significant.

Angiographic reperfusion

mTICI scores were not available for 13 patients in the non-GA group. Of the available scores, full recanalization (mTICI 2b/3) was reached in 113/265 (43%) of patients in the non-GA group versus 34/70 (49%) in the non-GA group. All scores on the mTICI are summarized in Table 2.

DISCUSSION

Our study suggests that patients with anterior circulation AIS treated with IAT, who did not receive GA have a higher probability of good clinical outcome compared to patients who received GA. Furthermore we observed that IAT was initiated sooner after symptom onset in patients treated without GA as compared to GA. We did not find major differences with regard to safety parameters between the two treatment modalities.

Our findings are consistent with earlier findings in both terms of clinical and safety outcomes between the two treatment types. However, previous studies reported an imbalance in baseline NIHSS in favor of non-GA treated patients, which could have influenced outcome. In contrast, our study had equal scores on baseline NIHSS. Hence, difference in baseline stroke severity is not the reason for improved clinical outcome following non-GA patients in our cohort.

How can we explain improved outcome in patients treated without the use of GA? First of all it is known that inhaled and/or intravenous anesthetic agents can alter blood CO₂ levels and blood pressure shifts, which can lead to changes in cerebral autoregulation and consequently in decrease of cerebral bloodflow (CBF), leading to extension of ischemic injury. Use of propofol and induction dosages of fentanyl predicted postinduction hypotension in a study of Reich

and colleagues.¹⁹ Furthermore some anesthetic gases might act as a vasodilator, resulting in the reverse 'Robin Hood' syndrome, with steal from blood flow of the affected vascular territories towards unaffected territories, further compromising flow in the ischemic area.²⁰ There are data that support these findings in AIS patients treated with IAT. Davis et al. found that lower blood pressures were associated with worse outcomes in patients undergoing CS or GA, and the mean systolic blood pressure in patients undergoing CS was 135 mmHg compared with 104 mmHg in patients with GA.²¹ Additionally, in a retrospective study of 126 patients with a middle cerebral artery stroke treated with IAT, Jumaa et al. showed that final infarct volume was significantly larger in intubated patients versus non-intubated patients (mean infarct volume (cm³) 147 vs 80.2, p=0.002).⁷ In our study we were unable to collect adequate information on type of anesthetic agents, blood pressure, CO₂ and CBF during treatment nor final infarct volumes to confirm these data.

Another reason often suggested for the difference in outcome, could be a higher rate of aspiration and pneumonia in intubated patients and contribution of pneumonia to poor outcome.⁹ However, we found a lower rate of pneumonia in the GA group and therefore this phenomenon cannot explain the differences in clinical outcome in our study. Conversely, lack of airway protection by the absence of intubation could lead to higher rates of pulmonary aspiration in non-GA patients. Patients with AIS of large cerebral artery may have a degree of dysphagia and are unlikely to have been fasted before intervention. The urgent need for conversion to GA may occur, accompanied by a higher risk of aspiration. Most previous studies did not examine the rate of conversion from non-GA to GA. In our study only 10 patients in the non-GA group were converted to general anesthesia. No effect on clinical outcome was seen in these patients. The small number of converted patients in our study demonstrates that in current medical practice, the risk of conversion to GA is relatively small, thereby not clearly influencing clinical outcome in the non-GA group.

The most important factor leading to poor outcome could be that GA may lead to treatment delay resulting in a prolonged onset to recanalization time and therefore reduce the chance of good clinical outcome. However, two previous studies that investigated this perception, found no difference in time to treatment between GA and non-GA, and between intubated and non-intubated state respectively.^{6,7} In our cohort, IAT in patients treated under GA was started 20 minutes later than in patients treated without GA. Since time from stroke onset to treatment is an important factor for outcome after acute stroke treatment, this may account for difference in clinical outcome. To our knowledge, this is the first study to demonstrate a difference in time to treatment between GA and non-GA. Future studies need to confirm this and should use specific time points to provide insight into the point at which most time is lost.

The main reason for neurointerventionalists to use GA is to minimize patient movement. Awake patients could be agitated during treatment resulting in head movements that affect DSA images. As a result, longer times to recanalization may occur. Major concern, of course, is increasing risk of procedural complications such as vessel perforation or dissection

and subsequent intracranial hemorrhage. In our group of non-GA patients, rate of vessel perforation was low and SICH was seen as often as in patients treated under GA. Other studies showed similar safety result, indicating that a non-GA approach seems to be a safe choice.

As we know from previous studies, higher recanalization leads to better clinical outcome.²² In a meta-analysis from Brinjikji et al., which included all available studies on anesthesia and IAT of AIS, a significant difference was found in recanalization grades in favor of non-GA.¹⁰ In our study, full recanalization was reached in similar percentages of patients in both treatment groups. So, we can conclude that higher recanalization may not account for better outcomes in the non-GA group in our cohort of patients.

The effect of anesthesia on clinical outcome in AIS patients remains a black box, containing several factors that could influence outcome. Our study did not answer the question which individual parameters are responsible for worse clinical outcome in patients treated under GA. Faster initiation of treatment from stroke onset could be one of the major factors in this study.

Limitations

Our study does have several limitations. One of the major limitations is the retrospective and non-randomized nature. Choice of anesthesia was based on standard local strategy or preference of the neurointerventionalist. The latter could have led to selection bias or confounding by indication or center, although a standard strategy regarding anesthetic management for acute stroke interventions is applied in most centers. Also, the majority of centers and operators preferred not to use GA, therefore group sizes were unequal. Optimal method would include randomization between GA and non-GA. Currently the ANSTROKE trial (Sedation Versus General Anesthesia for Endovascular Therapy in Acute Stroke - Impact on Neurological Outcome) is randomizing AIS patients between GA and sedation only.²³ Furthermore, mRS scores were only available at discharge. It is preferable to assess the effect of anesthesia on clinical outcome over a longer period of time.

Conclusion

Overall, the results of our study are in line with previous studies and show that patients who do not receive GA have a higher probability of good clinical outcome and do not have higher complication rates than patients who undergo GA. Local anesthesia, with the possible use of conscious sedation, during intra-arterial treatment for acute ischemic stroke seems a good strategy if possible.

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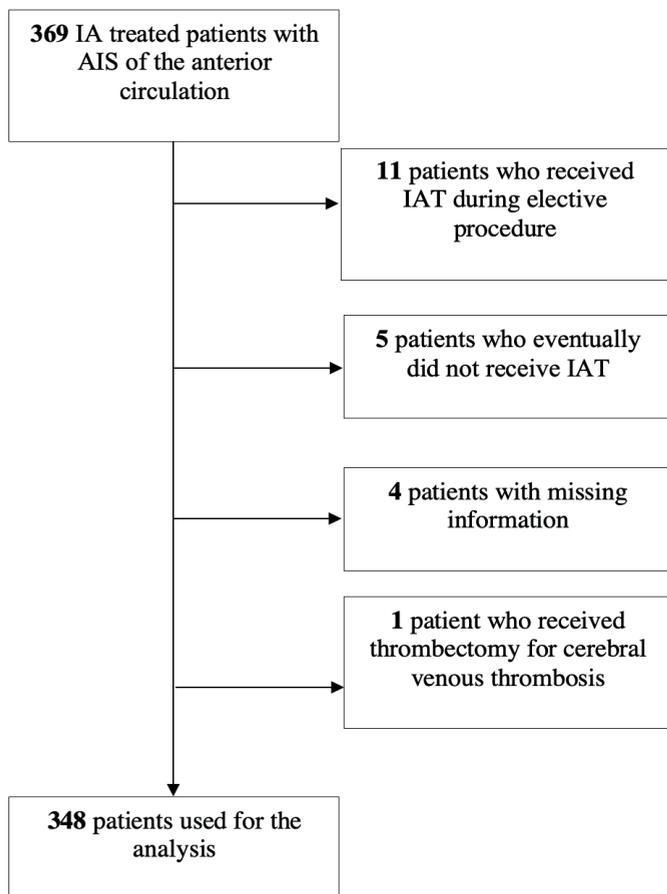
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SUPPLEMENTARY APPENDIX

■ Patient flow-chart



IA indicates intra-arterial; AIS, acute ischemic stroke, IAT, intra-arterial treatment





CHAPTER 7

The effect of anesthetic management during intra-arterial therapy for acute stroke in MR CLEAN

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ABSTRACT

Background

The aim of the current study was to assess the influence of anesthetic management on the effect of treatment in MR CLEAN.

Methods

MR CLEAN was a multicenter, randomized, open label trial of IAT versus no IAT. The intended anesthetic management at the start of the procedure was used for this post-hoc analysis. The primary effect parameter was the adjusted common odds ratio (acOR) for a shift in direction of a better outcome on the modified Rankin Scale (mRS) at 90 days, estimated with multivariable ordinal logistic regression analysis, which included a term for general anesthesia (GA).

Results

GA was associated with significant ($P=0.011$) effect modification, resulting in estimated decrease of 51% (95%CI; 31% to 86%) in treatment effect compared to Non-GA. We found a shift in the distribution on the mRS in favor of Non-GA compared to control group [acOR 2.18 (95%CI; 1.49 to 3.20)]. The shift in distribution between GA and control group was in similar direction [acOR 1.12 (95%CI; 0.71 to 1.78)] with loss of statistical significance.

Conclusions

In this post-hoc analysis, we found that the type of anesthetic management influences outcome following intra-arterial therapy. Only treatment without general anesthesia was associated with a significant treatment benefit in MR CLEAN.

Classification of Evidence

This study provides Class II evidence that for patients with acute ischemic stroke undergoing intra-arterial treatment, mRS scores at 90 days improve only in patients treated without general anesthesia.

INTRODUCTION

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

Controversy exists about the optimal anesthetic management during intra-arterial treatment. A recent consensus statement from a task force of US-based neuro-anesthesiologists found the available data inconclusive.⁶ Current evidence is based on the comparison of outcome after IAT in series of patients from surveys and treatment arms of randomized trials. Reported outcomes are better when IAT is performed without general anesthesia (Non-GA), which means applying local anesthesia in the groin, with or without subsequent use of conscious sedation.⁷⁻⁹ The Non-GA approach may lead to faster treatment initiation and may avoid complications associated with intubation. Furthermore, it is known that most anesthetic agents used for GA induce sympatholysis which may lead to hypotension and decreased cerebral perfusion.^{10,11} On the other hand, general anesthesia (GA) reduces patient movement during the procedure and may therefore decrease procedural times and procedure-related complications. The choice between the anesthetic approaches is most often based on the preference of the interventionist or custom of the center.

In this post hoc analysis, we investigated the influence of anesthetic management on the effect of treatment in the MR CLEAN trial.

METHODS

Methodology informing classification of evidence

We seek to answer the following research question: Does general anesthetic management in patients with acute ischemic stroke caused by an intracranial occlusion of the anterior circulation modify the treatment effect of intra-arterial therapy found in the MR CLEAN trial? Class II level of evidence is assigned to this question.

Patients and procedures

Patient eligibility and methods of MR CLEAN have been reported previously.^{1,12} MR CLEAN was a randomized clinical trial of IAT versus no IAT in patients with a proximal arterial occlusion in the anterior circulation demonstrated on vessel imaging, treatable within 6 hours after symptom onset. The primary outcome was the score on the modified Rankin Scale (mRS)

at 90 days. Use of GA was prospectively recorded as part of the intervention Case Report Form, which was in use during the trial. Patients receiving treatment under GA were intubated, or received a laryngeal mask. Patients converted to GA during IAT were scored as Non-GA according to intention to treat principle. No data were collected on the use of conscious sedation, blood pressure, or cerebral blood flow (CBF) during IAT. The steering committee gave no recommendations about type of anesthetic management and left this decision to the discretion of the MR CLEAN centers. Nevertheless, the majority of centers adhered to a fixed protocol regarding type of anesthetic management throughout the trial.

Outcome and safety measures

The primary outcome measure was the mRS score at 90 days. The mRS is a 7-point scale ranging from 0 (no symptoms) to 6 (dead). A score of 2 points or less indicates functional independence.¹³

Secondary outcome measures included the proportion of patients who reached functional independence (mRS 0-2) at 90 days and neurological assessment with the National Institute of Health Stroke Score (NIHSS; range 0 to 42, with higher scores indicating more severe neurologic deficits) at 24 hours and 5-7 days or discharge if earlier. Radiological outcome measures included the modified Thrombolysis in Cerebral Infarction (TICI) 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 non-contrast CT (NCCT) at 5-7 days. The modified TICI score is a 4-point scale, which ranges from 0 (no reperfusion) to 3 (complete antegrade reperfusion of the previously ischemic territory, with absence of visualized occlusion in all distal branches).¹⁴

Serious adverse events included hemorrhagic complications, progression of ischemic stroke, recurrent ischemic stroke and death. Symptomatic intracranial hemorrhage was defined as neurological deterioration of 4 or more points on the NIHSS and intracranial hemorrhage confirmed by neuroimaging. Progression of ischemic stroke was defined as neurological deterioration with an increase of 2 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. Procedure related safety parameters included vessel perforations, dissections, and new emboli outside of the target downstream territory (ENT).¹⁴

Statistical analysis

The primary effect parameter was the adjusted common odds ratio (acOR) for a shift in direction of a better outcome on the mRS, estimated with multivariable ordinal logistic regression analysis, which included a term for GA. This was used to estimate acORs for GA and Non-GA versus control. The acOR and all secondary effect parameters were adjusted for potential imbalances in known prognostic variables adapted from the original trial protocol statistical analysis plan: age, stroke severity (NIHSS) at baseline, time since onset to randomization, previous stroke, atrial fibrillation, diabetes mellitus and presence of intracranial carotid artery

(ICA) terminus occlusion. For the primary outcome we also explored the effect of center and pre randomization mRS by additional adjustments with these variables. If patients were allocated to the intervention arm, but IAT was withheld, patients were excluded from all analyses. Furthermore, a sensitivity analysis was conducted in order to limit the potential effect of confounding by indication by excluding centers without a fixed protocol for either GA or Non-GA. The direct comparison between GA and Non-GA groups was conducted as secondary analyses for the primary and secondary outcome parameters.

The adjusted and unadjusted common odds ratios were reported with 95% confidence intervals (CI) to indicate statistical precision. Binary outcomes were analyzed with logistic regression and reported as adjusted and unadjusted odds ratios with 95% confidence intervals. All p-values are 2-sided. Statistical analyses were performed with Stata/SE 13.1 (StataCorp, Texas, USA).

Standard Protocol Approvals, Registrations, and Patient Consents

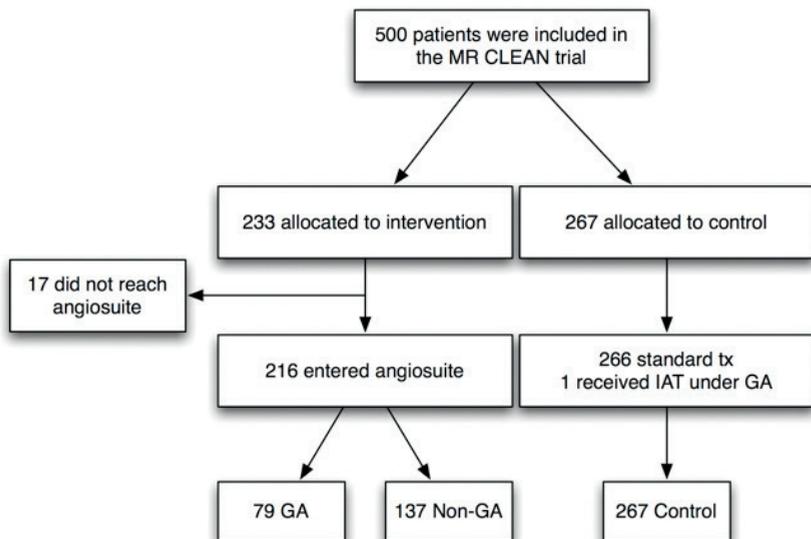
All patients or their legal representatives provided written informed consent before randomization. A central medical ethics committee and the research board of each participating center approved the study protocol. The design and data collection were performed by members of the executive committee and the local investigators of each participating centers. The study sponsors were not involved in the study design, study conduct, protocol review, or manuscript preparation or review. The MRCLEAN is registered under number NTR1804 in the Dutch trial register and under ISRCTN10888758 in the ISRCTN register.

RESULTS

Patient and center characteristics

Patients were recruited from December 2010 until March 2014. Of the 500 patients, 233 patients (47%) were allocated to the intervention arm and 267 patients (53%) to the control arm. One patient received IAT after being allocated to the control group. Seventeen patients (7%), randomized to intervention, did not receive IAT and were excluded from the analysis. Of 216 patients, 79 patients (37%) had GA and 137 (63%) were treated in a Non-GA setting (Figure 1). Three of the 16 centers used general anesthesia exclusively, with an additional four centers demonstrating a greater than 50% usage of GA. Conversion to GA occurred in 6/137 (4.4%) of the cases because of severe movement and discomfort. Risk factors for poor outcome, clinical risk factors for stroke and pre-randomization treatment details were evenly distributed between groups (Table 1).

■ **Figure 1.** Flow diagram of patients included in the MR CLEAN.



Patients included in MR CLEAN subdivided in intra-arterial therapy under general anesthesia (GA), intra-arterial treatment without general anesthesia (Non-GA) and control arm of the trial.

■ **Table 1.** Clinical characteristics at baseline of patients included in the MR CLEAN, subdivided in intra-arterial therapy under general anesthesia (GA), intra-arterial treatment without general anesthesia (Non-GA) and control arm of the trial.

	GA (N=79)	Non-GA (N=137)	Control (N=267)
Age in years - median (IQR)	63 (51-76)	66 (56-76)	65 (55-76)
Male sex - n (%)	47 (59.5)	79 (57.7)	157 (58.8)
NIHSS score - median (IQR)	18 (15-21)	17 (14-21)	18 (14-22)
Glasgow Coma Score - median (IQR)	13 (11-15)	13 (11-15)	13 (11-15)
Clinical localization: Left hemisphere - n (%)	36 (45.6)	68 (49.6)	153 (57.3)
History of ischemic stroke - n (%)	13 (16.5)	16 (11.7)	25 (9.4)
Atrial fibrillation - n (%)	26 (32.9)	36 (26.3)	69 (25.8)
Diabetes mellitus - n (%)	7 (8.9)	24 (17.5)	34 (12.7)

Table 1. Clinical characteristics at baseline of patients included in the MR CLEAN, subdivided in intra-arterial therapy under general anesthesia (GA), intra-arterial treatment without general anesthesia (Non-GA) and control arm of the trial. (continued)

	GA (N=79)	Non-GA (N=137)	Control (N=267)
Pre-stroke modified Rankin Scale score – n (%)			
0	60 (76.0)	116 (84.7)	214 (80.2)
1	10 (12.7)	10 (7.3)	29 (10.9)
2	2 (2.5)	9 (6.6)	13 (4.9)
>2	7 (8.8)	2 (1.4)	11 (4.0)
Systolic blood pressure – mean mmHg (SD) [#]	141 (26)	149 (27)	145 (24)
Treatment with IV alteplase – n (%)	67 (84.8)	120 (87.6)	242 (90.6)
Time from onset to start of IV alteplase – minutes median (IQR)	80 (59-105)	85 (70-110)	87 (65-116)
Extent of infarct on CT as measured by NCCT ASPECTS – median (IQR) [*]	9 (7-10)	9 (7-10)	9 (8-10)
Intracranial arterial occlusion [*]			
Intracranial ICA – n (%)	0 (0)	1 (0.7)	3 (1.1)
ICA-T – n (%)	21 (26.6)	34 (24.8)	75 (28.2)
M1 segment – n (%)	51 (64.6)	92 (67.2)	165 (62.0)
M2 segment – n (%)	6 (7.6)	10 (7.3)	21 (7.9)
A1/2 segment – n (%)	1 (1.2)	0 (0)	2 (0.8)
Time from onset to randomization – minutes median (IQR) [‡]	212 (154-276)	203 (156-243)	196 (149-266)

Abbreviations: IQR = interquartile range; NIHSS = National Institutes of Health Stroke Scale range 0 to 42, higher scores indication more severe neurological deficits; SD = standard deviation; IV = intravenous; ASPECTS = Alberta Stroke Program Early CT Score, range 0 to 10, higher scores indicate less early ischemic changes; ICA = Internal Carotid Artery (intracranial segment); ICA-T = Internal Carotid Artery with involvement of the M1 segment; M1/2 = Middle cerebral artery segments; A1/A2 = Anterior cerebral artery segments.

[#]Systolic blood pressure at baseline was missing in 1 patient.

^{*}ASPECTS was not available in 4 patients: NCCT was not performed in 1 patient; 3 patients had ACA territory strokes.

^{*}Vessel imaging was not performed in 1 patient and level of occlusion is not available.

[‡]Randomization time was missing in 2 patients.

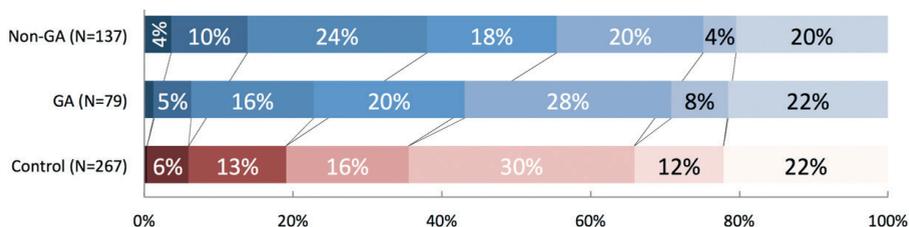
Primary outcome

No patients were lost to follow-up. The overall effect of treatment in MR CLEAN consisted of a significant shift in direction of a better outcome in the distribution of the mRS (acOR 1.67 [95%CI; 1.21 to 2.30]). The overall treatment effect was modified by anesthetic management (p=0.011). Treatment under GA was associated with a decrease of 51% (95%CI 31% to 86%) of this primary effect parameter. The effect of treatment in Non-GA was significant (acOR 2.18 [95%CI; 1.49 to 3.20]). The shift in distribution between GA and control was in the same direction (acOR 1.12 [95%CI; 0.71 to 1.78]), but the effect was smaller and not statistically significant (Table 2). The shift towards better outcome was consistent for all categories of the

mRS, except for dead (Figure 2). The acOR was not affected by adjustment for center (2.18 [95%CI 1.49 to 3.20] for Non-GA vs control, and 1.11 [95%CI 0.70 to 1.77] for GA vs control) nor for pre randomization mRS (acOR 2.14 [95%CI 1.46 to 3.13] for Non-GA vs control & 1.15 [95%CI 0.73 to 1.82] for GA vs control).

The effect of GA, if directly compared to Non-GA, resulted in a decrease of 0.58 (95%CI 0.34 to 0.97) for improvement on the mRS in the adjusted analyses (Supplemental Table e-1). If converted patients were taken out of the Non-GA and added to GA group, the acOR was almost identical (0.58 [95%CI 0.35 to 0.97]).

■ **Figure 2.** Modified Rankin Scale at 90 days by intention to treat groups.



The number and percentages of patients are shown in each cell according to distribution of the modified Rankin Scale (range 0 to 6, with 0 indicating no symptoms, 1 no clinically significant disability, 2 slight disability (able to look after own affairs without assistance but unable to carry out all previous activities), 3 moderate disability (requires some help but able to walk unassisted), 4 moderately severe disability (unable to attend to bodily needs without assistance and unable to walk unassisted), 5 severe disability (requires constant nursing care and attention), and 6 dead). We found a shift in the distribution on the modified Rankin Scale in favor of the Non-GA group compared to MR CLEAN control group [acOR 2.18 (95%CI; 1.49 to 3.20)]. The shift in distribution between GA and MR CLEAN control group was in similar direction [acOR 1.12 (95%CI; 0.71 to 1.78)].

Secondary outcomes and safety parameters

In this study, we found an absolute risk difference of 19% for functional independence at 3 months (mRS 0-2) in favor of the Non-GA group compared to control [aOR 2.96 (95%CI 1.78 to 4.92)]. The absolute difference in functional independence was 4% in favor of the GA group compared to control [aOR 1.17 (95%CI 0.60 to 2.29)]. In Non-GA patients the NIHSS had improved 3.0 points more after 24 hours and 4.8 points more after 1 week than in controls. We found less infarct reduction relative to control in the GA group (12.7 ml) as compared to Non-GA (21.8 ml). No effect on improvement on the NIHSS was observed in patients treated under GA compared to controls (Table 2).

■ **Table 2.** Primary and secondary outcomes of patients included in the MR CLEAN.

Outcome	GA (N=79)	Non-GA (N=137)	Control (N=267)	Effect parameter	Unadjusted effect GA vs Control (95%CI)	Unadjusted effect Non-GA vs Control (95%CI)	Adjusted effect GA vs Control (95%CI)	Adjusted effect Non-GA vs Control (95%CI)
Primary								
mRS at 90 days – median (IQR)	4 (3-5)	3 (2-4)	4 (3-5)	cOR	1.23 (0.79 to 1.91)	2.02 (1.39 to 2.95)	1.12 (0.71 to 1.78)	2.18 (1.49 to 3.20)
Secondary – clinical								
mRS 0-1 at 90 days – n. (%)	5 (6.3)	19 (13.9)	16 (6.0)	OR	1.06 (0.38 to 3.00)	2.53 (1.25 to 5.09)	1.07 (0.37 to 3.13)	2.60 (1.26 to 5.36)
mRS 0-2 at 90 days – n. (%)	18 (22.8)	52 (38.0)	51 (19.1)	OR	1.25 (0.68 to 2.30)	2.59 (1.63 to 4.11)	1.17 (0.60 to 2.29)	2.96 (1.78 to 4.92)
mRS 0-3 at 90 days – n. (%)	34 (43.0)	76 (55.5)	96 (35.6)	OR	1.37 (0.82 to 2.28)	2.26 (1.48 to 3.42)	1.31 (0.74 to 2.32)	2.59 (1.63 to 4.14)
NIHSS after 24 hours – mean (SD) [‡]	15.5 (7.8)	12.6 (9.0)	16.1 (7.5)	Beta	-0.60 (-2.67 to 1.47)	-3.51 (-5.20 to -1.83)	-0.64 (-2.41 to 1.13)	-3.00 (-4.39 to -1.54)
NIHSS at 5-7 days or discharge – mean (SD) [‡]	13.2 (8.5)	7.8 (7.1)	13.0 (7.9)	Beta	0.13 (-2.00 to 2.25)	-5.26 (-7.00 to -3.51)	0.07 (-1.83 to 1.98)	-4.76 (-6.32 to -3.20)
Secondary - radiological								
Intra-cranial occlusion on follow-up CTA [*] – n./total n. (%)	16 / 63 (25.4)	23 / 111 (20.7)	139 / 207 (67.2)	OR	0.17 (0.09 to 0.31)	0.13 (0.07 to 0.22)	0.15 (0.08 to 0.29)	0.12 (0.07 to 0.21)
Final infarct volume on follow-up NCCT – n./total n. (%) [*]	46 / 79 (58.2)	88 / 137 (64.2)	163 / 267 (61.0)					

■ **Table 2.** Primary and secondary outcomes of patients included in the MR CLEAN. (continued)

Outcome	GA (N=79)	Non-GA (N=137)	Control (N=267)	Effect parameter	Unadjusted effect GA vs Control (95%CI)	Unadjusted effect Non-GA vs Control (95%CI)	Adjusted effect GA vs Control (95%CI)	Adjusted effect Non-GA vs Control (95%CI)
Volume in milliliters – mean (SD)	82.3 (76.9)	67.7 (70.6)	92.3 (73.3)	Beta	-9.9 (-33.9 to 14.0)	-24.6 (-43.6 to -5.6)	-12.7 (-36.0 to 10.7)	-21.8 (-40.2 to -3.5)
Secondary – time difference in GA versus Non-GA in min (SD)					Unadjusted effect GA versus Non-GA (95%CI)		Adjusted effect GA versus Non-GA (95%CI)	
Door to groin puncture	162 (69)	134 (60)	- (-)	Beta	28 (10.0 to 45.7)		31 (13.4 to 49.5)	
Randomization to groin puncture	79 (64)	50 (32)	- (-)	Beta	14 (5.6 to 22.9)		16 (7.0 to 24.2)	
Procedural duration	76 (35)	79 (41)	- (-)	Beta	-3.6 (-14.6 to 7.3)		-6.5 (-17.4 to 4.5)	
Onset to revascularization or last angiogram	334 (86)	349 (81)	- (-)	Beta	15 (-8.9 to 39)		7.6 (-6.5 to 22)	

Primary and secondary outcomes subdivided in intra-arterial treatment under general anesthesia (GA), intra-arterial treatment without general anesthesia (Non-GA) and control arm of the trial. The table lists numbers of patients and percentages in each treatment group, type of effect parameter (OR or linear regression coefficient), unadjusted and adjusted for age, NIHSS at baseline, time to randomization, previous stroke, atrial fibrillation, diabetes mellitus and presence of ICA terminus occlusion.

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.

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

The effect of GA, if directly compared to Non-GA, resulted in a decrease for improvement on the mRS in the unadjusted, as well as the adjusted analyses (Supplemental Table e-1). If a patient received treatment under GA, the average score on the NIHSS was higher after 24 hours (2.43 [95%CI 0,20 tot 4,67]), and this difference further increased at 5-7 days or discharge (4.69 [95%CI 2.49 tot 6.89]).

We found no major differences between groups in terms of safety outcomes, except for progressive ischemic stroke. Progression of ischemic stroke occurred more often in patients treated under GA (30% GA vs 18% control, P=0.017) (Table 3).

Procedural related outcomes and safety

On average, time from door to groin puncture was 32 minutes longer in the GA group (p=0.001), and time from randomization to groin puncture was 16 minutes longer (p<0.001). We found no significant differences between GA and non-GA patients in procedure duration, and time from onset to revascularization or, in case no revascularization was reached, time from onset to last angiogram (Table 2).

The rate of recanalization (mTICI 2b/3) on post treatment DSA was 63% in the Non-GA group and 52% in the GA group, for a difference of 11% (p=0.19). Two vessel perforations occurred in the Non-GA group, both patients died as a result. In total, four patients (two in each group) suffered from procedural related dissections (Table 3).

Table 3. Safety parameters and Serious Adverse Events within 90-days after randomization in GA, Non-GA and control arm.

	GA (N=79)	Non-GA (N=137)	Control (N=267)
Safety parameters:			
Death			
Within 7 days – n (%)	6 (7.6)	8 (5.8)	11 (4.1)
Within 30 days – n (%)	12 (15.2)	18 (13.1)	27 (10.1)
Vessel perforations – n (%)	0 (-)	2 (1.5)	0 (-)
Procedure related dissections – n (%)	2 (2.5)	2 (1.5)	0 (-)
ENT – n (%)	8 (10.1)	12 (8.8)	0 (-)
Serious adverse events:*			
Patients with at least one SAE – n (%)	43 (54.4)	57 (41.6)	113 (42.3)
Symptomatic ICH – n (%)			
Any type	6 (7.6)	11 (8.0)	17 (6.4)
Parenchymal hematoma type 1 (PH1) [^]	0 (-)	0 (-)	2 (0.75)
Parenchymal hematoma type 2 (PH2) [^]	5 (6.3)	8 (5.8)	14 (5.2)

Table 3. Safety parameters and Serious Adverse Events within 90-days after randomization in GA, Non-GA and control arm. (continued)

	GA (N=79)	Non-GA (N=137)	Control (N=267)
Hemorrhagic infarction type 1 (HI1) ^{&}	0 (-)	1 (0.73)	0 (-)
Hemorrhagic infarction type 2 (HI2) ^{&}	0 (-)	1 (0.73)	1 (0.37)
Subarachnoid hemorrhage	1 (1.3)	1 (0.73)	0 (-)
Recurrent acute ischemic stroke – n (%)	4 (5.1)	8 (5.8)	1 (0.4)
Progressive ischemic stroke – n (%) [#]	24 (30.4)	17 (12.4)	47 (17.6)
Pneumonia – n (%)	11 (13.9)	13 (9.5)	41 (15.4)
Other complication – n (%)	10 (12.7)	11 (8.0)	33 (12.4)

Abbreviations: SAE = Serious Adverse Event; ICH = Intra Cerebral Hemorrhage, ENT= embolization into new territory.

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

[^]Parenchymal hematoma defined as; PH1 Blood clot(s) ≤ 30% of infarct area with some mild space-occupying effect; PH2 Blood clots > 30% of infarct area with significant mild space-occupying effect.

[&]Hemorrhagic infarcts defined as; HI1 small petechiae along the margins of the infarct; HI2 with more confluent petechiae within the infarct area.

[#]Difference between GA versus control was statically significant (P=0.017).

Sensitivity analysis

A sensitivity analysis of the primary outcome, which only included patients in centers that used either GA or Non-GA exclusively (N=236 in 10 centers), showed similar differences in effect between Non-GA versus control [2.78 (95%CI; 1.57 to 4.94)] and GA versus control [1.21 (95%CI; 0.57 to 2.56)], although the effect modification was not statistically significant (P=0.065) anymore.

DISCUSSION

In this post hoc analysis of MR CLEAN, the method of anesthesia appears to influence outcome following intra-arterial treatment. Specifically, non-general anesthesia was associated with a significant benefit of intra-arterial treatment, whereas there was no benefit of IAT in the subgroup of patients treated under general anesthesia.

Our findings expand upon earlier reports, which demonstrated worse outcomes after IAT under general anesthesia. However, these studies could not examine the influence of the anesthetic approach on treatment effect because of the absence of a control group without IAT. There is currently equipoise within the treating community regarding the optimal anesthetic approach. In a recent survey of neurointerventional practitioners, 49% of respondents reported using

general anesthesia primarily.¹⁵ The results of our analysis however strongly challenge the use of general anesthesia as a first-line approach.

Nevertheless, there are patients who will need GA due to a decreased level of consciousness for airway protection or poor cooperation due to agitation or pain.⁶ Consequently, it is important to elucidate the mechanisms by which general anesthesia negates the benefits of intra-arterial therapy. A recent study suggests that this detrimental effect is ultimately mediated through infarct growth.¹⁶ The authors demonstrated that GA was an independent predictor of final infarct volume $>70 \text{ cm}^3$ (OR 4.0, $P=0.004$). In line with this finding, we found less infarct reduction relative to control in the GA group. The unadjusted difference in volume between GA and Non-GA was 15ml (Supplemental Table e-1). Final infarct volumes of patients with neurological deterioration before day 3 are not included in this analysis and might have further influenced a difference in infarct growth.

One potential mechanism by which general anesthesia may be related to infarct growth and worse outcome is the time delay associated with intubation. In MR CLEAN, the time from randomization to groin puncture was 16 minutes longer in the GA group on average. However, this did not translate to a significant difference in the time from onset to revascularization. Another potential mechanism is uncorrected anesthesia-induced blood pressure reduction and altered cerebral hemodynamics at the introduction of GA and during GA. Most anesthetic agents, for example propofol or induction dosages of thiopental, are known to be associated with hypotension.¹⁷ Lower mean arterial blood pressures have been associated with poorer clinical outcomes in patients treated under GA compared to conscious sedation.^{11,18} Furthermore, anesthetic agents may cause disturbance in cerebral autoregulation, potentially impairing cerebral blood flow and perfusion.¹⁰ The effect of anesthetic agents in patients suffering from acute ischemic stroke, which in itself can injure cerebral autoregulation, requires further investigation.

Another potential disadvantage of GA management is the increased risk of aspiration and at times aspiration pneumonia following intubation.^{7,19} On the other hand, emergency intubation may still be required during the non-GA approach, possibly accompanied by even a higher risk of aspiration and airway trauma.^{19,16} Because the incidence of pneumonia was equal between the groups in our study, combined with a low rate (6/137) of emergency endotracheal intubations in the Non-GA group, this probably does not explain poorer outcome in the GA group. In MR CLEAN, conversion to GA occurred in 4.4%, and direct availability of anesthetic team during treatment without Non-GA is recommended.

Those in favor of general anesthesia have cited greater procedural safety and shorter duration of the treatment secondary to decreased patient motion. Indeed, there were two vessel perforations leading to death in the Non-GA group, whereas no such events were noted in the GA group. However, there were no overall differences in procedure-related serious adverse events. Similarly, there was a decrease in procedure duration among GA patients, but this was

not significant and did not lead to a difference in overall time to revascularization. Decrease in patient motion could potentially lead to a higher revascularization rate. On the contrary, we found an absolute difference in recanalization of 11% in favor of patients treated without GA. This may have contributed to the better outcome in the Non-GA group. However, a difference in recanalization rate of this size is not sufficient enough to explain the treatment modification by GA that we observed in our study.

Our study is a post hoc analysis and may be affected by selection bias. However, there were no differences in baseline stroke severity on the NIHSS between the anesthesia groups. Moreover, 10 out of the 16 MR CLEAN centers used one approach exclusively, mitigating potential bias related to clinical patient characteristics at presentation (eq levels of agitations or clinical instability that are no evident from the NIHSS) In addition, the sensitivity analysis showed similar adjusted common odd ratios between Non-GA vs control. We do not know the mechanism or cause of the treatment effect modification and therefore, it may well be so that neuro-anesthesia in experienced hands leads to similar outcomes as Non-GA.

Our results should be confirmed in future trials that randomize between types of anesthesia. Currently three trials are randomizing AIS patients between general anesthesia and conscious sedation.²⁰⁻²²

Data on the type of anesthetics used during GA were not collected in MR CLEAN. Moreover, there were no data on the use of conscious sedation in the Non-GA group. As previously mentioned, also no systematically collected data on blood pressure, nor cerebral perfusion were prospectively collected during the time of anesthesia. These limitations prevent us from studying the explanatory factors and possible underlying mechanisms that might explain worse outcomes under general anesthesia. Furthermore, safety concerns might be underestimated due to sample size.

Conclusion

In this post-hoc analysis of MR CLEAN, we found that the type of anesthetic management appears to influence outcome following intra-arterial therapy. Only treatment without general anesthesia was associated with a significant treatment benefit in MR CLEAN. This finding may have major implications for current interventional practice. Confirmation of these results is necessary, and randomized controlled trials are ongoing.

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CHAPTER 7

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SUPPLEMENTAL MATERIAL

■ **Table e-1.** Primary and secondary outcomes of direct comparison of GA or Non-GA management in patients allocated to intervention.

Outcome	Effect parameter	GA (N=79)	Non-GA (N=137)	Unadjusted effect of GA (95%CI)	Adjusted effect of GA (95%CI)
Primary					
mRS at 90 days – median (IQR)	cOR	4 (3-5)	3 (2-4)	0.63 (0.39 to 1.02)	0.58 (0.34 to 0.97)
Secondary – clinical					
mRS 0-1 at 90 days – n. (%)	OR	5 (6.3)	19 (13.9)	0.42 (0.15 to 1.17)	0.40 (0.13 to 1.23)
mRS 0-2 at 90 days – n. (%)	OR	18 (22.8)	52 (38.0)	0.48 (0.26 to 0.90)	0.41 (0.20 to 0.85)
mRS 0-3 at 90 days – n. (%)	OR	34 (43.0)	76 (55.5)	0.61 (0.35 to 1.06)	0.54 (0.28 to 1.02)
NIHSS after 24 hours – mean (SD) [‡]	Beta	15.5 (7.8)	12.6 (9.0)	2.91 (0.47 to 5.36)	2.43 (0.20 to 4.67)
NIHSS at 5-7 days or discharge – mean (SD) [‡]	Beta	13.2 (8.5)	7.8 (7.1)	5.39 (3.06 to 7.72)	4.69 (2.49 to 6.89)
Secondary - radiological					
Intra-cranial occlusion on follow-up CTA [‡] – n. / total n. (%)	OR	16 / 63 (25.4)	23 / 111 (20.7)	1.30 (0.63 to 2.70)	1.19 (0.55 to 2.58)
Final infarct volume on follow-up NCCT – n. / total n. (%) [*]		46 / 79 (58.2)	88 / 137 (64.2)		
Volume in milliliters – mean (SD)	Beta	82.3 (76.9)	67.7 (70.6)	14.66 (-11.42 to 40.75)	4.64 (-21.09 to 30.37)

Primary and secondary outcomes subdivided in intra-arterial treatment under general anesthesia (GA), intra-arterial treatment without general anesthesia (Non-GA). The table lists numbers of patients and percentages in each treatment group, type of effect parameter (OR or linear regression coefficient), unadjusted and adjusted for age, NIHSS at baseline, time to randomization, previous stroke, atrial fibrillation, diabetes mellitus and presence of ICA terminus occlusion. 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.

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





CHAPTER 8

Improving workflow for endovascular treatment in acute ischemic stroke

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In progress ■

ABSTRACT

Introduction

Time to treatment is one of the most important prognostic factors for endovascular treatment (EVT) of acute ischemic stroke (AIS). We studied the effect of workflow improvements on time to treatment in our high-volume comprehensive stroke center.

Methods

We performed a prospective sequential cohort study: period I (during workflow improvements, April 2014–December 2016) compared to period II (after workflow improvements, January 2017–January 2018). We included consecutive AIS patients treated with EVT with referrals from 13 primary stroke centers. Workflow improvements were: switching from primary general anesthesia to local anesthesia, optimization of transfers through a regional protocol, one stop CT/CT-angiography, preparation of IVT during image acquisition, digital image transfer, referral without consultation, and preparation of the angio-suite prior to patient arrival. Primary outcome was the door (first hospital)-to-groin time (FDGT). Secondary outcomes included functional outcome (modified Rankin Scale [mRS] after 90 days), successful reperfusion (eTICI 2b-3), and symptomatic intracranial hemorrhage (sICH). Time periods were compared using (ordinal) logistic regression and multivariable Cox regression analysis.

Results

We included 439 patients (256, 58% period I, 183 (42%) period II). Median FDGT was shorter for patients in period II (115 vs. 148 minutes, adjusted hazard ratio 1.83, 95%CI 1.49–2.26). Patients in period II had a higher chance of achieving excellent functional outcome (mRS 0-1 at 90 days, aOR 2.21, 95%CI 1.30 – 3.76). Rates of successful reperfusion were better in period II (71% vs. 57%, aOR 1.89, 95%CI 1.23 – 2.91). Mortality and sICH rates were similar.

Conclusion

Innovations to improve workflow for patients receiving EVT led to shorter door-to-groin times and were associated with improved functional outcomes.

INTRODUCTION

Onset-to-treatment time is an important prognostic parameter for functional outcome after endovascular treatment (EVT) for acute ischemic stroke (AIS).¹ Since the worldwide implementation of EVT in 2015, the clinical and radiological stroke work-up has evolved rapidly and has become more complex. In the pre-EVT era, only a clinical diagnosis of ischemic stroke, a non-contrast CT scan (NCCT) to rule out hemorrhage, and a few clinical parameters were required to make treatment decisions regarding intravenous thrombolysis (IVT). Nowadays, at least a CT-angiography (CTA) is required to confirm large vessel occlusion. Moreover, for patients with symptoms >6 hours or unknown time of onset, CT- or magnetic resonance-perfusion imaging has to be performed to determine the amount of salvageable tissue.²⁻⁵ Logistics are complicated even further since only comprehensive stroke centers are capable of EVT, making as-fast-as-possible inter-hospital transport of patients with AIS an everyday challenge.

Further evolution of the AIS treatment paradigm introduced new bottlenecks in standard stroke care.⁶ For both IVT and EVT, several innovations to improve in-hospital logistics as well as the introduction of treatment times (door-to-needle [DNT] and door-to-groin [DGT] times) resulted in significantly decreased treatment times in several studies.⁷⁻¹¹ However, substantial differences between countries' population and hospital density necessitate tailored solutions. With this knowledge, a multidisciplinary initiative was set up to improve intra- and inter-hospital logistics in both primary and intervention stroke centers in our acute stroke care region, the greater Amsterdam area.

The aims of this study were (1) to analyze the effect of workflow improvements in both primary and comprehensive stroke centers on EVT treatment times and (2) to evaluate whether these workflow improvements were associated with improved functional outcome of AIS patients treated with EVT.

METHODS

Patient selection

We performed a prospective sequential cohort study comparing the time period before workflow improvements to that after introduction of workflow improvements. The study took place in the greater Amsterdam area, a mixed urban and rural area with 2.75 million inhabitants, including 13 primary stroke centers performing IVT and one comprehensive stroke center performing EVT. We included consecutive patients with AIS of the anterior circulation treated with EVT between April 1st, 2014 and January 1st, 2018. Patients arrived either directly at the intervention center (direct patients) or were transferred from a primary stroke center (transfer patients). We excluded patients with an occlusion of the posterior circulation and patients with a peri-procedural stroke, e.g. during aneurysm coiling.

Initial workflow and regional protocol

A uniform regional protocol of Emergency Medical Services in the greater Amsterdam area was applied for all patients with suspected stroke: patients with symptom onset <6 hours were brought to the closest primary stroke center capable of administering IVT, and eligible patients were transferred to the intervention center for EVT.¹² Patients admitted primarily at the intervention center were directly presented at the CT-suite of the Emergency Department (ED).¹¹ The stroke team consisted of a neurologist (staff or resident), neurology nurse, ED doctor, ED nurse, radiologist (or resident), and radiology technician. Neurological deficits were scored with the National Institutes of Health Stroke Scale (NIHSS). Thereafter, NCCT and/or CTA imaging was acquired. After establishing eligibility for IVT, the neurology nurse prepared alteplase, which was administered intravenously according to international guidelines. Starting in April 2014, in patients with a suspected large vessel occlusion, a CTA was performed to determine EVT eligibility. If CTA showed a proximal intracranial occlusion of the anterior circulation, the neuro-interventionist was contacted. For patients presented in a primary stroke center, transport to the intervention center was initiated after EVT eligibility was confirmed by the local neurologist. Only in case of significant clinical deterioration or improvement, or absence of imaging from the primary stroke center, neuro-imaging was repeated in the intervention center.

Workflow improvements

Between January 2015 and October 2017, the following improvements in workflow were implemented. First, in January 2015, we switched from performing EVT routinely under general anesthesia to local anesthesia.¹³ Second, in January 2016, the StrokeNet protocol was introduced. StrokeNet is a collaboration between all 14 stroke hospitals and the Emergency Medical Services in the greater Amsterdam area and aims to homogenize and improve stroke care in the region. A protocol was drafted containing requirements for each participating center to ensure a 24/7 stroke service including the capability to provide IVT, a work-up with CTA to determine eligibility for EVT, and the presence of a web-based software program to share imaging with the intervention center. A teleradiology system (EVOCS, Fysicon, Oss, the Netherlands) was introduced to allow easier consultation of interventional neuroradiologists by the referring physician to determine eligibility for EVT and to obviate the need of repeat imaging on arrival in the intervention center.¹⁴

Third, in June 2016, the acute stroke scanning protocol in the comprehensive stroke center was changed. Previously, IVT was started after NCCT acquisition and CTA was performed thereafter. In the new situations, all imaging was done sequentially, i.e. NCCT directly followed by CTA and CT perfusion (CTP), prior to IVT administration.

Fourth, representatives of the intervention center visited primary stroke centers in the region and helped addressing bottlenecks in local logistics (e.g. not awaiting clinical improvement of IVT before referral for EVT¹⁵, EVT in older patients¹⁶, and treatment of patients with tandem occlusions¹⁶).

Fifth, in 2017, we introduced a direct referral system enabling neurologists at the primary stroke centers to independently initiate transfer for patients they deemed eligible for EVT, and only contacting the intervention center after initiation of transport. From October 2017 on, this was possible 24/7. Lastly, in 2017, preparation of the angiosuite as soon as the decision for EVT was made, before patient arrival, was incorporated in the local EVT protocol.⁶

Data collection

For the current study, we included data of patients who underwent EVT after the last patient was randomized in the MR CLEAN trial (April 2014).¹⁷ In addition to registration in our local prospective consecutive database of patients treated with EVT, patients that underwent EVT were registered in the MR CLEAN-Registry.¹⁸ All imaging data were core-lab adjudicated by the MR CLEAN Registry imaging committee. We collected data on the following time points: time of stroke onset (defined as time of witnessed onset of stroke symptoms or, when exact onset was unknown, time of last seen well), door of first hospital (door at primary stroke center for transfer patients and door of comprehensive stroke center for both transfer and direct patients), timing of NCCT and CTA at primary stroke center (transfer patients) and comprehensive stroke center (direct patients, but also for transfer patients in case of repeated imaging), administration of intravenous alteplase (needle), arrival at angiosuite, groin puncture, and end of procedure time (sheath withdrawal). The first door to groin puncture time (FDGT) was defined as the time difference between arrival at the first hospital and groin puncture in the angiosuite. Therefore, for patients who were initially presented in a primary stroke center, the door-time of the primary stroke center was used to calculate the FDGT. Functional outcome was measured with the modified Rankin Scale score (mRS) at 90 days and was obtained by a dedicated stroke-nurse through a structured telephone interview.¹⁹

Endpoints

Our primary endpoint was the FDGT. Secondary endpoints included functional outcome at 90 days, rates of successful reperfusion (defined as modified Thrombolysis In Cerebral Infarction (mTICI)²⁰ score of 2b or 3 for patients treated in 2014, and extended Thrombolysis In Cerebral Infarction (eTICI)²¹ score of 2b, 2c or 3 for patients treated from 2015), frequency of symptomatic intracranial hemorrhage (sICH, according to the Heidelberg criteria), and other time intervals.²²

Statistical analyses

We stratified patients according to two periods: period I (prior and during workflow improvements, April 2014–December 2016) compared with period II (after workflow improvements, January 2017–1 January 2018). Intergroup comparisons were performed using the chi-square test, independent samples T-test, or Mann-Whitney U test, as appropriate. Time intervals were expressed as medians with interquartile range and 90th percentile.²³ No imputation was used for descriptive variables and the number of missing values is reported. For regression analyses, missing variables were imputed with multivariate imputation by chained equations with five imputations. The following variables were included: age at

stroke, sex, systolic blood pressure, diastolic blood pressure, baseline NIHSS, history of atrial fibrillation, diabetes, hypertension, hypercholesterolemia, coronary artery disease, ischemic stroke, peripheral arterial disease, use of antiplatelets, statins and anti-hypertensive agents, IVT yes or no, baseline ASPECTS score, baseline collateral score, location of intracranial occlusion, pre-stroke mRS, performed procedure, symptomatic intracranial hemorrhage, post-intervention eTICI scores, mRS at 90 days, door-to-door times, door-to-needle times, door-to-groin times, door-to-groin times with door comprehensive stroke center, onset-to-door times, onset-to-needle times, onset-to-groin times, onset-to-end of procedure times, general anesthesia, off hours presentation.

To establish the overall effect of our workflow improvements, we performed time to event analyses using multivariable Cox regression models to determine whether the likelihood of patients having undergone groin puncture at any given time differed between Period I vs. Period II. We report unadjusted and adjusted Hazard Ratio's (HR) with corresponding 95% confidence intervals (CI). A HR > 1 indicates that patients in period II were more likely to have undergone groin puncture at a given time point compared to period I – thus indicating that EVT was initiated faster in period II. We adjusted for the following pre-specified prognostic factors: age, baseline NIHSS, pre-stroke mRS, systolic blood pressure, IVT use, onset-to-door time, ASPECTS score, collateral scores, and off hours presentation (defined as Monday – Friday between 5PM and 8AM and weekends). In an attempt to evaluate the effect of innovations separately, we stratified our cohort into 5 innovation groups: no innovations (April 2014 – December 2014), introduction of local anesthesia (LA) (January 2015 – December 2015), introduction of local anesthesia and StrokeNet (January 2016 – June 2016), introduction of local anesthesia, StrokeNet and parallel workflow (July 2016 – December 2016), and all innovations (January 2017 – January 2018). We reported median FDGT and adjusted HRs per group (using 'the April 2014 – December 2014' time period as reference group). We adjusted for the same variables as our primary analysis. To illustrate the observed improvement in FDGT per innovation, we plotted the percentage of patients that underwent groin puncture per time point, and their corresponding FDGTs in a cumulative event plot using unimputed data.

For functional outcome, we plotted the percentages of the mRS score at 90 days for patients for both time periods. We used multivariable ordinal logistic regression analysis to estimate the adjusted common odds ratio (acOR) with corresponding 95% CI for a shift in the direction of better functional outcome on the mRS. We adjusted for the following pre-specified prognostic factors: age, baseline NIHSS, pre-stroke mRS, systolic blood pressure, IVT use, onset-to-door time, occlusion location, collaterals, ASPECTS score, and successful reperfusion. For sICH and successful reperfusion, we used multivariable binary logistic regression analysis and adjusted for the following pre-specified prognostic factors: previous stroke, use of anticoagulation, baseline NIHSS, systolic blood pressure, IVT use, and onset-to-groin time.

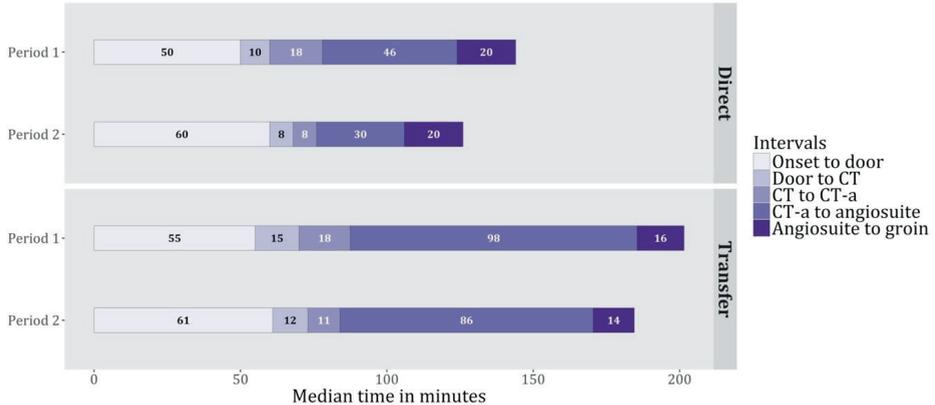
RESULTS

Of 486 patients treated with EVT in the study period, 47 patients were excluded because of a posterior circulation occlusion (n=45) or a peri-interventional stroke (n=2, Supplemental Figure 1). Therefore, 439 patients were included in the analysis. Of these, 256 (58%) patients were treated in period I, and 183 (42%) patients in period II.

Baseline characteristics

Patients presenting during period II were more often male (46% in period II vs. 57% in period I, $p=0.029$), and less often had a history of coronary artery disease (23% vs. 13%, $p=0.012$), Supplemental Table 1. EVT under general anesthesia was less common during period II (7% vs. 30%). Median baseline ASPECTS scores were higher during period II (9 (interquartile range [IQR] 8 – 10) vs. 8 (IQR 7 – 10), $p<0.001$). Additionally, collateral scores were better during period II ($p=0.079$). There was no significant difference in stroke severity (median baseline NIHSS 16 vs. 17, $p=0.128$), rate of IVT administration (76% vs. 78%, $p=0.593$), or transfer rate (73% vs. 68%, $p=0.294$). When looking at subgroups according to transfer status, onset to door times were significantly longer for both transfer and direct patients during period II (direct patients 60 vs. 50 minutes, $p=0.017$, and transfer patients 61 vs. 55 minutes, $p=0.022$, Figure 1 and Supplemental table 2).

■ **Figure 1.** Workflow for direct vs. transfer patients during Period 1 and 2.



Treatment times

Median FDGT was significantly shorter in period II vs. period I: (115 vs. 148 minutes, $p<0.001$, Table 1 and Supplemental table 2).

■ **Table 1.** Outcome measures: time intervals and clinical outcomes

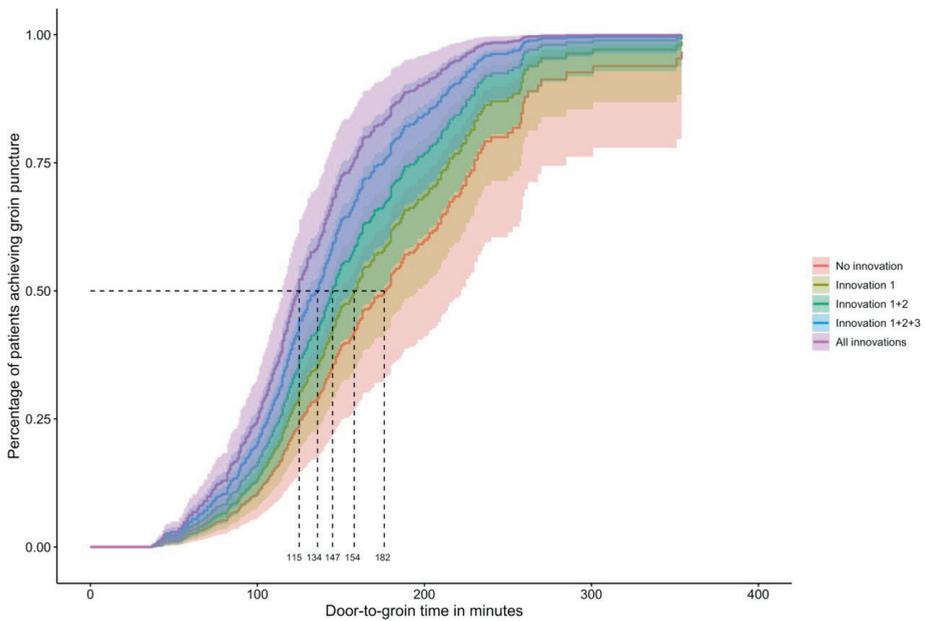
Time intervals in minutes	Period II (n=183)	Period I (n=256)	P-value	Unadjusted Hazard Ratio (95% CI)	Adjusted Hazard Ratio (95% CI)
Door first hospital to groin puncture	115 (90 - 141)	148 (116 - 190)	<0.001	1.74 (1.44 - 2.11)	1.83 (1.49 - 2.26)
Door intervention center to groin puncture	35 (23 - 75)	57 (34 - 100)	<0.001	1.89 (1.55 - 2.31)	2.08 (1.68 - 2.56)
Onset to groin	183 (147 - 236)	210 (170 - 264)	0.002	1.13 (0.93 - 1.37)	1.81 (1.46 - 2.24)
Clinical outcomes - n (%)	Period II (n=183)	Period I (n=256)		Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Median mRS at 90 days (IQR)	4 (2 - 5)	3 (1 - 6)	0.119	1.26 (0.89 - 1.78)*	1.13 (0.77 - 1.65)*
mRS 0-1 at 90 days	51/174 (29)	36/246 (15)	<0.001	2.13 (1.33 - 3.40)	1.98 (1.15 - 3.41)
mRS 0-2 at 90 days	78/174 (45)	87/246 (35)	0.050	1.37 (0.92 - 2.04)	1.19 (0.70 - 2.00)
mRS 0-3 at 90 days	96/174 (55)	119/246 (48)	0.170	1.23 (0.83 - 1.81)	1.00 (0.59 - 1.69)
Mortality at 90 days	46/174 (26)	61/246 (25)	0.704	1.15 (0.73 - 1.79)	1.39 (0.76 - 2.53)
Successful reperfusion ^a	127/179 (71)	140/245 (57)	0.004	1.85 (1.22 - 2.79)	1.89 (1.23 - 2.91)
Symptomatic ICH	9/179 (5)	11/247 (5)	0.782	1.07 (0.43 - 2.65)	0.96 (0.37 - 2.47)

Abbreviations: mRS, Modified Rankin Scale; eTICI, extended Thrombolysis in Cerebral Infarction; ICH, intracerebral hemorrhage; OR, odds ratio. ^aDefined as eTICI 2b-3.

*Adjusted common odds ratio

Patients were significantly more likely to have undergone groin puncture earlier at any given time point in period II when compared to period I (adjusted HR 1.83, 95% CI 1.49 – 2.26), indicating that the workflow from patient arrival to groin puncture was significantly faster in period II. The median door of intervention center to groin puncture and median onset to groin time were also significantly shorter in period II (DGT 35 vs. 57 minutes, $p < 0.001$, adjusted HR 2.08, 95% CI 1.68 – 2.56 and OTG 183 vs. 210 minutes, $p < 0.001$, adjusted HR 1.81, 95% CI 1.46 – 2.24, respectively). Additional treatment times are presented in the Supplemental table 2. All in-hospital workflow times were significantly shorter for patients presented during period II. The angiosuite to groin time was significantly shorter only for transfer patients during period II, not for direct patients. In the analysis evaluating the incremental effect of all innovations, statistical significance was reached after introduction of LA, StrokeNet and parallel workflow (adjusted HR 1.62, 95% CI 1.06 – 2.74), and for all innovations (adjusted HR 2.06, 95% CI 1.39 – 3.06), Figure 2.

■ **Figure 2.** Change in FDGT per workflow improvement.



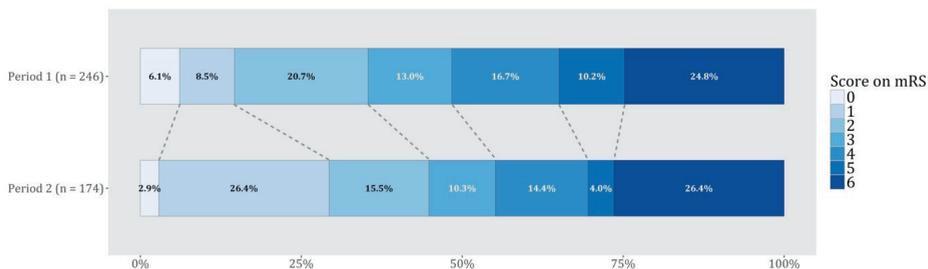
The coloured lines indicate the percentage of patients that underwent groin puncture per group for that particular FDGT: no innovations (red line), introduction of LA (yellow line), introduction of LA and StrokeNet (green line), introduction of LA, StrokeNet and parallel workflow (blue line), and all innovations (purple line).

adjusted HR for innovation 1 = 1.01, 95% CI 0.67 – 1.53,
 adjusted HR for innovation 1+2 = 1.05, 95% CI 0.68 – 1.62,
 adjusted HR for innovation 1+2+3 = 1.62, 95% CI 1.06 – 2.74,
 adjusted HR for all innovations = 2.06, 95% CI 1.39 – 3.06
 (no innovation = reference category).

Clinical outcomes

There was no overall shift towards a better outcome for patients presented during period II; adjusted common OR 1.13, 95% CI 0.77 – 1.65, Figure 3, Table 1. However, patients presented in period II did have a higher chance of achieving excellent functional outcome (mRS 0-1: 29% vs. 15%, aOR 2.21, 95% CI 1.30 – 3.76), Table 1. Rate of successful reperfusion was higher for patients presented in period II: 71% vs. 57%, aOR 1.89, 95% CI 1.23 – 2.91, Table 1 and Supplemental figure 2. There was no significant difference between the two groups in mortality (26% vs. 25%, aOR 1.19, 95% CI 0.67 – 2.12), and sICH (both 5%, aOR 0.96, 95% CI 0.37 – 2.47).

■ **Figure 3** - Functional outcome measured with the modified Rankin Scale score at 90 days (n=19 missing).



Unadjusted common OR 1.26 (95% CI 0.89 – 1.78), adjusted common OR 1.13 (95% CI 0.77 – 1.65).

DISCUSSION

This study showed that regional implemented innovations to improve workflow for patients receiving EVT led to substantially shorter treatment times. Also, patients were more likely to achieve an excellent functional outcome. There was no difference in sICH and mortality rates.

We analyzed transfer and direct patients separately as they oppose different bottlenecks and require separate workflow adjustments. In our cohort, the most notable improvement in workflow for patients directly admitted to the intervention center was observed in the time intervals 'CT to CTA' and 'CTA to angiosuite'. We believe that the direct sequential imaging introduced in our new protocol for our intervention center was essential in achieving this improvement. Importantly, the DNT for patients that received intravenous alteplase did not prolong despite this implementation. Together with the shortened 'CTA to angiosuite' times, this likely indicates that the sequential imaging intervention did not just 'shift' time of intravenous alteplase administration from before to after CTA acquisition, but actually saved time in the total workflow. For transfer patients, the largest delay in DGT was the transfer itself (represented as the CTA to angiosuite time), which is comparable to results found in other studies.^{24,25} As this transfer is already classified as Urgency 1 response by the ambulance services, decreasing this transfer time is challenging. Interestingly, the overall median angiosuite to groin time did not change for patients treated in period I and II. We did see a decrease in angiosuite to groin time for transfer patients specifically, which could be

explained by the fact that the neuro-interventional team is pre-notified that the patient is coming, resulting in enough time to clear the angi-suite and prepare for the EVT procedure.

Apart from improvement in treatment times, we also saw that the rate of successful reperfusion was higher for patients presented in period II. This is similar to at least one other study.²⁶ As the rate of successful reperfusion might influence the association between time period and functional outcome, we added this as a covariate in the adjusted analyses. A potential reason for not finding a significant difference between the two groups in the majority of our outcomes is the lack of power, despite the higher rates of successful reperfusion in Period II.

One of the strengths of this study is that it reflects daily clinical practice in a large region in the Netherlands, with 13 primary stroke centers serviced by one intervention center. Our center has a high treatment volume, and a large proportion of patients were transferred from primary stroke centers. Also, we used the first door-to-groin time as primary outcome, which includes the in-hospital logistics at the primary stroke center and therefore assessed the whole chain of care. Only few other studies report the FDGT as primary outcome.^{27,28} An important limitation of our study is that we are unable to differentiate precisely the effect of each innovation separately. Earlier studies presented a pre- and post-intervention method (with all innovations implemented as 1 package), which makes it statistically easier to find the effect of the interventions as one package.^{11,26} In our study however, innovations were implemented over several years. For our primary analysis, we combined these into one period and compared them to the post-intervention period II. In an additional analysis, we attempted to evaluate the effect of the innovations separately, however, as time passes with the implementation of innovations, the learning curve for the treatment naturally progresses as well. Therefore, for all studies investigating the effect of interventions on workflow, it is difficult to separate an overall learning effect from an intervention effect. Second, our baseline characteristics suggest that there might be some patient selection (for example baseline ASPECTS score) possibly leading to better functional outcomes during Period 2. We adjusted for these variables in our regression analyses. A factor that we unfortunately could not adjust for is the use of CT-perfusion, an imaging modality that since 2018 (after the time period of our study) plays an important role in the selection of patients for EVT presenting outside the standard six hour window.^{3,4,29}

Future perspectives could focus on other workflow improvements, such as specifically trained EVT nurses instead of anesthesiologists at the procedure to relieve the workload for the anesthesiologist, a special EVT pager for transfer patients that includes the neuro-interventionist, direct presentation of transfer patients at the angi-suite, and use of artificial intelligence for automated thrombus detection, ASPECTS, and collateral scoring.

To conclude, our study shows that region-wide innovations in workflow for stroke patients can shorten EVT treatment times as well as, increase the odds of excellent functional recovery.

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SUPPLEMENTAL MATERIAL

■ **Supplemental table 1.** Baseline characteristics

	Period II (n=183)	Period I (n=256)	P-value
Mean age (SD)	68 ± 15	67 ± 15	0.300
Male – n (%)	85/183 (46)	146/256 (57)	0.029
Mean systolic blood pressure (SD) ^a	149 ± 25	145 ± 23	0.088
Mean diastolic blood pressure (SD) ^b	83 ± 17	82 ± 15	0.550
Median NIHSS (IQR)	16 (12 – 20)	17 (13 – 21)	0.128
IVT – n (%)	139/183 (76)	200/256 (78)	0.593
Off hours – n (%)	60/183 (33)	69/255 (27)	0.195
Transferred patients – n (%)	133/183 (73)	174/256 (68)	0.289
General anesthesia – n (%)	13/183 (7)	77/256 (30)	<0.001
Mean glucose (SD) ^c	7.48 ± 2.39	7.49 ± 2.89	0.968
Cardiovascular history – n (%)			
Previous stroke/TIA	31/182 (17)	40/256 (16)	0.694
Atrial fibrillation	36/182 (20)	65/256 (25)	0.170
Diabetes mellitus	30/182 (17)	37/255 (15)	0.572
Hypertension	79/176 (45)	108/255 (42)	0.602
Hypercholesterolemia	34/174 (20)	24/255 (9)	0.003
Coronary artery disease	41/182 (23)	34/255 (13)	0.012
Peripheral artery disease	9/182 (5)	10/255 (4)	0.605
Pre stroke mRS – n (%)			0.184
0	119/177 (67)	189/251 (75)	
1	27/177 (15)	30/251 (12)	
≥ 2	31/177 (18)	32/251 (13)	
Prior medication use – n (%)			
Antiplatelet therapy	46/180 (26)	64/253 (25)	0.951
Antihypertensive agents	100/180 (56)	124/251 (49)	0.207
Anticoagulation ^d	44/180 (24)	57/254 (22)	0.627
Statins	71/182 (39)	75/253 (30)	0.041
Imaging characteristics			
Median ASPECTS at baseline (IQR) ^e	9 (8 – 10)	8 (7 – 10)	<0.001
Location of occlusion – n (%)			0.763

■ **Supplemental table 1.** Baseline characteristics (continued)

	Period II (n=183)	Period I (n=256)	P-value
Intracranial ICA	7/168 (4)	11/232 (5)	
ICA-T	34/168 (20)	59/232 (25)	
M1	102/168 (61)	132/232 (57)	
M2	23/168 (14)	27/232 (12)	
Other (M3, M4, A1, A2)	2/168 (1)	3/232 (1)	
Collateral grade - n (%)			0.079
Absent collaterals	7/166 (4)	17/224 (8)	
Filling < 50% of occluded area	54/166 (33)	94/224 (42)	
> 50% but less < 100%	80/166 (48)	86/224 (38)	
100% of occluded area	25/166 (15)	27/224 (12)	

Abbreviations: SD, standard deviation; NIHSS, National Institutes of Health Stroke Scale; IQR, interquartile range; IVT, intravenous thrombolysis; mRS, Modified Rankin Scale; DOAC, direct oral anticoagulation; ASPECTS, Alberta Stroke Program Early CT Score; interquartile range; ICA, internal carotid artery; ICA-T, internal carotid artery terminus; MCA, middle cerebral artery; ACA, anterior cerebral artery.

Missing data = ^a3 (0.7%), ^b4 (0.9%), ^c73 (16.6%), ^e34 (7.7)

^aHeparin, vitamin K antagonist, direct oral anticoagulant.

■ **Supplemental table 2.** Treatment times, presented as medians with interquartile range and 90th percentile

	Period II (n=183)	Period I (n=256)	Missing - n (%)	P-value
Onset to door	60 (42 - 98, 169)	53 (38 - 74, 118)	37/439 (8.4)	0.002
Onset to IVT	90 (65 - 122, 178)	80 (63 - 107, 149)	5/339 (1.5)	0.063
Door to needle	22 (17 - 32, 46)	26 (20 - 36, 49)	9/339 (2.7)	0.026
Door to door	93 (79 - 115, 163)	120 (100 - 150, 177)	40/307 (13.0)	<0.001
Door first hospital to groin puncture	115 (90 - 141, 186)	148 (116 - 190, 230)	18/439 (4.1)	<0.001
Door intervention center to groin puncture	35 (23 - 57, 89)	57 (34 - 100, 132)	27/439 (6.2)	<0.001
Onset to groin	183 (147 - 236, 322)	210 (170 - 264, 306)	4/439 (0.9)	0.002
Duration of procedure	52 (34 - 74, 89)	57 (39 - 80, 100)	21/439 (4.8)	0.026
Onset to last angio run	234 (186 - 294, 362)	264 (217 - 304, 370)	47/439 (10.7)	0.002
Onset to end procedure	244 (195 - 302, 366)	273 (225 - 316, 376)	22/439 (5.0)	0.001

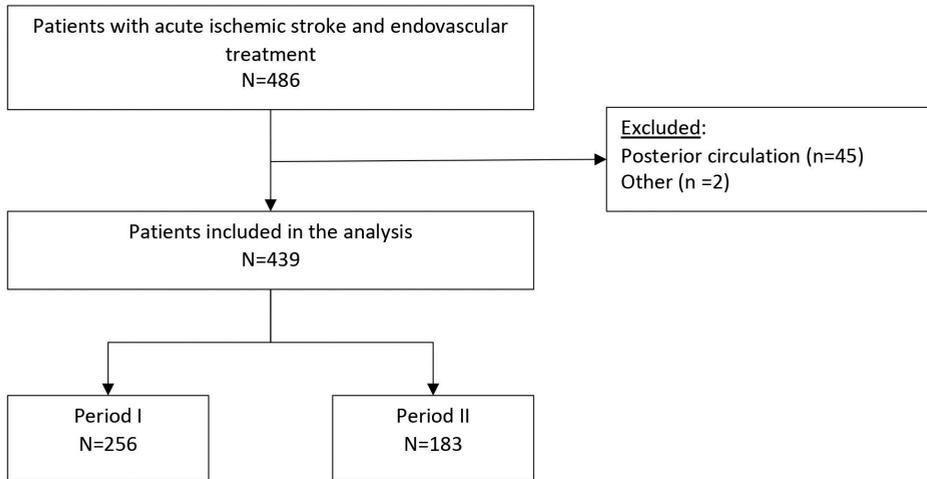
Abbreviations: IVT, intravenous thrombolysis.

■ **Supplemental table 3.** Supporting data of Figure 2: workflow for direct vs. transfer patients

	Direct patients				Transfer patients			
	Period II (n=50)	Period I (n=82)	Missing - n (%)	P-value	Period II (n=133)	Period I (n=174)	Missing - n (%)	P-value
Onset to groin	146 (127 - 205)	170 (134 - 210)	3/132 (2.3%)	0.192	190 (156 - 237)	227 (180 - 275)	1/307 (0.3%)	<0.001
Onset to door	60 (45 - 106)	50 (39 - 68)	2/132 (1.5%)	0.017	61 (40 - 95)	55 (38 - 76)	35/307 (11.4%)	0.022
Door to CT	8 (5 - 12)	10 (8 - 14)	2/132 (1.5%)	0.012	12 (7 - 19)	15 (10 - 21)	88/307 (28.7%)	0.012
CT to CTA	8 (6 - 11)	18 (9 - 48)	2/132 (1.5%)	<0.001	11 (6 - 19)	18 (12 - 37)	87/307 (28.3%)	<0.001
CTA to angiosuite	30 (21 - 47)	46 (30 - 56)	18/132 (13.6%)	0.010	87 (68 - 108)	98 (79 - 126)	103/307 (33.6%)	0.002
Angiosuite to groin puncture	20 (12 - 25)	20 (12 - 30)	19/132 (14.4%)	0.798	14 (9 - 16)	16 (11 - 25)	37/307 (12.1%)	<0.001

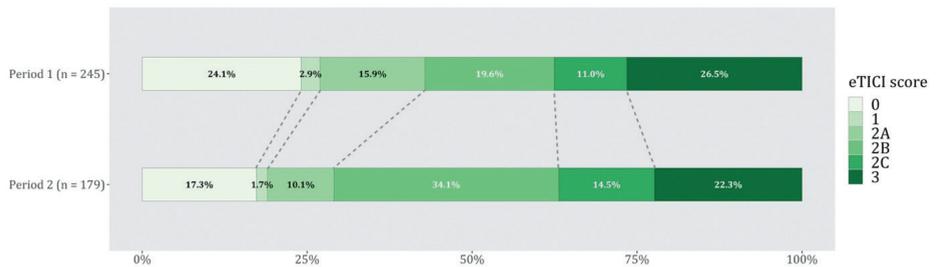
Abbreviations: C.T, computed tomography; CT-a, computed tomography angiography.

■ **Supplemental figure 1.** Flowchart for patient selection.



Other: EVT was performed as part of endovascular coiling procedures of intra-cerebral aneurysms because of secondary thrombus formation

■ **Supplemental figure 2.** eTICI scores for patients treated in period I vs. period II (p=0.008).







CHAPTER 9

| General discussion

The primary goal of this thesis was to provide evidence for the long-term clinical benefit and cost-effectiveness of endovascular treatment for patients with acute ischemic stroke caused by large vessel occlusion of the anterior circulation. Secondary aims included the influence of anesthetic management on clinical outcome after EVT and implementation of work-flow innovations to improve regional stroke care in the greater Amsterdam Area.

Until 2015 the only proven effective acute treatment for acute ischemic stroke patients was intravenous thrombolysis with recombinant tissue plasminogen activator given within 4.5 hours of symptom onset.^{1,2} The treatment effect of IVT is however limited, especially in patients with acute ischemic stroke caused by an intracranial proximal large vessel occlusion.^{3,4} MR CLEAN was the first randomized controlled trial to demonstrate clinical effectiveness of EVT with respect to functional recovery at 90 days in patients with acute ischemic stroke caused by a proximal intracranial arterial occlusion of the anterior circulation.⁵ It showed a clear benefit in shift towards a better outcome on the modified Rankin Scale score in favor of intervention. After presentation of the results of the MR CLEAN trial, several trials were halted either because pre-defined stopping criteria were reached or the loss of clinical equipoise. These trials all confirmed the positive results of MR CLEAN, as well as a meta-analysis of individual patient data from these trials.⁶ Within a year hereafter EVT was incorporated in Dutch as well as in international guidelines as standard stroke care. This has major implications for the outcome in acute ischemic stroke patients: it has been estimated that about 2000 patients in the Netherlands are eligible for EVT each year.⁷ Based on results of MR CLEAN and the meta-analysis this would mean an extra 300-400 patients could live independently after stroke yearly.

LONG TERM CLINICAL OUTCOME AND COST-EFFECTIVENESS OF ENDOVASCULAR TREATMENT FOR ACUTE ISCHEMIC STROKE

Long term clinical outcome

All above results and conclusions are based on the effect of EVT at a maximum follow-up of 90 days after stroke onset. Longer term follow-up data give important information regarding recurrent events and mortality, as well as the long-term treatment effect. This may have implications for (individual) treatment decisions, as well as decisions on implementation and reimbursement of new treatments.

We studied clinical outcome after EVT at two years in patients included in the MR CLEAN trial. Our study showed that the beneficial effect of EVT in AIS patients on functional outcome and quality of life was consistent on the longer-term as was reported at 90 days, without difference in mortality between the two treatment arms. We found an odds ratio of 1.68 towards a better outcome measured on the mRS at two years of follow-up, compared to an odds ratio of 1.67

as was reported at 90 days in the original trial. These outcomes are consistent with the known literature on longer term outcomes after EVT.⁸

Our long-term data gave us the opportunity to assess mortality rates and the occurrence of recurrent major vascular events in patients with AIS caused by a LVO during two years after randomization in the MR CLEAN study. We found a slight difference in mortality rates in favor of the intervention group (26.0% (intervention group) versus 31.0% (control group)) compared to the difference in mortality at 90 days (21.0% (intervention group) versus 22.0% (control group)). We assumed this might well be explained by the natural course of AIS caused by LVO in patients with poor outcome at 90 days (mRS category 4 and 5), which was larger in the control group (42.0% (control group) versus 28.0% (intervention group)).

We observed only very few major recurrent vascular events, including recurrent strokes, during the 2-year follow-up (overall rate of 8 events per 474 person-years at risk (rate 1.6%)), with no significant difference between the treatment arms. Compared to other studies this rate is remarkably low. However, it is important to notice that these studies did not specifically look at recurrent vascular events in AIS patients caused by large vessel occlusion with moderate to severe neurological deficit, as in our study. Most studies investigated the long-term prognosis by different stroke subtypes based on etiology (i.e. cardio-embolic infarction, atherothrombotic infarction, lacunar infarction), included patients with brain hemorrhage, and report different outcomes and outcome rates. For example, one study published in 2001 found cumulative probabilities of recurrent stroke rates at one-, five- and ten-years of follow-up of respectively 13.5%, 38.7 % and 53.9% in a mixed patient population consisting of 339 patients with intracerebral hemorrhage (8.8%), cardioembolic cerebral infarction (20.9%), lacunar infarction (13.9%) and atherosclerotic cerebral infarction (56.3%).⁹ Another study, dated from 2004, with a comparable patient population regarding different stroke subtypes, showed an overall recurrence rate of stroke within the first year of stroke of 6.5%.¹⁰ Additionally, they found a difference in recurrence rate between the different stroke subtypes, with the highest rates among patients with cardio-embolic infarction. More recent studies on the long-term risk of recurrent stroke in large patient populations, were mainly performed in patients with transient ischemic attack (TIA) or minor stroke. Amarenco and colleagues found that the rate of cardiovascular events, including stroke, in a cohort of 3847 patients with TIA or minor stroke was 6.4% in the first year and the second through fifth year after the initial event.¹¹ In a Dutch study consisting of 971 patients with TIA or nondisabling ischemic stroke of atherosclerotic origin, who were classified as respectively small vessel disease (SVD) or large vessel disease (LVD) based on neuroimaging, they found that new vascular events occurred in 56 of 312 SVD patients (3.3%/year) and in 128 of 659 LVD patients (2.9%/year).¹²

One potential explanation for the low rate in our study might be the etiology of stroke. Among patients with AIS caused by a LVO, the stroke might either be caused by artery-to-artery or cardiogenic embolic disease or extra- or intracranial atherosclerosis. These can nowadays be treated more effectively as compared to the patients in the aforementioned studies, which

were mainly performed before treatments were optimized and available on a large scale.^{13,14} Of course, we could well have missed important recurrent events in our study. We had a substantial proportion of patients who were lost to follow-up, and these patients had worse clinical characteristics and worse functional outcomes at 90 days compared to the patients with available follow-up.

Future data on the recurrent events in AIS stroke patients with LVO are needed to have better understanding in the natural history of the disease and eventually optimize individual treatment decisions. Investigators of clinical stroke trials should be encouraged to include long-term follow-up data in the design of their trials.

Economic evaluation: cost-effectiveness and budget impact analysis

Before decisions are made on reimbursement and large-scale implementations, regulatory offices and health care insurance organizations often demand cost-effectiveness evaluations. Awaiting (long-term) clinical and cost-effectiveness of EVT, as well as a budget impact analysis, EVT for AIS patients was only temporarily reimbursed in the Netherlands by the Ministry of Health from 2013. Before publication of the results of the beneficial clinical effect of EVT from 2015 and onwards, valid cost-effectiveness data were lacking.¹⁵ In general, most published studies on cost-effectiveness of EVT are model based, mainly with the use of Markov modeling.¹⁶⁻¹⁸ Input data for the models were retrieved from different sources (i.e., data from the literature and expert opinion).

In our study we were able to retrieve empirical data alongside a clinical trial up to two years from a societal perspective. The results resemble therefore more everyday practice. On the other hand, modeling in economic studies has some important advantages: it creates a possibility to use large numbers of input data to minimize uncertainty and generate life-time horizons.

We found that EVT dominated standard care with €13,247 saved per extra patient with a good outcome (mRS 0-2) and €76,937 saved per additional QALY over a period of two years. These results indicate that EVT is cost-effective, and even cost saving, over two years from a societal perspective in AIS patients caused by LVO. One comparable economic study on EVT for AIS using empirical data alongside a randomized clinical trial, reported an ICER per one QALY gained of \$14 881 (90% CI, \$8595-\$47,007), indicating cost-effectiveness.¹⁹ However, follow-up was up to 90 days and costs included initial hospital stay costs only. However, as seen in our study, costs associated with rehabilitation and nursing home stay that follow the initial hospital stay, play an important part in the difference in costs between the treatment strategies.

Unfortunately, mainly due to missing data, we were not able include costs associated with productivity loss by absenteeism from work or impaired productivity while at work. In our patient population, with a median age of 65 years, the number of patients who are an

active member on the workforce will only have a limited size. Given the convincing evidence that EVT is an efficient and cost-effective treatment modality, extending the scope to the employer's perspective might be redundant and will only further support to implement EVT as soon as possible. Of course, it would have given interesting additional information regarding the impact of LVO stroke in the working population on resumption of work. For example, more insight could have been gained in which factors after stroke play an important role in the ability to return to work, to eventually work towards optimization of vocational rehabilitation.

The second part of our economic evaluation was a budget impact analysis (BIA). In our BIA, we showed that introduction of endovascular treatment as a replacement for usual care in eligible patients in the Netherlands could result in substantial budget savings from €2.9 million in 2015 to €58.9 million in 2021. These results leave room for budget cuts or for additional expenditures in other areas of medicine.

We did not look at different scenarios, for example scenarios concerning the organization of EVT nationwide. It would be interesting to study the impact on costs of implementing EVT in such a way to achieve a geographically optimal spread of EVT centers across the nation. EVT is a complex treatment with regard the logistics to guarantee 24/7 coverage of the treatment and infrastructure to transfer eligible patients to a EVT center fast. Also, treatment itself requires specific skills and sufficient experience by the interventionist and the team.^{20,21}

Because of the relatively low numbers of eligible patients, centralization could be necessary to warrant optimal patient care, improve outcome, and reduce associated costs. After the results of the MR CLEAN and other trials, the Minister of Health developed quality criteria, in which it is required that each neuro-interventionist should perform 20 EVT procedures each year to maintain level of expertise. This has led to the registration of intervention centers including 24/7 available EVT by a dedicated team consisting of a vascular neurologist, neuro-interventionist and anesthesiologist.

Implications of the results

The results of both the 2-year clinical follow-up as well as economic evidence has led to the decision of the government in the Netherlands to reimburse EVT for AIS patients, as well as prioritizing (regional) organization for acute stroke. Fortunately, since EVT is accepted as standard care in international stroke guidelines in 2015, many other countries made efforts to optimize access and delivery of EVT for all eligible patients. However, in a survey of the national scientific societies and stroke experts in 44 European countries published in 2019, major inequalities in acute stroke treatment between and within these countries was observed.²² In 13 countries the annual number of EVT per million inhabitants was fewer than 10. This is in large contrast with annual rates of 100 per million inhabitants, reported in three other countries. In 28 countries full 24/7 EVT coverage was lacking, of which in 20 countries there were no plans to provide full national access to EVT in the near future. According to the survey, the most common reasons for not providing EVT to all eligible patients were the shortcoming

of trained personnel (34 countries), lack of facilities (22 countries) and lack of reimbursement and/or funding (16 countries). We think our results can serve both as a motivation for and as a blueprint on how in these countries EVT can further be implemented and organized.

ANESTHETIC MANAGEMENT: IMPACT ON CLINICAL OUTCOME AND TREATMENT EFFECT OF ENDOVASCULAR TREATMENT

An important topic of controversy is the optimal anesthetic management during EVT. EVT can be performed under general anesthesia (GA) with intubation, or without general anesthesia (with or without the use of conscious sedation and/or local anesthetics) (Non-GA).

The mode of anesthesia during EVT is mainly based on the preference of the interventionist or local treatment protocol. In a survey published in 2014 among neuro-interventionist, most respondents (49%) reported using general anesthesia primarily.²³ However, a literature review and meta-analysis published in 2015 based on retrospective case series, showed that GA may be associated with a lower rate of successful recanalization and worse clinical outcome.²⁴

We studied the association between type of anesthesia and clinical outcome in a large cohort of patients with AIS treated with EVT before start of the MR CLEAN trial (MR CLEAN pre-trial cohort) and found that use of non-general anesthesia was associated with better clinical outcome on the modified Rankin scale. Given the retrospective and non-randomized nature of the study these results need to be interpreted carefully. In a post-hoc analysis in the MR CLEAN trial itself we were able to investigate the influence of anesthetic management on treatment effect. The results showed that only treatment without general anesthesia was associated with a significant treatment benefit of EVT.

For both the retrospective study as well as the post-hoc analysis in MR CLEAN, one of the major concerns is selection bias based on clinical presentation (i.e., patients with worse baseline clinical characteristics are more likely to be treated under general anesthesia), and/or confounding by indication. In the MR CLEAN trial, no recommendations about type of anesthetic management were given and this decision was left to the discretion of the participating centers. However, most MR CLEAN centers adhered to a fixed protocol regarding type of anesthetic management possibly limiting the effect of confounding by indication. In 2018 the HERMES collaboration published the results of pooled data from all patients included in randomized trials to study the functional outcome in ischemic stroke patients with large vessel anterior circulation occlusion undergoing EVT under GA versus non-GA versus standard care.²⁵ In line with our results, it also showed that GA was associated with worse outcomes after EVT. An important difference compared to the results of the MR CLEAN post-hoc analysis was that the treatment effect of EVT under GA remained significant. Different theories exist on why treatment under GA is more harmful, most important that it could lead to treatment

delay and reduced cerebral perfusion due to use of anesthetic agents that may induce blood pressure lowering.

In the meanwhile, three smaller single center randomized clinical trials were published, and investigated GA versus conscious sedation and found either no difference or minor benefit from GA^{26–28}. GA was done under strict protocols to maintain blood pressure. In the case of non-GA, conscious sedation was applied with the use of the same anesthetic drugs at lower doses without intubation. The strict treatment protocols might explain the difference effect of anesthesia on clinical outcome compared to our study and the HERMES meta-analysis.

Taken all data together, GA should be avoided whenever possible. Based on the meta-analysis of 1764 patients, EVT remained however clinical effective under GA. When GA is medically necessary, close attention should be paid to minimizing delays to anesthetic induction and start of procedure and maintaining physiological parameters such as blood pressure whenever possible.

ORGANIZATION OF (REGIONAL) STROKE CARE: REDUCING TIME-TO-TREATMENT

Since EVT for AIS is a relatively new and highly specialized time depended acute treatment, nationwide and regional (re) organization to guarantee optimal patient care is still needed. The most important goal is to transfer all AIS patients eligible for EVT to a comprehensive stroke center where EVT can be performed as fast as possible.

Between 2000 and 2006 the Acute Brain Care protocol was implemented at the Amsterdam Medical University Center and led to a reduction of the Door-to-Needle times for IVT of 30 minutes.²⁹ For EVT we aimed to achieve similar results regarding Door-to-Groin times in the Greater Amsterdam Area. We studied the effect of the introduction of several workflow improvements on DNT and DGT for AIS patients receiving acute reperfusion therapy in our intervention center. The results showed that these innovations led to substantially shorter DGT times and better functional outcomes. The most effective improvement in workflow was observed in time from CT to CTA and CTA to angiosuite. We assumed this was probably because of introduction of sequential imaging (CT and CTA in one session). An important observation was that transferred patients still receive EVT significantly later as compared to patients that come directly to the intervention center.

An important improvement for transferred patients could be direct transfer from the ambulance to the angiosuite. Several studies evaluated direct presentation to the angiosuite and showed significant reductions in DGT's.^{30–32} There are however some important clinical scenarios to consider in case of direct presentation at the angiosuite: 1) the patient is neurologically deteriorated at arrival, for example by intracranial hemorrhage, 2) the patient is neurologically improved because of reperfusion and 3) the thrombus is distally migrated and

no longer accessible for EVT. For all scenarios repeated imaging is indicated. In our center, it is possible to perform a non-contrast CT at the angiosuite to detect intracerebral hemorrhage, and for improved patients a DSA can be directly done to see if the thrombus has resolved or is distally migrated. One major disadvantage of direct presentation is therefore the redundant occupation of the on-call neuro-intervention team and angiosuite. Another disadvantage might be the complications related to the DSA. In the Greater Amsterdam Area, we therefore choose to present transferred patients at the CT-room of the Emergency Department (ED) and do a quick clinical and neurological examination and compare it to the initial clinical score. If unchanged, the patient is directly transferred to the angiosuite, where the pre-notified neuro-intervention team is ready to start the procedure. In case of deterioration or improvement, repeated imaging (non-contrast CT and/or CTA) is done. Furthermore, instable patients can directly get adequate support from ED nurses and doctors. Approximately 30% of transferred patients received repeated imaging in our study, most often because of clinical improvement (52%) or deterioration (24%). Therefore, in our opinion this workflow is still feasible in our patient population.

FUTURE DIRECTIONS

The evidence for the overall favorable short -and long-term clinical effect of EVT for AIS patients caused by LVO is convincing and does not need further confirmation. The same applies for the evidence on its cost-effectiveness.

The acceptance of EVT as standard treatment modality for eligible stroke patients has led to a rapidly evolving field of acute reperfusion therapy. More and more patients can be treated now, because of the revolution of expanding time windows by imaging selections, up to 24 hours after symptom onset, but most probably also because of higher awareness among physicians and patients after publication of the positive results of EVT.^{33,34}

Nevertheless, despite the strong benefit of EVT resulting in a better functional outcome, still a substantial number of patients remain to have a poor outcome (67% in MR CLEAN). To raise the number of patients with good clinical outcome we need to keep making efforts to further reduce time to treatment in pre -and in-hospital work-flow protocols and interventions, gain more insight in clinical factors which influence outcome, and if possible, interact on these factors by effective interventions.

For the purpose of reducing time to reperfusion therapy, future improvements could for example be direct triage to an intervention center of patients with a high suspicion of LVO AIS and the use of artificial intelligence (AI) for automatic imaging detection (e.g. thrombus, ASPECTS and collateral scoring).

In several studies, direct triage to a comprehensive stroke center reduces treatment delays and improves overall outcomes after acute stroke.³⁵ Numerous randomized clinical trials

evaluated the effect of telemedicine, in which a stroke neurologist or neurointerventionalist can participate in mobile triage and treatment, and found an overall improvement in stroke treatment timing, overall clinical outcomes and cost-effectiveness.³⁶⁻³⁸ A more complex pre-hospital stroke treatment and management innovation are so called Mobile Stroke Units (MSUs). A MSU is a CT-equipped stroke ambulance and is mostly staffed with paramedics, a physician, and a radiology technologist. It links the stroke physician (usually at a tertiary hospital) to the patient via a telemedicine connection. After completion of evaluation, including brain imaging, IVT is started in the ambulance while the patient is being transferred to the stroke center. Multiple studies have shown that a MSU can significantly reduce treatment time with a tenfold increase of patients treated within the first 60 min of symptom onset. Two German studies indicate that the MSU model is cost effective by reducing disability and improving quality adjusted life years after stroke.³⁹

It is important to notice that the studies on telemedicine and MSU's were performed in geographically large countries with long interhospital distances. In a small country like the Netherlands these high-cost interventions might be futile.

The main goal is to identify patients with an LVO-stroke in a pre-hospital setting to immediately transport these patients to the nearest comprehensive stroke center in an efficient and cost-effective manner, tailored to the local situation. A more easy and less costly pre-hospital option is for example to use of clinical scales to detect possible LVO stroke in a pre-hospital setting. However, the sensitivity and specificity of these scales is not high.^{40,41} Recently the first results of the electroencephalography (EEG) controlled triage in the ambulance for acute ischemic stroke study (ELECTRA- STROKE study) were published and showed promising results.⁴² In this ongoing Dutch trial, the primary aim is to determine the diagnostic accuracy of dry electrode EEG for LVO stroke detection in the prehospital setting. With the use of dry electrodes, EEG preparation time can be less than five minutes.⁴³ In the first phases of the study, dry electrode EEG recordings were performed in controlled in-hospital settings to gain insight in technical and logistical feasibility of dry EEG, and to assess which EEG features are most useful for LVO stroke detection in the ambulance. The first results showed that median EEG-recording-time was 3 min (IQR 3-5) and that combined weighted phase lag index and relative theta power, best identified LVO stroke (sensitivity 100%; specificity 84%). These data are promising but need to be further validated in the prehospital setting.

Recently several artificial intelligence (AI) based automatic analysis platforms for detecting LVO on CTA images have been introduced and are increasingly used. Studies on the diagnostic accuracy, transfer times and potential cost-effectiveness of AI show promising results.^{44,45} However, more real-life data with relevant clinical outcome parameters should be used to gain insights into how to apply AI tools in a sensible and safe way. Also, other imaging parameters possibly interesting for AI including CT-perfusion analysis, collateral status assessment, or ASPECT scoring need to be further investigated in the AI setting as these parameters have a large impact on the growing late presenting stroke population.

In the Netherlands a consortium named Collaboration for New Treatments in Acute Stroke (CONTRAST) was set up to further improve outcome and treatment of AIS patients. Main aims of CONTRAST are to improve microvascular reperfusion and to increase the number of patients who potentially benefit from EVT by extending the indication by integration of translational research and pragmatic randomized clinical trials.

There are still many patients in which quick and adequate recanalization after EVT is achieved, but who remain severely neurologically and functionally disabled. This might be due to local hypoperfusion of the microvasculature, which in cardiology is described as the ‘no reflow’ phenomenon.^{46,47} In ischemic stroke various processes have been described that result in incomplete reperfusion: distal microvascular damage or dysfunction because of tissue necrosis and cell death (due to late intervention), but also to distal microvascular occlusion caused by pericyte contraction, microthrombi or cellular plugs.⁴⁸⁻⁵⁰ Furthermore, there might be an interaction between thrombi and mechanical devices with adhesive properties, which might be influenced by thrombus content and surface.^{50,51} Numerous observational studies that assessed the effects of periprocedural use of antiplatelets and unfractionated heparin during EVT in AIS patients showed a potential beneficial effect on functional outcome.⁵²⁻⁵⁴ The Multicenter Randomized Clinical trial of Endovascular treatment for Acute ischemic stroke in the Netherlands investigating the effect on outcome of periprocedural MEDication (MR CLEAN MED), hypothesizes that periprocedural antithrombotic treatment improves microvascular reperfusion in AIS undergoing EVT, and thereby clinical outcome. In this trial heparin, antiplatelet agents, both, or neither is given to the patient directly before start of EVT. However, in February 2021, the trial was permanently stopped for safety concerns after advice of the Data and Safety Monitoring Board

(DSMB) to unblind the outcome data. Analysis of the data by the trial steering committee showed that periprocedural intravenous aspirin and unfractionated heparin during EVT are both associated with an increased risk of symptomatic intracranial hemorrhage, without evidence for a beneficial effect on functional outcome.⁵⁵ The investigators did find higher recanalization rates in the unfractionated heparin group but stated that this benefit did not outweigh the risk of intracranial hemorrhage. Furthermore, generally used dosages of intravenous unfractionated heparin and aspirin were used in the trial, and the authors suggest to further evaluate lower dosages, also used in clinical practice, in future studies.

In most large EVT trials all eligible patients received IVT as part of the standard treatment. For example, in MR CLEAN a total of 89% (445/500) of patients received IVT. Potential benefits of IVT given prior to EVT include early recanalization, fewer stent retriever passes, improvement of microvascular reperfusion and lysis of distal thrombi. Possible disadvantages might be increased hemorrhagic complications, thrombus fragmentation and delayed start of EVT. In the MR CLEAN NOIV the primary aim was to assess the effect of direct EVT compared with IVT followed by EVT on functional outcome. The results were published in the NEJM in November 2021 and showed that EVT alone was neither superior nor noninferior to intravenous

alteplase followed by EVT regarding functional outcome at 90 days, and that the incidence of symptomatic intracerebral hemorrhage was similar in the two groups.⁵⁶ Although small, there were important between group differences with respect to the presence of atrial fibrillation, age, and occlusion location, with more prognostically unfavorable baseline characteristics in the EVT-alone group. This could have affected the result towards a more favorable outcome in the EVT plus IVT group. Moreover, the trial included only patients directly presented at an intervention center. This way the results cannot well be extrapolated to care settings in which patients need to be transferred to EVT centers. In these patients, times from stroke onset to EVT is substantially longer, which may have a large impact on clinical outcome.

Another potential mechanism to further improve outcome is improvement of collateral perfusion and reduction of blood pressure. As shown in observational studies, nitroglycerin may interact on both; it may increase intracranial blood flow and results in reduction of blood pressure.⁵⁷⁻⁵⁹ The Multicenter Randomized trial of Acute Stroke treatment in the Ambulance with a nitroglycerin Patch (MR ASAP) investigates the effect of administering transdermal nitroglycerin, by a patch given in the ambulance, on final clinical outcome of AIS and ICH patients. Unfortunately, the trial has been stopped as of June 24th 2021 due to safety concerns by the DSMB. Also, a recent trial (RIGHT-2) did not show a positive of prehospital treatment with transdermal prehospital treatment with transdermal on functional outcome in patients with presumed stroke.⁶⁰

Based on inclusion criteria and positive results from several trials, selected AIS patients presenting between 6-24 hours of symptom onset can now be treated directly with EVT conform Dutch guidelines.^{33,34} These include patients with a small ischemic core and large penumbra based on advanced neuroimaging (CTP or MRI DWI), in combination with moderate to severe neurological deficit at presentation. The MR CLEAN LATE studies the effect of EVT in patients who present between 6-24 hours after symptom onset or last seen well. Compared to published trials, inclusion criteria are broad, and imaging selection criteria for patients are not only based on infarct cores, but also include the presence of collaterals in the infarcted area, which can be assessed by standard CTA. Presence of collateral flow has been shown to be an adequate parameter for patient selection.⁶¹ As the standard CTA is already performed in these patients to confirm LVO, it may lead to substantial benefits for centers with limited access to advanced neuroimaging and software, and possibly in shorter times to treatment. As a result, a higher number of eligible patients that benefit from EVT can be reached. On January 27th of 2022 the last patient was included, and results are expected fall 2022.

CONCLUSIONS

Our results show that the beneficial effect of EVT in patients with acute ischemic stroke caused by a proximal intracranial occlusion of the anterior circulation is sustained during at least two years, which is consistent with other studies on longer-term outcomes after EVT. Together with

CHAPTER 9

the cost-effectiveness results, this has led to further implementation and re-imburement of EVT for AIS patients in the Netherlands.

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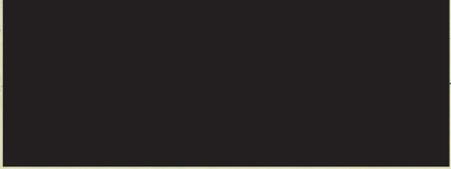
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APPENDICES

SUMMARY

Acute ischemic stroke occurs when there is a sudden disruption of blood flow to brain tissue. In about one third of AIS patients, this is caused by a thrombo-embolic occlusion of one of the large vessels of the proximal intracranial circulation, also called large vessel occlusions. In absence of revascularization, hypoxic damage in a large vascular territory of the brain will develop fast, with a high chance of permanent severe neurological deficit. AIS is a disease with a high incidence and prevalence and a leading cause of death and disability worldwide. In the Netherlands approximately 30.000 to 35.000 patients suffer from AIS annually, of whom 8500 to 9000 dies.

Acute reperfusion therapies focus at restoring blood flow as soon as possible to prevent permanent damage of brain tissue and subsequently poor clinical outcome. Until 2015 the only proven acute reperfusion therapy consisted of intravenous treatment with recombinant tissue plasminogen activator given within 4,5 hours of onset. This therapy has important contraindications and has a limited effect on recanalization in AIS patients with LVO. A new therapy to intra-arterially remove the blood clot was explored, which showed promising results. However, large randomized clinical trials to prove its clinically effectiveness remained absent for a long time, and this therapy was only performed outside standard protocols in selected patients. In 2015 the results of the MR CLEAN trial were presented. In MR CLEAN 500 patients of 18 years or older with AIS caused by LVO in the anterior cerebral blood circulation were randomized to receive EVT plus usual care or usual care alone within 6 hours of symptom onset. The patients were included in 16 comprehensive stroke centers in the Netherlands between 2010 and 2014. The trial showed that EVT was effective and safe. Shortly hereafter, the results were confirmed in several other clinical trials and in a meta-analysis of all trials, and EVT has since then become the standard care for AIS patients with LVO.

In the years following the publication of these trials, acute reperfusion therapy, now consisting of IVT and EVT, was extensively studied and rapidly evolving with one of the biggest changes being the expanding time window by imaging selection.

An important issue already raised during the execution of the MR CLEAN trial, was the need for the longer-term clinical effect and cost-effectiveness of EVT before nationwide re-imburement and large-scale implementation eventually could start. The focus of this thesis is to provide information on the long-term clinical follow-up, cost-effectiveness, and optimization of implementation of EVT for AIS patients.

Chapter 1 is a general introduction and describes the background and rationale of this thesis.

Mainly due to granting issues, the extended follow-up study started more than two years later than the original MR CLEAN study. This posed a big challenge regarding data collection as well as methodological issues. In **Chapter 2** we present a detailed design and statistical analysis plan of the extended, two-year clinical follow-up study of the MR CLEAN trial, in which we also

elaborate on the methods how we dealt with the late start of the study. Results of the two-year clinical follow-up study are presented in **Chapter 3**. We found that the positive effect on functional outcome according to the modified Rankin scale score of endovascular treatment in acute ischemic stroke patients was similar at 2 years as was reported at 90 days. The adjusted common odds ratio was 1.68 (95 % confidence interval [CI] 1.15 to 2.45, $p=0.007$) for a shift toward better outcomes on the modified Rankin Scale in favor of endovascular treatment. This result was consistent in different subgroups, i.e., groups based on stroke severity, age, internal carotid artery involvement, time to randomization and early ischemic changes on CT. Also, quality of life at two years was higher in patients randomized to endovascular treatment compared to patients in the conventional treatment group (mean health utilities 0.48 versus 0.38, mean difference 0.10 [95% CI 0.03 to 0.16,] $p=0.006$). There was an overall low rate of recurrent major vascular events during two years of follow up, with no significant difference between to two treatment groups.

One of the major incentives to perform this extended clinical follow-up study of the MR CLEAN was to provide important information for cost-effectiveness analyses, and thereby justify decisions on reimbursement and implementation of EVT nationally, and even internationally.

Chapter 4 covers an economic evaluation, in which we aim to assess whether endovascular therapy plus usual care is cost-effective in comparison to usual care alone in AIS patients. We performed this study parallel to the MR CLEAN trial and its two-year follow-up study. Its results show that endovascular treatment dominated standard treatment with \$18,233 saved per extra patient with a good outcome and \$105,869 saved per additional QALY. In other words: endovascular treatment for AIS is cost-effective; it both improves quality of life and is cost saving compared to usual care. To further guide reimbursement decisions and influence future price and volume negotiations between for example insurer and health care provider we performed a budget impact analysis (BIA) as part of the economic evaluation (**Chapter 5**). The BIA estimates that introduction of EVT as a replacement for usual care in eligible patients in the Netherlands results in budget savings from €2.9 million in 2015 to €58.9 million in 2021. These substantial savings provide room for reallocation of budgets to address other demands for health care in this or other disease areas.

Because of its pragmatic design with broad inclusion criteria to represent every day clinical practice the best possible way, the MR CLEAN-pre-trial and MR CLEAN trial provided a unique opportunity to study the effect of different clinical and imaging parameters on patient's outcome. An important clinical parameter is the mode of anesthesia during endovascular treatment. The type of anesthesia may for example influence time to treatment, influence hemodynamics and subsequently on cerebral perfusion, or carry a risk for aspiration. All these factors can play an important role in clinical outcome after EVT. Until now, the anesthetic approach during EVT is mostly based on the availability of anesthesia and/or the preference of the neurointerventionist or the treating team of the intervention center. To provide more evidence to optimize treatment strategy we investigated the effect of anesthetic management

APPENDICES

during EVT on clinical outcome in AIS patients. In **Chapter 6** we present the results of the association between type of anesthesia and clinical outcome in a large cohort of patients with AIS treated with EVT between 2002 and 2013 (MR CLEAN pre-trial cohort). These data showed that AIS patients treated without general anesthesia during EVT have a higher probability of good clinical outcome compared to patients treated with general anesthesia. In the MR CLEAN trial itself we were able to further expand on this research question and observed that there was only a significant treatment effect in patients treated with EVT without general anesthesia (**Chapter 7**). These results suggest performing EVT without general anesthesia whenever possible. Of course, ideally these results need to be confirmed in randomized clinical trials.

Since EVT has become the standard care from 2015, ongoing efforts by national and international collaborations are made to further implement and optimize treatment.

One of the most important aspects in optimizing treatment is to further reduce onset-to-treatment time, as it is one of the most important prognostic factors for clinical outcome. Logistics around EVT for AIS are and have become more complex because of rapid development in clinical and radiological stroke work-up and as-fast-as possible transportation of AIS patients to a EVT capable comprehensive stroke center. **Chapter 8** describes the results of innovations we made to local workflow protocol in the Greater Amsterdam Area. The effects of these improvements on treatment times were assessed. Improvements included: switching from primary general anesthesia to local anesthesia, optimization of transfers through a regional protocol, one stop CT/CT-angiography, preparation of IVT during image acquisition, digital image transfer, referral without consultation, and preparation of the angio-suite prior to patient arrival. Results showed that innovations to improve workflow for EVT led to shorter door-to-groin times and are associated with improved functional outcomes.

The final part, **Chapter 9**, is a general discussion of this thesis, in which the current results and its implications are discussed, and future perspectives are given.

The most important conclusion of this thesis is that the beneficial effect on functional outcome and quality of life of EVT in patients with AIS is sustained over at least two years. Furthermore, during this time horizon EVT compared to usual care is highly cost-effective and will lead to substantial budget savings for total health care costs. These findings have led to further implementation and reimbursement of EVT for AIS nationwide, and hopefully will help decision making in other countries around the world, in which EVT is not yet implemented as standard care.

NEDERLANDSE SAMENVATTING

Bij een acuut herseninfarct is er sprake van een plotse afsluiting van bloedtoevoer naar hersenweefsel. In ongeveer een derde van patiënten met een acuut herseninfarct wordt dit veroorzaakt door een thrombo-embolische afsluiting van een groot proximaal bloedvat naar de hersenen, dit wordt ook wel 'Large Vessel Occlusion' (LVO) genoemd. Als er geen herstel van de bloedvoorziening is (reperfusie), treedt er binnen zeer korte tijd hypoxisch-ischemische schade op in een groot vasculair verzorgingsgebied in de hersenen met daaropvolgend een grote kans op blijvende ernstige neurologische uitval. Het acute herseninfarct is een ziekte met een hoge incidentie en prevalentie, en vormt één van de belangrijkste oorzaken van overlijden en invaliditeit wereldwijd. In Nederland worden zo'n 30.000 tot 35.000 patiënten per jaar getroffen door een herseninfarct, waarvan 8500 tot 9000 komen te overlijden.

Acute reperfusie therapie is erop gericht de bloedstroom naar de hersenen zo snel mogelijk te herstellen om permanente schade aan hersenweefsel, en daarmee ook een slechte klinische uitkomst, te voorkomen. Tot 2015 was intraveneuze behandeling met recombinant tissue plasminogen activator (IVT) binnen 4,5 uur na het ontstaan van de klachten, de enige klinisch bewezen behandeling. Deze behandeling kent echter een aantal belangrijke contra-indicaties en heeft een beperkt effect bij patiënten met een acuut herseninfarct door een LVO. Een nieuwe behandeling werd onderzocht waarbij via een endovasculaire benadering het bloedstolsel werd verwijderd (EVT). Deze behandeling liet veel belovende resultaten zien, maar gerandomiseerde klinische trials die de klinische effectiviteit van de behandeling bewezen bleven lange tijd uit. Hiermee werd deze behandeling alleen nog toegepast buiten standaard protocollen in een kleine selectie van patiënten. In 2015 verschenen de resultaten van de MR CLEAN studie. In deze studie werden 500 patiënten van 18 jaar of ouder met een acuut herseninfarct veroorzaakt door een LVO gerandomiseerd tussen standaardbehandeling of EVT plus standaardbehandeling, waarbij de behandeling binnen 6 uur na het ontstaan van de klachten moest kunnen plaatsvinden. De patiënten werden geïncludeerd in 16 Nederlandse stroke centra tussen 2010 en 2014. De resultaten lieten zien dat EVT klinisch effectief en veilig was. Kort hierna werden deze resultaten bevestigd in verschillende andere klinische trials, en een meta-analyse van deze trials, waarop EVT nu standaardbehandeling is voor patiënten met een acuut herseninfarct.

In de daaropvolgende jaren werd acute reperfusie therapie, nu bestaande uit IVT en EVT, intensief bestudeerd, met als gevolg snelle ontwikkelingen, waarvan de belangrijkste de uitbreiding van het 'behandelwindow' voor beide behandelingen door selectie van patiënten op basis van beeldvormende technieken.

Een belangrijk punt, welke al naar voren kwam toen het MR CLEAN onderzoek nog liep, was de noodzaak voor klinisch bewijs voor langetermijneffecten en de kosteneffectiviteit van EVT, voordat daadwerkelijke vergoeding door de overheid en daarmee implementatie op grote schaal kon worden bewerkstelligd.

Het hoofddoel van dit proefschrift was om informatie te verschaffen over het lange termijn klinische effect, kosteneffectiviteit en optimalisatie van implementatie van EVT voor patiënten met een acuut herseninfarct.

Hoofdstuk 1 is een algemene introductie, en beschrijft de achtergrond en rationale achter dit proefschrift.

Vanwege de lange duur tot het verkrijgen van subsidie, kon de verlengde follow-up studie van de MR CLEAN pas twee jaar na het starten van oorspronkelijke MR CLEAN trial beginnen. Dit bracht grote uitdagingen met zich mee om nog zoveel mogelijk kwalitatief goede data te verkrijgen en stelde ons voor een aantal methodologische problemen. **Hoofdstuk 2** bevat een gedetailleerde beschrijving van het ontwerp en het statistisch analyse plan van de 2 jaar follow-up studie van de MR CLEAN. Hierin beschrijven we ook hoe we zijn omgegaan met de latere start van de studie, zowel praktisch als op methodologisch gebied. De resultaten van 2-jaar follow-up studie worden beschreven in **hoofdstuk 3**. We vonden dat het positieve klinische effect van EVT op functionele uitkomst op basis van de Modified Rankin Scale score (mRS schaal), min of meer gelijk was op 2 jaar vergeleken met de uitkomst op 3 maanden, met een Odds Ratio van 1,68 (95% CI 1,15-2,45, P=0,007) richting een betere uitkomst op de mRS schaal. Dit effect bleef gelijk in verschillende subgroepen gebaseerd op ernst van het herseninfarct, leeftijd, betrokkenheid van arteria carotis interna, tijd tot randomisatie en vroege ischemische veranderingen op CT-hersenen. Daarnaast was de kwaliteit van leven gemeten met de EQ5D in de behandelde groep groter in vergelijking met patiënten in de controlegroep (0,48 versus 0,38, gemiddeld verschil 0.10 (95% CI 0.03-0.16, p=0.006). In de gehele groep van patiënten in de studie was het voorkomen van nieuwe ernstige vasculaire events gedurende follow-up laag, zonder significant verschil tussen beide behandelarmen.

Een van belangrijkste redenen om deze lange termijn studie van de MR CLEAN uit te voeren was mede om informatie te verkrijgen voor een gedegen kosteneffectiviteit studie, waarmee uiteindelijke beslissingen over vergoeding en implementatie van EVT voor het acute herseninfarct in Nederland konden worden genomen, en mogelijk ook internationaal.

Hoofdstuk 4 is een economische analyse, met als doel de kosteneffectiviteit van EVT in combinatie met standaardbehandeling versus standaardbehandeling alleen bij patiënten met een acuut herseninfarct te onderzoeken. De studie werd uitgevoerd parallel aan de MR CLEAN hoofdstudie en de lange termijn follow-up studie. De resultaten laten zien dat EVT 18,233 dollar per patiënt met een goede uitkomst op de mRS en 105,869 dollar per QALY bespaard ten opzichte van de standaardbehandeling. Met andere woorden: EVT is kosteneffectief; het verbetert zowel de kwaliteit van leven, en bespaart ook geld in vergelijking met de standaardbehandeling. In aanvulling werd ook een Budget Impact Analyse (BIA) gedaan, om zo verdere beslissingen over vergoeding van EVT en eventuele prijsonderhandelingen tussen bijvoorbeeld zorgverzekeraar en zorgaanbieder te ondersteunen (**Hoofdstuk 5**). De BIA laat zien dat introductie van EVT als vervanging voor de eerdere standaardtherapie kan resulteren

in besparingen van €2.9 miljoen in 2015 tot €58.9 miljoen in 2021. Deze substantiële bedragen bieden ruimte voor zorguitgaven binnen andere gebieden van het gezondheidszorg budget waar deze nodig zijn.

Het ontwerp van MR CLEAN pre-trial en MR CLEAN trial was erop gericht de dagelijkse klinische praktijk zoveel mogelijk na te bootsen, met daardoor brede inclusiecriteria. Dit heeft de unieke mogelijkheid geboden om effecten op de uitkomst van verschillende klinische en radiologische parameters te bestuderen. Een belangrijke klinische parameter is wijze van anesthesie welke wordt toegepast tijdens EVT. De wijze van anesthesie kan bijvoorbeeld invloed hebben op tijd tot start van de behandeling, een effect hebben op hemodynamiek en daarmee cerebrale perfusie en brengt een mogelijk risico op aspiratie met zich mee. Al deze factoren kunnen een belangrijke invloed hebben op de klinische uitkomst van de patiënt na EVT. De wijze van anesthesie wordt momenteel nog steeds bepaald door de acute beschikbaarheid van anesthesie en/of de voorkeur van de behandelaar of het behandelend team van het stroke centrum. Om meer bewijs te krijgen over de optimale wijze van anesthesie en daarmee de behandeling en klinische uitkomst te optimaliseren, hebben we het effect van de anesthesie tijdens EVT op klinische uitkomst bestudeerd. In **hoofdstuk 6** worden de resultaten beschreven van de associatie tussen type anesthesie en klinische uitkomst in een groot cohort van patiënten behandeld met EVT (MR CLEAN pre-trial cohort) tussen 2002 en 2013. De data laten zien dat patiënten met een acuut herseninfarct behandeld met EVT zonder gebruik van algehele anesthesie een hogere kans op een betere uitkomst hadden in vergelijking met patiënten behandeld onder algehele anesthesie. We konden deze vraag verder onderzoeken in de MR CLEAN trial (**hoofdstuk 7**), waarbij de resultaten in lijn waren met de eerdere bevindingen: er was alleen een significant behandel-effect in de groep patiënten behandeld zonder algehele anesthesie. Deze resultaten suggereren dat EVT indien mogelijk zonder algehele anesthesie moet worden uitgevoerd. Uiteraard moeten deze resultaten idealiter bevestigd worden in gerandomiseerde trials.

Sinds EVT nu onderdeel is van de standaardbehandeling voor patiënten met een acuut herseninfarct, zijn nationale en internationale samenwerkingsverbanden bezig met het verder optimaliseren en implementeren van deze behandeling. Gezien één van belangrijkste prognostische factoren voor een goede klinisch uitkomst bij een acuut herseninfarct tijd van ontstaan klachten tot start behandeling is, is één van de hoofddoelen dan ook zo snel mogelijk te kunnen starten met reperfusie therapie vanaf start symptomen. De logistiek rondom EVT wordt meer en meer complex door de snelle ontwikkelingen van de afgelopen jaren met betrekking tot klinische en radiologische work-up, als ook het zo snel mogelijk transporteren van de patiënt van centrum van primaire presentatie naar een stroke centrum met EVT-mogelijkheden.

Hoofdstuk 8 beschrijft de resultaten van verschillende innovaties die wij binnen onze workflow voor patiënten met acuut herseninfarct in regio Amsterdam/Noord-Holland hebben doorgevoerd. Hierbij werd het effect van deze innovaties op behandel-tijden en klinische

APPENDICES

uitkomst bestudeerd. De innovaties betroffen onder andere: behandeling onder lokale anesthesie (tenzij medisch niet mogelijk), implementatie van een regionaal protocol, one-stop CT/CTA, digitale verzending van beeldvorming en klaarmaken van de interventiekamer voordat patiënt arriveert. De resultaten lieten zien dat deze innovaties hebben geleid tot kortere tijden tot presentatie in het primaire ziekenhuis en tot het aanprikken van de lies voor EVT in het behandelcentrum, en dat deze innovaties geassocieerd waren met een betere functionele uitkomst na drie maanden.

Het laatste deel van dit proefschrift is een algemene discussie waarin alle resultaten en mogelijke implicaties op klinische praktijk worden beschouwd, en toekomstige perspectieven worden beschreven.

De belangrijkste conclusie van dit proefschrift is dat het gunstige effect op de functionele uitkomst van endovasculaire behandeling bij patiënten met een acuut herseninfarct standhoudt over de langere termijn van twee jaar. Daarnaast is gebleken dat endovasculaire behandeling zeer kosteneffectief is, en dat de introductie van deze behandeling zal leiden tot substantiële besparingen. Deze bevindingen tezamen hebben geleid tot vergoeding en verdere implementatie van EVT voor het acuut herseninfarct in Nederland. Hopelijk zullen onze resultaten ook helpen bij het maken van beslissingen rondom vergoedingen en implementatie in andere delen van de wereld met een vergelijkbaar zorgstelsel, waar EVT nog niet (volledig) geïmplementeerd is als standaardbehandeling.

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PhD period: 2013-2022

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Co-promotores: Prof.dr. Charles Majoie and Prof.dr. Robert van Oostenbrugge

1. PhD training

General courses	Year	Workload (ECTS)
Basic Course Legislation and Organization for Clinical Researchers (BROK)	2013	1.0
Scientific writing in English	2013	1.5
Clinical Epidemiology	2013	0.6
Practical biostatistics	2013-2014	1.4
Evidence Based Searching	2014	0.1

Specific courses	Year	Workload (ECTS)
Course Health Technology Assessment, University Medical Center Groningen, Zeist	2013	1.5

Seminars, workshops and masterclasses	Year	Workload (ECTS)
Nacholing Nederlandse Neurovasculaire werkgroep, Utrecht	2014	0.5
Masterclass 'The imaging-based quest to find new treatments: conquering stroke and TIAs severe heterogenetity', Prof. A. Demchuk. Amsterdam.	2016	0.1
First International Health Economic Workshop in collaboration with MR CLEAN team, Amsterdam	2018	0.75

(Inter)national conferences	Year	Workload (ECTS)
European Stroke Conference 2013. London, United Kingdom.	2013	0.75
European Stroke Conference 2014. Nice, France.	2014	0.75
World Stroke Congress 2014. Istanbul, Turkey.	2014	0.75
European Stroke Organization Conference 2015. Glasgow, United Kingdom.	2015	0.75
European Stroke Organization Conference 2016. Barcelona, Spain.	2016	0.75
International Stroke Conference 2016. Los Angeles, United States of America.	2016	0.75

APPENDICES

Nederlandse Vereniging voor Neurologie Wetenschapsdagen	2016	0.5
Amsterdam Neuroscience Kikckoff meeting	2016	0.25

2. Presentations

Poster presentations	Year	Workload (ECTS)
Differences in clinical outcome after endovascular treatment for ischemic stroke in the MR CLEAN pre-trial cohort: General versus Local anesthesia-World Stroke Congress 2014. Istanbul, Turkey.	2014	0.5
Cost-effectiveness and Long-Term follow-up of endovascular treatment for acute ischemic stroke alongside a multicenter randomized clinical trial in the Netherlands (CLOT-MR CLEAN)-European Stroke Conference 2014. Nice, France.	2014	0.5
Malignant middle cerebral artery infarctions in patients included in the MR CLEAN trial- European Stroke Conference 2015. Glasgow, United Kingdom.	2015	0.5
Kosteneffectiviteit van endovasculaire behandeling voor het acute herseninfarct-resultaten van de mr clean trial- Nederlandse Vereniging voor Neurologie Wetenschapsdagen, 2016.	2016	0.5
Long term outcome after endovascular treatment for acute ischemic stroke - two year follow-up of the MR CLEAN trial- Amsterdam Neuroscience Kikckoff meeting, 2016.	2016	0.5
Oral presentations	Year	Workload (ECTS)
Breïnbrekers- Afspraken over acute beroerte behandeling in de praktijk-Thema avond Stroke, TraumaNet AMC and Regionaal Overleg Acute Zorg Noord-Holland/Flevoland.	2015	0.5
Lange termijn uitkomsten na endovasculaire behandeling voor een acuut herseninfarct- twee jaar klinische follow-up van de MR CLEAN trial- Nederlandse Vereniging voor Neurologie Wetenschapsdagen 2016.	2016	0.5
Ruimte voor endovasculaire behandeling voor het herseninfarct- "Begin van een nieuw tijdperk"- Topics in Intensive Care, Lunteren.	2016	0.5
Long term outcome after intra-arterial treatment for acute ischemic stroke: Results of two year clinical follow-up of the MR CLEAN trial- Masterclass Prof. A. Demchuk. Amsterdam.	2016	0.5
Economic evaluation alongside the multicenter randomized clinical trial of endovascular treatment for acute ischemic stroke in The Netherlands - MR CLEAN trial- European Stroke Organization Conference 2017. Prague, Czech Republic.	2017	0.5

Cost-effectiveness analysis- Insights from the economic evaluation of MR CLEAN- First International Health Economic Workshop in collaboration with MR CLEAN team, Amsterdam.	2018	0.5
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3. Teaching

Lecturing	Year	Workload (ECTS)
Neurological examination training for medical students	2016	0.3
Amstel Academie (Acute neurology)	2018	0.5

Tutoring, Mentoring and Supervising	Year	Workload (ECTS)
Scientific internship, D.Koelman	2013/2014	1.0
Scientific internship, L. Koelman	2014/2015	1.0
Bachelor thesis, S. Kooiker	2016	1.0

Parameters of Esteem

Awards and prices	Year
Second prize winner of the 2015 Stroke Progress and Innovation Award for the publication entitled "Type of Anesthesia and Differences in Clinical Outcome After Intra-Arterial Treatment for Ischemic Stroke"	2016
Best oral presentation for presentation entitled 'Lange termijn uitkomsten na endovasculaire behandeling voor een acuut herseninfarct- twee jaar klinische follow-up van de MR CLEAN trial,', Nederlandse Vereniging voor Neurologie Wetenschapsdagen 2016.	2016
Second place AMC Graduate School PhD Publication Award for the publication entitled "Two-year outcome after endovascular treatment for acute ischemic stroke"	2017

DANKWOORD

Heel graag wil ik iedereen bedanken die op enige wijze heeft bijgedragen aan de afronding van dit proefschrift. Het was een lange en leerzame weg, en dit boekje was nooit tot stand gekomen zonder jullie steun. Er is een aantal mensen die ik in het bijzonder wil bedanken.

Mijn dank gaat allereerst uit naar alle patiënten en hun naasten die hebben willen deelnemen aan de onderzoeken.

Mijn promotores prof dr. Yvo Roos en prof. dr. Marcel Dijkgraaf.

Geachte prof. dr. Yvo Roos, beste Yvo,

Tijdens mijn co-schap neurologie in het AMC heb jij mij weten te inspireren om verder te gaan in de neurologie. Jouw enthousiasme voor het vak, pragmatische klinische blik en aanstekelijk plezier in wat je doet zijn een inspiratiebron. Na het afronden van mijn studie geneeskunde trok ik mijn stoute schoenen aan en nam contact met je op. Een paar weken later had je een prachtige promotieplek voor me en was je zelfs op mijn afstudeerceremonie om dit met me te delen. Fantastisch! Daarna zijn we met vol enthousiasme begonnen aan het project. Ik heb veel gehad aan de gesprekken en meetings. Ook weer door je scherpe klinische blik en pragmatiek is hier een onderzoek uit gekomen met invloed op de dagelijkse klinische praktijk. Je begeleiding heeft onder andere geresulteerd in een aantal belangrijke publicaties, met als kers op de taart een publicatie in de *The New England Journal of Medicine*! Voor jou niet het eerste artikel in zo'n prestigieus tijdschrift, maar dank dat je me deze mogelijkheid hebt geboden. Ik denk dat we samen heel trots kunnen zijn. Naast de wetenschap, heb je me ook geïntroduceerd binnen de vakgroep neurologie, eerst als ANIOS, en later (gelukkig) als AIOS. Hier was je nog een tijdje mijn opleider, en nu nog steeds een fijne samenwerking als supervisor. Ook al ben je razend druk, ik heb het gevoel dat jouw deur altijd open staat om zowel werk-gerelateerde- als privékwesities te bespreken, dat waardeer ik enorm. Ik zou nog heel lang door kunnen gaan, maar ik wil je nogmaals bedanken voor alles wat we samen hebben gedaan, wat je voor me betekent en al hebt betekend. Hopelijk werken we nog heel lang samen!

Geachte prof. dr. Marcel Dijkgraaf, beste Marcel.

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Mijn co-promotores prof. Majoie en prof. Van Oostenbrugge

Geachte prof. dr. Charles Majoie, beste Charles.

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Geachte prof. dr. Robert van Oostenbrugge, beste Robert,
Bedankt voor je betrokkenheid bij al mijn projecten. Bij de MR CLEAN hoofdstudie zaten we samen in het 'SAE' team. Dit was veel werk, maar ik kon altijd op een snelle reactie en oplossing van jouw kant rekenen. Voor de lange termijn studie en economische analyse toonde je altijd veel interesse en had je waardevolle inbreng. Tijdens de MR CLEAN exec meetings en congressen (destijds nog live) bracht je veel Limburgse goedlachse gezelligheid. Dank voor de bijzondere tijden.

Geachte leden van de promotiecommissie, geachte prof. dr. J. Horn, prof. dr. R.M.A. de Bie, dr. M.E.S. Sprengers, prof. dr. W.S. Schlack, prof. dr. J.L. Saver en prof. dr. M.J. Postma, hartelijk dank voor het kritisch beoordelen van dit proefschrift en voor het zitting nemen in de commissie.

Beste (overige) leden van het MR CLEAN executive committee

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APPENDICES

Alle MR CLEAN principal investigators en inkluderend artsen, bedankt voor jullie tomeloze betrokkenheid en inzet voor de trial en al haar substudies. Naast dagelijkse drukke klinische praktijk, was het mogelijk de inclusies en benodigde data zelfs voor de beoogde einddatum compleet te krijgen. Dit was nooit, maar dan ook nooit, zonder jullie gelukt.

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Beste stafleden en collega AIOS (kinder) neurologie en KNF van het Amsterdam UMC, locatie AMC. Bedankt voor de leerzame en leuke tijd tijdens de opleiding.

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.

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1. van Voorst H, Kunz WG, **van den Berg LA**, Kappelhof M, Pinckaers FME, Goyal M, Hunink MGM, Emmer BJ, Mulder MJHL, Dippel DWJ, Coutinho JM, Marquering HA, Boogaarts HD, van der Lugt A, van Zwam WH, Roos YBWEM, Buskens E, Dijkgraaf MGW, Majoie CBLM; MR CLEAN Registry investigators. Quantified health and cost effects of faster endovascular treatment for large vessel ischemic stroke patients in the Netherlands. *J Neurointerv Surg*. 2021 Dec;13(12):1099-1105.

2. **van den Berg LA**, Berkhemer OA, Fransen PSS, Beumer D, Lingsma H, Majoie CBM, Dippel DWJ, van der Lugt A, van Oostenbrugge RJ, van Zwam WH, Roos YB, Dijkgraaf MGW; MR CLEAN Investigators. Economic Evaluation of Endovascular Treatment for Acute Ischemic Stroke. *Stroke*. 2022 Mar;53(3):968-975.

3. Guglielmi V, Compagne KCJ, Sarrami AH, Sluis WM, **van den Berg LA**, van der Sluijs PM, Mandell DM, van der Lugt A, Roos YBWEM, Majoie CBLM, Dippel DWJ, Emmer BJ, van Es ACGM, Coutinho JM; MR CLEAN trial and MR CLEAN Registry Investigators. Assessment of Recurrent Stroke Risk in Patients With a Carotid Web. *JAMA Neurol*. 2021 Jul 1;78(7):826-833.

4. van Kranendonk KR, Treurniet KM, Boers AMM, Berkhemer OA, **van den Berg LA**, Chalos V, Lingsma HF, van Zwam WH, van der Lugt A, van Oostenbrugge RJ, Dippel DWJ, Roos YBWEM, Marquering HA, Majoie CBLM; MR CLEAN Investigators. Stroke Clinical and Imaging Markers Associated With Hemorrhagic Transformation in Patients With Acute Ischemic Stroke. *2019 Aug;50(8):2037-2043*.

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APPENDICES

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Lucie Anne van den Berg was born on August 19th, 1987, in Rotterdam and grew up in Velp, both in the Netherlands. She graduated from the Stedelijk Gymnasium Arnhem in 2005. In the same year she started her study Medicine at the University of Amsterdam. During her study she worked as an assistant at the Netherlands Brain Bank of the Dutch Institute of Neurosciences. In 2012 she earned her degree of Doctor of Medicine (MD). In the year thereafter she began her PhD project '*Cost-effectiveness analyses and Long-Term follow-up in patients randomized in a multicenter randomized clinical trial of endovascular treatment for acute ischemic stroke in The Netherlands*' at the Department of Neurology of the Amsterdam University Hospital (Prof. Roos, Prof. Dijkgraaf, Prof. Majoie and Prof. Oostenbrugge). Besides this PhD project she was part of the project and fellow-coordinator of '*StrokeNet: gestroomlijnde zorg rondom acute behandeling voor patiënten met herseninfarct in de regio Noord-Holland*'.

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