ENDOVASCULAR TREATMENT OF ISCHEMIC STROKE

Treat the right patient, at the right time, in the right place

Esmee Venema

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Endovascular Treatment of Ischemic Stroke

Treat the right patient, at the right time, in the right place

Endovasculaire behandeling van het herseninfarct

Behandel de juiste patiënt, op het juiste moment en de juiste plaats

Proefschrift

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

Prof.dr. R.C.M.E. Engels

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Chapter 1

General introduction

One in six people will ever in their life suffer a stroke and over 35,000 stroke patients are annually admitted to a hospital in the Netherlands.[1,2] The effect of stroke is devastating: it is a significant cause of long-term disability and the second leading cause of death worldwide.[3,4]

Stroke is caused by a sudden interruption in the blood supply to the brain due to a thrombus that occludes an artery (ischemic stroke) or by a ruptured artery that leads to a bleeding in the brain tissue (hemorrhagic stroke). The vast majority of strokes are ischemic (87%), with atherosclerosis and cardio-embolism as main underlying causes.[3] In ischemic stroke, the impaired blood flow results in a lack of oxygen and glucose in the underlying brain tissue. Neurons will be damaged and, due to their high energy demand, die quickly. The loss of neurological function depends on the size and location of the brain tissue that is affected, and may include paralysis of one side of the body, sensory disturbances, impaired vision, and speech and language difficulties.

Acute treatment of ischemic stroke

During the acute phase of ischemic stroke, on average 1.9 million neurons are destroyed each minute that the artery is blocked.[5] Since neurological function loss can be reversible if the blood flow is restored in time, treatment has to be started as soon as possible. Intravenous treatment with alteplase (IVT) to dissolve the blood clot is standard of care for ischemic stroke patients presenting within 4.5 hours after stroke onset.[6-8] However, IVT is less effective in the subgroup of patients with a large vessel occlusion (LVO), a thrombus in one of the proximal intracranial arteries in the anterior circulation, which account for approximately 24% to 46% of all ischemic strokes.[9-11] These patients are often severely affected and have a poor prognosis despite treatment with IVT.[12,13]

Endovascular treatment

A more effective treatment option for patients with LVO is endovascular treatment (EVT), which consists of mechanical clot removal (thrombectomy, Figure 1.1), and originally of delivery of a thrombolytic agent at the site of the occlusion. From 1998, multiple trials demonstrated that this treatment is effective in reopening the occluded vessel and restoring the blood flow, but these studies were not able to show an effect on functional outcome of patients.[14-19] The breakthrough came in 2015, when The Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands (MR CLEAN) was the first to prove the safety and clinical effectiveness of EVT in patients presenting within 6 hours after onset of stroke.[20] Four other randomized controlled trials (RCTs) were stopped early after publication of the MR CLEAN results and showed similar effectiveness.[21-24] EVT soon became standard of care in developed countries.[25]

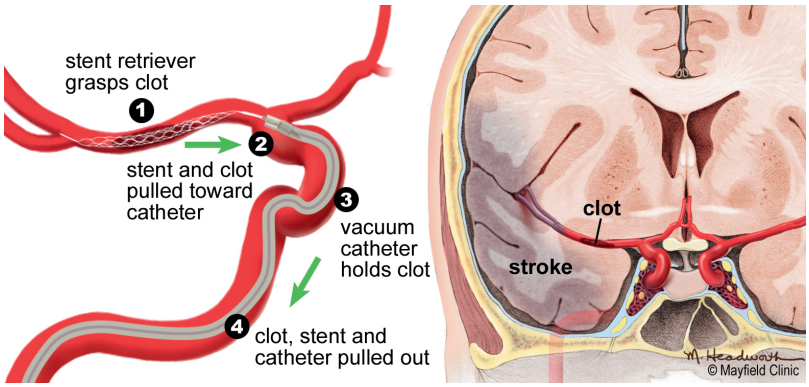

Figure 1.1 Illustration of mechanical thrombectomy, reprinted with permission of MayfieldClinic.com. All rights reserved. No reuse permitted.

Treatment benefit

Endovascular treatment aims to improve functional outcome of ischemic stroke patients. Therefore, the primary outcome in most EVT trials was the modified Rankin Scale (mRS), an ordinal scale that measures the degree of disability during daily life activities.[26] This scale ranges from 0 (no symptoms) to 5 (severe disability), with an extra category of 6 to account for death (Table 1.1).

Table 1.1 Modified Rankin Scale.

Grade	Description
0	No remaining symptoms
1	No significant disability despite symptoms; able to perform all usual activities
2	Slight disability; unable to perform all previous activities, but independent
3	Moderate disability; requiring some help, but able to walk without assistance
4	Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance
5	Severe disability; bedridden, requiring constant nursing care and attention
6	Dead

In a patient-level pooled meta-analysis of five RCTs, the chance of achieving a good functional outcome, defined as an mRS score of 0–2, increased with EVT from 26.5% to 46%. The analysis revealed an astonishingly low number needed to treat of 2.6 to reduce disability by at least one level on the mRS.[27] However, this is the average treatment effect for the overall group of patients included in the trials, while the effect will likely vary between individual patients. Some patients will benefit more from EVT than other patients due to heterogeneity of baseline risk and relative treatment effect.[28-31] The baseline risk of good outcome without treatment, or in other words, the natural history of disease, can be affected by prognostic factors such as age or severity of symptoms. Changes in baseline risk will affect the absolute benefit of a certain treatment, ie, the difference between outcome with and without treatment (Figure 1.2A). The relative treatment effect can be modified by predictive factors, for example when the treatment has a larger effect if started earlier after onset of symptoms (Figure 1.2B). Relative effects appear to be more stable across populations with different baseline risks, and are therefore useful when comparing two treatments or when combining the results of different trials in a meta-analysis. However, the absolute treatment benefit is what matters for a patient and is therefore more relevant for clinical decision-making.[32] As an extreme example, a relative risk of 5 might increase the probability of the outcome with only 0.04% if that outcome is very rare (baseline risk = 0.01%).

Subgroup analysis are often performed to compare the relative treatment effect between different subgroups of patients within a trial population.[33-35] However, these analyses are mostly underpowered, assess only one variable at a time, without taking into account a patient's full baseline risk, and are prone to false-negative and false-positive results.[36,37] When multiple patient characteristics are evaluated simultaneously, more clinically relevant heterogeneity in treatment effect between individual patients will be found.[28,29,38]

Treatment delay and workflow

Early initiation of EVT is associated with better clinical outcomes as the treatment effect strongly declines over time. Every hour of delay between symptom onset and start of EVT results in a 3-5% decreased probability of achieving functional independence.[39,40] It is estimated that every 20 minutes decrease in time to treatment may lead to an average benefit equivalent to 3 months of disability-free life.[41] Reducing delay will also increase the number of stroke patients that can be treated within the recommended 6 hour time-window. Although recent trials have shown that EVT can also be beneficial 6-24 hours after onset of symptoms, this applies to a selected group of patients with sufficient viable brain tissue on additional imaging only.[42,43] Efficient workflow processes that decrease the time from onset to treatment are therefore important to increase the number of patients eligible for EVT and improve the overall outcome of treated patients.

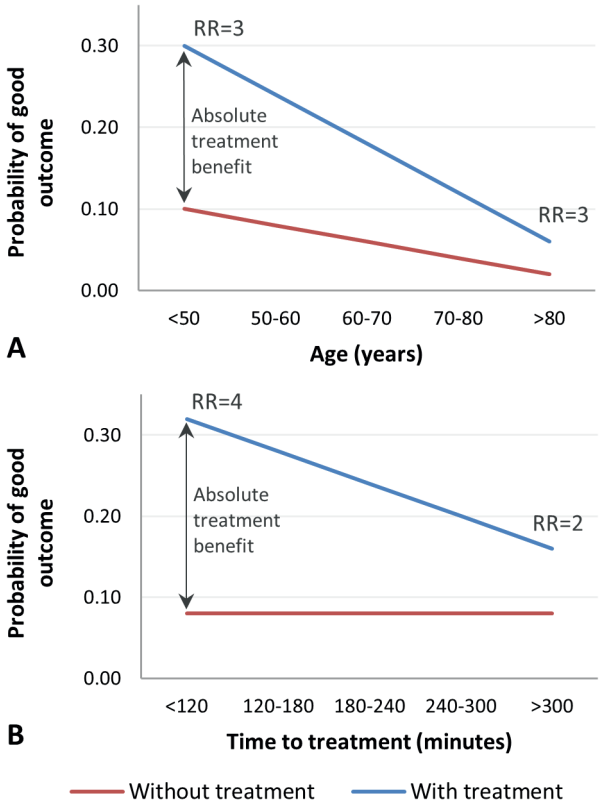

Figure 1.2 Example to illustrate the hypothetical effect of (A) decreasing baseline risk with older age, assuming the same relative treatment effect (relative risk (RR) = 3) for all age categories; and (B) smaller relative treatment effect with increasing time to treatment, assuming a constant baseline risk.

Previously, several quality improvement initiatives resulted in significantly shorter door-to-needle times and a higher percentage of patients treated with IVT.[44-46] These studies showed that in-hospital workflow processes can be streamlined using pre-notification of hospitals by the emergency medical services, rapid stroke team activation, readily available imaging facilities, and frequent feedback to the stroke team on time performance measures. Efficient workflow processes for EVT will also require interdisciplinary teamwork and communication between the emergency department and the neuro-interventional team. In the prehospital setting, potential EVT candidates should be recognized by the emergency medical services and transported to a hospital without any further delay. Potential workflow improvements include direct transportation to an intervention center with facilities for EVT instead of transportation to the closest hospital, and the use of air transportation or mobile stroke units. However, it is unknown how these interventions affect the delivery of EVT.

Prehospital triage

In current clinical practice, most suspected stroke patients are transported to the nearest primary stroke center for rapid IVT and further evaluation. When eligible for EVT, patients have to be transferred to an intervention center. Due to the importance of early treatment, it has been suggested that patients with ischemic stroke due to LVO would benefit from direct transportation to a center capable of performing EVT.[47] LVO can only be assessed with computed tomography (CT) imaging in the hospital, but several prehospital stroke scales have been developed to estimate the likelihood of LVO in patients presenting with stroke symptoms in the ambulance, based on the neurological examination and severity of symptoms.[48,49] Although potentially beneficial for LVO patients, bypassing the nearest primary stroke center might be harmful for the majority of stroke patients because of the time-depending effect of IVT.[6,50] Prehospital triage of suspected stroke patients therefore requires a trade-off between the harm of delaying IVT versus the potential benefit of rapid EVT.

Methods used in this thesis

Prediction modeling

A clinical prediction model estimates the probability of an individual to have a certain disease (diagnosis) or develop a certain clinical outcome (prognosis) based on the combination of a number of characteristics.[51] Such models enable researchers or clinicians to make predictions for individual patients based on the effect of multiple factors combined. It can be used to inform individuals about their expected outcome and to select the right patients for a certain treatment or study.[52] In contrast to etiological studies, a prediction model is not used to suggest a causal relationship between predictors and outcome. Also, it does not provide relative risk estimates such as an odds ratio or risk ratio, but it provides the absolute probability of a certain disease or outcome for an individual patient.

The development of a prediction model consists of several important steps, including careful predictor selection and model specification.[52-54] The validity of the model should be evaluated at least in the derivation cohort (internal validation), and preferably also with external validation to assess generalizability of the model in other populations or settings.[55-57] Performance measures often used in validation studies are discrimination and calibration. Discrimination assesses whether models are able to distinguish between patient with low risk and high risk of the outcome, while calibration describes the agreement between observed and predicted values.[53]

Decision analyses

Decision analyses are designed to compare strategies in situations with decisional uncertainty. It provides a framework to combine all available evidence and uncertainties, to balance the harms and benefits of each alternative, and to make informed decisions.[58-61] A decision tree is a visual representation of all these alternatives and the consequence of

each choice. The expected outcome per strategy is calculated by multiplying the outcome values with the probability that the outcome will occur. According to the basic principles of decision analyses, the strategy with the highest outcome value would be preferred. Uncertainty concerning estimated model parameters and assumptions can be explored using sensitivity analyses in which parameters are varied over a range of estimates to assess its effect on the decision.[62]

Table 1.2 Overview of the data sources used in this thesis.

Study	Design	Location of participating centers	Time frame of patient inclusion	Number of patients used for the analyses in this thesis
MR CLEAN	Phase III, multicenter RCT with open-label treatment and blinded outcome evaluation	The Netherlands	December 2010 – March 2014	500 (Chapters 3 and 6)
MR CLEAN Registry	Nationwide, prospective, observational study	The Netherlands	March 2014 – November 2017	3156 (Chapter 4) 3260 (Chapter 5) 1526 (Chapter 7)
IMS III	Phase III, multicenter RCT with open-label treatment and blinded outcome evaluation	The United States, Canada, Australia, and several countries in Europe	August 2006 – April 2012	260 (Chapter 3)
HERMES	Individual patient data from seven RCTs	The United States, Canada, Australia, New Zealand, Korea, and several countries in Europe	2010 – 2015	1242 (Chapter 4) 781 (Chapter 5)

Data sources

The analyses in this thesis were performed using clinical data from multiple sources (Table 1.2).

- The **MR CLEAN trial** randomized patients with ischemic stroke due to a proximal LVO between EVT (within 6 hours after stroke onset) plus usual care, versus usual care alone.[20,63]
- The **MR CLEAN Registry** included all consecutive patients treated in the Netherlands after the final MR CLEAN inclusion, to monitor the implementation, outcome and safety of EVT in routine clinical practice.[64]
- The **IMS III trial** (Interventional Management of Stroke) randomized ischemic stroke patients to EVT after IVT versus IVT alone. Patient inclusion was not restricted to patients with a proven LVO on non-invasive vessel imaging and the trial was stopped early because of futility.[17,65]

- The **HERMES collaboration** (Highly Effective Reperfusion Using Multiple Endovascular Devices) combined data from seven international randomized controlled trials (RCTs), including MR CLEAN.[20-24,66,67] Patient enrollment was performed according to the specific inclusion and exclusion criteria of each trial.

Aim and outline of this thesis

The overall aim of this thesis is to increase the benefit of endovascular treatment for ischemic stroke by optimizing prediction of outcome and treatment effect, reducing treatment delay, and improving prehospital triage strategies.

This translates into the following research questions:

1. Which are the right patients to treat?
   a. Can we reliably and accurately predict outcome and treatment benefit of EVT for individual patients?
2. How can we treat patients at the right time?
   a. What are the main causes of prehospital and in-hospital delay of EVT?
   b. How do workflow improvements effect treatment delay and outcome?
3. How to direct patients to the right place?
   a. Which factors should influence the decision to transport individual patients directly to an intervention center?
   b. What is the optimal prehospital triage strategy for suspected stroke patients?

The first part of this thesis covers the development and validation of prediction models for outcome and treatment benefit of EVT ("treat the right patient"). **Chapters 2 and 3** describe the development and first external validation of a clinical decision tool to predict outcome with and without EVT (MR PREDICTS). In **Chapter 4**, this model is externally validated and updated with data from the HERMES collaboration and the MR CLEAN Registry. **Chapter 5** contains the development and validation of MR PREDICTS@24H, a post-procedural tool to predict functional outcome at 3 months more accurate with clinical data available within 24 hours after EVT.

The second part of this thesis is focused on rapid initiation of EVT ("treat at the right time"). **Chapter 6** aims to identify treatment delay in the MR CLEAN trial and factors associated with such delay. In **Chapter 7**, the effect of inter-hospital transfer on time to treatment and functional outcome is assessed by comparing patients transferred from a primary stroke center with patients directly admitted to an intervention center in the MR CLEAN Registry. **Chapter 8** reports the results of a systematic review and meta-analysis on the effectiveness of workflow improvements on time to treatment and outcome.

The third part of this thesis evaluates prehospital triage strategies for suspected stroke patients to reduce treatment delay and further improve effectiveness of EVT ("treat in the right place"). **Chapter 9** describes a decision-analytic model to determine the optimal prehospital transportation strategy for individual patients and to assess the factors that should influence this decision. In **Chapter 10**, this model is applied to the United States to evaluate the effect of several policies on outcomes of the ischemic stroke population. **Chapter 11** contains the study protocol of PRESTO, a multicenter observational cohort study to prospectively validate prehospital stroke scales for the prediction of LVO in the prehospital setting.

The main results of this thesis are summarized and discussed in **Chapter 12**, providing recommendations for future research and current clinical practice.

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Part I

Treat the right patient

Chapter 2

Towards personalized endovascular treatment of patients with ischemic stroke: a study protocol for development and validation of a clinical decision aid

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Abstract

Introduction

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

Methods and analysis

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

Ethics and dissemination

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

Introduction

In 2015, five consecutive randomized controlled trials (RCTs) showed that endovascular treatment (EVT) within 6 hours after stroke onset, improves functional outcome of patients with a proximal occlusion in the anterior circulation.[1-6] This was a major breakthrough in the field, and EVT is now implemented in updated guidelines on ischemic stroke management.[7]

Ideally, EVT will be targeted at patients who are expected to have optimal benefit: personalized treatment. In this study protocol we present seven steps for development and validation of a clinical decision aid to predict which individual patients with ischemic stroke will benefit most from EVT.[8,9]

Strengths and limitations of this study

- *Multiple characteristics will be evaluated simultaneously to show clinically relevant heterogeneity in treatment benefit between patients.*
- *Multivariable prediction modelling substantially increases statistical power compared to other approaches and is more robust, especially in small datasets.*
- *We will use a relatively small cohort for the development of a prediction model.*
- *Using a proportional odds model requires the assumption that the odds ratio are the same for each cut-off of the modified Rankin Scale.*

Methods and analysis

Step 1: Problem definition and data inspection

Problem definition

RCTs provide estimates of treatment effects for average patients. However, it is important to take potential heterogeneity of treatment effects into account. Clinically relevant differences in the absolute effect of a treatment can be caused by 1) differences in the relative treatment effect (predictive effects) and 2) differences in baseline risk on the outcome of interest (prognostic effects).[10,11] For example, in the Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands (MR CLEAN) trial, there is no predictive effect of age; the relative treatment effect is constant across age subgroups.[1] This is demonstrated by a non-significant test for interaction between age and treatment (Figure 2.1A). However, variation in baseline risk on favorable outcome according to age results in a larger absolute treatment benefit in younger patients (Figure 2.1B).

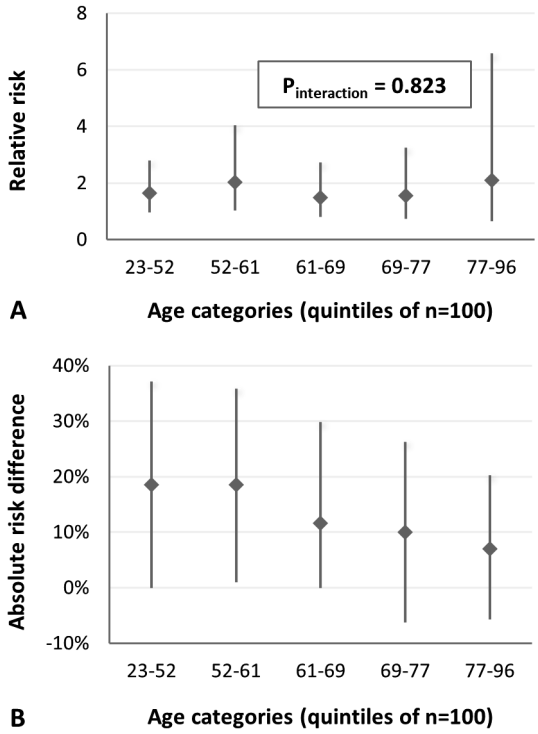

Figure 2.1. Relative risk (A) and absolute risk difference (B) for functional independence (mRS 0-2) in MR CLEAN sort by age**.** MR CLEAN, Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands; mRS, modified Rankin Scale

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

Development data

We will use data of the MR CLEAN trial (n=500), which was a phase 3, multicenter clinical trial with randomized treatment group assignment, open-label treatment, and blinded end-point evaluation. EVT plus usual care (which could include intravenous administration of alteplase) was compared with usual care alone. EVT consisted of arterial catheterization with a microcatheter to the level of occlusion and delivery of a thrombolytic agent, mechanical thrombectomy, or both.[1]

Severity of stroke was assessed at baseline with the National Institutes of Health Stroke Scale (NIHSS; range 0–42). Baseline Computed tomography (CT) was evaluated with the Alberta Stroke Program Early Computed Tomography Score (ASPECTS; range 0–10). Baseline imaging (CT angiography) was used to determine the location of occlusion and to grade the quality of collateral flow to the ischemic area with a 4-point scale. Detailed information about the MR CLEAN trial can be found in the study protocol and the publication of the main results.[1,12]

Endpoints of interest

Primary outcome will be the modified Rankin Scale (mRS), a 7-point scale ranging from 0 (no symptoms) to 6 (death) at 90 days after stroke.[13] We will provide estimates of treatment benefit as the absolute increase in probability on functional independence (defined as mRS 0–2) and survival (defined as mRS 0–5).

Step 2: Coding of variables

As variables, we will use patient characteristics that are expected to predict outcome, or that are expected to interact with treatment, based on expert opinion and the recent literature (Table 2.1). Non-linearity of continuous variables will be tested by comparing the 2 log likelihood of models with linear and restricted cubic spline (RCS) functions.[14]

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

Step 3 and 4: Model specification and estimation

We will test the effect of variables on functional outcome and treatment effect with proportional odds regression modelling. All variables from Table 2.1 will be tested for effect on outcome and interaction with treatment effect. Prognostic variables (main effects) and predictive variables (interaction effects) with a p-value of 0.15 in univariable and multivariable analyses will be included in our final model. A p-value of 0.15 was chosen to make the predictor selection less data driven and prevent overfitting.[14,15] We will perform shrinkage of all regression coefficients with ridge regression to prevent overfitting of the model.[14] Predicted probabilities for each of the mRS categories, with and without treatment, will be derived from the ordinal model. All statistical analyses will be performed within the computing environment R version 3.2.2 (The R Foundation).

Table 2.1. Patient characteristics that are expected to predict outcome (prognostic), or that are expected to interact with treatment (predictive).

	% of data complete in MR CLEAN	Prognostic	Predictive
Clinical			
Age[6,24]	100%	X	
Baseline NIHSS[25,26]	100%	X	
History of diabetes mellitus[27]	100%	X	
History of previous stroke[28]	100%	X	
History of atrial fibrillation[29]	100%	X	
Pre-stroke mRS score[28]	100%	X	
Systolic blood pressure[30]	100%	X	
IV treatment with alteplase[31-33]	100%	X	
Time from stroke onset to groin puncture[34,35]	100%*	X	X
Radiological			
ASPECTS[6,36]	99.2%	X	
Location of intracranial occlusion on non-invasive vessel imaging[37,38]	99.8%	X	
Collateral score on CTA[38,39]	98.4%	X	X

*Of patients undergoing endovascular treatment.
ASPECTS, Alberta Stroke Program Early CT score; CTA, computed tomography angiography; IV, intravenous; 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.

Step 5: Model performance

Model performance will be expressed in discrimination and calibration. Discrimination will be quantified with the c-statistic. The c-statistic is similar to the area under the curve (AUC) for binary outcomes and estimates the probability that out of two randomly chosen patients, the patient with the higher predicted probability of a good outcome will indeed have a better outcome. Calibration refers to the agreement between predicted and observed risks and will be assessed graphically with calibration plots, and expressed as calibration slope and intercept. The calibration slope describes the relative overall effect of the variables in the validation sample, and is ideally equal to 1.

The intercept indicates whether predictions are systematically too high or too low, and should ideally be zero.[16] We will calculate a general c-statistic to express the performance of our ordinal model and additional calibration plots with specific c-statistics for the predictions of favorable functional outcome (mRS 0-2) and survival (mRS 0-5).

Step 6: Model validity
The c-statistic will be internally validated with a bootstrap procedure (500 samples with replacement) to estimate the degree of optimism in parameter estimates.[8] After penalization of the regression coefficients we will externally validate the model on data of patients in the Interventional Management of Stroke III trial (IMS III) with an occlusion in the anterior circulation on non-invasive vessel imaging.[17] Coefficients of the final model will be fitted on the combined development and validation datasets.

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

Step 7: Model presentation
The final model will be online available to be used in clinical practice, both for mobile devices and as a web-application. It will provide predictions of all mRS categories for each individual patient, both with and without EVT.

Ethics and dissemination

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

Discussion

Compared to the current subgroup analyzes on the effect of EVT, our modelling approach has multiple advantages. First, it accounts for the fact that patients have multiple characteristics that simultaneously affect the likelihood of treatment benefit.[18] Thus, our model will show more clinically relevant heterogeneity in treatment benefit between patients. Second, a multivariable prediction model substantially increases statistical power to identify heterogeneity in treatment effects compared to other approaches.[19] These include neural network and decision trees. We use regression modelling since it is considered more robust, especially in relatively small datasets.[20,21]

There are some differences between patients included in MR CLEAN and IMS III that may influence the external validity of our model. IMS III had different inclusion criteria, used older devices and used older treatment paradigms than MR CLEAN. In order to overcome these limitations, we will use only those patients in IMS III with an occlusion in the intracranial anterior circulation on noninvasive vessel imaging. We will compare the baseline

characteristics of the derivation and validation cohort and describe relevant differences that might lead to an under- or overestimation of the model performance. Interestingly, a substantial treatment effect in the IMS III patients with proven intracranial large vessel occlusion has been reported.[22]

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

We will use a proportional odds model to analyze the full mRS score as outcome. Formally this model requires the assumption that the odds ratio are the same for each cut-off of the mRS. However, previous studies have shown that even if the proportionality assumption is violated, proportional odds analysis is still more efficient than dichotomization.[23] In addition, all recent RCTs on the effect of EVT used the full mRS and analyzed their results with proportional odds regression.

Conclusion

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

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Chapter 3

Selection of patients for endovascular treatment of ischemic stroke: development and validation of a clinical decision tool in two randomized trials

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Abstract

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

Design
Multivariable regression modeling with data from two randomized controlled clinical trials.

Setting
Sixteen hospitals in the Netherlands (derivation cohort) and 58 hospitals in the United States, Canada, Australia and Europe (validation cohort).

Participants
500 patients from the Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands (MR CLEAN) trial (derivation cohort) and 260 patients with proven intracranial occlusion from the Interventional Management of Stroke III (IMS III) trial (validation cohort).

Main outcome measures
The primary outcome was the modified Rankin Scale (mRS) at 90 days after stroke. We constructed an ordinal logistic regression model to predict outcome and treatment benefit, defined as the difference between the predicted probability of good functional outcome (mRS 0–2) with and without EVT.

Results
Eleven baseline clinical and radiological characteristics were included in the model. The externally validated c-statistic was 0.68 (95% confidence interval (CI) 0.64 to 0.73) for the ordinal model and 0.73 (95% CI 0.67 to 0.79) for the prediction of good functional outcome, indicating moderate discriminative ability. The mean predicted treatment benefit varied between patients in the combined derivation and validation cohort from -2.3% to 24.3%. There was benefit of EVT predicted for some individual patients from groups in which no treatment effect was found in previous subgroup analyses, such as those with no or poor collaterals.

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

Trial registration

clinicaltrials.gov NCT00359424 (IMS III) and isrctn.com ISRCTN10888758 (MR CLEAN).

Box 3.1 Research in context.

What is already known on this topic

- *Endovascular treatment improves functional outcome in patients with acute ischemic stroke caused by a proximal occlusion.*
- *There is large variation in the selection of candidates for endovascular treatment in current practice because of the uncertainty of treatment benefit in specific subgroups.*

What this study adds

- *A newly developed clinical decision tool combines multiple baseline clinical and radiological characteristics and shows large variations in treatment benefit between patients.*
- *Selection of individual patients for endovascular treatment should therefore not be based on single patient characteristics.*
- *This model is the first step towards individualized selection of patients for endovascular treatment of ischemic stroke and may be used as a tool for assisting clinical decision making.*

Box 3.2 Descriptions of ASPECTS and collateral score.

ASPECTS

A quantitative grading system to assess early ischemic changes on a non-contrast CT scan. Scores ranges from 0 to 10, with 10 points for a normal CT scan and 1 point subtracted for every defined region with evidence of early ischemic changes.[16]

Collateral score

A 4 point scale to grade the collateral flow of the occluded territory on vessel imaging, with 0 representing absent collateral flow, 1 representing poor collateral flow (<50% filling), 2 representing moderate collateral flow (between 50% and 100% filling), and 3 representing good collateral flow (100% filling).[17]

Background

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

Clinicians combine multiple clinical features in their clinical decision making on how to treat an individual patient. For example, consider a 70-year old man who is admitted 40 minutes after onset of symptoms, with a severe left hemisphere ischemic stroke and a National Institutes of Health Stroke Scale (NIHSS) score of 22, an Alberta Stroke Program Early Computed Tomography Score (ASPECTS) of 7 and a M1 occlusion but no collaterals on computed tomography angiography (CTA). A previous subgroup analysis using data of the MR CLEAN trial suggested no treatment effect for patients with no or poor collaterals.[15] But if this man can be treated very early after onset of stroke, will he benefit from EVT? Or consider a diabetic woman with high systolic blood pressure, aged 80, who arrived in a primary stroke center too late for treatment with intravenous (IV) alteplase, with a NIHSS score of 22, ASPECTS of 9, and a carotid-T occlusion with good collaterals on CTA. Should she be transferred to an intervention center 40 miles away if EVT just within the 6-hour time window is possible?

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

Methods

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

Derivation cohort

We used data from all 500 patients of MR CLEAN (derivation cohort) for the development of our model.[5] MR CLEAN was a phase III multicenter clinical trial with randomized treatment-group assignment, open-label treatment and blinded outcome evaluation. EVT plus usual care was compared with usual care alone (control group). Usual care could include treatment with IV alteplase if eligible. Enrolled patients were 18 years or older (no upper age limit), had a score of 2 or higher on the NIHSS (range 0 to 42), an occlusion of the proximal intracranial carotid artery, middle cerebral artery (M1 or M2), or anterior cerebral artery (A1 or A2), established with CTA. The start of EVT had to be possible within six hours after stroke onset. The imaging committee evaluated the findings on baseline non-contrast computed tomography (NCCT) for the ASPECTS and non-invasive baseline vessel imaging (CTA, magnetic resonance angiography, or digital subtraction angiography) for the location of the occlusion and collateral score.

More detailed information about MR CLEAN can be found in the study protocol and the publication of the main results.[5,18]

Model development

Patient characteristics obtained before treatment that are expected to predict outcome or to interact with treatment, based on expert opinion or recent literature, were specified in our statistical analysis plan.[19] We used ordinal logistic regression modeling, which assumes proportional odds, to test the effect of age, baseline NIHSS score, systolic blood pressure, treatment with IV alteplase, history of ischemic stroke, atrial fibrillation, diabetes mellitus, prestroke mRS, ASPECTS, location of occlusion, collateral score and time to treatment, as well as the corresponding interactions with treatment. Primary outcome was the mRS score, a 7-point scale ranging from 0 (no symptoms) to 6 (death), at 90 days after stroke.[20] For additional analyses, we derived the probabilities for good functional outcome (mRS 0–2) from the ordinal model. Treatment benefit was defined as the difference between the predicted probability of good functional outcome with and without EVT.

In our final multivariable model we selected the main effects or interaction terms with a P value of <0.15 in univariable and multivariable analyses. Location of occlusion was analyzed categorically and ASPECTS and collateral score were analyzed continuously. Continuous variables were not dichotomized. Non-linearity of continuous variables was tested with restricted cubic spline functions.[21] In the final model we used restricted cubic spline functions for age and systolic blood pressure. As a measure for time to treatment we used the time from stroke onset to groin puncture. Since groin puncture was not performed in control subjects, time to groin puncture was not observable in the control arm. Single imputation based on regression using age, NIHSS score, inter-hospital transfer, hospital of first presentation and time to randomization, was used to assign time to expected groin puncture (R^2=0.89). Since all other variables were more than 98% complete within the derivation

cohort, we used simple imputation by the mean for continuous variables and simple imputation by the mode for categorical variables.

Internal validation with bootstrapping was used to estimate the degree of optimism in the final model. Regression coefficients were reduced with penalized regression to correct for this optimism.[21,22] Coefficients of non-linear terms and interaction terms were reduced with a larger penalty than the main effects.[22]

External validation

External validation of our model was performed in the Interventional Management of Stroke III (IMS III) trial.[23] The IMS III trial (n=656) was a phase III multicenter clinical trial with randomized treatment group assignment, open label treatment, and blinded outcome evaluation. The trial tested the approach of IV alteplase followed by EVT, as compared with standard IV alteplase. Further details on the methods used in the trial have been reported extensively.[23,24]

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

Model performance in the validation cohort was expressed by discrimination and calibration. Discrimination was quantified with the concordance or c-statistic, which varies between 0.5 for a non-informative model and 1 for a perfectly discriminating model.[25] We calculated the general c-statistic of our ordinal model and an additional c-statistic for the predictions of good functional outcome (mRS 0–2).

Calibration refers to the level of agreement between predicted risks and observed outcome; this was assessed graphically with a validation plot for the prediction of good functional outcome (mRS 0–2) expressed as calibration slope and intercept. The calibration slope describes the effect of the predictors in the validation sample versus the derivation sample, and is ideally equal to 1. The intercept indicates whether predictions are systematically too high or too low, and should ideally be zero.[26]

After external validation, the regression coefficients were fitted on a dataset combining all patients in the derivation and validation cohort. To assess if our model could be used to select individual patients for EVT, we estimated the individual predictions for all 760 patients

included in this combined dataset. We created a scatterplot with the predicted probabilities of good functional outcome (mRS 0–2) for these patients without EVT on the x-axis and the predicted probabilities with EVT on the y-axis. We made additional plots for the predictions of patients with no or poor collaterals and patients with low ASPECTS scores, since pre-specified subgroup analyses showed that these groups had no or very limited benefit of treatment.

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

Patient involvement

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

Results

Table 3.1 shows that baseline patient characteristics and important characteristics of workflow and outcome were similar between the derivation cohort (n=500) and validation cohort (n=260). The validation cohort was somewhat more homogeneous, by not including patients with baseline disability (premorbid mRS ≥3) or patients not treated with IV alteplase.

Most variables were predictors of outcome (Table 3.2). The strongest predictors in multivariable analysis were age (P<0.001), baseline NIHSS (P<0.001), systolic blood pressure (P<0.001), history of ischemic stroke (P=0.03), diabetes mellitus (P=0.02), prestroke mRS (P=0.003), ASPECTS (P=0.001), location of occlusion (P=0.03) and collateral score (P<0.001). Interactions with relative treatment effect were found in univariable analysis for history of ischemic stroke, atrial fibrillation, collateral score and time to groin puncture (all P≤0.10, Figure 3.1). In the multivariable model, the effects of EVT were similar as in univariable analysis, with larger effects in patients without previous ischemic stroke (P=0.07), in patients with better collateral scores (P=0.07), and in patients with shorter times to groin puncture (P=0.13). Atrial fibrillation was not significant in multivariable analysis as either a main effect (P=0.67) or interaction effect (P=0.27), and was therefore excluded from the model.

The final multivariable model included age, baseline NIHSS score, systolic blood pressure, IV treatment with alteplase, history of ischemic stroke, diabetes mellitus, pre-stroke mRS, ASPECTS, location of occlusion, collateral score and time from onset to groin puncture. We added terms representing the interaction between treatment and each of previous stroke,

Table 3.1. Overview of the derivation and validation cohort.

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

Values are numbers (percentages) unless stated otherwise.
ASPECTS, Alberta Stroke Program Early CT score; EVT, endovascular treatment; ICA-(T), internal carotid artery (with terminal segment); IQR, interquartile range; IV, intravenous; mRS, modified Rankin Scale; mTICI, modified thrombolysis in cerebral infarction scale; NCCT, non-contrast computed tomography; NIHSS, National Institutes of Health Stroke Scale.

collateral score and time to groin puncture. The internally validated c-statistic for ordinal outcome was 0.74 without interaction terms and this increased to 0.75 by adding interaction with treatment. The c-statistic for good functional outcome was 0.79.

External validation

Similar effects were found for most variables in the validation cohort except for systolic blood pressure, diabetes mellitus and the interaction between history of ischemic stroke and treatment effect. The externally validated c-statistic was 0.69 (95% CI 0.64 to 0.73) for the ordinal model and 0.73 (0.67 to 0.79) for the prediction of good functional outcome (Figure 3.2).

Table 3.2. Main effects in derivation cohort (n=500).

	Univariable model		Multivariable model	
	Common odds ratio (95% CI)	**p-value**	**Common odds ratio (95% CI)**	**p-value**
Intra-arterial treatment	1.66 (1.21 to 2.28)	0.002	1.86 (1.34 to 2.59)	<0.001
Age (per year)		<0.001		<0.001
<65 years	0.97 (0.95 to 0.99)		1.00 (0.97 to 1.02)	
>=65 years	0.92 (0.89 to 0.94)		0.92 (0.89 to 0.95)	
Baseline NIHSS (per point)	0.91 (0.88 to 0.94)	<0.001	0.93 (0.90 to 0.96)	<0.001
Systolic blood pressure (per 10 mmHg)		<0.001		<0.001
<130 mmHg	1.12 (0.88 to 1.41)		1.24 (0.97 to 1.59)	
>=130 mmHg	0.76 (0.70 to 0.83)		0.77 (0.70 to 0.85)	
Treatment with IV alteplase	1.85 (1.12 to 3.08)	0.02	1.62 (0.94 to 2.79)	0.08
History of ischemic stroke	0.48 (0.29 to 0.80)	0.005	0.53 (0.31 to 0.92)	0.03
Atrial fibrillation	0.52 (0.36 to 0.73)	<0.001	0.92 (0.62 to 1.36)	0.67
Diabetes mellitus	0.37 (0.23 to 0.59)	<0.001	0.54 (0.33 to 0.90)	0.02
Prestroke mRS	0.63 (0.52 to 0.77)	<0.001	0.72 (0.58 to 0.90)	0.003
ASPECTS (per point)	1.16 (1.07 to 1.26)	<0.001	1.16 (1.06 to 1.28)	0.001
Level of occlusion on non-invasive imaging		0.02		0.03
ICA-(T)	1.0 (reference)		1.0 (reference)	
M1	1.53 (1.08 to 2.17)		1.43 (0.98 to 2.07)	
M2	2.11 (1.15 to 3.88)		2.35 (1.20 to 4.60)	
Collateral score	1.95 (1.62 to 2.36)	<0.001	1.61 (1.31 to 1.96)	<0.001
Time from onset stroke to groin puncture (per 30 minutes)	0.94 (0.88 to 1.00)	0.07	0.93 (0.86 to 1.00)	0.04

Presented common odds ratios reflect the effect on the reversed modified Rankin Scale (odds ratio >1 corresponds with better functional outcome).
ASPECTS, Alberta Stroke Program Early CT score; CI, confidence interval; CTA, computed tomography angiography; EVT, endovascular treatment; ICA-(T), internal carotid artery (with terminal segment); IQR, interquartile range; IV, intravenous; mRS, modified Rankin Scale; NCCT, non-contrast computed tomography; NIHSS, National Institutes of Health Stroke Scale.

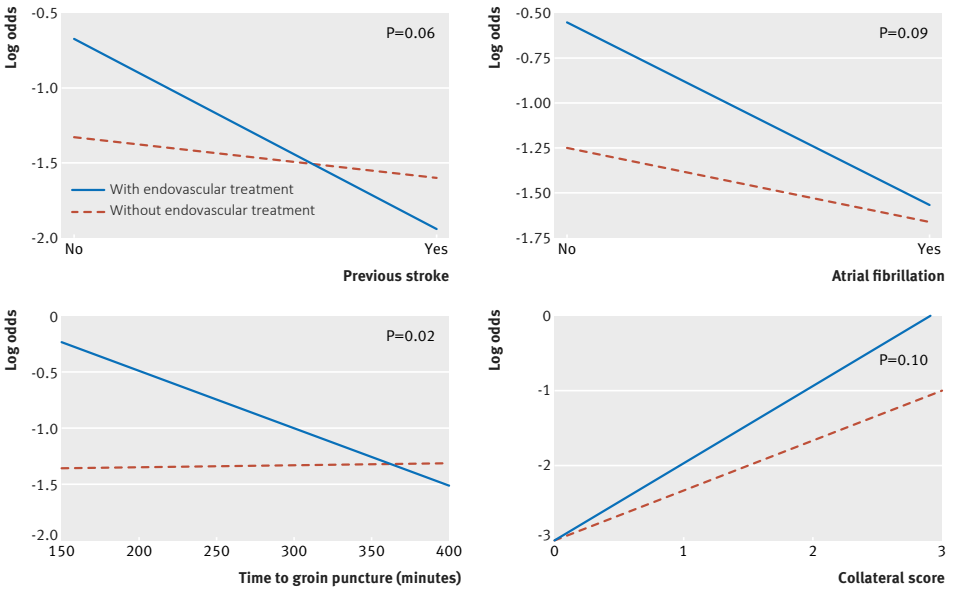

Figure 3.1. Univariable interaction effects in the derivation cohort (n=500). Interaction with treatment is expressed as the log odds for good functional outcome (modified Rankin Scale 0–2) with and without endovascular treatment on the y-axis. Variables on the x-axis are expressed continuously (time to groin puncture) or categorically (previous stroke, atrial fibrillation and collateral score).

The expected benefit of EVT varied largely between patients in the combined derivation and validation cohort (Figure 3.3A). Mean predicted absolute treatment benefit was an 11.8% higher probability of mRS 0–2 compared to the probability without EVT, and varied from -2.3% to 24.3% between individual patients in the combined derivation and validation cohort. The individual predictions for patients with no or poor collaterals (score 0–1) or low ASPECTS (score 0–5) illustrate the substantial variation in outcome and treatment benefit in these groups (Figures 3.3B and 3.3C). For some patients, who have multiple characteristics that negatively affect treatment benefit, the model predicts no benefit or even harm.

We calculated the predicted probabilities of good functional outcome with and without EVT for the two patients described in the introduction (Figure 3.4). The first patient is expected to benefit from EVT despite absent collaterals and moderate ASPECTS. The probability of achieving good functional outcome increases by 11 percentage points, from 16% without EVT to 27% with EVT. The predictions for the second patient illustrate that a good collateral score does not guarantee a large treatment benefit. The 80-year old patient has a low probability of achieving good functional outcome (3% without EVT and 5% with EVT), with some shift on the total mRS scale.

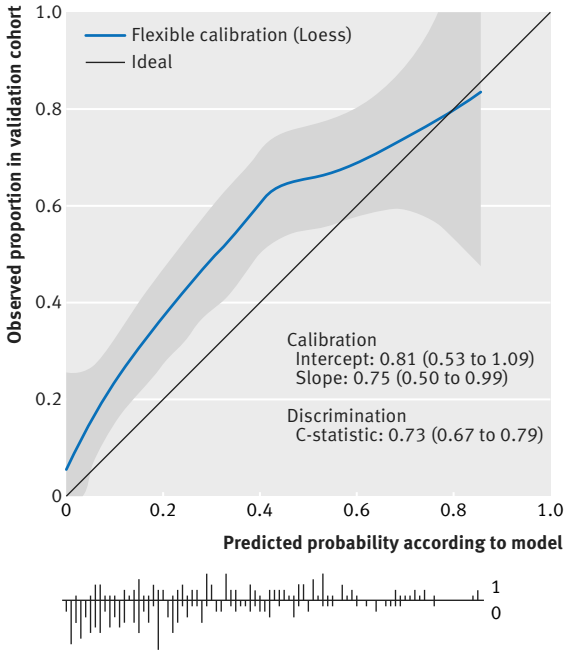

Figure 3.2. Calibration plot for predicted good functional outcome, defined as modified Rankin Scale (mRS) 0-–2, in the validation cohort (n=260). The calibration slope reflects the strength of the predictors. The calibration intercept reflects the calibration-in-the-large, indicating whether predicted probabilities are systematically too low or too high. The overall observed proportion of patients with mRS 0–2 in the validation cohort was higher as to be expected using our model. The linear bar chart shows the distribution of patients with (=1) or without (=0) an observed outcome of mRS 0–2. Discrimination between low and high likelihood of good functional outcome was moderate (c-statistic 0.73, 95% CI 0.67 to 0.79).

We implemented our model in a web-application that provides predictions of outcome for individual patients based on baseline clinical and radiological characteristics for use in clinical practice. It shows bar charts with the expected distribution of mRS categories with and without EVT, the predicted probabilities of good functional outcome and the predicted absolute treatment benefit (Figure 3.4). This web-application was made accessible online at www.mrpredicts.com.

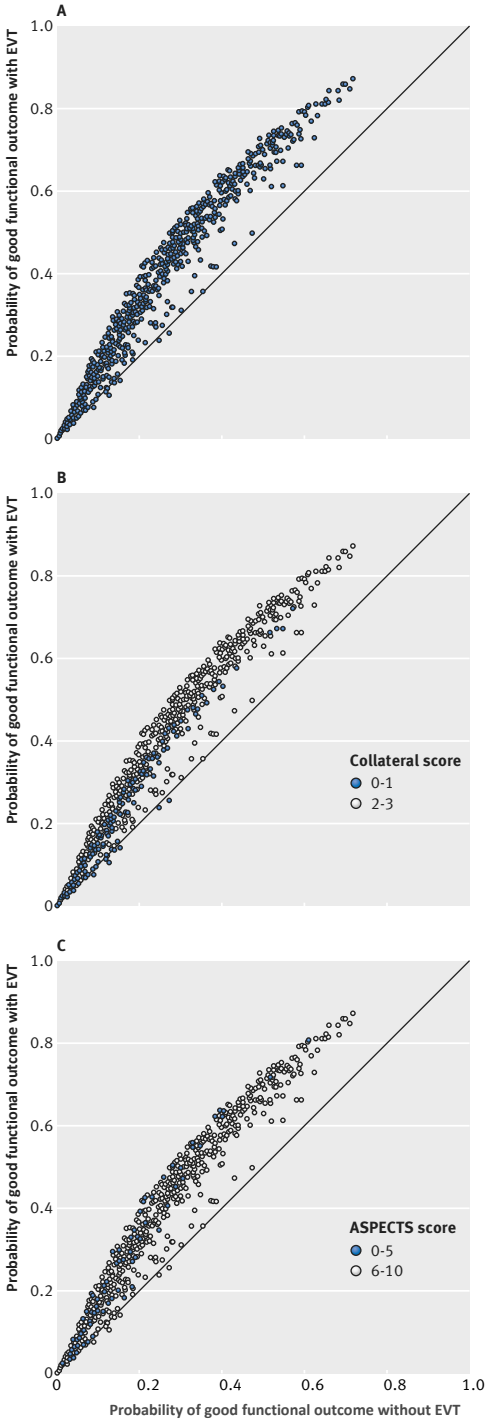

Figure 3.3. (A) Predicted probabilities of good functional outcome (modified Rankin Scale (mRS) score 0–2) for all individual patients in combined derivation and validation cohort (n=760). Each dot represents one individual patient, with the probability of good functional outcome (mRS score 0–2) without endovascular treatment (EVT) expressed on x-axis, and probability for good functional outcome with EVT on y-axis. Above the diagonal line the predicted probability of good functional outcome with EVT is higher than that without EVT. The farther above this line, the larger the predicted effect of treatment. (B) Patients highlighted with no or poor collaterals (score 0–1). (C) Patients highlighted with low Alberta Stroke Program Early CT Score (ASPECTS, score 0–5).

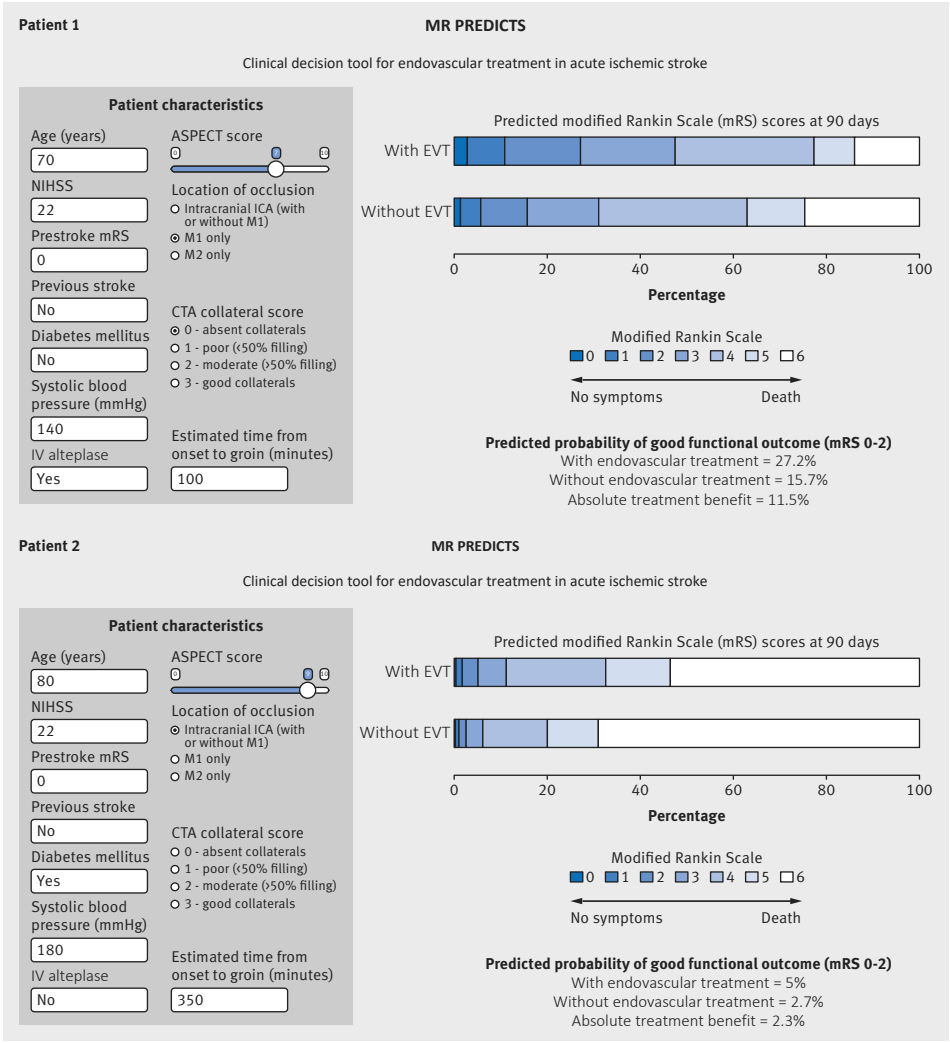

Figure 3.4. A stylized representation of the clinical decision tool. Baseline characteristics and predicted probabilities of good functional outcome (modified Rankin Scale (mRS) score 0–2) for two examples (see introduction). ASPECT, Alberta Stroke Program Early Computed Tomography Score; EVT, endovascular treatment; NIHSS, National Institutes of Health Stroke Scale; ICA, internal carotid artery; CTA, computed tomography angiography.

Discussion

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

Strengths and weaknesses in relation to other studies

Two risk scores have been described previously for the prediction of functional outcome after EVT.[27,28] These scores are of limited value because they were developed on older cohorts of patients who were treated before the introduction of stent-retrievers and contain only a small number of clinical variables. Furthermore, they do not provide individual predictions and most of the variables and outcome measures in these studies had been dichotomized, which is considered to be statistically inefficient and biologically implausible.[29] Our model combines eleven baseline clinical and radiological characteristics simultaneously to provide individualized predictions of the effect of EVT. In contrast, conventional subgroup analyses focus mainly on predictive effects and assess the effect of only one variable at a time. Previous subgroup analyses of EVT trials have tested whether there are differences in effect of EVT based on for example: time to treatment,[30-34] stroke severity,[12,35] and collateral score.[15] Analyzing one variable at a time may provide mechanistic insights to inform future studies and shape clinical considerations. However, they are of limited value in individual patient care, because treatment benefit is influenced by multiple individual factors simultaneously.[13,14] Furthermore, even with similar relative treatment effect, individual patients may have different absolute treatment effects due to different baseline risks. More targeted individual treatment decisions can be obtained by using a more complex multivariable modeling approach to identify individual patients with large or small expected treatment benefit.[13]

We found modest interaction with treatment for history of ischemic stroke, collateral score and time from stroke onset to groin puncture. For collateral score and time to groin puncture, interaction with effect of EVT was already shown in previous subgroup analyses.[15,30] Both variables are clinically likely to cause interaction with EVT. However, previous stroke has not been studied for interaction with treatment before, and was an unexpected finding in our study. It may be a chance finding, since it was not reproduced in the validation cohort and we have no clinical explanation. When the regression coefficients were fitted on data of the combined derivation and validation cohort and the coefficients of interaction terms were reduced to prevent overfitting, the interaction effect for previous stroke in the final model was small. Further validation should reveal whether the relative effect of EVT is modified by experience of a previous stroke.

Our study has several limitations. The discriminative ability of the model in the external validation was modest. It should be emphasized however, that the c-statistic for the ordinal

outcome is a conservative measure. It assesses discrimination between exact categories of the mRS, instead of discrimination between 2 groups with different outcome (for example mRS 0–2 versus mRS 3–6). Externally validated c-statistics of all cut-offs were better than the ordinal c-statistic (eg, 0.73 for good functional outcome and 0.75 for mortality). Nevertheless, the relatively small sample size and inclusion of interaction terms in the model may have resulted in some optimism and overfitting, despite shrinkage of the regression coefficients. The calibration was also suboptimal; despite the fact that most patients were treated with first generation thrombectomy devices, patients in the IMS III trial had a better outcome than predicted by our model. This could be explained by the patient selection in IMS III (eg, premorbid mRS 0–2, age <82 years, treatment with IV alteplase),[36] which resulted in a better prognosis overall. Patients in the IMS III control group had better outcomes than patients in the control group in MR CLEAN (mRS 0–2 = 39% (IMS III with occlusion on CTA) versus 19% (MR CLEAN)), leading to inadequate calibration of our model.[5,36]

Implications for clinicians

Despite its limitations, the currently developed model is the first to predict the effect of EVT for individual patients upon arrival at the emergency department. When compared to other models used in neurovascular practice, HAS-BLED (c-statistic = 0.65) and CHA_2DS_2-VASc (c-statistic = 0.61), it performs accurately.[37,38] The predictions made by our decision tool often agree with clinical intuition, which should not be surprising. However, estimates derived from large datasets are preferable to the subjective opinion of a physician, whose experience, no matter how vast, can never match the information contained in large datasets.[39]

Currently, some centers withhold EVT in specific subgroups of patients (eg, low ASPECTS, no collaterals, age >80 years, or M2 occlusion). Indeed, our model predicts no benefit of EVT for some individual patients, especially when a patient has more than one characteristic that negatively affects the effect of EVT. The decision not to treat may be particularly relevant in patients who have to be transferred to an intervention center. The model may help to identify patients without expected benefit of EVT and topple the balance in favor of no treatment. But, perhaps more importantly, our study shows that treatment should not be withhold based on a single characteristic. Some patients belonging to one of the subgroups that are considered as having no benefit of EVT, such as poor collaterals or low ASPECTS, may still benefit from EVT substantially if other characteristics are favorable. This emphasizes the importance of making personalized treatment decisions, instead of using average treatment effects, and shows the need for combining multiple clinical and radiological baseline characteristics instead of withholding treatment based on a single characteristic.[40]

This is the first model for EVT decision making. The predictions of our model should be considered as a starting point for clinical decision making, and not as a final recommendation. Our model was developed using the MR CLEAN database, consisting of an unselected population with few selection criteria. Therefore, our model is likely applicable in centers

that use few clinical and radiological selection criteria. Future analyses within larger studies may refine the current recommendations and improve the validity of the model.

Conclusion

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

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Chapter 4

Improving selection of patients for endovascular treatment of ischemic stroke: validation and updating of MR PREDICTS with data from 4,398 patients

Submitted

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Research in context

Evidence before this study

We searched PubMed for articles published in any language before March 1, 2020, using a search strategy that included the keywords "ischemic stroke", "prediction", "prognostic", "endovascular", "intra-arterial", and "thrombectomy". Included were pre-intervention models that were developed or validated to predict functional outcome following endovascular treatment of anterior circulation stroke within six hours after symptom onset. Over 25 models could be identified, of which several concerned modifications of existing models. The number of variables in each model ranges between two and eleven, with age and stroke severity as most frequently used predictors. All models have certain methodological shortcomings in their development that could lead to bias, often due to limited sample size and overfitting. Predictive performance of the models is moderate with c-statistics ranging between 0.60 and 0.80, and extensive external validation is often lacking. Two models identified subgroups of patients with small treatment benefit, defined as poor outcome irrespective of reperfusion status, but these results need further validation in larger samples.

Added value of this study

To our knowledge, MR PREDICTS is the only model that predicts outcome with and without endovascular treatment to estimate individual treatment benefit and thereby improve patient selection. The model was validated and updated using high-quality data from international trials and a large nationwide registry, and performed reasonably well in the prediction of functional independence. Predictions can be adapted to different settings and populations using the online tool that is available for clinicians and researchers at www.mrpredicts.com.

Implications of all available evidence

Because of the substantial treatment effect and small potential harm of endovascular treatment, most patients arriving within 6 hours at an endovascular-capable center should be treated regardless of their clinical characteristics. MR PREDICTS can be used to support clinical judgement when there is uncertainty about the treatment indication, when resources are limited, or before a patient is to be transferred to an intervention center.

Abstract

Background

Benefit of early endovascular treatment (EVT) for ischemic stroke varies considerably among patients. The MR PREDICTS decision tool, previously derived from the MR CLEAN trial, predicts outcome and treatment benefit based on baseline characteristics. Our aim was to externally validate and update MR PREDICTS with data from international trials and daily clinical practice.

Methods

We used individual patient data from six randomized controlled trials within the HERMES collaboration (ESCAPE, REVASCAT, SWIFT-PRIME, EXTEND-IA, THRACE, and PISTE) to validate the original model. Then, we updated the model and performed a second validation with data from the observational MR CLEAN Registry. The primary outcome was functional independence (defined as modified Rankin Scale 0–2) three months after stroke. Treatment benefit was defined as the difference between the probability of functional independence with and without EVT. Discriminative performance was evaluated using a concordance (c) statistic.

Findings

We included 1242 patients from HERMES (633 assigned to EVT, 609 assigned to control) and 3156 patients from the MR CLEAN Registry (all of whom underwent EVT within 6.5 hours). The c-statistic for functional independence was 0.74 (95% CI 0.72 to 0.77) in HERMES and, after model updating, 0.80 (0.79-0.82) in the Registry. Median predicted treatment benefit of routinely treated patients (Registry) was 10.6% (IQR 6.4% to 14.5%). Patients with low (<1%) predicted treatment benefit (n=105/3156 (3.3%)) had low rates of functional independence, irrespective of reperfusion status, suggesting potential absence of treatment benefit.

Interpretation

MR PREDICTS performed reasonably well in a heterogeneous population. Our updated model can be used to support treatment decisions when there is uncertainty about the treatment indication, when resources are limited, or before a patient is to be transferred to an intervention center.

Introduction

Endovascular treatment (EVT) within 6 hours after symptom onset is safe and effective for patients with ischemic stroke due to a proximal intracranial occlusion in the anterior circulation.[1] Benefit of this treatment varies considerably among patients due to differences in prognostic factors and heterogeneity of treatment effect. For this reason, we have developed the MR PREDICTS decision tool with data from the Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands (MR CLEAN) to predict treatment benefit in individual patients.[2-4] This prediction model combines eleven patient and imaging characteristics at baseline to estimate -outcome with and without EVT. It emphasizes the importance of personalized treatment decisions by combining multiple individual factors to estimate treatment effects in individual patients.[5,6] MR PREDICTS is meant to support clinicians in decision making for EVT, so as to treat patients that are most likely to benefit from EVT and avoid futile treatment.

A previous external validation with data from the Interventional Management of Stroke (IMS) III trial showed moderate discriminative ability.[3,7] However, the field of EVT is developing very quickly and quality of care is improving with, for example, shorter treatment times.[8] Patients treated in clinical practice are less selected and may therefore differ from those included in randomized trials.[6] Furthermore, it is unclear if MR PREDICTS is reflecting practice in other healthcare systems and countries. In the present study, we therefore aim to externally validate and update the MR PREDICTS decision tool with data from multiple international trials and a Dutch national registry, which reflects daily clinical practice.

Methods

First, we performed external validation of MR PREDICTS using individual patient data from randomized controlled trials (RCTs) within the HERMES collaboration to assess its predictive ability and estimate relative treatment effects.[1] We then updated the model and performed a second validation with data from patients routinely treated with EVT in the MR CLEAN Registry.[8]

HERMES collaboration

The HERMES collaboration consists of patient-level data from seven RCTs comparing EVT with usual care in patients with anterior circulation ischemic stroke: MR CLEAN;[4] Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion with Emphasis on Minimizing CT to Recanalization Times (ESCAPE);[9] Extending the Time for Thrombolysis in Emergency Neurological Deficits–Intra-Arterial (EXTEND-IA);[10] Randomized Trial of Revascularization with Solitaire FR Device versus Best Medical Therapy in the Treatment of Acute Stroke Due to Anterior Circulation Large Vessel Occlusion Presenting Within Eight

Hours of Symptom Onset (REVASCAT);[11] Solitaire with the Intention for Thrombectomy as Primary Endovascular Treatment (SWIFT PRIME);[12] Thrombectomie des Artères Cerebrales (THRACE);[13] and The Pragmatic Ischaemic Thrombectomy Evaluation (PISTE).[14] Enrolled patients were 18 years or older and had an intracranial large vessel occlusion in the anterior circulation on non-invasive imaging. Specific inclusion criteria for pre-stroke disability, National Institutes of Health Stroke Scale (NIHSS) score, Alberta Stroke Program Early Computed Tomography Score (ASPECTS), occlusion location, and collateral score varied among the studies. EVT was mainly performed with second-generation neuro-thrombectomy devices. All participants provided informed consent according to each trial protocol and each study was approved by the local ethics and research board. The methods and design for the patient-level pooling have been described previously.[1]

For this validation study, we included all patients with an occlusion of the intracranial carotid artery (ICA), internal carotid artery terminus (ICA-T), or middle cerebral artery (segment M1 or M2) on non-invasive imaging. Patients from the MR CLEAN trial (ie, the derivation cohort) and patients with missing outcomes were excluded, according to HERMES policy. Missing predictor values were replaced with the mean or the mode, or by single regression imputation when more than 5% was missing.

MR CLEAN Registry

The MR CLEAN Registry is a prospective, observational study, which included all patients treated with EVT in the Netherlands. Registration started in March 2014, directly after the final inclusion in the MR CLEAN trial. There was no upper age limit and no minimal ASPECTS or collateral score required. All data were centrally collected and checked for completeness and consistency. An imaging assessment committee assessed imaging characteristics without knowledge of outcome or detailed clinical characteristics and an adverse event committee scored the safety parameters. Functional outcome at 3 months was systematically assessed by experienced and trained research nurses. The central medical ethics committee of the Erasmus MC University Medical Center, Rotterdam, The Netherlands, evaluated the study protocol and granted permission to carry out the study as a registry (MEC-2014-235). Detailed methods of the MR CLEAN Registry have been reported previously.[8]

For this validation study, we included patients treated between March 16, 2014, and November 1, 2017. We used the following inclusion criteria: age ≥18 years; occlusion of the ICA(-T) or middle cerebral artery (segment M1 or M2) on non-invasive imaging; start of treatment within 6.5 hours after onset or last seen well; and treatment in a center that participated in the MR CLEAN trial. Following MR CLEAN Registry policy, missing baseline and outcome values were imputed using multiple imputation based on relevant covariates.

Statistical analyses

MR PREDICTS is a multivariable ordinal logistic regression model that predicts the modified Rankin Scale (mRS) score at 90 days after stroke. Definitions of predictor variables were

used as described in the MR PREDICTS paper.[3] The probability of functional independence, defined as an mRS score of 0–2, was derived from the ordinal model.

External validation was performed using the coefficients and intercept of the original model. We used individual patient data and did not account for potential clustering of patients within the HERMES dataset in the six constituting trials. After the first validation, the model was updated based on the full HERMES dataset, which includes the MR CLEAN trial. The model coefficients were refitted with a separate intercept for the derivation versus validation cohort. We assessed extension of the model with baseline glucose based on previously published studies, using a likelihood-ratio test.[15–17] Non-significant variables were removed. Then, a second validation using this updated model was performed with data from the MR CLEAN Registry.

Model performance was evaluated according to discrimination (ie, the ability to distinguish between patients with a low and high probability of a good outcome) and calibration (ie, the level of agreement between predicted and observed outcome). Discriminative ability was quantified with Harrell's concordance (c) statistic, which varies between 0.5 for a non-informative model and 1 for a perfectly discriminating model.[18] We calculated the c-statistic for the prediction of functional independence (mRS 0–2) and for the full ordinal analysis. Calibration was assessed graphically with a plot for the prediction of functional independence and was quantified by the calibration intercept and slope.[19] The intercept should ideally be equal to 0 and the calibration slope equal to 1. Bootstrap resampling with 2000 replications was performed to construct the 95% confidence intervals of the model performance measures (50th and 1950th performance estimates).

Treatment benefit was defined as the difference in the probability of functional independence with and without EVT. The predicted treatment benefit of individual patients in HERMES was compared with the observed benefit (ie, the difference between treated patients and control patients) in quintiles of predicted benefit. We calculated the "c-for-benefit" using the outcomes of patient pairs that were matched on predicted benefit but discordant for treatment assignment.[20] Because of the lack of a control group in the MR CLEAN Registry, we compared outcome of patients with successful reperfusion (defined as an extended Thrombolysis in Cerebral Infarction (eTICI) score 2B-3) and non-successfully treated patients (eTICI 0–2A) to estimate the observed treatment benefit.[21] We classified patients according to their predicted treatment benefit: low (predicted benefit <1%), moderate (1-10%), and high (>10%), to compare baseline characteristics and observed outcomes.

All statistical analyses were performed with R statistical software (version 3.6.3). The online tool was developed with the R Shiny package (version 1.4.0).

Results

First validation: HERMES collaboration

After exclusion of 21 patients because of missing mRS scores, 1242 patients were included in the HERMES validation cohort (633 assigned to EVT, 609 assigned to control). Patients in this cohort had less pre-stroke disability (mRS ≥2: 1.9% versus 9.2%), better collateral scores (grade 2-3: 86% versus 67%) and shorter workflow times (onset to groin puncture: 228 versus 260 minutes) than patients in the derivation cohort (Table 4.1). Collateral score was missing because of insufficient baseline CT angiography imaging in 68 patients (5.5%), and onset to groin puncture was missing in 102 patients (8.2%). All other variables were more than 95% complete.

Most predictor effects were similar to the derivation cohort (Table 4.2). No significant effect was found for treatment with IV alteplase (odds ratio 0.96, 95% confidence interval (CI) 0.68 to 1.35) and previous stroke (0.99, 95% CI 0.72 to 1.34). The interaction between EVT and time from onset to groin puncture was confirmed in the validation cohort with a decreasing treatment effect over time (P=0.02), but there was no statistically significant interaction between EVT and previous stroke (P=0.13), or EVT and collateral score (P=0.26). Discriminative ability of the model was moderate, with a c-statistic of 0.74 (95% CI 0.72 to 0.77) for the prediction of functional independence and 0.68 (95% CI 0.66 to 0.70) for the ordinal model (Table 4.3).

Overall, patients did better than predicted by the model (Figure 4.1A). The predicted versus observed proportion of functional independence was 25% versus 35% in the control group and 39% versus 54% in the intervention group (average treatment benefit: 14% predicted versus 19% observed). The observed treatment benefit was particularly higher than predicted in the quintile of patients with the lowest predicted benefit (Figure 4.2). These patients were less often treated with IV alteplase (76% versus 93%, P<0.001), and had less favorable clinical and imaging characteristics (Supplementary Table 4.1).

Model updating

The addition of baseline glucose as non-linear predictor significantly improved model fit (chi-square value 9.1 with 2 degrees of freedom; P=0.01) in the full HERMES dataset (including MR CLEAN). No significant effect was found for treatment with IV alteplase (chi-square value 0.42 with 1 degree of freedom; P=0.52) and previous stroke (chi-square value 1.8 with 2 degrees of freedom; P=0.41), and these variables were therefore excluded. Then, the model coefficients were refitted based on the complete dataset with a separate intercept for the derivation versus validation cohort (see Supplementary material for the regression equation). The apparent c-statistic of this model was 0.79 for functional independence and 0.72 for the ordinal outcome.

Table 4.1. Baseline characteristics of the derivation and validation cohorts.

	Derivation cohort	Current validation cohorts	
	MR CLEAN (n=500)	**HERMES (n=1242)**	**MR CLEAN Registry (n=3156)**
Age, years	65 (14)	66 (13)	70 (14)
Male sex	292 (58%)	630 (51%)	1640 (52%)
Baseline NIHSS score	18 (14 to 22)	17 (13-20)	16 (11 to 19)
Baseline systolic blood pressure, mmHg	145 (25)	145 (24)	150 (25)
Baseline glucose level, mg/dL	121 (106 to 141)	119 (104 to 140)	123 (106 to 146)
Treatment with IV alteplase	445 (89%)	1109 (89%)	2410 (77%)
Allocation to EVT	233 (47%)	633 (51%)	NA
Medical history			
Ischemic stroke	54 (11%)	133 (11%)	527 (17%)
Diabetes mellitus	68 (14%)	215 (17%)	502 (16%)
Pre-stroke mRS			
0	404 (81%)	647 (84%)	2093 (68%)
1	50 (10%)	112 (14%)	408 (13%)
≥2	46 (9.2%)	15 (1.9%)	585 (19%)
Baseline imaging			
ASPECTS on NCCT	9 (8 to 10)	8 (7 to 9)	9 (7 to 10)
Collateral score on CTA			
0	26 (5.3%)	5 (0.6%)	186 (6.3%)
1	135 (27%)	113 (14%)	1069 (36%)
2	199 (40%)	348 (42%)	1152 (39%)
3	134 (27%)	363 (44%)	557 (19%)
Location of occlusion on non-invasive vessel imaging			
ICA-(T)	138 (28%)	284 (25%)	795 (27%)
M1	319 (64%)	777 (68%)	1764 (59%)
M2	39 (7.9%)	84 (7.3%)	441 (15%)
Workflow			
Onset to groin puncture, minutes	260 (210 to 311)	228 (173 to 290)	194 (150 to 250)
Onset to reperfusion, minutes	340 (274 to 395)	291 (231 to 357)	250 (199 to 311)

Data are reported as n (%), mean (SD), or median (IQR).
ASPECTS, Alberta Stroke Program Early CT Score; CTA, computed tomography angiography; EVT, endovascular treatment; ICA(-T), intracranial carotid artery (terminus); IV, intravenous; M1, middle cerebral artery segment 1; M2, middle cerebral artery segment 2; mRS, modified Rankin Scale score; NA, not applicable; NCCT, non-contrast computed tomography; NIHSS, National Institutes of Health Stroke Scale.

Table 4.2. Main effects in the derivation and validation cohorts.

	Derivation cohort	Current validation cohorts	
	MR CLEAN (n=500)	HERMES (n=1242)	MR CLEAN Registry (n=3156)
Endovascular treatment	1.86 (1.34 to 2.59)	1.94 (1.58 to 2.37)	NA
Age (per year)*			
<65 years	1.00 (0.97 to 1.02)	0.98 (0.97 to 1.00)	1.01 (1.00 to 1.02)
>=65 years	0.92 (0.89 to 0.95)	0.95 (0.94 to 0.97)	0.93 (0.93 to 0.94)
Baseline NIHSS (per point)	0.93 (0.90 to 0.96)	0.93 (0.91 to 0.95)	0.92 (0.90 to 0.93)
Baseline systolic blood pressure (per 10 mmHg)*			
<130 mmHg	1.24 (0.97 to 1.59)	1.07 (0.92 to 1.24)	1.05 (0.94 to 1.17)
>=130 mmHg	0.77 (0.70 to 0.85)	0.90 (0.85 to 0.96)	0.92 (0.89 to 0.96)
Treatment with IV alteplase	1.62 (0.94 to 2.79)	0.96 (0.68 to 1.35)	1.32 (1.13 to 1.55)
Previous stroke	0.53 (0.31 to 0.92)	0.99 (0.72 to 1.34)	0.83 (0.68 to 1.02)
Diabetes mellitus	0.54 (0.33 to 0.90)	0.60 (0.46 to 0.79)	0.61 (0.51 to 0.75)
Pre-stroke mRS	0.72 (0.58 to 0.90)	0.58 (0.44 to 0.76)	0.68 (0.64 to 0.73)
ASPECTS (per point)	1.16 (1.06 to 1.28)	1.13 (1.06 to 1.19)	1.08 (1.04 to 1.12)
Level of occlusion on non-invasive imaging			
ICA-(T)	1.0 (reference)	1.0 (reference)	1.0 (reference)
M1	1.43 (0.98 to 2.07)	1.84 (1.45 to 2.34)	1.52 (1.30 to 1.77)
M2	2.35 (1.20 to 4.60)	2.56 (1.63 to 4.03)	1.48 (1.18 to 1.85)
Collateral score	1.61 (1.31 to 1.96)	1.39 (1.21 to 1.60)	1.38 (1.27 to 1.50)
Time from onset stroke to groin puncture (per 30 minutes)	0.93 (0.86 to 1.00)	0.92 (0.89 to 0.95)	0.90 (0.88 to 0.93)

Presented common odds ratios with 95% confidence intervals reflect the effect on the reversed modified Rankin Scale (odds ratio >1 corresponds with better functional outcome).
*Modeled using a restricted cubic spline function.
ASPECTS, Alberta Stroke Program Early CT Score; ICA(-T), intracranial carotid artery (terminus); IV, intravenous; M1, middle cerebral artery segment 1; M2, middle cerebral artery segment 2; mRS, modified Rankin Scale score; NA, not applicable; NIHSS, National Institutes of Health Stroke Scale.

Second validation: MR CLEAN Registry

In total, 3156 patients were included (Table 4.1, Supplementary Figure 4.1). Compared to patients in the derivation cohort, patients in the MR CLEAN Registry were less often treated with IV alteplase (77% vs 89%), more often had a pre-stroke disability (mRS ≥2: 19% versus 9%), and were treated faster (onset to groin puncture: 194 versus 260 minutes). Overall, 3% of all data points were missing.

The predictor effects were similar as in the derivation cohort (Table 4.2). Discriminative ability was moderate to good, with a c-statistic of 0.80 (95% CI 0.79 to 0.82) for functional independence and 0.74 (95% CI 0.73 to 0.75) for the full mRS. Calibration was best when

Table 4.3. Model performance measures.

	Derivation cohort	Previous validation cohort	Current validation cohorts	
	MR CLEAN (n=500)	**IMS III (n=260)**	**HERMES (n=1242)**	**MR CLEAN Registry (n=3156)**
Discrimination				
C-statistic – mRS 0–2	0.79	0.73 (0.67 to 0.79)	0.74 (0.72 to 0.77)	0.80 (0.79 to 0.82)
C-statistic – ordinal mRS	0.75	0.69 (0.64 to 0.73)	0.68 (0.66 to 0.70)	0.74 (0.73 to 0.75)
Calibration				
Intercept	NA	0.81 (0.53 to 1.09)	0.63 (0.51 to 0.76)	-0.13 (-0.21 to -0.05)
Slope	NA	0.75 (0.67 to 0.79)	0.95 (0.81 to 1.09)	1.00 (0.92 to 1.08)

The concordance (c) statistic is a measure for the ability to distinguish between patients with a low and high probability of good outcome. It can vary between 0.5 for a non-informative model and 1 for a perfectly discriminating model. The calibration intercept reflects the calibration-in-the-large, indicating whether predicted probabilities are systematically too low or too high, and should ideally be equal to 0. The calibration slope reflects the strength of the predictors and should ideally be equal to 1.
mRS, modified Rankin Scale; NA, not applicable.

using the intercept of the HERMES validation cohort, with slightly worse outcomes than predicted (40.9% versus 42.9% functional independence, Figure 4.1B). Treatment benefit was predicted for 3145/3156 patients (99.7%) with a median benefit of 10.6% (IQR 6.4% to 14.5%). The subgroup of patients with low predicted benefit (n=105 (3.3%)) achieved low rates of functional independence irrespective of reperfusion status (3/58 (5.2%) with successful reperfusion, 3/47 (6.4%) without reperfusion), suggesting potential absence of treatment (Figure 4.3). The majority of these patients had pre-stroke disability (53%), absent collaterals (63%), or other unfavorable prognostic characteristics (Supplementary Table 4.2), but none of these features was fully predictive of a low treatment benefit.

Final model

The regression equation of the updated model is provided in the Supplementary material. The intercept, that reflects the baseline risk of outcome not explained by the predictor variables, can be adjusted to obtain predictions for a setting or population similar to that of the MR CLEAN derivation cohort, the HERMES validation cohort, or the MR CLEAN Registry. The web application was updated with the new model coefficients for use in clinical practice and research (www.mrpredicts.com).

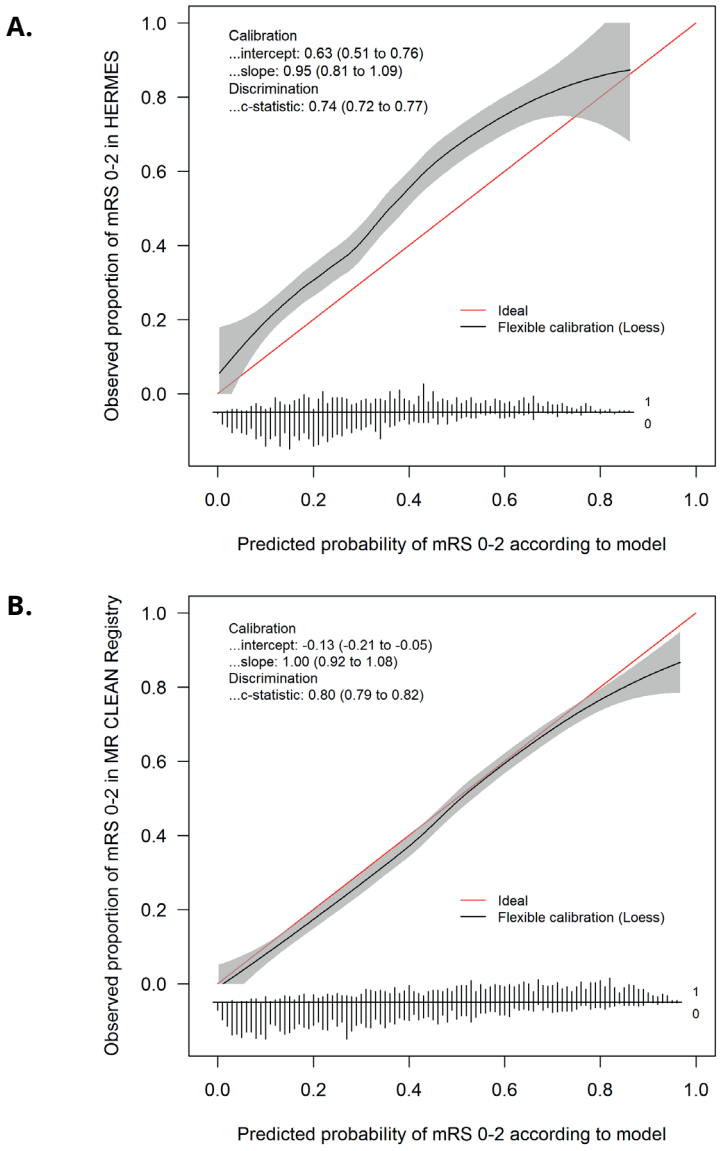

Figure 4.1. Calibration of functional independence, defined as a modified Rankin Scale (mRS) score of 0–2, in the HERMES validation cohort (A, n=1242) and, after model updating, in the MR CLEAN Registry (B, n=3156). The linear bar chart shows the distribution of patients with (=1) or without (=0) an observed outcome of mRS 0–2.

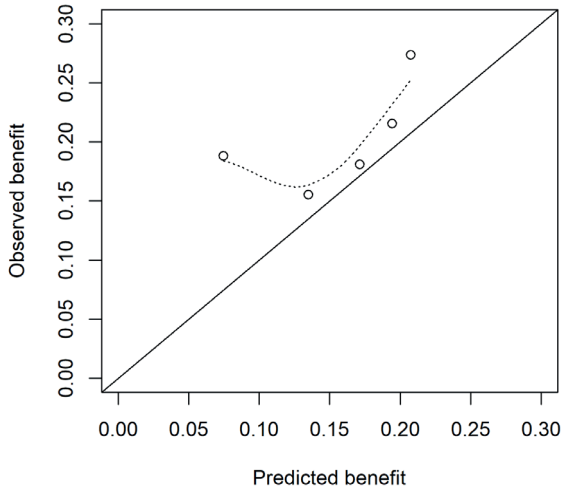

Figure 4.2. Calibration of treatment benefit in the HERMES validation cohort (n=1242), defined as the difference in the observed proportion of functional independence (modified Rankin Scale (mRS) score 0–2) in treated patients and control patients. Patients were classified into quintiles according to their predicted treatment benefit. The c-for-benefit was 0.53 (95% CI 0.50 to 0.56).

Discussion

We externally validated and updated the MR PREDICTS decision tool with high-quality individual patient data from recent international randomized controlled trials and a large nationwide registry. Predictors included in the final model were age, baseline NIHSS, systolic blood pressure, baseline glucose, diabetes mellitus, pre-stroke mRS, ASPECTS, occlusion location, collateral score on non-invasive imaging and (estimated) time from symptom onset to groin puncture. Treatment effect was modified by onset to treatment time, collateral score and the baseline probability of good outcome. The updated model showed moderate to good discriminative ability and good calibration in data from daily clinical practice.

The original model included three interaction terms for differential relative treatment effects. The interaction between EVT and onset to groin was confirmed in the HERMES validation cohort, but we did not confirm a differential relative treatment effect for collateral score or previous stroke. Only 118 out of 829 (14%) patients in the HERMES validation cohort had absent or poor collaterals and these patients might have been selected based on favorable CT-perfusion characteristics. Because collateral flow is an important determinant for outcome and treatment effect in less selected populations[22,23], and we previously found a similar interaction between EVT and collateral score in the IMS III validation, we kept this in the model. Since we have no clinically plausible explanation for the interaction between EVT and prior stroke, we believe that this is more likely to be a spurious finding and we excluded it from the final model.

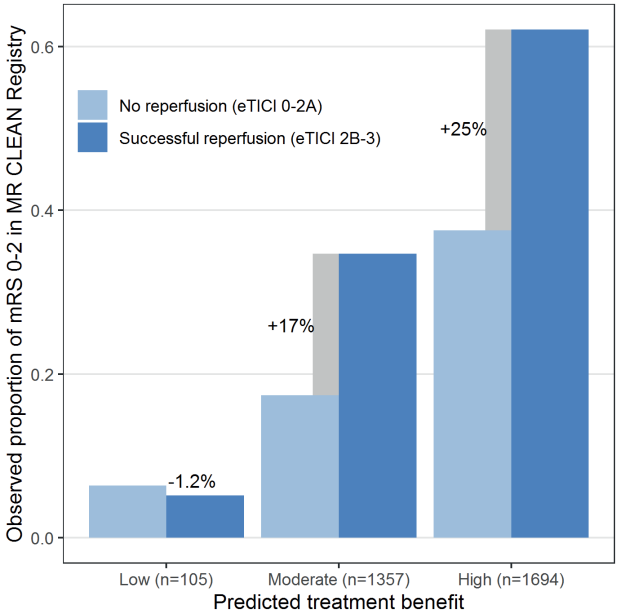

Figure 4.3. Estimated treatment benefit in the MR CLEAN Registry validation cohort (n=3156), defined as the difference in the observed proportion of functional independence (modified Rankin Scale (mRS) 0–2) in patients with and without successful reperfusion (extended Thrombolysis in Cerebral Infarction (eTICI) ≥2b). Patients were classified into three categories: low predicted benefit (<1%), moderate predicted benefit (1%-10%), and high predicted benefit (>10%). The c-for-benefit was 0.58 (95% CI 0.55 to 0.60).

Ischemic core volume is often suggested as an additional predictor of functional outcome after EVT.[24–26] The DAWN and DEFUSE-3 trials successfully used CT perfusion or MR diffusion-weighted imaging to select patients that benefit from EVT more than 6 hours after last seen well.[27,28] Two trials within the HERMES collaboration used CT perfusion or MR perfusion-diffusion imaging as an additional selection tool for some or all of their patients (EXTEND-IA and SWIFT-PRIME), one used collateral score (ESCAPE), and one used ASPECTS (REVASCAT). Core volume was shown to be an independent prognostic factor of functional outcome in previous analyses of the MR CLEAN and HERMES data, although it did not modify the relative treatment effect of EVT.[25,29] We did not add ischemic core volume to our model, because we only had CT perfusion or MR diffusion imaging data available for a subgroup of patients (n=900 (72%)), which might affect the validity of the model. A prediction model based on perfusion imaging characteristics may be useful. It would require large, representative registries in addition to the more selective trial data.

Discriminative performance was modest, especially in the clinical trial population, although predictor effects were comparable in the different cohorts. Previous research has shown that the c-statistic is not only related to model validity, but also to heterogeneity of patients

in the validation cohort.[30] The strict selection criteria of some trials might have caused less heterogeneity and therefore a slightly lower c-statistic (ie, when patients in the validation cohort are more alike, it is harder for the model to distinguish between low and high risk patients). The reported c-for-benefit would be considered weak when rated on the scale of a conventional c-statistic, but adjusted benchmarks are required to correctly interpret this novel measure.[20] Treatment benefit and overall outcomes in the HERMES trials were systematically higher than predicted, which might be explained by the selection of patients with favorable characteristics, inclusion of high-quality centers with ample experience, and fast workflow times in these studies. The good calibration in the MR CLEAN Registry shows that the model predicts well in a broad population of patients treated in routine clinical practice.

MR PREDICTS was updated based on the best evidence currently available for patients treated within 6 hours after stroke onset. An important feature of the model is that it predicts outcome with and without treatment, and therefore estimates expected average treatment benefit. Predicted treatment benefit appears substantial in most patients and the potential harm of EVT is small. Although we identified a small subgroup of patients with low treatment benefit, we cannot predict definite harm. Therefore, most patients arriving within 6 hours at an endovascular-capable center should be treated regardless of their clinical characteristics. Our model can be helpful in discussions about treatment decision when there is difficulty in translating trial results to individual patients. For example, a very old patient with multiple comorbidities but favorable imaging characteristics. In those situations, it is important to combine the prognostic effect of multiple factors simultaneously. The MR PREDICTS tool can also be used as an adjunct to clinical judgement when a patient has to be transported from a primary stroke center to an intervention center, when resources are limited, or when physicians explore the boundaries of treatment indications. Although individual outcomes vary, consistent and careful use of our model will on the long run benefit care for the patient with acute ischemic stroke.

Conclusion

MR PREDICTS performed reasonably well in a heterogeneous population from international trials and daily clinical practice. Our updated model can be used to support treatment decisions when there is uncertainty about the treatment indication, when resources are limited, or before a patient is to be transferred to an intervention center.

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Supplementary material

MR PREDICTS regression equation

Variable definitions

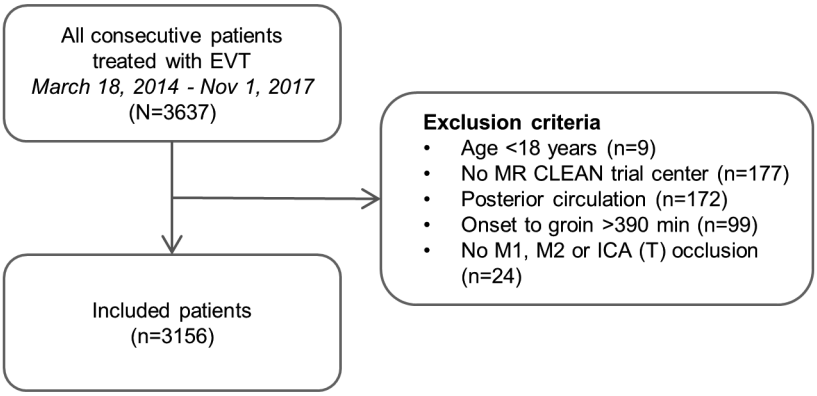
- EVT 0=no, 1=yes
- age numeric, in years
- NIHSS numeric, range 0–42
- premrs numeric, range 0–5
- diabetes 0=no, 1=yes
- BP numeric, in mmHg
- glucose numeric, in mg/dL
- ASPECTS numeric, range 0–10
- location categorical: "ICA-(T)", M1", "M2"
- collaterals numeric, range 0–3
- onsetgroin numeric, in minutes

Intercept

	First validation cohort (HERMES)	Second validation cohort (Registry)
mRS 0	-1.22797	-1.84370
mRS 0-1	0.0274482	-0.309062
mRS 0-2	0.978621	0.818420
mRS 0-3	1.80475	1.58490
mRS 0-4	2.98749	2.27731
mRS 0-5	3.64836	2.63582

Predicted probability (R code)

plogis(0.401027*EVT - 0.0120204*age - 1.92034e-05*pmax(age-46,0)^3 + 4.97121e-05*pmax(age-67.5,0)^3 - 3.05088e-05*pmax(age-81,0)^3 - 0.0738649*NIHSS - 0.433080*premrs - 0.461911*diabetes + 0.00125678*BP - 3.37399e-06*pmax(BP-115,0)^3 + 6.43166e-06*pmax(BP-144,0)^3 - 3.05768e-06* pmax(BP-176,0)^3 - 0.00469915*glucose + 4.50623e-07*pmax(glucose-94.5,0)^3 - 7.20996e-07*pmax(glucose-122,0)^3 + 2.70374e-07*pmax(glucose-167,0)^3 + 0.120994*ASPECTS + 0.504772*(location=="M1") + 0.887365*(location=="M2") + 0.256451*collaterals + (0.231751*EVT*collaterals) - 0.00219134*onsetgroin - (0.00118786*EVT*onsetgroin) + intercept)



Supplementary Figure 4.1. Patient selection in the MR CLEAN Registry validation cohort.

Supplementary Table 4.1. Baseline characteristics of the HERMES validation cohort (n=1242) according to quintile of predicted treatment benefit.

	Lowest quintile	Second quintile	Middle quintile	Fourth quintile	Highest quintile	p-value
Age, years	75 (10)	69 (13)	64 (13)	61 (13)	60 (12)	<0.001
Male sex	120 (48%)	128 (52%)	120 (48%)	127 (51%)	135 (54%)	0.60
Baseline NIHSS score	20 (17 to 22)	18 (16 to 21)	17 (13 to 20)	15 (12 to 18)	14 (11 to 17)	<0.001
Baseline systolic blood pressure, mmHg	158 (27)	148 (24)	144 (22)	143 (20)	137 (22)	<0.001
Treatment with IV alteplase	190 (76%)	214 (86%)	232 (93%)	237 (96%)	237 (95%)	<0.001
Previous stroke	43 (18%)	27 (11%)	24 (9.7%)	15 (6.2%)	24 (9.6%)	0.002
Pre-stroke mRS						<0.001
0	113 (70%)	112 (81%)	134 (89%)	134 (88%)	154 (91%)	
1	41 (25%)	26 (19%)	13 (8.7%)	17 (11%)	15 (8.8%)	
≥2	8 (4.9%)	1 (0.7%)	3 (2.0%)	3 (1.3%)	1 (0.6%)	
ASPECTS	8 (6 to 9)	8 (6 to 9)	8 (7 to 9)	8 (7 to 9)	8 (7 to 9)	<0.001
Collateral score						<0.001
0	3 (1.8%)	1 (0.6%)	1 (0.6%)	0 (0%)	0 (0%)	
1	38 (23%)	31 (20%)	18 (11%)	121 (7.5%)	141 (7.8%)	
2	80 (49%)	75 (48%)	60 (36%)	69 (43%)	64 (36%)	
3	42 (26%)	51 (32%)	90 (53%)	79 (49%)	101 (56%)	
Occlusion location						<0.001
ICA	107 (46%)	68 (29%)	48 (21%)	35 (16%)	26 (12%)	
M1	116 (50%)	150 (65%)	167 (71%)	170 (75%)	174 (78%)	
M2	8 (3.5%)	14 (6.0%)	19 (8.1%)	21 (9.3%)	22 (9.9%)	
Onset to groin puncture, minutes	270 (220 to 340)	223 (181 to 285)	235 (182 to 299)	215 (159 to 271)	214 (159 to 264)	<0.001

Data are reported as n (%), mean (SD), or median (IQR).
ASPECTS, Alberta Stroke Program Early CT Score; ICA(-T), intracranial carotid artery (terminus); IV, intravenous; M1, middle cerebral artery segment 1; M2, middle cerebral artery segment 2; mRS, modified Rankin Scale score; NIHSS, National Institutes of Health Stroke Scale.

Supplementary Table 4.2. Baseline characteristics of MR CLEAN Registry validation cohort (n=3156) according to category of predicted treatment benefit: low (<1%), moderate (1-10%), or high (>10%).

Characteristic	Low benefit (n=105)	Moderate benefit (n=1357)	High benefit (n=1694)	p-value
Age, years	79 (13)	72 (14)	68 (14)	<0.001
Male sex	45 (43%)	698 (51%)	897 (53%)	0.12
Baseline NIHSS score	20 (18 to 24)	17 (13 to 21)	14 (10 to 18)	<0.001
Baseline systolic blood pressure, mmHg	167 (29)	151 (26)	148 (24)	<0.001
Treatment with IV alteplase	65 (63%)	1008 (75%)	1337 (79%)	<0.001
Previous stroke	22 (21%)	277 (21%)	228 (14%)	<0.001
Pre-stroke mRS				<0.001
0	30 (31%)	811 (61%)	1252 (75%)	
1	15 (15%)	159 (12%)	234 (14%)	
≥2	51 (53%)	358 (27%)	176 (11%)	
ASPECTS	8 (6 to 9)	9 (7 to 10)	9 (8 to 10)	<0.001
Collateral score				<0.001
0	62 (63%)	124 (9.8%)	0 (0%)	
1	35 (35%)	797 (63%)	237 (15%)	
2	2 (2.0%)	281 (22%)	869 (54%)	
3	0 (0%)	67 (5.3%)	490 (31%)	
Occlusion location				<0.001
ICA	53 (53%)	391 (30%)	351 (22%)	
M1	44 (44%)	698 (54%)	1022 (63%)	
M2	3 (3.0%)	198 (15%)	240 (15%)	
Onset to groin puncture, minutes	279 (220 to 330)	213 (170 to 270)	171 (135 to 225)	<0.001

Data are reported as n (%), mean (SD), or median (IQR).
ASPECTS, Alberta Stroke Program Early CT Score; ICA(-T), intracranial carotid artery (terminus); IV, intravenous; M1, middle cerebral artery segment 1; M2, middle cerebral artery segment 2; mRS, modified Rankin Scale score; NIHSS, National Institutes of Health Stroke Scale.

Chapter 5

Multivariable outcome prediction after endovascular treatment for ischemic stroke (MR PREDICTS@24H): a post-procedural tool to predict functional outcome at 3 months

In preparation

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Research in context

Evidence before this study

We searched the Cochrane Library, Embase, Medline, Web of Science, and Google Scholar for prognostic models that were developed to predict functional outcome at 3 months in patients who underwent endovascular treatment for ischemic stroke in the anterior circulation and included at least post-procedural characteristics. Search terms used included stroke, embolectomy/thrombectomy/endovascular treatment, predict*/prognos*. The search yielded 9 models, of which 3 were externally validated. All validated models originated from before the landmark trials that demonstrated the efficacy of endovascular treatment. A few non-validated models included post-procedural stroke severity and showed it to be a major prognostic factor for functional outcome at 3 months.

Added value of this study

The novel prognostic model MR PREDICTS@24H was developed and validated using data from recent clinical trials and routine practice. It includes 9 pre- and post-procedural characteristics, including the National Institutes of Health Stroke Severity (NIHSS) score after endovascular treatment, and can be applied one day after the intervention to predict functional outcome at 3 months. This post-procedural tool is online available for clinical use at www.mrpredicts.com.

Implications of all the available evidence

MR PREDICTS@24H is a simple prognostication tool that can provide patients, family members, and physicians with reliable outcome expectations. It can assist physicians in personalizing their patient's treatment and rehabilitation plans. To make MR PREDICTS@24H applicable to an even wider range of patients (ie, endovascular treatment between 12-24h after symptom onset, posterior circulation stroke), it needs to be further externally validated.

Abstract

Introduction

Prediction of functional outcome after endovascular treatment (EVT) for ischemic stroke in individual patients is challenging. We aimed to develop and validate a post-procedural model to predict functional outcome at 3 months after EVT (MR PREDICTS@24H).

Methods

We used data from seven randomized controlled trials within the HERMES collaboration and included 781 ischemic stroke patients who had undergone EVT within 12 hours of symptom onset. We assessed 19 variables, routinely available one day after EVT, using univariable and multivariable ordinal regression with stepwise backward selection (p<0.157) to predict functional outcome (modified Rankin Scale (mRS) score) at 3 months after EVT. Probabilities for functional independence (mRS 0–2) and survival were derived from the ordinal model. For external validation we used data of the Dutch MR CLEAN Registry (n=3260). Model performance was expressed with discrimination (c-statistic) and calibration (intercept and slope).

Findings

Nine variables were included in the final model: age, baseline National Institutes of Health Stroke Severity (NIHSS), pre-stroke mRS, diabetes mellitus, occlusion location, collateral score, reperfusion after EVT, NIHSS at 24h after EVT, and symptomatic intracranial hemorrhage. External validation showed excellent discriminative ability with a c-statistic of 0.91 for functional independence and 0.89 for survival. Calibration slopes were excellent (functional independence: 1.07, survival: 1.01), but intercepts were suboptimal (functional independence: 0.29, survival: -0.91), which we resolved by providing separate intercepts of HERMES and the MR CLEAN Registry.

Interpretation

MR PREDICTS@24H is online available for clinical use (www.mrpredicts.com) and can be applied one day after EVT to accurately predict functional outcome at 3 months. It may provide patients, family members, and caregivers with reliable outcome expectations, and may assist physicians in adapting and personalising their patients' treatment and rehabilitation plans.

Introduction

Since the implementation of endovascular treatment (EVT) in daily clinical practice, physicians are confronted with questions from patients and family members about the extent of recovery they can expect, most often quite early after EVT. While at group level almost half of all patients treated with EVT recover to functional independence, outcome of individual patients is highly variable and depends on multiple factors.[1] For the treating physicians it is therefore difficult to accurately predict individual outcomes after stroke. Results from previous research suggest that well-validated prognostic models are more accurate in predicting outcome than physicians.[2,3] For patients undergoing EVT, most existing prediction models are based on pre-procedural data only and primarily serve to identify patients who may benefit from EVT.[4-6] A clinical prognostic model that can be used after EVT and takes into consideration both pre- and post-procedural variables – such as age, reperfusion grade, and stroke severity one day after EVT – could provide physicians, patients, and family members with more reliable outcome expectations. The only currently existing validated models that were designed for prognostication and include post-procedural variables were developed before the landmark trials were published.[7-9]

The purpose of the present study was therefore to develop and externally validate a prognostic model that can be applied one day after EVT to predict functional outcome at 3 months, using data from recent clinical trials and routine clinical practice.

Methods

Derivation cohort

The model was developed in patient-level data from seven randomized controlled trials (RCTs) on EVT within the HERMES collaboration: MR CLEAN,[10] ESCAPE,[11] EXTEND-IA,[12] SWIFT PRIME,[13] REVASCAT,[14] THRACE,[15] PISTE.[16] These RCTs compared EVT – primarily performed with stent retrievers – with standard care in adult patients with ischemic stroke caused by a large vessel occlusion in the anterior circulation confirmed on computed tomography angiography (CTA) or magnetic resonance angiography (MRA). Inclusion criteria varied between the RCTs.[1] All participants provided informed consent according to each trial protocol, and each RCT was approved by the local ethics committee.

For this study, we included all patients from the intervention group who underwent groin puncture within 12 hours of symptom onset for a large vessel occlusion of the intracranial carotid artery (ICA), internal carotid artery terminus (ICA-T), or middle cerebral artery (segment M1 or M2). Following HERMES policy, patients with missing outcomes were excluded. Missing predictor data were imputed by multiple regression imputation based on relevant covariates, intervention, and outcome.

Outcome measures

The primary outcome was functional outcome at 3 months, assessed with the modified Rankin Scale (mRS). The mRS is an ordinal scale used to measure the degree of disability in daily activities, and ranges from 0 (no symptoms) to 6 (death).[17] We derived the probabilities for functional independence (defined as mRS 0–2) and survival from the ordinal model.

Model development

To identify predictors of functional outcome after EVT, we pre-specified 19 pre- and post-procedural variables that can be assessed one day after EVT, based on recent literature, expert opinion, and clinical relevance. These variables were: age, sex, pre-stroke disability assessed with the mRS, diabetes mellitus (yes/no), hypertension (yes/no), previous stroke (yes/no), baseline stroke severity assessed with National Institutes of Health Stroke Scale (NIHSS), serum glucose, systolic blood pressure, IV treatment with alteplase (yes/no), baseline location of intracranial large vessel occlusion, baseline collateral score (range 0-3), baseline Alberta Stroke Program Early CT Score (ASPECTS), time from symptom onset to groin puncture, duration of the procedure (groin puncture to last contrast bolus injection), general anesthesia (yes/no), radiological reperfusion grade (modified Treatment in Cerebral Infarction (mTICI) score) after EVT on digital subtraction angiography (DSA), NIHSS one day after EVT, and symptomatic intracranial hemorrhage (sICH) within one day after EVT (as defined by each RCT). To adjust for clustering of data, trial was added as fixed effect.

We used ordinal logistic regression modelling, which assumes proportional odds, to determine the association of the potential predictors with functional outcome. We tested non-linearity of the relation between continuous variables (age, systolic blood pressure, glucose, NIHSS at baseline, ASPECTS, time to groin puncture, duration of the procedure, NIHSS at 24h) and the log odds of mRS with restricted cubic spline functions with three knots.

We used univariable and multivariable regression analysis with stepwise backward selection. All variables with P<Akaikes Information Criterion (AIC; ie, P<0.157 for 1 degree of freedom) were included in the final model, called Multivariable outcome prediction at 24 hours after endovascular treatment for ischemic stroke (acronym: MR PREDICTS@24H). Predictor effects were expressed as adjusted (common) odds ratios (a(c)OR) with 95% confidence intervals (CI). To obtain more insight in the relative importance of post-intervention stroke severity, we assessed the predictive performance of a model without NIHSS at 24h. In addition, we added follow-up infarct volume (FIV) assessed between 12 hours and 2 weeks, which was first tested for non-linearity, to the final model to assess its predictive value.

We assessed the internal validity of the final regression model with bootstrap resampling to calculate the degree of optimism in model performance. To correct for this optimism we reduced the regression coefficients using penalized regression.

Validation cohort

For external validation we used data from the MR CLEAN Registry, a nationwide prospective, observational study for 18 centers that provide EVT in the Netherlands.[18] Data were collected from all consecutive patients with ischemic stroke who had undergone EVT since March 2014, after the last patient was included in MR CLEAN. The central medical ethics committee of the Erasmus MC University Medical Center, Rotterdam, the Netherlands evaluated the research protocol of the MR CLEAN Registry and granted permission to carry out the study as a registry (MEC-2014-235).

We included ischemic stroke patients enrolled in the MR CLEAN Registry, treated with EVT between March 16, 2014 and November 1, 2017 in a center that participated in the MR CLEAN trial. Included patients were aged 18 years or older, had an occlusion of the ICA(-T) or middle cerebral artery (M1 or M2) on CTA or MRA, and had undergone groin puncture within 12 hours after symptom onset. Reperfusion grade was scored according to the extended TICI (eTICI) score, which includes TICI 2C, but was analyzed in the validation according to the mTICI score (ie, TICI 2C was added to TICI 2B). Missing data, including mRS, were imputed according to MR CLEAN Registry policy by multiple regression imputation based on relevant baseline covariates and outcomes.

Model validation and updating

External validation was performed with the regression coefficients of MR PREDICTS@24H and the intercept of the MR CLEAN trial (ie, the most representative cohort for routine practice). Model performance was assessed in terms of discrimination and calibration. Discrimination refers to the ability of the model to distinguish between patients with good and poor outcome. The discriminative ability of the model at internal and external validation was quantified with the concordance statistic (c-statistic).[19] We calculated the c-statistic for the ordinal mRS and for the predictions of functional independence (mRS 0–2) and survival. Calibration refers to the level of agreement between predicted probabilities and observed outcomes. We assessed calibration of predictions graphically by plotting predicted probability of functional independence or survival based on the derivation cohort against the observed proportion of functional independence or survival in the validation cohort. Calibration was quantified with the calibration slope and calibration intercept of these plots. The calibration slope should ideally be equal to 1, describing that the effect of predictors is equal in the derivation cohort versus those in the validation cohort. The intercept should ideally be 0, and indicates whether the predictions based on the model are systemically too high or too low in the validation cohort.[19] The 95% confidence intervals of the c-statistic, calibration slope, and calibration intercept were calculated with bootstrap resampling with 2000 replications by taking the 50th and 1950th performance estimates.

After validation on the MR CLEAN Registry data, we updated the regression coefficients of the predictors. Additionally, we replaced the variable mTICI for eTICI, which is reported to be more predictive of outcome.[20,21] Using these updated coefficients, the model intercept

was calculated for HERMES and the MR CLEAN Registry separately, to represent the baseline risk of both settings and populations. We implemented the updated final model in a web application that provides predictions of functional outcome at three months for individual patients with acute ischemic stroke based on routinely available information one day after EVT. It displays the expected distribution of mRS categories after EVT and the predicted probabilities of functional independence and survival. The intercept can be selected by users depending on the setting or patient population. The HERMES intercept reflects the baseline risk of patients included in these RCTs, while the intercept of the MR CLEAN Registry is more representative of the broad population treated in daily clinical practice. .

Statistical analyses were performed with R statistical software (version 3.5.1), the rms library (version 5.1-2), and the R Shiny package (version 1.2.0).

Results

Derivation cohort

The HERMES cohort consisted of 781 patients with a median age of 67 years (IQR 57–76). 414 (53%) patients were men, and their median baseline NIHSS score was 17 (IQR 14–21) (Table 5.1). Successful reperfusion (ie, mTICI ≥2B) was achieved in 544/715 (75%) patients. The median NIHSS at 24h was 9 (IQR 4–16). In total, 48% of patients achieved functional independence and 86% survived up to 3 months.

Model development

All pre-specified variables, with the exception of treatment with IV alteplase, previous stroke, and hypertension, were predictors of outcome in univariable analysis (Table 5.2). Given their non-linear effect on outcome, restricted cubic splines with three knots were used for age, serum glucose, stroke onset to groin puncture time, and NIHSS at 24h. Based on multivariable analysis, 9 pre- or post-procedural variables were included in the final model: age, baseline NIHSS, pre-stroke mRS, diabetes mellitus, occlusion location, collateral score, mTICI score after EVT, NIHSS at 24h, and sICH. This model had a c-statistic of 0.85 for the ordinal outcome, which decreased to 0.73 without NIHSS at 24h. By adding FIV to the final model, the c-statistic increased from 0.85 to 0.86. The internally validated c-statistic of the final model, corrected for optimism, was 0.84 for the ordinal mRS, 0.91 for functional independence, and 0.87 for survival (Table 5.3).

Patient population in validation cohort

The MR CLEAN Registry consisted of 3260 patients (Figure 5.1). The median age was 72 years (IQR 61–80), 1684 patients (52%) were men, and median baseline NIHSS was 16 (IQR 11–19) (Table 5.1). Patients in the validation cohort less often had atrial fibrillation (23% versus 34%), but more often pre-stroke disability (mRS ≥1: 32% versus 17%) and worse collateral scores (good collaterals: 19% versus 41%) than in the derivation cohort. Fewer patients in

Table 5.1. Overview of derivation cohort and validation cohort.

	Derivation cohort HERMES (n=781)	Validation cohort MR CLEAN Registry (n=3260)
Baseline patient characteristics		
Age (years)	67 (57–76)	72 (61–80)
Men	414/781 (53%)	1684/3260 (52%)
NIHSS	17 (14–21)	16 (11–19)
Systolic blood pressure (mmHg)	144 (130–159)	150 (131–165)
Serum glucose (mmol/L) (mg/dL)	6.7 (5.9–7.8) 121 (106–141)	6.8 (5.9–8.1) 122 (106–146)
Previous stroke	89/777 (11%)	544/3233 (17%)
Hypertension	426/779 (55%)	1676/3194 (52%)
Atrial fibrillation	217/640 (34%)	770/3217 (24%)
Diabetes mellitus	120/780 (15%)	524/3236 (16%)
Pre-stroke mRS		
0	501/605 (83%)	2160/3188 (68%)
1	76/605 (13%)	421/31888 (13%)
2	19/605 (3.1%)	239/3188 (7.5%)
≥3	9/605 (1.5%)	368/3188 (12%)
Baseline imaging characteristics		
Occlusion location		
ICA(-T)	198/733 (27%)	818/3121 (26%)
M1	473/733 (65%)	1804/3121 (58%)
M2 or other*	62/733 (8.5%)	499/3121 (16%)
ASPECTS	8 (7–9)	9 (7–10)
Collateral score		
0	5/602 (0.8%)	187/3053 (6.1%)
1	81/602 (14%)	1094/3053 (36%)
2	268/602 (45%)	1181/3053 (39%)
3	248/602 (41%)	591/3053 (19%)
Treatment characteristics		
Treatment with IV alteplase	678/781 (87%)	2445/3248 (75%)
Time from stroke onset to groin	240 (185–299)	195 (150–255)
General anesthesia	227/776 (29%)	775/3063 (25%)
Duration of the procedure	64 (40–91)	59 (38–83)
Outcome measures		
Reperfusion grade (mTICI)		
0	54/715 (7.6%)	531/3160 (17%)
1	19/715 (2.7%)	94/3160 (3.0%)

	Derivation cohort HERMES (n=781)	Validation cohort MR CLEAN Registry (n=3260)
Reperfusion grade (mTICI)		
2A	98/715 (14%)	592/3160 (19%)
2B	483/715 (68%)	1054/3160 (33%)†
3	61/715 (8.5%)	902/3160 (28%)
NIHSS at ±24h after EVT	9 (4–16)	10 (4–17)
SICH	28/770 (3.6%)	189/3245 (5.8%)
mRS score at 3 months	3 (1–4)	3 (2–6)
Functional independence at 3 months	371/781 (48%)	1235/3047 (41%)
Survival at 3 months	671/781 (86%)	2164/3047 (71%)

Categorical values are presented as n (%) and continuous values as median (IQR). Missing continuous values (n derivation cohort, n validation cohort) : age 0, 15; NIHSS baseline 4, 55; systolic blood pressure 1, 89; serum glucose 26, 371; ASPECTS 8, 109; time from stroke onset to groin 0, 15, duration of the procedure 174, 291; NIHSS at 24h 25, 333. * Other occlusion location (M3 or anterior cerebral artery segment 1 or 2) by core lab: HERMES (n=1), MR CLEAN Registry (n=25). † Extended TICI score MR CLEAN Registry: TICI 2B (n=715), TICI 2C (n=339).
ASPECTS, Alberta Stroke Program Early CT Score; ICA(-T), intracranial carotid artery (terminus); IV, intravenous; M1, middle cerebral artery segment 1; M2, middle cerebral artery segment 2; mRS, modified Rankin Scale score; mTICI, modified treatment in cerebral infarction; NIHSS, National Institutes of Health Stroke Scale; SICH, symptomatic intracranial haemorrhage.

the validation cohort had M1 occlusions (58% versus 64%), and time from stroke onset to groin puncture was shorter (median 195 (IQR 150–255) vs 240 (IQR 185–299)). 2245/3248 (75%) patients were treated with IV alteplase, compared to 678/781 (87%) patients in the derivation cohort. Other baseline patient, baseline imaging, and treatment characteristics were similar between the two cohorts. Successful reperfusion (ie, mTICI ≥2B) was achieved in 1956/3160 (62%) patients. NIHSS at 24h and functional outcome were less favorable than in the derivation cohort: median NIHSS at 24h was 10 (IQR 4–17), 41% of patients achieved functional independence, and 71% survived up to 3 months.

External validation

In the validation cohort, we found predictor effects similar to those in the derivation cohort (Table 5.4). The externally validated c-statistics were 0.84 (95% CI 0.83 to 0.84) for the ordinal mRS, 0.91 (95% CI 0.90 to 0.92) for functional independence, and 0.89 (95% CI 0.88 to 0.90) for survival (Table 5.3). Calibration plots showed that the observed proportion of patients achieving functional independence was systemically slightly higher than predicted based on the model (intercept 0.29, slope 1.07; Table 5.3). The observed probability of functional independence was 41%, while the model predicted 37% (Figure 5.2A). The predictions of survival were systemically too low (intercept -0.91, slope 1.01; Table 5.3). The observed probability of survival was 71%, while the model predicted 82% (Figure 5.2B).

Table 5.2. Main effects in derivation cohort (HERMES, n=781) presented as common odds ratios* with 95% confidence intervals.

	Univariable models	Multivariable model
Age, per year		
<65 years	0.99 (0.98 to 1.01)	1.00 (0.98 to 1.02)
≥65 years	0.95 (0.94 to 0.97)	0.94 (0.92 to 0.96)
Baseline NIHSS, per point	0.91 (0.88 to 0.93)	1.03 (1.00 to 1.06)
Systolic blood pressure, per 10 mmHg	0.88 (0.83 to 0.92)	0.96 (0.91 to 1.03)
Glucose, per 30 mmol/L		
<120 mmol/L	0.54 (0.40 to 0.73)	0.98 (0.73 to 1.32)
≥120 mmol/L	0.91 (0.83 to 0.99)	0.97 (0.90 to 1.03)
Treatment with IV alteplase	1.25 (0.86 to 1.82)	NA
Previous stroke	0.82 (0.55 to 1.21)	NA
Hypertension	0.89 (0.70 to 1.14)	NA
Atrial fibrillation	0.77 (0.59 to 1.02)	0.99 (0.70 to 1.41)
Diabetes mellitus	0.49 (0.35 to 0.70)	0.49 (0.33 to 0.73)
Pre-stroke mRS, per point	0.54 (0.44 to 0.67)	0.67 (0.51 to 0.87)
Occlusion location		
ICA(-T)	1.0 (reference)	1.0 (reference)
M1	1.67 (1.24 to 2.25)	1.25 (0.88 to 1.78)
M2 or other	2.37 (1.44 to 3.91)	1.99 (1.12 to 3.53)
Collateral score, per point	1.78 (1.44 to 2.20)	1.28 (1.03 to 1.58)
ASPECTS	1.21 (1.13 to 1.30)	1.00 (0.92 to 1.09)
Time from stroke onset to groin puncture, per 30 minutes		
<250 minutes	0.85 (0.77 to 0.93)	0.98 (0.88 to 1.09)
≥250 minutes	0.98 (0.92 to 1.05)	0.97 (0.90 to 1.04)
General anesthesia	0.72 (0.55 to 0.94)	0.97 (0.70 to 1.34)
Duration of the procedure, per 15 minutes	0.85 (0.80 to 0.89)	1.00 (0.99-1.00)
Post-procedural reperfusion grade (mTICI), per point	1.78 (1.54 to 2.07)	1.14 (0.96 to 1.36)
24h NIHSS, per point		
<12 points	0.72 (0.69 to 0.75)	0.71 (0.68 to 0.90)
≥12 points	0.85 (0.82 to 0.89)	0.86 (0.83 to 0.90)
SICH*	0.09 (0.04 to 0.18)	0.30 (0.12 to 0.74)

*Common odds ratios reflect the effect on the reversed modified Rankin Scale (an odds ratio >1 corresponds with better functional outcome). Variables with a p<AIC (Akaikes Information Criterion; p<0.157 for 1 degree of freedom) in univariable analysis, were entered into the multivariable model.
ASPECTS, Alberta Stroke Program Early CT Score; IV, intravenous; ICA(-T), intracranial carotid artery (terminus); M1, middle cerebral artery segment 1; M2, middle cerebral artery segment 2; mRS, modified Rankin Scale; mTICI, modified treatment in cerebral infarction; NA, not applicable; NIHSS, National Institutes of Health Stroke Scale; SICH, symptomatic intracranial hemorrhage.

Table 5.3. Performance measures with their 95% confidence intervals in derivation cohort (n=781) and validation cohort (n=3260).

	Ordinal mRS	Functional independence (mRS 0–2)	Survival (mRS 0–5)
Internal validation			
C-statistic	0.84	0.91	0.87
External validation			
C-statistic	0.84 (0.83 – 0.84)	0.91 (0.90 to 0.92)	0.89 (0.88 to 0.90)
Calibration intercept	NA	0.29 (0.20 to 0.39)	-0.91 (-1.01 to -0.81)
Calibration slope	NA	1.07 (1.00 to 1.14)	1.01 (0.93 to 1.09)

The c-statistic is a measure for the ability to distinguish between patients with a low and high probability of good outcome. It can vary between 0.5 for a non-informative model and 1 for a perfectly discriminating model. The calibration intercept reflects the calibration-in-the-large, indicating whether predicted probabilities are systematically too low or too high, and should ideally be equal to 0. The calibration slope reflects the strength of the predictors and should ideally be equal to 1.
mRS, modified Rankin Scale; NA, not applicable.

Final model (updated)

The regression equation of the updated final model, with separate intercepts to represent HERMES and the MR CLEAN Registry, is available in the Supplementary material. The online implementation is accessible for clinical use at www.mrpredicts.com (Figure 5.3).

Discussion

MR PREDICTS@24H can be used one day after EVT for ischemic stroke to accurately predict functional outcome at 3 months after EVT. The model consists of 9 readily available pre- or post-procedural clinical and radiological variables and showed good to excellent discriminative ability and excellent calibration slopes. Through validation and updating the model was further improved. Users are given the possibility to select the desired setting and population most comparable to their own clinical practice (HERMES versus MR CLEAN Registry).

Several other prognostic models for outcome of patients treated with EVT also combined pre- and post-procedural variables,[7-9,22-27] but only 3 models have been externally validated.[7-9] Of these, the SNARL score included symptomatic intracranial hemorrhage, NIHSS at baseline, age, reperfusion grade, and location of the occlusion, and concluded that adding post-procedural variables improves outcome prediction.[7] The POST score was based on age, infarct volume and hemorrhagic complications,[9] while the BRANCH scale included baseline

Table 5.4. Main effects of final model in derivation cohort and validation cohort presented as common odds ratios* with 95% confidence intervals.

	Derivation cohort HERMES (n=781)	Validation cohort MR CLEAN Registry (n=3260)
Age, per year		
<65 years	1.00 (0.98 – 1.02)	1.02 (1.00 – 1.03)
≥65 years	0.94 (0.92 – 0.96)	0.94 (0.93 – 0.94)
Baseline NIHSS, per point	1.03 (1.00 – 1.06)	1.00 (0.98 – 1.01)
Diabetes mellitus	0.49 (0.33 – 0.73)	0.57 (0.47 – 0.69)
Pre-stroke mRS, per point	0.67 (0.51 – 0.87)	0.60 (0.56 – 0.66)
Occlusion location		
ICA(-T)	1.0 (reference)	1.0 (reference)
M1	1.25 (0.88 – 1.78)	1.16 (0.99 – 1.36)
M2 or other	1.99 (1.12 – 3.53)	1.32 (1.05 – 1.65)
Collateral score, per point	1.28 (1.03 – 1.58)	1.15 (1.05 – 1.26)
Post-procedural reperfusion grade (mTICI), per point	1.14 (0.96 – 1.36)	1.12 (1.05 – 1.18)
24h NIHSS, per point		
<12 points	0.71 (0.68 – 0.90)	0.78 (0.76 – 0.80)
≥12 points	0.86 (0.83 – 0.90)	0.84 (0.82 – 0.86)
SICH*	0.30 (0.12 – 0.74)	0.17 (0.11 – 0.28)

*Common odds ratios reflect the effect on the reversed modified Rankin Scale (an odds ratio >1 corresponds with better functional outcome).
ICA(-T), intracranial carotid artery (terminus); M1, middle cerebral artery segment 1; M2, middle cerebral artery segment 2; mRS, modified Rankin Scale; mTICI, modified treatment in cerebral infarction; NIHSS, National Institutes of Health Stroke Scale; SICH, symptomatic intracranial hemorrhage.

blood glucose, reperfusion grade, age, baseline NIHSS score, change in blood glucose after 48h, and symptomatic intracranial hemorrhage. However, all three models were derived from cohorts of patients treated before the landmark trials were published and EVT became the standard of care using second-generation devices. These models showed good, but lower discrimination for the prediction of mRS 0–2 at 3 months than MR PREDICTS@24H, which includes age, baseline NIHSS, pre-stroke mRS, diabetes mellitus, occlusion location, collateral score, reperfusion grade, NIHSS at 24h, and symptomatic intracranial hemorrhage. In our study, we found NIHSS at 24h to be the strongest outcome predictor of all nine included variables. This substantiates previous findings that the post-procedural NIHSS score is a major predictor of long-term functional outcome.[7,23,25,28-30] Interestingly, time from stroke onset to groin puncture was not included in MR PREDICTS@24H. We want to emphasize that this does not mean that time is not important for the prediction of outcome after EVT, but suggest that the well-established effect of time on outcome[31] is captured in other (post-procedural) variables, such as the NIHSS at 24h.

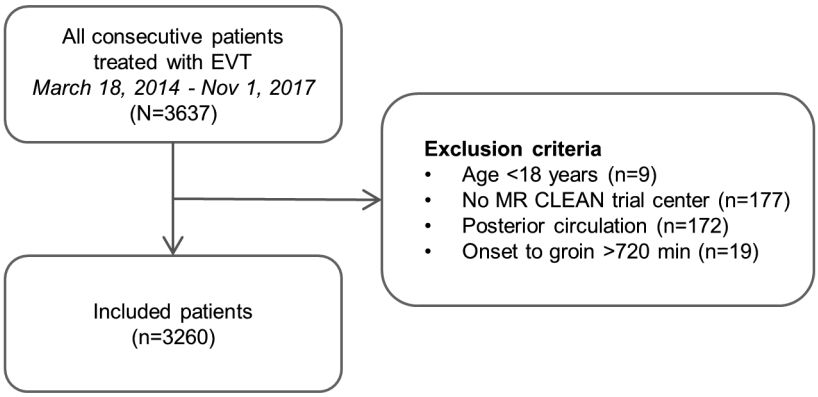

Figure 5.1. Flowchart of patients in validation cohort (MR CLEAN Registry).

Two models, the POST score and GADIS score,[9,27] included follow-up infarct volume, as this is known to be a strong independent predictor of outcome after EVT.[32] Similar to us, the authors of the SNARL score also explored follow-up infarct volume as a predictor of outcome, resulting in improved discriminative ability of the model. As FIV was assessed on follow-up between 12 hours and 2 weeks, the reported c-statistic of our model that includes FIV will therefore be an overestimation of the real model performance one day after EVT. In addition, in many countries including the Netherlands, patients do not routinely undergo follow-up CT or MRI in clinical practice. As MR PREDICTS@24H was specifically designed for use in clinical practice one day after EVT, FIV was not considered for inclusion in the model. Moreover, as there is a desire to inform patients and their family members quickly after treatment, other post-EVT variables beyond one day that may also influence functional outcome, such as the occurrence of pneumonia and the intensity and timing of rehabilitation, were not analyzed.

This model may be of use to neurologists, stroke physicians, and rehabilitation specialists, resulting in more homogeneous outcome prediction across different physicians. By providing more objective data of expected outcomes, the model can be used to guide physicians in adapting and personalizing their patients' treatment and rehabilitation plans, including discharge destination. It can assist them in medical decision making, while taking into consideration other factors, such as wishes of the patient or family members. For decisions relatively early after EVT, such as those concerning invasive treatments including gastrostomy, tracheostomy, and withholding or withdrawing life-sustaining treatments, accurate prediction of expected (poor) outcome in the patient is required. The accuracy of outcome prediction by physicians alone has shown to be insufficient for these types of decisions.[33] In addition, a more accurate estimation of a patients' prognosis could also be used in certain other situations, such as assisting families in planning long-term housing

arrangements. External factors, such as housing circumstances and social support become more important when a poor outcome is likely. As a prognostic model cannot replace clinical judgement, MR PREDICTS@24H should be used as a complementary tool to aid the treating physician.

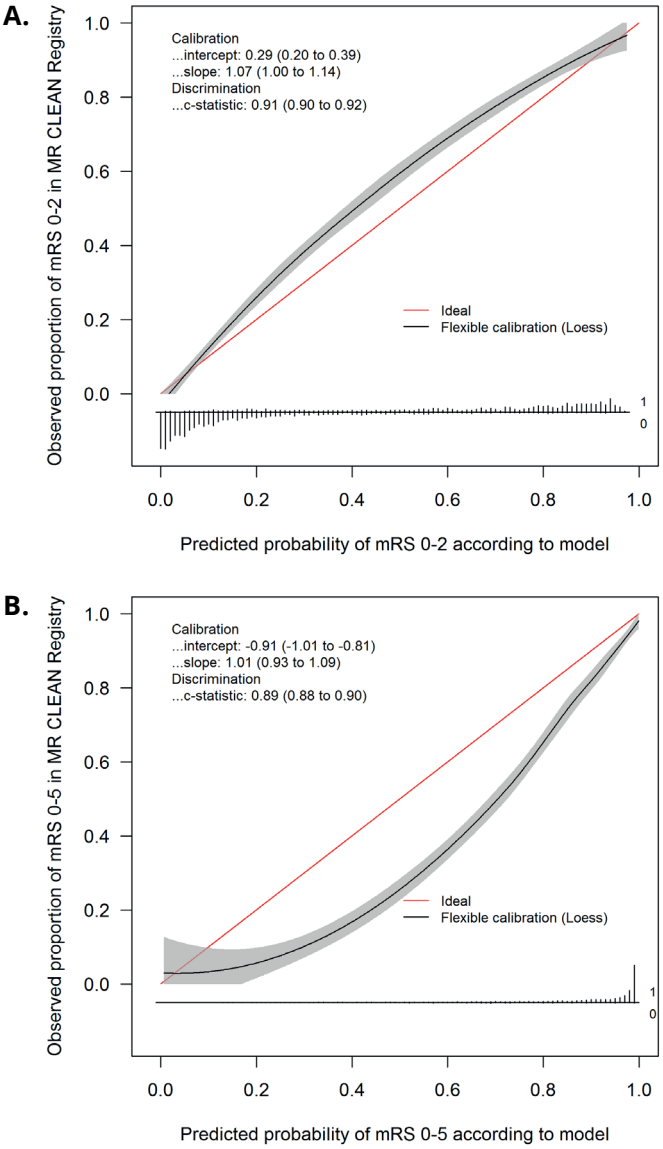

Figure 5.2. Calibration plots for (A) functional independence (modified Rankin scale (mRS) 0–2), and (B) survival (mRS 0–5) in the validation cohort (n=3260).
The overall observed proportion of patients with mRS 0–2 in the validation cohort was higher than the predicted proportion using our model, while the observed proportion of patients that survived was lower than predicted. The linear bar chart shows the distribution of patients with (=1) or without (=0) the observed outcome.

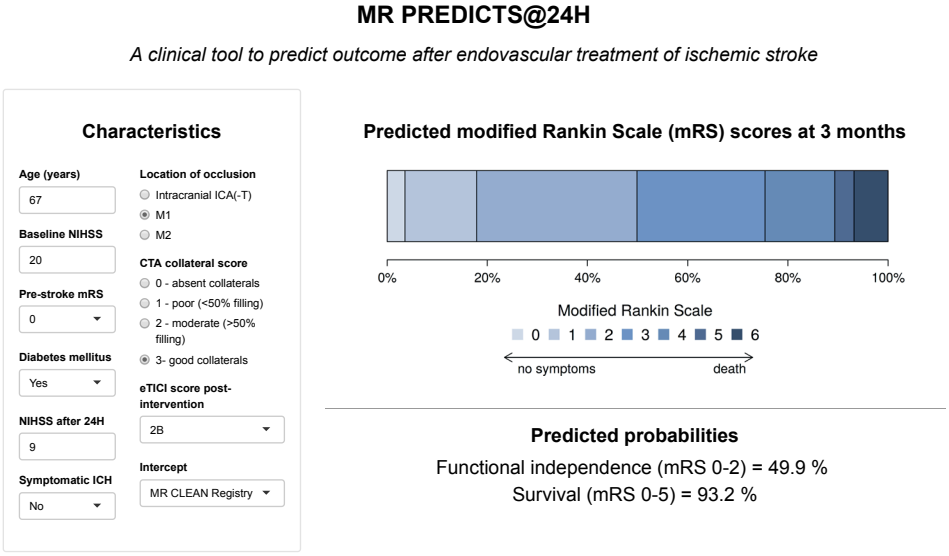

Figure 5.3. Screenshot of the online tool, which is available at www.mrpredicts.com.
CTA, computed tomography angiography; ICA(-T), intracranial carotid artery (terminus); ICH, intracranial hemorrhage; M1, middle cerebral artery segment 1; M2, middle cerebral artery segment 2; mRS, modified Rankin Scale; mTICI, modified treatment in cerebral infarction; NIHSS, National Institutes of Health Stroke Scale.

A major strength of this study is that it was developed on a large heterogeneous dataset generated from ischemic stroke patients treated with EVT in many different countries throughout Europe, North America, East Asia and Oceania. It was externally validated in a large Dutch registry that started after the RCTs from the derivation cohort were finished. This registry is more heterogeneous than RCTs in terms of patient characteristics, representing current clinical practice. This makes the model widely applicable and improves its applicability in daily clinical practice. However, the more liberal inclusion criteria are likely the cause of worse functional outcome and hence the suboptimal calibration, which we resolved by giving users the possibility to select the intercept based on the setting or treated patient population. Patients who had undergone EVT after 12 hours of symptom onset were not included in HERMES nor in the MR CLEAN Registry, as well as those that had undergone EVT for a posterior circulation stroke. To make MR PREDICTS@24H applicable for a wider range of patients, it needs to be externally validated and updated in datasets beyond the current development and validation data.

We believe that the biggest challenge will be to incorporate a tool like this into routine clinical practice, as unfortunately up to now prognostic models have to a limited extent been adopted by the stroke community.[34] This has several reasons, such as that the models are perceived as being too complicated to use, too generic or not intuitive enough, or may

require information that is not routinely available. Therefore we aimed to develop and directly externally validate a simple online clinical tool, based on routinely available important pre- and post-procedural variables. Whether MR PREDICTS@24hrs will be used in clinical practice and will lead to higher satisfaction of patients, families, and physicians with the quality of prognostic information given, requires further implementation research.

Conclusion

MR PREDICTS@24H includes nine variables and can be applied one day after EVT to accurately predict functional outcome at 3 months. The online tool may provide physicians, patients, and family members with reliable outcome expectations, and may assist physicians in personalizing their patients' treatment and rehabilitation plans.

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Supplementary material

MR PREDICTS@24H regression equation

Variable definitions

- age — numeric, in years
- nihss_baseline — numeric, range 0–42
- diabetes — 0=no, 1=yes
- premrs — numeric, range 0–5
- location — categorical: "ICA-(T)", M1", "M2"
- collaterals — numeric, range 0–3
- posttici — numeric, range 0–5 (ie, 2=TICI 2A, 3=TICI 2B, 4=TICI 2C, 5=TICI 3)
- nihss_24h — numeric, range 0–42
- sich — 0=no, 1=yes

Intercept

	HERMES trials	MR CLEAN Registry
mRS 0	-1.18876	-1.54221
mRS 0-1	0.564424	0.236233
mRS 0-2	2.07651	1.75612
mRS 0-3	3.48564	2.88320
mRS 0-4	5.01627	3.89115
mRS 0-5	5.74731	4.37647

Predicted probability (R code)

plogis(0.00820728*age - 4.847520e-05*pmax(age-50.6,0)^3 + 0.000119454*pmax(age-72,0)^3 - 7.09791e-05*pmax(age-86.5,0)^3 - 0.00325521*nihss_baseline - 0.567183*diabetes - 0.509292*premrs + 0.107328*(location=="M1") + 0.276687*(location=="M2") + 0.135082*collaterals + 0.0822202*posttici - 0.256114*nihss_24h + 0.000157732*pmax(nihss_24h-1,0)^3 -0.000301125*pmax(nihss_24h-11,0)^3 + 0.000143393*pmax(nihss_24h-22,0)^3 - 1.75500*sich + intercept)

Part II

Treat at the right time

Chapter 6

Workflow and factors associated with delay in the delivery of endovascular treatment for ischemic stroke in the MR CLEAN trial

J Neurointerv Surg, 2018

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*equal contribution

Abstract

Objective

The effect of endovascular treatment (EVT) for acute ischemic stroke is highly time-dependent. We investigated delay of EVT and factors associated with such delay.

Methods

MR CLEAN was a randomized trial of EVT plus usual care versus usual care alone (n=500). With multivariable linear regression, we analyzed the effect of intravenous treatment, general anesthesia, off-hours and inter-hospital transfer on time to admission at the emergency department (ED) of the intervention center and time to treatment. Furthermore, we assessed compliance with a target of 75 minutes for time from ED to treatment, and calculated the potential absolute increase of patients with a good outcome (modified Rankin Scale score ≤2), if this target had been achieved in all treated patients.

Results

Inter-hospital transfer prolonged time to ED with 140 minutes (95% confidence interval 129 to 150), but reduced time from ED to treatment with 77 minutes (64 to 91). Time from ED to treatment was increased with 19 minutes by general anesthesia (5 to 33) and total time was increased with 23 minutes during off-hours (6 to 40). The in-hospital target was achieved in 11.5% (22/191) of patients. Full compliance with the target time of 75 minutes from ED to treatment would have increased the proportion of patients with good outcome with 7.6% (6.7% to 8.5%).

Conclusion

Inter-hospital transfer is an important cause of delay in the delivery of EVT and every effort should be made to avoid transfers and reduce transfer-related delay. Furthermore, in-hospital workflow should be optimized to improve functional outcome after EVT.

Introduction

Endovascular treatment (EVT) with the use of stent retrievers has been proven safe and effective for patients with acute ischemic stroke due to a proximal intracranial arterial occlusion in the anterior circulation.[1] The effect of treatment is highly time-dependent and increased time from stroke onset to reperfusion is associated with a decreased likelihood of good functional outcome.[2-7] The Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands (MR CLEAN) showed a decrease in the effect of EVT on good outcome (risk difference between intervention and control) of 6.4% per hour delay in time to expected reperfusion.[3] It seems likely that reducing treatment delay will further increase the effect of EVT.

The timeline from stroke onset to reperfusion consists of several steps, and each step is prone to factors causing delay. An important potential cause of delay in the prehospital stage is referral to a community hospital without facilities for EVT (a primary stroke center), which necessitates inter-hospital transportation of patients to an intervention center. Other factors that may increase time to reperfusion are intravenous treatment with alteplase (IVT), the use of general anesthesia during the endovascular procedure, and inefficiency of in-hospital workflow, specifically outside working hours.[8-10] In-hospital workflow consists of all protocols and procedures in the emergency department (ED) of the primary stroke center, the ED of the intervention center, and the interventional suite.

In addition to the previously defined benchmark time of 60 minutes for IVT, various lenient or strict target times for EVT are now being suggested to improve in-hospital workflow.[11-13] The Highly Effective Reperfusion Evaluated in Multiple Endovascular Stroke Trials (HERMES) collaborators reported the 25th percentile of ED admission to groin puncture, which amounted to 75 minutes, and could very well serve as a benchmark time.[7]

Our aim was to investigate prehospital and in-hospital delay in the delivery of EVT in the MR CLEAN trial and to assess the impact of inter-hospital transfer and other factors on such delay.

Methods

Study design

MR CLEAN was a multicenter randomized clinical trial in the Netherlands comparing EVT plus usual care (intervention group) with usual care alone (control group).[14,15] MR CLEAN is registered with the ISRCTN registry (ISRCTN10888758).

Study setting and population

Patients of 18 years or older with a clinical diagnosis of acute stroke, a deficit on the National Institute of Health Severity of Stroke (NIHSS) scale of 2 points or more, and a proximal occlusion in the anterior circulation on vessel imaging were included. Detailed inclusion and exclusion criteria can be found in the study protocol.[14] Usual care could include IVT if indicated. The endovascular procedure had to be initiated within 6 hours after onset of stroke symptoms and could include intra-arterial delivery of a thrombolytic agent at the level of occlusion, mechanical thrombectomy, or both. In total 500 patients were enrolled from December 2010 to March 2014. Of these patients, 233 were allocated to the intervention arm and 267 were allocated to the control arm. EVT consisted of stent thrombectomy in the majority of cases (195/233, 84%).[14,15]

Study protocol

Inclusion in the study could occur in three settings: (1) patients arrived directly at an intervention center after onset of stroke symptoms; (2) patients were presented at a primary stroke center first before being transferred to an intervention center for study participation; or (3) patients suffering a stroke while already hospitalized. In the hospital of first presentation, a non-contrast CT (NCCT) was performed to exclude intracerebral hemorrhage. This was followed by standard medical treatment which could include IVT. Vessel imaging with computed tomographic angiography (CTA), magnetic resonance angiography (MRA), or digital-subtraction angiography (DSA), had to be performed before inclusion in the study in the intervention center, to assess the presence of an intracranial arterial occlusion.

Time points of various events were prospectively collected in the trial, including time of stroke onset, start of IVT, admission to the ED of the intervention center and time of randomization. In patients receiving EVT, timing of treatment was documented by the local interventionist. Time of imaging (ie, NCCT and CTA, MRA or DSA) was prospectively recorded in the intervention centers, but had to be collected retrospectively if performed in a primary stroke center.

Definitions and outcome measures

Stroke onset was defined as the time point when stroke symptoms were first noticed by the patient or an observer. In case the time of first symptoms was unknown, stroke onset was defined as the moment the patient was last seen well. We defined off-hours as weekend days or working days between 17:00 hours and 08:00 hours. Groin puncture was defined as the moment of placing a sheet in the groin, indicating the start of the endovascular procedure. Reperfusion was measured with the modified Thrombolysis in Cerebral Infarction (mTICI) score, which can range from grade 0 for no reperfusion, to grade 3 for full reperfusion.[16] We defined time of reperfusion as the first moment a mTICI score of 2b or 3 was reached. When reperfusion was not achieved, we used the timepoint when the last angiography run was done, which indicated the end of the endovascular procedure.

Time intervals of primary interest were: (1) time from stroke onset to admission at the ED of the intervention center as a measure for prehospital delay; (2) time from admission at the ED of the intervention center to groin puncture as a measure for in-hospital delay; and (3) time from stroke onset to groin puncture. Additionally, we compared the following time intervals between transfer patients and direct patients: (4) time from stroke onset IVT; (5) time from admission at ED to vessel imaging; (6) time from vessel imaging to randomization; and (7) time from groin puncture to reperfusion. If all vessel imaging was performed in the primary stroke center, the patient was excluded from analyses (5) and (6). Time of transportation from the primary stroke center to the intervention center was estimated for all transfer patients with the TomTom MyDrive application (version 4.1.4.3089, available at mydrive.tomtom.com).

Statistical analysis

For descriptive purposes, time intervals were reported as medians with interquartile range (IQR). To assess transfer-related treatment delay, we compared baseline characteristics and median time intervals of patients transferred from a primary stroke center versus patients directly arrived at the intervention center.

Using multivariable linear regression analyses we evaluated the effect of patient and workflow-related characteristics on time to treatment. Factors assessed were administration of IVT, use of general anesthesia during the endovascular procedure, admission during off-hours and inter-hospital transfer. We included the following potential confounders in these analyses: age, gender, baseline NIHSS score, history of ischemic stroke and prestroke modified Rankin Scale (mRS). Missing baseline characteristics were imputed with the mean (continue variables) or mode (categorical variables). Missing time variables were not imputed.

To assess the impact of in-hospital delay, we compared the time from admission at ED to groin puncture with the target time of 75 minutes. For each individual patient we estimated the excess delay by subtracting target time from the actual time. The mean excess delay of all treated patients was multiplied by an increase in treatment benefit (defined as the risk difference for good outcome (mRS score 0–2)) of 6.4% per hour, based on previous results of the MR CLEAN trial.[3] This provides an estimate of the potential increase in treatment benefit if the target time would have been achieved in all treated patients.

All statistical analyses were performed with R software (version 3.2.1, R Foundation).

Results

Of the 500 patients included in MR CLEAN, 281 (56.2%) arrived directly at an intervention center and 219 (43.8%) were transferred from a primary stroke center. Transfer patients were significantly younger than those arriving directly at an intervention center (62.2 versus 67.0 years) and were admitted more frequently during off-hours (63.4 versus 51.6%). Other baseline characteristics are shown in Table 6.1.

Table 6.1. Baseline characteristics of patients in the MR CLEAN trial, according to mode of arrival at the emergency department of the intervention center.

	Direct (n=281)	Transfer (n=219)	p-value
Age, years – mean (SD)	67.0 (13.6)	62.2 (13.6)	<0.01
Male sex – n (%)	156 (55.5)	136 (62.1)	0.16
Medical history – n (%)			
Atrial fibrillation	77 (27.4)	58 (26.5)	0.90
Hypertension	135 (48.0)	92 (42.0)	0.21
Hyperlipidemia	71 (25.3)	58 (26.5)	0.84
Diabetes mellitus	41 (14.6)	27 (12.3)	0.55
Previous ischemic stroke	33 (11.7)	21 (9.6)	0.53
Prestroke mRS – n (%)			0.09
0	220 (78.3)	184 (84.0)	
1	27 (9.6)	23 (10.5)	
2	19 (6.8)	6 (2.7)	
>2	15 (5.3)	6 (2.7)	
NIHSS score – median (IQR)	17 (14–22)	18 (15–22)	0.13
Location of occlusion – n (%)*			0.24
Internal carotid artery	72 (25.7)	66 (30.1)	
M1 middle cerebral artery segment	180 (64.3)	139 (63.5)	
M2 middle cerebral artery segment	27 (9.6)	12 (5.5)	
A1 or A2 anterior cerebral artery segment	1 (0.4)	2 (0.9)	
IVT – n (%)	249 (88.6)	196 (89.5)	0.87
Admission during off hours – n (%)†	141 (51.6)	128 (63.4)	0.01
Allocation to EVT – n (%)	132 (47.0)	101 (46.1)	0.92
Use of general anesthesia – n (%)‡	39 (32.5)	41 (42.3)	0.18

*One missing value. †25 missing values. ‡Only endovascular treated patients.
EVT, endovascular treatment; IVT, intravenous treatment; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale.

Table 6.2. Time intervals in the MR CLEAN trial according to mode of arrival at the emergency department of the intervention center, expressed as median (IQR).

All patients	**Direct (n=281)**	**Transfer (n=219)**
Stroke onset to IVT (n=444)	85 (65–110)	85 (66–110)
Stroke onset to admission to ED (n=471)	52 (34–75)	200 (166–245)
Admission to ED to vessel imaging (n=439)	39 (25–67)	24 (17–32)
Vessel imaging to randomization (n=460)	53 (34–80)	21 (15–33)
Endovascular treated patients	**Direct (n=132)**	**Transfer (n=101)**
Stroke onset to groin puncture (n=205)	233 (202–287)	315 (260–346)
Admission to ED to groin puncture (n=192)	170 (142–205)	96 (75–120)
Groin puncture to reperfusion (n=194)	56 (42–86)	61 (37–90)

ED, emergency department; IVT, intravenous treatment.

Median time from stroke onset to groin puncture was 233 minutes (IQR 202–287) in direct arrival patients, and 315 minutes (260–346) in transfer patients (Table 6.2). The median time of inter-hospital transportation was 30 minutes (23–41), but total time from onset to admission at the ED of the intervention center was 148 minutes longer in transfer patients than in direct arrival patients. In-hospital workflow was improved in transfer patients, with a decrease in median time from arrival to vessel imaging of 15 minutes and a decrease in time from vessel imaging to randomization of 32 minutes. Duration of the endovascular procedure from groin puncture to reperfusion was comparable (56 minutes in direct arrival patients versus 61 minutes in transfer patients). Overall, we observed an association between increasing time from onset of stroke to admission at ED and decreasing time from admission to groin puncture (Supplementary Figure 6.1). However, the average prehospital delay caused by inter-hospital transfer was only partially compensated by improved in-hospital workflow (Figure 6.1).

In multivariable analysis, the total time to treatment (groin puncture) was increased by 23 minutes during off-hours (95% confidence interval (CI) 6 to 40) and by 65 minutes due to inter-hospital transfer (95% CI 48 to 82) (Figure 6.2). Transfer prolonged time to admission to the ED by 140 minutes (129 to 150), but was associated with a shorter time to groin puncture (77 minutes, 95% CI 64 to 91). Time from ED to groin puncture was increased by an additional 19 minutes by the use of general anesthesia during the endovascular procedure (95% CI 5 to 33).

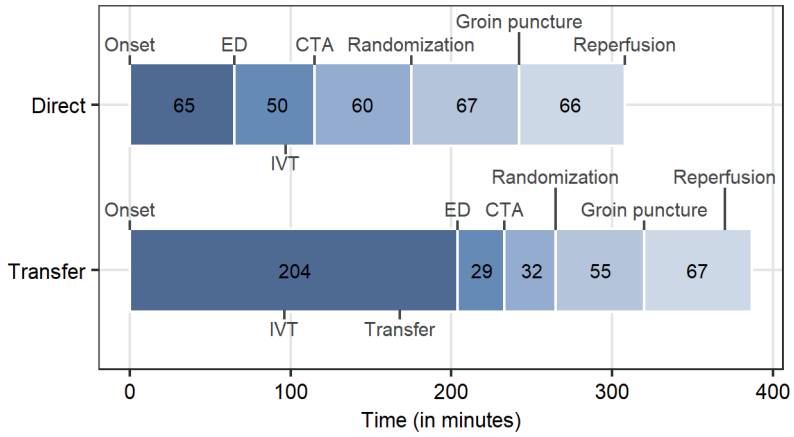

Figure 6.1. Mean time intervals in MR CLEAN (n=500) according to mode of arrival at the emergency department of the intervention center. CTA, computed tomography angiography; ED, emergency department; IVT, intravenous treatment.

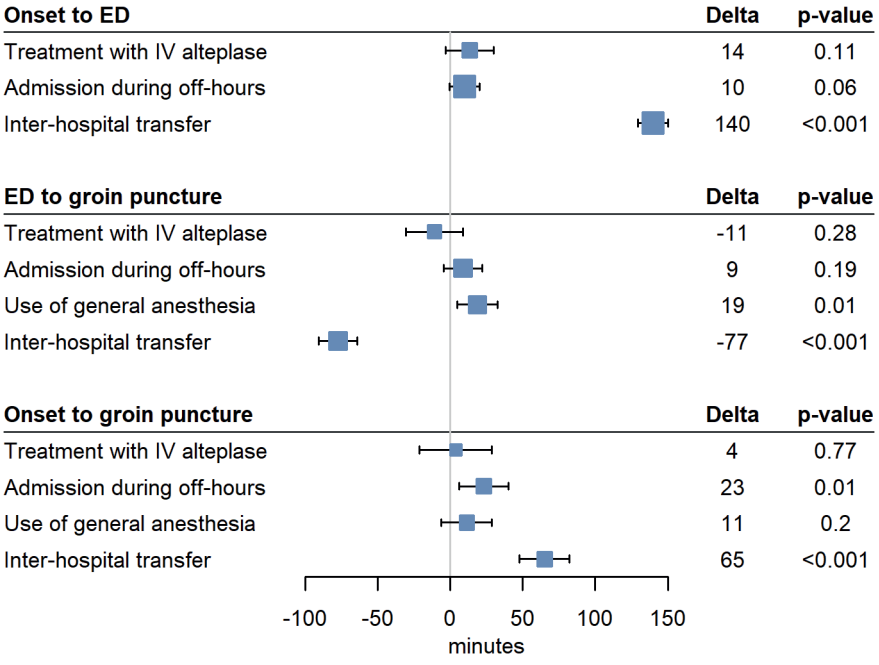

Figure 6.2. Effect of clinical factors on time intervals in MR CLEAN (n=500). ED, emergency department (of the intervention center).

In patients receiving EVT, time from admission to the ED to groin puncture was on average 145±61 minutes. The defined target time of 75 minutes was reached in only 11.5% (22/191) of the treated patients. However, if this target time had been achieved in all patients, mean time from onset to groin puncture would have been 71 minutes (95% CI 63 to 80) shorter. Because the risk difference of good functional outcome decreases with 6.4% per hour, the absolute treatment benefit (proportion of patients with mRS 0–2) in MR CLEAN could have been 7.6% (6.7% to 8.5%) higher.

Discussion

This study shows that inter-hospital transfer was the most important factor associated with treatment delay in MR CLEAN. Time from onset to treatment increases with more than one hour in patients transferred from a primary stroke center, despite improved in-hospital workflow times. Furthermore, only a few patients received EVT within the proposed target time of 75 minutes for time from admission to the ED to groin puncture, and enhancing this compliance by improving in-hospital workflow might further increase functional outcome after EVT.

Overall, the time intervals in MR CLEAN are longer than in several other trials on EVT, such as The Endovascular Treatment for Small Core and Proximal Occlusion Ischemic Stroke (ESCAPE), EXtending the time for Thrombolysis in Emergency Neurological Deficits with Intra-Arterial therapy (EXTEND-IA) and Solitaire With the Intention for Thrombectomy as Primary Endovascular Treatment (SWIFT PRIME).[17-19] For example, median time to reperfusion was 340 minutes in MR CLEAN versus 241 minutes in ESCAPE. This can be explained by the strong focus on improving workflow and reducing time delays in ESCAPE, while MR CLEAN did not require the participating investigators to be trained in delivery of fast care and logistics. Furthermore, the study design of these trials allowed verbal or deferred informed consent, while in MR CLEAN a written informed consent was required before randomization.[15,18] Trials with a shorter median time to groin puncture had a significant larger treatment effect (Supplementary Figure 6.2).

Total time to treatment was increased most by inter-hospital transfer, confirming the results of previous studies.[4,5,9,10] Transfer patients arrived 148 minutes later at the ED, while the median transportation time in our study was only 30 minutes. This suggests that that most delay was caused during work-up in the primary hospital. However, increased time to arrival at the ED was clearly associated with a decrease in the following time to groin puncture. This paradoxical effect was likely caused by the fact that this group consisted mainly of transfer patients who had already undergone part of the workup, the intervention center was pre-notified and clinical information was available before arrival at the ED, which made it possible for the staff to mobilize the neuro-interventional team and for the angiosuite to

be prepared in advance. This finding suggests that improvement of in-hospital workflow might lead to a shorter time from ED to treatment for patients who are directly admitted to an intervention center.

Our study has a number of limitations. Our analysis was restricted to data that was collected during the trial. We had no information available on the time of arrival in the primary stroke center and the time of departure to the intervention center to estimate door-in to door-out times, while this might have provided more insight into the various elements of delay. Also, the reported workflow times from this randomized study might not be representative for daily clinical practice, since the process of obtaining written informed consent and randomization can increase treatment delay substantially. Furthermore, the vessel imaging in MR CLEAN was often performed or repeated in the intervention center, while in daily routine transfer patients can be directly transferred to the interventional suite without any delay of additional imaging. Since the distances between hospitals in the Netherlands are very short and the median transportation time in this study was only 30 minutes, our results cannot be easily extrapolated to other countries. Transportation times in larger countries are usually longer, and the effect of inter-hospital transfer on treatment delay might therefore be much stronger in those countries. Last, inter-hospital transfer has not only a disadvantageous effect on time to treatment, but also on the number of patients that might be eligible for treatment.[20] We had no data on the patients in primary stroke centers who were not included in the trial because of the need for a transfer and the associated delay. Therefore, we were not able to quantify the impact of transfer delay on the likelihood of receiving EVT.

Overall, it remains clear that inter-hospital transfer causes significant pre-hospital delays in EVT, and that adequate measures have to be taken to shorten transfer times and, if possible, to reduce the number of transferred patients. This could be achieved by transporting ischemic stroke patients directly to an intervention center using prehospital triaging scales to select patients with a high risk of a large vessel occlusion.[21-23] These scales have to be implemented in regional care systems and protocols for prehospital triage to minimize transfer delays depending on the characteristics of the area.[24-26] In regions with very large distances, the additional use of air ambulance services for the transportation of EVT candidates might be beneficial. Another possibility would be to bypass the primary stroke center by using a mobile stroke unit; an ambulance with a CT scanner and a specialized team on board, allowing in-ambulance initiation and administration of IVT and direct transportation to the intervention center.[27-29]

The other important step in reducing treatment delay in EVT is improving in-hospital workflow. The reduced time from ED to groin puncture in transfer patients suggests that it should be possible to shorten the time delay in the ED. Previous studies have already shown that optimizing workflow and protocols can decrease time to treatment.[30,31] Pre-notification

of the interventional team as soon as a patient with a suspected large vessel occlusion is announced, direct transport from door to scanner, a parallel nature of care processes and optimizing the processes around IVT administration and initiation of EVT are all potential factors to reduce ED delay.[10,32,33] Providing reasonable time targets might also improve this process, as was shown with the introduction of door-to-balloon target times for percutaneous coronary intervention.[34]

In summary, inter-hospital transfer is an important cause of delay in the delivery of EVT and every effort should be made to avoid transfer and reduce transfer-related delay. Furthermore, in-hospital workflow can and should be optimized to improve functional outcome after EVT.

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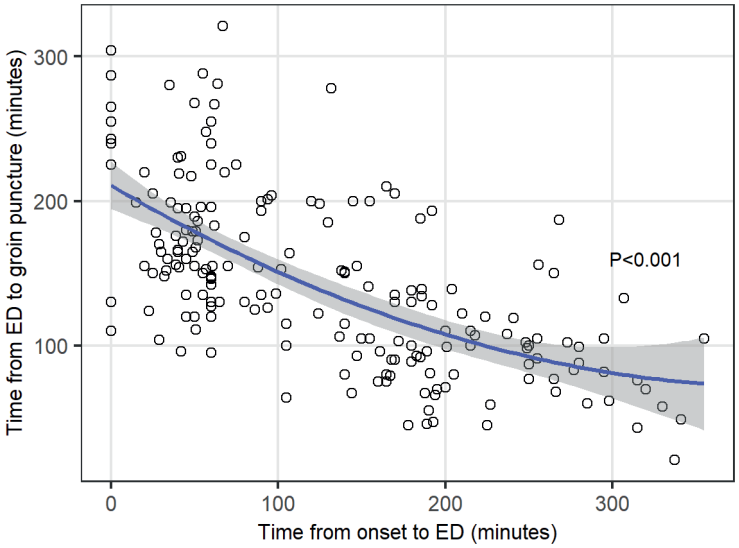
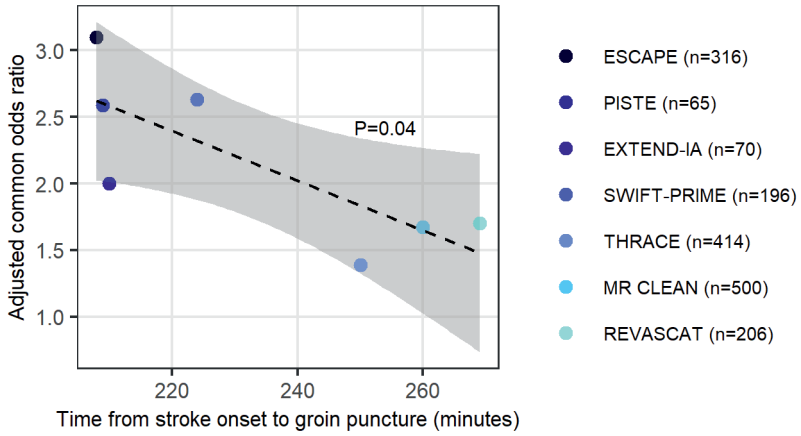
Supplementary material



Supplementary Figure 6.1. The relationship between time from stroke onset to admission to the emergency department (ED) of the intervention center and the following time to groin puncture. Each dot represents one patient, the blue line is the fitted regression line with 95% confidence bands.



Supplementary Figure 6.2. The relationship between the median time from stroke onset to groin puncture and the treatment effect on functional outcome (adjusted common odds ratio) of different trials. Each dot represents one trial, the dashed line is the fitted regression line with 95% confidence bands.

Chapter 7

Effect of inter-hospital transfer on endovascular treatment for ischemic stroke

Stroke, 2019

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*equal contribution

Abstract

Background and purpose

To assess the effect of inter-hospital transfer on time to treatment and functional outcome after endovascular treatment (EVT) for ischemic stroke, we compared patients transferred from a primary stroke center to patients directly admitted to an intervention center in a large nationwide registry.

Methods

The MR CLEAN (Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands) Registry is an ongoing, prospective, observational study in all centers that perform EVT in the Netherlands. We included adult patients with an acute anterior circulation stroke who received EVT between March 2014 to June 2016. Primary outcome was time from arrival at the first hospital to arterial groin puncture. Secondary outcomes included the 90-day modified Rankin Scale (mRS) and functional independence (mRS 0–2).

Results

In total, 821/1526 patients (54%) were transferred from a primary stroke center. Transferred patients less often had pre-stroke disability (227/800 (28%) versus 255/699 (36%), P=0.02) and more often received intravenous treatment with alteplase (659/819 (81%) versus 511/704 (73%), P<0.01). Time from first presentation to groin puncture was longer for transferred patients (164 versus 104 minutes, P<0.01, adjusted delay 57 minutes (95% CI 51 to 62)). Transferred patients had worse functional outcome (adjusted common odds ratio 0.75 (95% CI 0.62 to 0.90)) and less often achieved functional independence (244/720 (34%) versus 289/681 (42%), absolute risk difference -8.5% (95% CI -8.7 to -8.3)).

Conclusions

Inter-hospital transfer of patients with acute ischemic stroke is associated with delay of EVT and worse outcomes in routine clinical practice, even in a country where between-center distances are short. Direct transportation of patients potentially eligible for endovascular treatment to an intervention center may improve functional outcome.

Introduction

Endovascular treatment (EVT) has been proven effective in patients with ischemic stroke due to an intracranial large vessel occlusion (LVO) of the anterior circulation.[1] The effect of EVT is highly time-dependent and a reduction in onset-to-treatment time increases the chance of good functional outcome for the patient.[2,3]

Studies focusing on workflow characteristics identified inter-hospital transfer as one of the main causes of treatment delay in the recent randomized controlled trials.[4,5] Patients with ischemic stroke are often first presented at the nearest primary stroke center to provide rapid treatment with intravenous thrombolytics (IVT). If the diagnostic work-up indicates eligibility for EVT, the patient is then transferred to an intervention center with facilities for EVT ('drip-and-ship'). Analysis of data from a US registry suggested that this drip-and-ship method increases time to treatment and decreases the odds of good functional outcome in daily clinical practice.[6] However, the effect of inter-hospital transfer might be different in a more densely populated region with short between-center distances and a well-organized acute stroke care system.

We investigated the frequency of inter-hospital transfer and the characteristics of transferred patients in a large nationwide cohort in the Netherlands: the MR CLEAN (Multicenter Randomized Clinical trial of Endovascular treatment for Acute ischemic stroke in the Netherlands) Registry. We aimed to assess the effect of inter-hospital transfer on time to treatment and functional outcome in routine clinical practice.

Material and methods

Study design

Detailed methods of the MR CLEAN Registry have been reported previously.[7] The MR CLEAN Registry is an ongoing, prospective, observational study in all centers that perform EVT in the Netherlands. Registration started in March 2014, directly after the final inclusion in MR CLEAN. All eighteen intervention centers in the Netherlands, of which sixteen centers participated in the MR CLEAN trial, registered their patients. All data were centrally collected and checked for completeness and consistency. The imaging assessment committee assessed imaging and the adverse event committee scored the safety parameters.

The central medical ethics committee of the Erasmus MC University Medical Center, Rotterdam, The Netherlands, evaluated the study protocol and granted permission to carry out the study as a registry. Data will not be made available to other researchers as no patient approval has been obtained for sharing coded data. However, syntax and output files of statistical analyses are available from the corresponding author on reasonable request.

Study population

All consecutive patients with ischemic stroke in the anterior and posterior circulation who received arterial groin puncture in the angiosuite have been registered. For the current analysis, we used data of patients treated between March 2014-June 2016. We included patients adhering to the following criteria: age ≥ 18 years; treatment in a center that participated in the MR CLEAN trial; and presence of an intracranial proximal arterial occlusion in the anterior circulation (intracranial carotid artery (ICA/ICA-T), middle cerebral artery (M1/M2) or anterior cerebral artery (A1/A2)), demonstrated by computed tomography (CT) angiography. EVT could consist of arterial catheterization followed by mechanical thrombectomy and/or thrombus aspiration, with or without delivery of a thrombolytic agent. Patients arrived either directly at the intervention center or were transferred from one of the primary stroke centers (Figure 7.1). Emergency medical services in the Netherlands identify potential stroke patients using the Face, Arm, Speech Test (FAST) and transport patients with an onset time of less than 6 hours to the closest stroke center with IVT or EVT facilities.

Definitions and outcome measures

Time of stroke onset was defined as the moment of witnessed onset of stroke symptoms or, when exact onset was unknown, the moment that the patient was last seen well. Admission outside office hours was defined as time of arrival at the intervention center on working days between 17:00 hours and 8:00 hours, during weekend days or national festive days. All transfer patients received a non-contrast CT in the primary stroke center and most transfer patients received a CT angiography before transfer to an intervention center. Imaging was not routinely repeated upon arrival at the intervention center, but only in case of a clinical indication (e.g. deterioration or substantial improvement). Imaging characteristics were assessed based on the first scan made (for transferred patients in the primary stroke center, for direct patients in the intervention center). Transfer-related travel time between each primary stroke center and the receiving intervention center was estimated using the TomTom MyDrive application (version 4.2.1.3495, available on mydrive.tomtom.com). A ratio of 0.85 was subsequently applied on each calculated time to approach the transfer-related travel time that an ambulance would actually need. This ratio is based upon measured travel times of ambulances in a previous study in the Netherlands.[8] The door-in-door-out time in the primary stroke center was then estimated by subtracting the transfer-related travel time from the reported time from door of the primary stroke center to door of the intervention center.

Primary outcome was the time from first presentation to start of treatment, defined as the interval between arrival at the first hospital to arterial groin puncture. Secondary outcomes included: time from arrival at intervention center to groin puncture; time from stroke onset to groin puncture; the modified Rankin Scale (mRS) at 90 days after stroke; functional independence, defined as mRS score 0–2; mortality at 90 days; successful reperfusion at

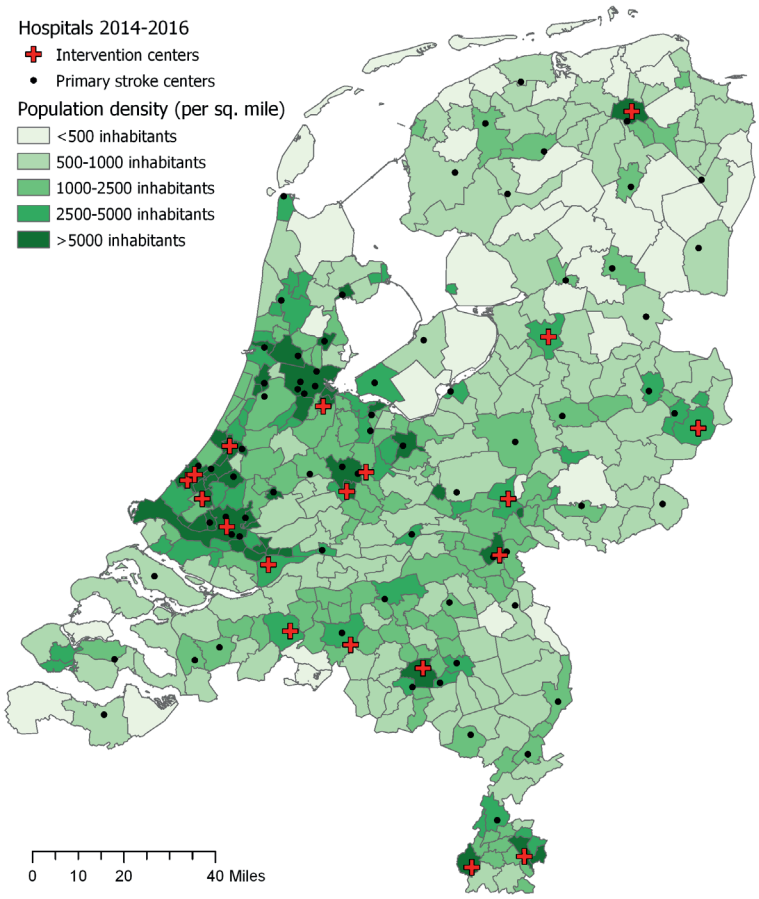

Figure 7.1. Map of the Netherlands including primary stroke centers, intervention centers and population density.

the end of EVT, defined as an extended Thrombolysis in Cerebral Infarction (eTICI) score ≥2B;[9] and occurrence of symptomatic intracerebral hemorrhage. Intracerebral hemorrhage was defined as symptomatic if patients died or deteriorated neurologically (an increase of ≥4 points on the National Institutes of Health Stroke Scale (NIHSS) score compared with the NIHSS before worsening), and the hemorrhage was related to the clinical deterioration (according to the Heidelberg Bleeding Classification).[10]

Statistical analysis

We compared patients transferred from a primary stroke center with patients who were directly admitted to an intervention center. Baseline characteristics were compared using Chi-square test for categorical variables, independent samples T-test for normally distributed

continuous variables, and Mann-Whitney U test for non-normal distributed continuous variables. Time intervals were expressed as medians with interquartile range (IQR). For regression analyses, missing data were imputed using multiple imputations by chained equations (MICE) based on relevant covariates and outcome.

Linear regression analyses were used to assess the effect of transfer on time intervals. Prespecified adjustments were made for age, baseline NIHSS score, prestroke mRS score, treatment with IVT, hypertension (baseline systolic blood pressure >185 mmHg and/or diastolic blood pressure >110 mmHg), location of occlusion, Alberta Stroke Program Early Computed Tomography Score (ASPECTS) on non-contrast CT, collateral score on CT angiograpy, the use of general anesthesia, and admission outside office hours. The effect of transfer on functional outcome was assessed using an ordinal logistic regression analysis for the shift in mRS score at 90 days. Binary logistic regression analyses were used for functional independence, mortality, successful reperfusion, and occurrence of symptomatic intracerebral hemorrhage. These analyses were adjusted for the following prespecified variables: age, baseline NIHSS score, prestroke mRS score, history of ischemic stroke or transient ischemic attack, treatment with IVT, location of occlusion, ASPECTS, collateral score, and time from onset to first hospital.

All analyses were performed using R software (Version 3.4.4, R Foundation) with the rms package (version 5.1-2).

Results

In total, 1627 consecutive patients treated with EVT for ischemic stroke were included in the MR CLEAN Registry between March 2014 and June 2016. We excluded 101 patients for the following reasons: age below 18 years (n=2); EVT performed in a non MR CLEAN center (n=20), and occlusion of the posterior circulation (n=79). The remaining 1526 patients were included in the analyses (Figure 7.2). Of these patients, 821 (53.8%) were transferred from a primary stroke center and 705 (46.2%) were presented directly to an intervention center. The percentage of transferred patients ranged between 3.4% and 77% per intervention center.

Baseline characteristics

Demographics and baseline stroke severity were similar in both groups: median age was 71 years for transferred patients versus 70 years for directly admitted patients, 53% of all patients were men, and median NIHSS at baseline was 16 for both groups (Table 7.1). Transferred patients were more often treated with IVT (80.5% versus 72.6%, P<0.01) and had less often pre-stroke disability (mRS≥1, 28.4% versus 36.5%, P=0.02). Imaging characteristics were less favorable for transferred patients, with lower ASPECTS (median 8 versus 9, P=0.01) and more often absent or poor collaterals (collateral score 0–1, 44.1% vs.

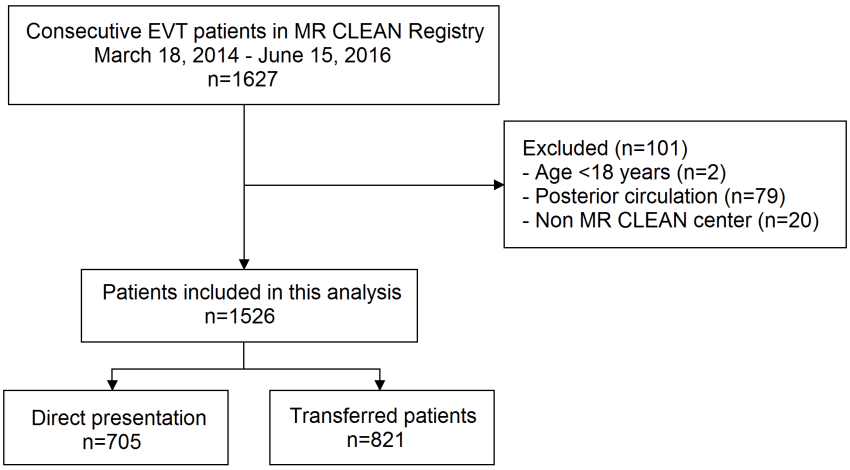

Figure 7.2. Flowchart of patient selection. EVT, endovascular treatment.

35.2%, P<0.01). Transferred patients less often had an occlusion of segment 2 of the middle cerebral artery (10.6% versus 14.4%, P=0.01). Imaging was repeated in 49/821 (6%) and 39/821 transfer patients (4.8%) for non-contrast CT and CT angiography, respectively.

Treatment times

The median time from arrival at the first hospital to groin puncture was longer for transferred patients than for patients who were directly admitted to an intervention center (164 versus 104 minutes, P<0.01, Table 7.2). The adjusted difference was 57 minutes (95% confidence interval (CI) 51 to 62 minutes), in favor of patients who were admitted directly (Table 7.3). After subtraction of the mean estimated transfer-related travel time (23 minutes), this time difference was 39 minutes. Transferred patients arrived slightly earlier after stroke onset at the first hospital (50 versus 55 minutes, P<0.01), but time from onset to arrival at the intervention center was much longer (174 versus 55 minutes, P<0.01). Median door-to-needle times for patients that received IVT were slightly longer for transferred patients (26 versus 24 minutes, P=0.02). Although the interval from arrival at the intervention center to start of treatment was shorter for transferred patients (47 versus 104 minutes, P<0.01, adjusted difference -58 minutes (95% CI -62 to -54)), the total time from onset to groin puncture was still substantially longer in these patients (230 versus 170 minutes, P<0.01, adjusted difference 40 minutes (95% CI 31 to 48)). The median duration of the endovascular procedure was similar in both groups (63 versus 62 minutes, P=0.79).

Clinical outcome

There was a significant shift towards worse functional outcome in transferred patients (adjusted common odds ratio (OR) 0.75, (95% CI 0.62 to 0.90); Figure 7.3). Transferred

Table 7.1. Baseline characteristics.

	Direct presentation n = 705	Transferred patients n = 821	P-value
Age, median (IQR)	70 (59 – 79)	71 (60 – 80)	0.45
Male sex, n (%)	371/705 (52.6)	438/821 (53.3)	0.78
Baseline NIHSS*, median (IQR)	16 (11 – 20)	16 (12 – 20)	0.19
Systolic blood pressure†, mean+SD	149±25	150±25	0.41
Treatment with IVT, n (%)	511/704 (72.6)	659/819 (80.5)	<0.01
Presentation outside office hours, n (%)	441/705 (62.6)	541/821 (65.9)	0.17
General anesthesia, n (%)	180/662 (27.2)	205/759 (27.0)	0.94
Medical history			
Ischemic stroke, n (%)	118/703 (16.8)	135/814 (16.6)	0.92
Myocardial infarction, n (%)	113/697 (16.2)	120/798 (15.0)	0.53
Diabetes mellitus, n (%)	126/700 (18.0)	136/817 (16.6)	0.49
Atrial fibrillation, n (%)	147/697 (21.1)	188/807 (23.3)	0.31
Prestroke mRS, n (%)			0.02
0	444/699 (63.5)	573/800 (71.6)	
1	97/699 (13.9)	98/800 (12.3)	
2	66/699 (9.4)	49/800 (6.1)	
≥3	92/699 (13.2)	80/800 (10.0)	
Imaging characteristics			
ASPECTS on first NCCT‡, median (IQR)	9 (7 – 10)	8 (7 – 10)	0.01
Collateral score on first CTA, n (%)			<0.01
Grade 0	42/674 (6.2)	56/743 (7.5)	
Grade 1	195/674 (28.9)	272/743 (36.6)	
Grade 2	259/674 (38.4)	288/743 (38.8)	
Grade 3	178/674 (26.4)	127/743 (17.1)	
Location of occlusion, n (%)			0.01
ICA	39/693 (5.6)	46/765 (6.0)	
ICA-T	142/693 (20.5)	180/765 (23.5)	
Proximal M1	161/693 (23.2)	210/765 (27.5)	
Distal M1	231/693 (33.3)	240/765 (31.4)	
M2	100/693 (14.4)	81/765 (10.6)	
Other§	20/693 (2.9)	8/765 (1.0)	

Number of missing values: *30, †43, ‡67.
§Occlusion in segment 1 or 2 of the anterior cerebral artery (A1: n=3; A2: n=3), segment 3 of the middle cerebral artery (M3: n=9), or no occlusion visible (n=13) on CTA after adjudication by the imaging assessment committee.
ASPECTS, Alberta Stroke Program Early CT Score; CTA, computed tomography angiography; M1, segment 1 of the middle cerebral artery; M2, segment 2 of the middle cerebral artery; mRS, modified Rankin Scale; NCCT, non-contrast computed tomography; NIHSS, National Institutes of Health Stroke Scale; ICA, internal carotid artery; ICA-T, internal carotid artery tandem; IVT, intravenous thrombolytics.

patients less often achieved functional independence when compared to directly admitted patients (mRS 0-2, 33.9% versus 42.4%, absolute risk difference -8.5% (95% CI -8.7 to -8.3)), also after adjustment (adjusted OR 0.69 (95% CI 0.54 to 0.89); Table 7.4). Mortality rates were not significantly different between the two groups (adjusted OR 1.27 (95% CI 0.97 to 1.66)). There were no significant differences in successful reperfusion rate (adjusted OR 1.13 (95% CI 0.91 to 1.39)) and occurrence of symptomatic intracerebral hemorrhage (adjusted OR 0.87 (95% CI 0.56 to 1.36)).

Table 7.2. Treatment times, presented as medians with interquartile range.

	Direct presentation n = 705	Transferred patients n = 821	P-value	Missing values n (%)
Onset to door first hospital	55 (37 – 105)	50 (35 – 80)	<0.01	197/1526 (12.9)
Onset to door intervention center	55 (37 – 105)	174 (139 – 220)	<0.01	30/1526 (2.0)
Onset to IVT	82 (63 – 125)	79 (60 – 115)	<0.01	218/1173 (18.6)
Door to needle	24 (18 – 34)	26 (20 – 36)	0.02	215/1173 (18.3)
Door to door*	NA	112 (91 – 140)	N/A	196/822 (23.5)
Primary stroke center to intervention center (estimated)	NA	21 (15 – 31)	NA	3/821 (0.4)
Door in door out† (estimated)	NA	88 (68 – 117)	NA	197/821 (24.0)
Door first hospital to groin puncture	104 (80 – 135)	164 (135 – 198)	<0.01	197/1526 (12.9)
Door intervention center to groin puncture	104 (80 – 135)	47 (31 – 70)	<0.01	30/1526 (2.0)
Onset to groin puncture	170 (135 – 246)	230 (190 – 277)	<0.01	0
Duration of procedure	62 (40 – 90)	63 (40 – 87)	0.79	163/1526 (10.7)
Onset to reperfusion	238 (185 – 314)	288 (244 – 343)	<0.01	91/1526 (6.0)

*Door primary stroke center to door intervention center. †Door primary stroke center to door intervention center, minus the estimated travel time from primary stroke center to intervention center.
IVT, intravenous thrombolytics; NA, not applicable.

Table 7.3. Outcome measures: time intervals (in minutes).

	Direct presentation n = 705	Transferred patients n = 821	Unadjusted beta (95% CI)	Adjusted beta* (95% CI)
Door first hospital to groin puncture	104 (80 – 135)	164 (135 – 198)	55 (50 to 61)	57 (51 to 62)
Door intervention center to groin puncture	104 (80 – 135)	47 (31 – 70)	-59 (-63 to -55)	-58 (-62 to -54)
Onset to groin puncture	170 (135 – 246)	230 (190 – 277)	36 (27 to 44)	40 (31 to 48)

*Adjusted for age, baseline National Institute of Health Stroke Severity score, prestroke modified Rankin Scale, treatment with intravenous thrombolytics, hypertension (baseline systolic blood pressure >185 mmHg and/or diastolic blood pressure >110 mmHg), location of occlusion, Alberta Stroke Program Early Computed Tomography Score, collateral score, use of general anesthesia and admission outside office hours.

Table 7.4. Outcome measures: clinical outcome.

	Direct presentation n = 705	Transferred patients n = 821	Unadjusted OR (95% CI)	Adjusted OR* (95% CI)
Functional independence at 90 days (mRS 0-2)	289/681 (42.4)	244/720 (33.9)	0.71 (0.58 to 0.88)	0.69 (0.54 to 0.89)
Mortality at 90 days	180/681 (26.4)	227/720 (31.5)	1.24 (0.99 to 1.55)	1.27 (0.97 to 1.66)
Successful reperfusion (eTICI ≥2B)	395/698 (56.6)	473/806 (58.7)	1.10 (0.90 to 1.35)	1.13 (0.91 to 1.39)
Symptomatic ICH	45/705 (6.4)	44/821 (5.4)	0.83 (0.54 to 1.27)	0.87 (0.56 to 1.36)

*Adjusted for age, baseline National Institute of Health Stroke Severity score, prestroke modified Rankin Scale, history of ischemic stroke, treatment with intravenous thrombolytics, location of occlusion, Alberta Stroke Program Early Computed Tomography Score, collateral score and time from onset to first hospital.
eTICI, extended Thrombolysis In Cerebral Infarction scale; ICH, intracerebral hemorrhage; mRS, modified Rankin Scale.

Discussion

In this large, nationwide cohort study, more than half of the patients treated with EVT were transferred from a primary stroke center. These patients had significant longer time intervals between first presentation and start of treatment, between symptom onset and start of treatment, and a lower chance of achieving good functional outcome. Even when we accounted for the travel time required to transfer a patient to an intervention center, start of treatment was still delayed by half an hour in transferred patients compared to patients who were directly admitted to an intervention center.

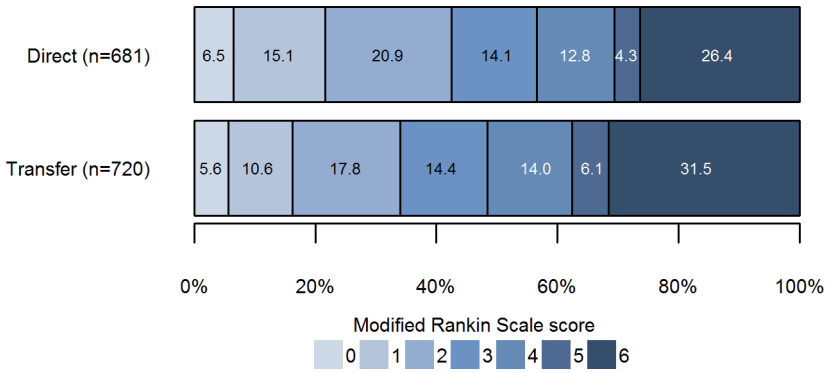

Figure 7.3. Functional outcome measured with the modified Rankin Scale score at 90 days, for patients presented directly in intervention center versus transferred from a primary stroke center (125 missing values). Transferred patients had worse functional outcomes than directly presented patients (adjusted common odds ratio 0.75 (95% CI 0.62 to 0.90)).

From earlier studies, we know that treatment delay translates to a decreased chance of achieving a favorable outcome.[2] However, because of selection bias and time delay associated with informed consent procedures, data from randomized trials may not always reflect daily practice. The STRATIS (Systematic Evaluation of Patients Treated With Neurothrombectomy Devices for Acute Ischemic Stroke) Registry included 984 patients from a large region in the United States of America after the implementation of EVT as standard care.[6] Similar to our study, the authors found that transferred patients had longer treatment times and worse functional outcomes when compared to direct admitted patients. However, their time analyses included only patients with successful reperfusion, which is not a fair representation of routine clinical practice. Also, distances between hospitals in rural areas of the USA are much larger than in our region, and time delays in primary hospitals – for instance because of initiation of IVT – are generally longer in the USA than in the Netherlands.[8,11,12] Results from an earlier small study in a region with short distances, including only one primary stroke center and one intervention center, showed that treatment times were longer for transferred patients, and the difference between the two groups for functional outcome was similar to our study.[13]

The Netherlands is a small, densely populated country, with 82 hospitals that provide 24/7 acute stroke care. Approximately 99.8% of the Dutch population has the ability to reach an emergency department within 45 minutes.[14] Our country has short between-center distances. This is emphasized by the fact that the mean transfer time was only 23 minutes, indicating that these results probably reflect the acute stroke care logistics in other highly populated regions. Although the observed in-hospital workflow times in this study were almost an hour shorter than in the MR CLEAN trial in the Netherlands,[15] there is still room

for improvement. It has been suggested that increased experience, reflected in higher volumes of patients treated with EVT, leads to shorter treatment times and, subsequently, improved functional outcomes.[16] Workflow times in our cohort do gradually decrease over time from 2014 until 2016. A decline in the median door-to-groin time (with the door of the first hospital as start) was observed for both transfer patients (187 to 149 minutes) and direct patients (123 to 97 minutes). However, the times achieved in our cohort are still longer when compared to other studies reporting workflow times. Additional interventions to optimize patient transfer management (eg, holding the initial ambulance primary stroke center until the decision of EVT eligibility has been made, streamlining transfer protocols, improving cloud-based image sharing, and transporting transfer patients directly to the angio-suite) might be useful to further reduce transfer-related delay in the future.[17-20]

Pre-hospital transportation of stroke patients suspected of LVO directly to an intervention center decreases time to EVT, but the potential harm of delaying IVT should be taken into account as well. We know, however, that the chance of achieving recanalization with IVT prior to thrombectomy in patients with LVO is low.[21] Therefore, we should focus on finding an algorithm to predict LVO early, so that emergency medical services can present these patients directly to the intervention center.[22,23] Implementing such a triage protocol has already shown to be feasible and seems to improve treatment times.[24] One ongoing randomized trial in Catalonia, Spain, is evaluating the effect of the mothership vs. the drip-and-ship strategy on functional outcome, among patients with a high likelihood of having a LVO identified with the Rapid Arterial Occlusion Evaluation (RACE) scale (Direct Transfer to an Endovascular Center Compared to Transfer to the Closest Stroke Center in Acute Stroke Patients With Suspected Large Vessel Occlusion (RACECAT), URL: www.clinicaltrials.gov. Unique identifier: NCT02795962). While this trial will provide class I evidence on whether a mothership model improves functional outcome, it will be challenging to translate its results to regions with other geographical and demographical conditions. Modeling studies showed that differences in transportation times and treatment times affect the optimal transportation strategy and that triage protocols should therefore be based on regional characteristics and individual likelihood of LVO.[25-28]

There were a number of baseline imbalances between the two groups. First, transferred patients more often received IVT. One of the reasons that could explain this observation is that patients who passed the time window for IVT are probably more often directly transported to an intervention center. Second, transferred patients more often had proximal occlusions (ie, ICA, ICA-T, and proximal M1) when compared to directly admitted patients. It could be that physicians hesitate to transport a patient with a more distal occlusion towards the intervention center, as earlier studies showed that these occlusions generally respond well to IVT.[29] Another observation that might be explained by a selection mechanism in the intervention center is that transferred patients less often had prestroke disability. This suggests that patients with favorable characteristics are more likely to be transferred

to an intervention center. However, imaging characteristics, assessed at the hospital of first presentation, were slightly less favorable for transferred patients. After adjustment for these baseline imbalances, we still found an 8.5% decrease in the chance of achieving functional independence after inter-hospital transfer.

Strengths of our study include that the analyses were performed with data from one of the largest cohorts of consecutive patients treated with EVT, with individual patient data from all stroke intervention centers in the Netherlands. It strongly reflects daily clinical practice, including a relatively large number of transferred patients. A number of limitations also warrant comment. Despite the fact that the MR CLEAN Registry is a nationwide study with consecutive inclusion of patients, our study is not completely free from a risk of selection bias. Patients with an LVO who did not receive EVT, for example due to clinical improvement on arrival, were not included in the study. Some patients who were initially admitted to a primary stroke center may not have been transferred to an intervention center because the time window would have been passed by the moment they would arrive in the intervention center or because there was uncertainty about treatment eligibility in case of an M2 occlusion. These patients could have been treated if they had been transported directly to the intervention center. Since the MR CLEAN Registry only contains data of patients who actually received EVT, we cannot estimate the size and impact of this patient population. The negative effect of a drip-and-ship strategy might therefore be larger in real life. Another limitation of our study is that we had no recorded door in door out times available to distinguish between in-hospital delay in the primary stroke center and delay due to the actual travel time between the primary stroke center and intervention center. We estimated the average inter-hospital travel times using the TomTom MyDrive application and then calculated the estimated door in door out times. Also, we used multiple imputation for time from first presentation to groin puncture, since time of arrival in the first hospital was missing for 13% of the patients. The difference between transferred patients and directly admitted patients in time from first presentation to groin puncture was comparable with the difference in time from onset to groin puncture, a variable that was available for all patients. We therefore believe that it has little impact on the validity of our results. Last, even though we adjusted for differences in prognostic factors, residual confounding might still influence our results.

Conclusions

In conclusion, these results from a large national cohort show that inter-hospital transfer of ischemic stroke patients eligible for EVT is associated with longer treatment times and worse functional outcome in clinical practice, even in a country where between-center distances are short. Direct transportation of EVT candidates to an intervention center might reduce treatment delay and thereby may improve functional outcome.

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Chapter 7.1

Response by Venema et al to letter regarding article, "Effect of inter-hospital transfer on endovascular treatment for ischemic stroke"

Stroke, 2019

Esmee Venema, Adrien E. Groot, and Jonathan M. Coutinho

In Response:

We read with interest the letter by Drs Seners and Baron regarding our recent publication about the effect of inter-hospital transfer on time to treatment and functional outcome of stroke patients undergoing endovascular treatment (EVT) in the MR CLEAN Registry.[1]

We agree that our results apply only to those patients with a large vessel occlusion (LVO) who effectively received groin puncture in an intervention center. As we stated in our discussion, the MR CLEAN (Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke) Registry does not contain data of patients with an LVO who did not undergo EVT. Due to this limitation, it is impossible to fully estimate the effect of first presentation in a primary stroke center versus direct transportation to an intervention center for the total LVO stroke population. A subset of the patients presenting in a primary stroke center with an LVO might not receive EVT due to clinical improvement on arrival at the intervention center. Assuming that the thrombus has resolved due to prior IV treatment with alteplase, these patients are indeed likely to have a more favorable outcome, and excluding them will lead to an underestimation of good functional outcome in the total transfer population. Direct transportation to an intervention center could have a negative effect on functional outcome of these patients because it delays IV treatment. On the other hand, there might also be patients in the transfer group that did not receive EVT because the remaining time window did not allow for transportation to the intervention center or because there was uncertainty about treatment eligibility (eg, in case of an M2 occlusion). These patients could potentially have been treated with EVT if they had been transported directly to an intervention center. Excluding these patients will, therefore, lead to an overestimation of good functional outcome in the transfer population. In other words, due to the limitations inherent to our study population, our results could both overestimate and underestimate the true difference in clinical outcome of patients between the drip-and-ship and mothership models.

Drs Seners and Baron refer to a study of Gerschenfeld et al, [2] in which all patients that were transferred for EVT - including those who eventually did not receive EVT - were included. However, patients who received only IV alteplase and were not transferred to an intervention center, were not included in the analysis. The reasons for withholding EVT in these 144 patients in the drip-and-ship paradigm and 122 patients in the mothership paradigm are not clearly described. Also, due to the small sample size, this study was likely underpowered to detect a difference in clinical outcome in the first place.

In conclusion, our results suggest that, if treated with EVT, patients directly transported to an intervention center have a shorter time to treatment and better functional outcome compared to patients transferred from a primary stroke center. Caution is warranted when generalizing these results to the total LVO stroke population and, similar to our colleagues, we look forward to the results of ongoing randomized trials that directly compare the drip-

and-ship versus mothership approach. Still, even the results of these trials cannot be directly translated to regions with other geographical and organizational characteristics, and modeling studies will therefore be required.[3]

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This letter was written in response to:
Seners P, Baron JC. Letter by Seners and Baron Regarding Article, "Effect of Interhospital Transfer on Endovascular Treatment for Acute Ischemic Stroke". *Stroke* 2019; **50**(9) :e259.

Chapter 8

Effect of workflow improvements in endovascular stroke treatment: a systematic review and meta-analysis

Stroke, 2019

Paula M. Janssen, Esmee Venema, and Diederik W.J. Dippel

Abstract

Background and purpose

Rapid initiation of endovascular stroke treatment is associated with better clinical outcome. The effect of specific improvements is not well known. We performed a systematic review and meta-analysis on the effectiveness of specific workflow improvements on time to treatment and outcome.

Methods

A random effects meta-analysis was used to evaluate the difference in mean time to treatment between intervention group and control group. Secondary outcomes included good functional outcome at 90 days (modified Rankin Scale score 0–2).

Results

Fifty-one studies (3 randomized controlled trials, 13 pre-post intervention studies, and 35 observational studies) with in total 8,467 patients were included. Most frequently reported workflow intervention types concerned anesthetic management (n=26), in-hospital patient transfer management (n=14), and prehospital management (n=11). Patients in the intervention group had shorter time to treatment intervals (weighted mean difference 26 minutes; 95% CI 19 to 33; P<0.001) compared with controls. Subgroup meta-analysis of intervention types also showed a shorter time to treatment in the intervention group: a mean difference of 12 minutes (95% CI 6 to 17; P<0.001) for anesthetic management, 37 minutes (95% CI 22 to 52; P<0.001) for prehospital management, 41 minutes (95% CI 27 to 54; P<0.001) for in-hospital patient transfer management, 47 minutes (95% CI 28 to 67; P<0.001) for teamwork, and 64 minutes (95% CI 24 to 104; P=0.002) for feedback. The mean difference in time to treatment of studies with multiple interventions implemented simultaneously was 50 minutes (95% CI 31 to 69; P<0.001) in favor of the intervention group. Patients in the intervention group had increased likelihood of favorable outcome (risk ratio 1.39; 95% CI 1.15 to 1.66; P<0.001).

Conclusions

Interventions in the workflow of endovascular stroke treatment lead to a significant reduction in time to treatment and results in an increased likelihood of favorable outcome. Acute stroke care should be reorganized by making use of the examples of workflow interventions described in this review to ensure the best medical care for stroke patients.

Introduction

Multiple trials have shown the benefit of endovascular recanalization therapy in selected stroke patients.[1-3] Earlier treatment is associated with better functional outcome.[4] The time from symptom onset to treatment is influenced by prehospital and in-hospital processes. Healthcare systems are being reorganized to offer stroke patients rapid and effective medical care. Stroke services had already changed their workflow since treatment with intravenous alteplase for selected stroke patients was proven effective.[5] Implementation of new strategies to improve the workflow process for treatment with intravenous alteplase has led to a significant reduction of in-hospital delay.[6]

Providing an optimal diagnostic process and rapid endovascular stroke treatment requires close collaboration of the emergency medical service, emergency department team, stroke team, neurointerventional team, and anesthesia team. Diagnostic imaging and endovascular treatment facilities should be available in very little time. Several strategies to reduce the time to endovascular stroke treatment have been proposed.[7-9] However, the effect of individual and combined strategies on reducing time to treatment is unclear. We performed a systematic review and meta-analysis on the effectiveness of specific workflow improvement interventions for rapid delivery of endovascular stroke treatment.

Methods

This systematic review and meta-analysis was performed according to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines.[10] All data and supporting materials are available within the article and its Supplementary material.

Search strategy

Medline, EMBASE, Cochrane Central, and Web of Science were searched for studies that evaluated the effect of one or more workflow interventions on time to endovascular stroke treatment, from database inception to November 14th, 2017. Google Scholar and Google were searched at November 14th, 2017, and the first 200 hits were included. We developed a broad search strategy consisting of a combination of the 2 main topics of this study: endovascular stroke treatment and workflow intervention. The complete search strategy is available in the Supplementary material. We restricted our search to studies published in English and excluded conference abstracts.

Eligibility criteria

Studies were included if ≥1 (prehospital or in-hospital) interventions in the workflow of endovascular stroke treatment were assessed and effect on time to treatment intervals was reported. Endovascular stroke treatment was defined as mechanical thrombectomy or intra-arterial fibrinolysis in an acute stroke patient with an intracranial large vessel occlusion.

Interventions only aimed at the duration of the endovascular treatment itself, for example type of mechanical thrombectomy device used, were excluded. Interventions intended only to increase the accuracy of patient selection, for example the introduction of a new imaging protocol, were also excluded. Studies were included in the systematic review when time to endovascular treatment was reported, from symptom onset to start treatment, or any time window between symptom onset and start treatment. Randomized and non-randomized controlled trials and pre-post intervention studies were included. Observational studies, or post-hoc analyses of observational data in trials were only included when a control group was reported. Reviews, editorials, and guidelines were excluded. Two authors (Drs Janssen and Venema) independently assessed the eligibility of all retrieved studies. Title and abstracts were first screened to identify potentially eligible articles, and then full texts were read to confirm inclusion. Reference lists of identified eligible papers and review papers were scanned for additional relevant studies.

Risk of bias assessment

The risk of bias of each included study was assessed against the following key criteria: random sequence generation; allocation concealment; blinding of participants, personnel and outcomes; incomplete outcome data; and selective outcome reporting; in accordance with the methods recommended by the Cochrane Library.[11] The following judgements were used: low risk, high risk, or unclear risk of bias (either lack of information or uncertainty on the potential for bias). Summary of risk of bias per key criterion was provided for all included articles separately.

Data extraction and outcome variables

Data was extracted from published reports by 2 authors (Drs Janssen and Venema). Workflow interventions were described and divided into six predefined categories: (A) anesthetic management, (B) prehospital management, (C) in-hospital patient transfer management, (D) teamwork, (E) feedback, and (F) other workflow interventions. Other collected data on study characteristics included study design, study period, stroke type (anterior or posterior circulation stroke, or both), and sample size.

The primary outcome measure in this study was the difference in time to treatment between the intervention group and control group. Other study outcomes were good functional outcome, defined as modified Rankin Scale (mRS) score 0–2 at 90 days after endovascular treatment, symptomatic intracranial hemorrhage, and mortality.

Statistical analysis

Mean time to treatment with standard deviation (SD) for the intervention group and control group was retrieved from each included study. When mean values with SD were not available in the publication nor obtained from the authors of the original publication, we used reported median time to treatment with interquartile range (IQR) to estimate the sample mean and SD using the method described by Wan et al.[12] The absolute difference of mean

time to treatment with 95% confidence intervals (CI) was calculated for each study using a two-sample t-test.

Studies were included in the meta-analysis when mean time to treatment with SD or median time to treatment with IQR was available for both groups. Weighted difference in mean time to treatment with 95% CI was calculated using a random-effects inverse variance model, with the estimate of heterogeneity being taken from the Mantel-Haenszel model. Subgroup analysis of the difference in mean time to treatment was performed for the predefined workflow intervention categories A to E and for studies implementing multiple interventions simultaneously.

Data on binary outcomes (good functional outcome, symptomatic intracranial hemorrhage, and mortality) was pooled using random-effect meta-analysis and expressed as risk ratios. Publication bias was assessed by constructing a funnel plot. All statistical analyses were conducted with Stata, version 15 (Statacorp LLC, College Station, TX).

Results

Our literature search identified 4,127 potentially relevant unique articles; 211 articles were retained for full-text review (Figure 8.1). A total of 51 studies met the inclusion criteria and were included in the qualitative synthesis.[2,13-62] We contacted authors from 31 of 51 studies with requests for additional data necessary for our meta-analysis. These additional data were provided for 17 of 31 studies. The sample mean difference in time to treatment with SD could be estimated from published data from 8 of 31 studies. After exclusion of the remaining 6 studies because of lack of sufficient data, a total of 45 studies was included in the meta-analysis on effect of workflow interventions on the time to treatment.

Fifty-one studies with 8,467 patients (4,037 intervention group and 4,430 control group) reported the effect of 25 different workflow interventions on the time to endovascular treatment (Table 8.1 and 8.2). Two studies reported the effect on time to treatment of two interventions separately.[50,55] Most frequently reported workflow intervention types concerned anesthetic management (n=26), in-hospital patient transfer management (n=14), and prehospital management (n=11). Ten studies reported the effect on time to treatment of multiple interventions implemented simultaneously. Time to treatment was shorter in the intervention group in 48 of 53 interventions (91%) reported in the 51 included studies. Included studies differed in study design, with 3 studies randomizing patients for the workflow intervention of interest in our study, 13 pre-post intervention studies, and the remaining 35 studies reporting observational data mostly from hospital stroke registries or randomized controlled trials investigating the effect of endovascular stroke treatment versus conservative treatment. Data collection was performed retrospectively in 34 studies, and 16 studies collected data from ≥1 center. Risk of bias assessment is reported in Supplementary Table 8.1.

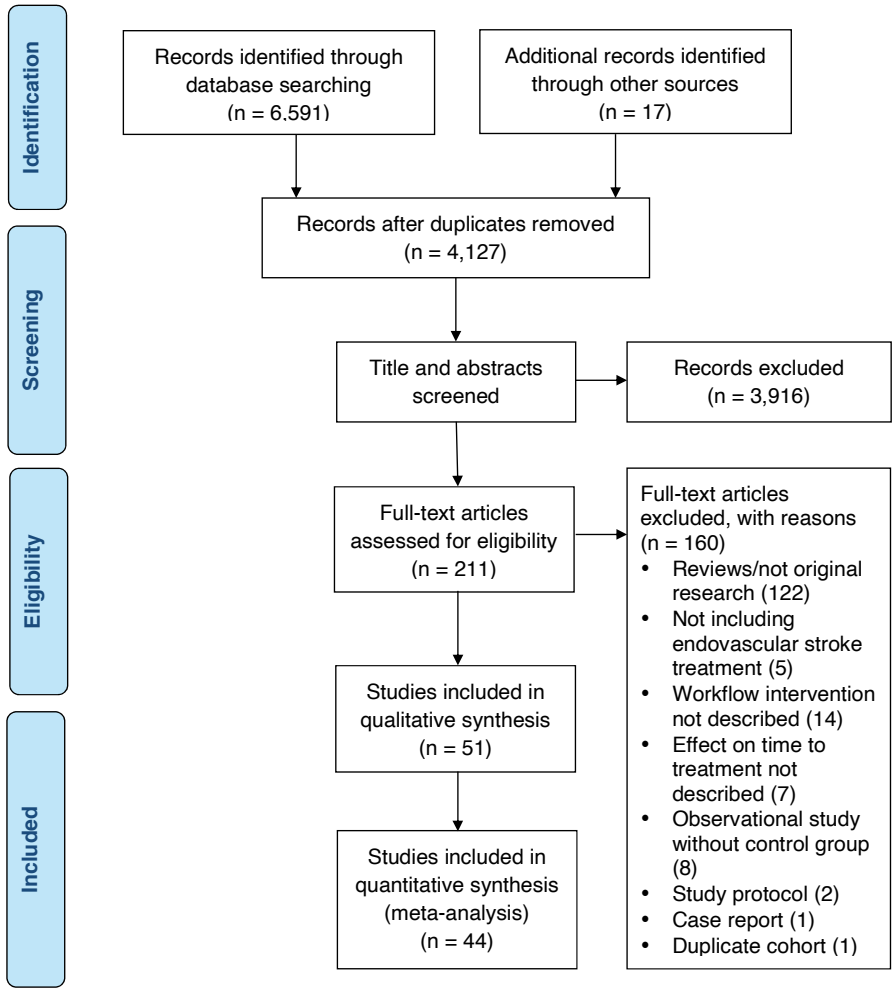

Figure 8.1. Flowchart of included and excluded articles, following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines.

Random effects meta-analysis of 45 studies (with 47 interventions), including 7,482 patients (3,480 intervention group and 4,002 control group) showed a difference in mean time to treatment of 26 minutes (95% CI 19 to 32; P<0.001) in favor of the intervention group (Figure 8.2). I^2 value was 85.4%, and Chi-squared value was 314.87 (degrees of freedom 46; P<0.001), indicating considerable heterogeneity between studies.

Table 8.1. Studies included in systematic review.

Author	Country	Study Design	Study Period*	Anterior, posterior circulation stroke or both	Intervention group (n)	Control group (n)	Type of intervention
Abou-Chebl et al[13]	USA	Retrospective cohort study; multicenter	2005–2009	Anterior	552	428	A
Abou-Chebl et al[14]	USA	Post hoc analysis retrospective NASA Registry; multicenter	2012–2013	Both	68	159	A
Abou-Chebl et al[15]	Canada, Europe, USA	Post hoc analysis IMS III trial; multicenter	2006–2012	Both	269	147	A
Aghaebrahim et al[16]	USA	Prospective pre-post study; single center	2012–2013/ 2013–2014	Both	108	178	B1, C1–3, D1–2, E1, F1
Alotaibi et al[17]	Canada	Retrospective pre-post study; single center	2011–2014/ 2014–2016	Both	28	17	E2
Van den Berg et al[18]	The Netherlands	Retrospective cohort study; multicenter	2002–2010	Anterior	278	70	A
Berkhemer et al[19]	The Netherlands	Post-hoc analysis MR CLEAN trial; multicenter	2010–2014	Anterior	137	79	A
Bracard et al[2]	France	Post-hoc analysis THRACE trial; multicenter	2010–2014	Both	74	69	A
Cerejo et al[20]	USA	Retrospective cohort study; single center	2014	Anterior	5	5	B2
Davis et al[21]	Canada	Retrospective cohort study; single center	2003–2009	Both	37	39	A
Eesa et al[22]	Canada	Retrospective cohort study; single center	2005–2009	Both	71	30	A
Frei et al[23]	USA	Retrospective pre-post study; single center	2012–2013/ 2013–2015	Both	267	113	B1, D2–4, F1–3
Goyal et al[24]	Canada, Europe, USA	Post-hoc analysis IMS III trial; multicenter	2006–2012	Both	17	64	B3
Goyal et al[25]	Europe, USA	Post-hoc analysis SWIFT PRIME trial; multicenter	2012–2014	Anterior	61	35	A
Hassan et al[26]	USA	Retrospective cohort study; multicenter	2006–2010	Both	83	53	A
Henden et al[27]	Sweden	Randomized controlled trial; single center	2013–2016	Anterior	45	45	A
Herrmann et al[28]	Germany	Pre-post study; retrospective data pre-intervention, prospective data post-intervention; single center	2006–2009/ 2009–2010	Both	23	48	F4

Table 8.1. Continued

Author	Country	Study Design	Study Period*	Anterior, posterior circulation stroke or both	Intervention group (n)	Control group (n)	Type of intervention
Jadhav et al[29]	USA	Retrospective cohort study; single center	2013–2016	Both	111	150	C2
Jagani et al[30]	USA	Retrospective cohort study; single center	2008–2015	Both	61	38	A
Janssen et al[31]	Germany	Retrospective cohort study; single center	2012–2014	Anterior	31	53	A
Jeon et al[32]	Korea	Retrospective pre-post study; single center	2014–2016/ 2016	Not specified	19	93	B1, C3, D2, E1, F1–2
John et al[33]	USA	Retrospective cohort study; single center	2008–2012	Anterior	99	91	A
Jumaa et al[34]	USA	Retrospective cohort study; single center	2006–2009	Anterior	73	53	A
Just et al[35]	Canada	Retrospective cohort study; single center	2000–2013	Both	67	42	A
Kamper et al[36]	Germany	Retrospective pre-post study; single center	2002–2006/ 2007–2010	Posterior	20	18	F5
Koge et al[37]	Japan	Retrospective pre-post study; single center	2008–2014/ 2014–2016	Not specified	23	19	D3–4, E1
Komatsubara et al[38]	Japan	Pre-post study; retrospective or prospective data collection not specified; single center	2012–2014/ 2014–2015	Both	14	14	E1, F1, F6
Li et al[39]	USA	Retrospective cohort study; single center	2006–2012	Both	74	35	A
Liang et al[40]	USA	Retrospective cohort study; single center	2015–2016	Not specified	22	17	B4
Mascitelli et al[41]	USA	Retrospective pre-post study; single center	2014/ 2014–2015	Both	29	27	B1, E1–2, F1
McTaggart et al[42]	USA	Retrospective cohort study; multicenter	2015–2016	Anterior	22	48	B4–5, C2, D2
Mehta et al[43]	USA	Pre-post study; retrospective data pre-intervention, prospective data post-intervention; single center	2007–2011/ 2011–2013	Anterior	51	93	C3, D2–4
Menon et al[44]	Canada, Ireland, South Korea, UK, USA	Prespecified secondary analysis ESCAPE trial; multicenter	2013–2014	Anterior	136	15	A

Author	Country	Study Design	Study Period*	Anterior, posterior circulation stroke or both	Intervention group (n)	Control group (n)	Type of intervention
Miley et al[45]	USA	Retrospective cohort study; multicenter	2005–2008	Both	52	39	A
Mundiyanapurath et al[46]	Germany	Prospective cohort study; single center	2013–2014	Both	15	29	A
Nichols et al[47]	USA	Post-hoc analysis IMS II trial; multicenter	2003–2006	Anterior	40	17	A
Pedragosa et al[48]	Spain	Prospective cohort study; multicenter	2008–2010	Not specified	25	20	B6
Pfaff et al[49]	Germany	Prospective cohort study with historical controls; single center	2014	Both	3	16	C4
Pfaff et al[50]	Germany	Prospective cohort study with historical controls; single center	2014–2016	Anterior	22	28	A
Pfaff et al[50]	Germany	Prospective cohort study with historical controls; single center	2014–2016	Anterior	28	28	C4
Psychogios et al[51]	Germany	Retrospective cohort study; single center	2016	Not specified	30	44	C4
Qureshi et al[52]	USA	Retrospective cohort study; multicenter	2007–2012	Not specified	66	117	C3
Ragoschke et al[53]	Germany	Pre-post study; retrospective data pre-intervention, prospective data post-intervention; single center	2006–2010/ 2010–2014	Both	174	81	C5
Rai et al[54]	USA	Prospective pre-post study; single center	2011–2014/ 2015	Both	30	64	B1, D2–4, F2
Ribo et al[55]	Spain	Retrospective cohort study; single center	2015–2016	Not specified	74	87	C1
Ribo et al[55]	Spain	Retrospective cohort study; single center	2015–2016	Not specified	40	87	C2
Schonenberger et al[56]	Germany	Randomized controlled trial; single center	2014–2016	Anterior	77	73	A
Schregel et al[57]	Germany	Retrospective pre-post study; single center	2008–2014/ 2014–2015	Both	90	278	C3, D2, E1
Simonsen et al[58]	Denmark	Randomized controlled trial, single center	2015–2017	Anterior	63	65	A
Singer et al[59]	Austria, Germany	Post-hoc analysis ENDOSTROKE registry; both retrospective and prospective data collection; multicenter	2011–2012	Both	36	691	A

Table 8.1. Continued

Author	Country	Study Design	Study Period*	Anterior, posterior circulation stroke or both	Intervention group (n)	Control group (n)	Type of intervention
Slezak et al[60]	Switzerland	Prospective cohort study; single center	2010–2015	Anterior	135	266	A
Sugg et al[61]	USA	Retrospective cohort study; single center	2007–2009	Both	57	9	A
Tsujimoto et al[62]	Japan	Retrospective cohort study; single center	2011–2013	Both	6	16	B7

ENDOSTROKE, Endovascular Stroke Treatment; ESCAPE, Endovascular Treatment for Small Core and Anterior circulation Proximal Occlusion with Emphasis on Minimizing CT to Recanalization Times; IMS, Interventional Management of Stroke; MR CLEAN, Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in The Netherlands; NASA, North American Solitaire Stent-Retriever Acute Stroke; SWIFT PRIME, Solitaire with the Intention for Thrombectomy as Primary Endovascular Treatment for Acute Ischemic Stroke; THRACE, Thrombectomie des Artères Cerebrales.
*Study period for pre/post intervention group.

The mean time to treatment was shorter in the intervention group compared to controls in the predefined workflow intervention categories (Table 6.3). The weighted difference in mean time to treatment was 12 minutes (95% CI 6 to 17; P<0.001) for anesthetic management, 37 minutes (95% CI 22 to 52; P<0.001) for prehospital management, 41 minutes (95% CI 27 to 54; P<0.001) for in-hospital patient transfer management, 47 minutes (95% CI 28 to 67; P<0.001) for teamwork, and 64 minutes (95% CI 24 to 104; P=0.002) for feedback. The weighted difference in mean time to treatment of studies with multiple interventions implemented simultaneously was 50 minutes (95% CI 31 to 69; P<0.001) in favor of the intervention group. Forest plots of the difference in mean time to treatment for each type of workflow intervention are showed in Supplementary Figure 8.1. The description of used time intervals in the studies, mean (SD) estimates for each study group, and a subgroup analysis per time interval is provided in Supplementary Table 8.2.

Twenty studies reported the occurrence of favorable outcome, defined as score 0–2 on the modified Rankin Scale at 90 days (Supplementary Table 8.3). Meta-analysis showed that patients in the intervention group had a higher likelihood of favorable outcome (absolute risk difference 12.2%; risk ratio (RR) 1.39; 95% CI 1.15 to 1.66; P<0.001) in comparison with controls. Data from 21 studies reporting the prevalence of symptomatic intracranial hemorrhage showed no difference between patients in the intervention groups and controls (RR 0.88; 95% CI 0.71 to 1.09; P=0.239). Mortality was assessed in 25 studies. Twelve studies reported in-hospital mortality, 2 studies reported mortality at 30 days, and 11 studies reported mortality at 3 months. Patients in the intervention groups had a lower risk of overall mortality (absolute risk difference 7.4%; RR 0.74; 95% CI 0.63 to 0.87; P<0.001) compared with controls.

Table 8.2. Categories of workflow interventions in endovascular stroke treatment.

Anesthetic Management
A = Non-general anesthesia versus general anesthesia
Prehospital Management*
B1 = Pre-notification ED team, CT technologist, and stroke team by EMS
B2 = Mobile Stroke Treatment Unit with CT scanner, point of care laboratory testing, vascular neurologist available via telemedicine
B3 = 'Ship and drip' for transfer patients versus 'drip and ship'
B4 = CT-angiography at primary stroke center versus at intervention center
B5 = Cloud based image sharing between primary stroke center and intervention center
B6 = Use of telemedicine assessment by a stroke neurologist at primary stroke center
B7 = Air transfer versus ground transfer
In-hospital Patient Transfer
C1 = Transporting patients directly to CT scanner by EMS
C2 = Transporting (transfer) patients directly to angiosuite by EMS
C3 = 'No turn around' approach (not returning to ED after imaging for decision-making)
C4 = Single room used for CT, angiography, and EVT
C5 = Single room for patient evaluation, CT, angiography, and EVT
Teamwork
D1 = Early communication between ED team and stroke team regarding plan of care
D2 = Early activation neurointerventional team
D3 = Parallel processing from ED/hospital ward to CT: clinical assessment, laboratory tests, imaging, patient/family education by the teams in a parallel workflow
D4 = Parallel processing from CT to angiosuite: neurointerventional team meets patient at CT, teams evaluate CT/CTA and make treatment decision while angiosuite is set up, patient/family education
Feedback
E1 = Education and feedback all teams
E2 = Smartphone application/digital system for real-time window from stroke onset to puncture for all teams, visualizing performance metrics
Other
F1 = Limiting non-essential interventions (e.g. ECG, chest X-ray, additional venous access, bladder catheter placement)
F2 = Standard angiography set for all of the devices needed for EVT
F3 = No groin shaving
F4 = Standard operating procedure for intubation at the intensive care unit prior to EVT
F5 = Standard operating procedure for EVT
F6 = Not waiting for effect intravenous alteplase versus waiting for 1 hour

CT, computed tomography; CTA, computed tomography angiography; ECG, electrocardiogram; ED, emergency department; EMS, emergency medical service; EVT, endovascular treatment.
*Prehospital management includes all interventions performed before the patient arrives at the intervention center.

We found no evidence of a potential publication bias in the funnel plot that was constructed after exclusion of two studies with a very large absolute difference in time to treatment between intervention group and controls (Figure 8.3).[34,36]

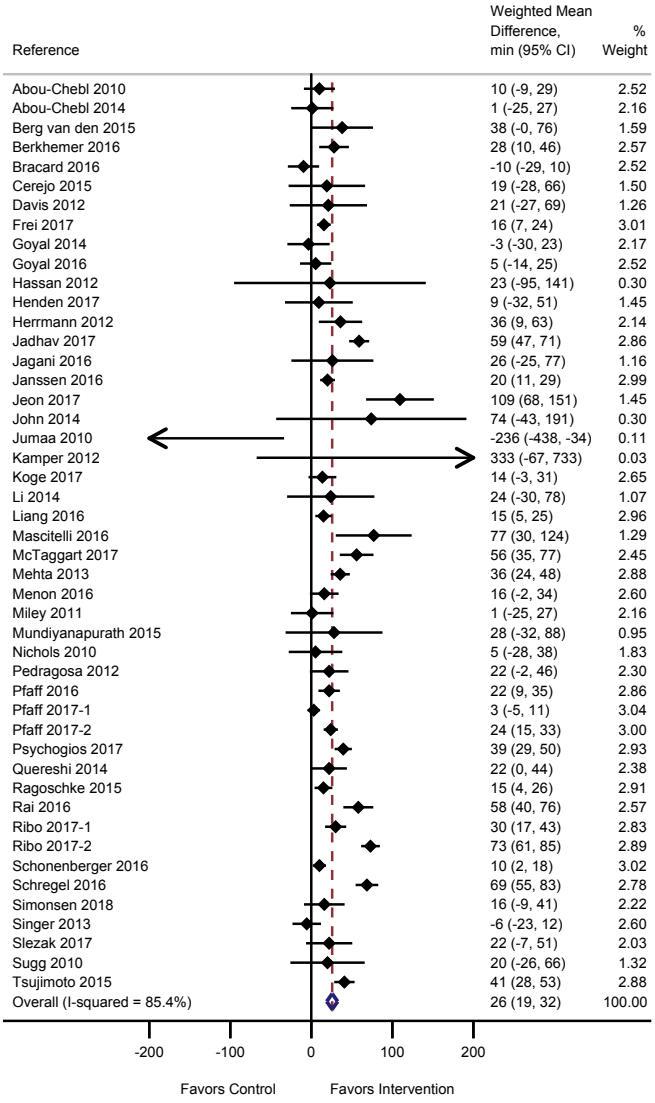

Figure 8.2. Forest plot of weighted difference in mean time to treatment for workflow interventions in endovascular stroke treatment, using random effect meta-analysis.

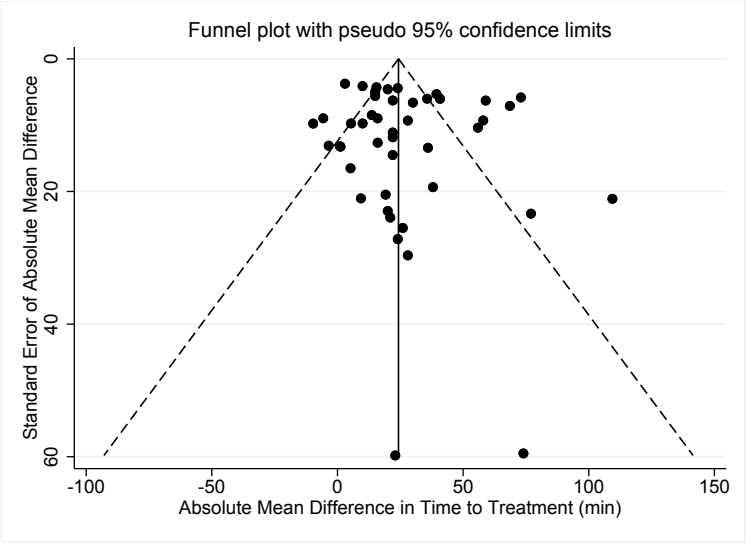

Figure 8.3. Funnel plot to detect potential publication bias in 43 studies of workflow interventions improvements in endovascular stroke treatment.

Table 8.3. Random-effects meta-analysis of difference in mean time to treatment for categories of workflow interventions in endovascular stroke treatment.

	Number of studies	Number of patients (intervention/control group)	Weighted mean difference, minutes (95% CI)
All interventions	47	3,480/4,002	26 (19 to 32) P<0.001
Anesthetic management	23	2,283/2,445	12 (6 to 17) P<0.001
Prehospital management	10	442/463	37 (22 to 52) P<0.001
In-hospital patient transfer management	13	730/1150	41 (27 to 54) P<0.001
Teamwork	7	502/708	47 (228 to 67) P<0.001
Feedback	4	161/417	64 (24 to 104) P=0.002
Multiple interventions simultaneously	8	531/735	50 (31 to 69) P<0.001

Discussion

Our systematic review and meta-analysis showed that interventions in the workflow of endovascular treatment for acute ischemic stroke led to a significant reduction in time to treatment. This applied to all categories of studied interventions, which were interventions aimed at using local anesthesia or conscious sedation, optimizing prehospital management, reducing in-hospital patient transfer, improving teamwork, and supplying feedback on achieved time intervals to the team. These workflow interventions led to higher likelihood of favorable functional outcome after 3 months.

The favorable effect of workflow interventions on the time to treatment are consistent with previous studies including acute stroke patients treated with intravenous alteplase. Implementation of a national quality improvement initiative organized by the American Heart Association/American Stroke Association, including more than 70,000 patients, resulted in significant shorter door-to-needle time and significant higher percentage of patients treated with intravenous alteplase within 60 minutes.[63] Workflow improvement strategies were promoting pre-notification of hospitals by EMS, rapid activation of the entire stroke team, rapid acquisition of brain imaging, and provision of feedback to the stroke team on performance. A single center study showed that the introduction of multiple concurrent strategies aimed at reducing in-hospital delay in treatment of acute stroke patients with intravenous alteplase led to a remarkable time reduction and final median door-to-needle time of 20 minutes.[6]

Our results are also consistent with studies on workflow improvement for reperfusion treatment of patients with myocardial infarction with ST-segment elevation. A study on time-saving strategies in the workflow for patients with acute myocardial infarction, including 365 hospitals, showed that rapid activation and availability of the entire team and use of real-time data feedback by the staff in the ED and angiography suite, reduced mean door-to-balloon time with 8 to 19 minutes.[64]

The workflow interventions in this review can easily be implemented in any intervention center. A time-saving effect of >1 hour could be achieved by providing feedback on time-intervals to the entire team. Implementation of regular feedback in the four included studies in this meta-analysis was executed by supplying time intervals and outcome to the entire team daily using an online bulletin or email, reviewing each patient during weekly or monthly meetings, or comparing actually achieved times to target times every 3 months.[32,37,41,57] Evaluation of time intervals can simply be added to existing regularly meetings at intervention hospitals. Optimizing in-hospital teamwork by using parallel processing instead of sequential processing in the workflow, and by early activation of all team members, requires multidisciplinary protocols or standard operating procedures. The time-investment to draft and implement such protocols seems well worthwhile, since our meta-analysis showed a

mean time reduction of 47 minutes.[22,32,37,42,43,54,57] Effects of multiple interventions cannot be simply added, but implementing multiple interventions at the same time still led to a very large time reduction of 50 minutes and is probably preferred above implementing 1 intervention at a time.

Anesthetic management in endovascular stroke treatment is a much discussed topic, since it possibly influences both time to treatment intervals as cerebral perfusion and thereby indirect functional outcome. A meta-analysis including 4,716 patients undergoing endovascular stroke treatment showed a difference in time to treatment of 14 minutes in favor of patients receiving local anesthesia or conscious sedation compared with general anesthesia, and a higher odds of good functional outcome.[65] Which studies were used for comparing time to treatment by type of anesthesia management and the way missing data was handled was not disclosed. Our meta-analysis included additional studies on anesthetic management and showed a comparable difference in time to treatment of 12 minutes in favor of patients receiving local anesthesia or conscious sedation. Both meta-analyses included many observational studies with possible selection bias. Only 3 randomized controlled trials, randomizing patients for local anesthesia or conscious sedation versus general anesthesia, were included in our meta-analysis, showing a non-significant difference in treatment intervals in two studies,[27,58] and a significant difference in time to treatment in 1 study of 10 minutes in favor of conscious sedation (95% CI 2 to 18).[56] We did not find studies comparing conscious sedation with local anesthesia. Regarding anesthetic management in endovascular stroke treatment and its effect on time to treatment, results of included randomized and non-randomized studies in our analysis varied between a significant positive effect or a significant negative effect of local anesthesia or conscious sedation, and a non-significant difference compared with general anesthesia. By combining these results in a meta-analysis, we showed a potential positive effect of non-general anesthesia on workflow.

The favorable effect of reducing time to treatment on functional outcome as described in previous studies is confirmed by our study.[4,66] Analysis of 5 endovascular stroke treatment trials showed a 4% absolute risk difference for a good functional outcome per hour of delay between symptom onset and reperfusion.[4] Our meta-analysis showed a difference in time to treatment effect of 26 minutes, with a total absolute risk difference of good functional outcome of 12%, which is higher compared to the ~2% absolute risk difference per half hour as seen in the meta-analysis of 5 endovascular stroke treatment trials. However, selection bias could have occurred in the non-randomized studies included in our meta-analysis and differences in baseline characteristics might have influenced our results. The effect of time to treatment on functional outcome might be stronger in clinical practice compared to a selected patient population from randomized controlled trials.[67] Furthermore, some workflow improvements, such as anesthetic management, have an effect on functional outcome which is not completely explained by the difference in time to treatment.[1]

A meta-analysis of 5 large endovascular stroke trials showed no effect of time to treatment on rates of mortality and symptomatic intracranial hemorrhage.[4] Our study showed no difference in rate of symptomatic intracranial hemorrhage, but a significantly lower mortality among patients in the intervention group. However, possible selection bias in the non-randomized studies included in our meta-analysis, could have influenced the effect of time to treatment on mortality.

This study has several limitations. To perform the meta-analysis, we estimated the mean time to treatment for 8 studies using the median time to treatment, IQR, and sample size. Since the meta-analysis is aimed at the difference in time to treatment between groups, rather than the actual time intervals per group, we assume that using the estimation of the mean time to treatment has no significant effect on the primary outcome. Considerable heterogeneity between included studies was observed. Therefore, we used a random-effects inverse variance model for our meta-analysis and categorized the interventions to perform separate analyses for each intervention type. Forty-eight of 51 included studies used a non-randomizing study design, with a high risk of selection bias. Furthermore, most data was collected retrospectively in a single center, without blinding of personnel and participants, possibly leading to performance bias. Multiple pre-post intervention studies were included in our meta-analysis, in which learning effect over time can also effect time to treatment. Therefore, generalizability is difficult to assess for the individual studies. However, since we included multiple studies on the same subject, these results can give us valuable insight on the possible effects in general practice, which is very promising. One of the purposes of a systematic review is to identify gaps in our knowledge and point out clinical areas that would benefit from more research. The 7 subcategories of pre-hospital intervention with only a limited number of studies, suggest that more work can be done in this area. Intervention studies and modelling of pre-hospital workflow may provide more insights and effective pre-hospital management strategies may have a relatively large effect on outcome.

In conclusion, interventions in the workflow of endovascular stroke treatment lead to a significant reduction in time to treatment. Reduction of any delay in time to treatment, by workflow interventions aimed at any interval between symptom onset and treatment, leads to a higher chance of good functional outcome for each individual patient. Acute stroke care should be reorganized by making use of the examples of workflow interventions described in this review to ensure the best medical care for patients with acute ischemic stroke.

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Supplementary material

Literature search strategy

Embase

('cerebrovascular accident'/exp OR 'brain ischemia'/exp OR 'occlusive cerebrovascular disease'/de OR 'middle cerebral artery occlusion'/de OR 'basilar artery obstruction'/de OR 'stroke patient'/de OR 'brain infarction'/exp OR ((cerebrovascular NEAR/3 accident*) OR cva OR stroke* OR ((brain OR cerebr* OR 'basilar arter*') NEAR/3 (ischemi* OR ischaemi* OR occlu* OR infarct*))):ab,ti) AND ('thrombectomy'/exp OR 'endovascular surgery'/de OR 'intraarterial drug administration'/de OR (thrombectom* OR endovascular* OR intravascul* OR endo-vascular* OR intra-vascul* OR intraarterial* OR intra-arterial*):ab,ti) AND ('workflow'/de OR 'therapy delay'/de OR 'time to treatment'/de OR 'time factor'/de OR (workflow* OR work-flow* OR pathway* OR ((therap* OR treat* OR puncture* OR reperfusion* OR admission OR care) NEAR/6 (delay* OR time-to OR door-to OR picture-to OR arrival* OR onset*)) OR ((Streamlin* OR speed OR rapid OR optimi*) NEAR/3 (treat* OR therap* OR recanal* OR reperfus* OR revascular*)) OR ((Intrahospital* OR Intra-hospital* OR prehospital* OR pre-hospital*) NEAR/3 (time OR period* OR delay*)) OR (time NEAR/3 (factor* OR lapse)) OR timing):ab,ti) NOT ([Conference Abstract]/lim OR [Letter]/lim OR [Note]/lim OR [Editorial]/lim) AND [english]/lim

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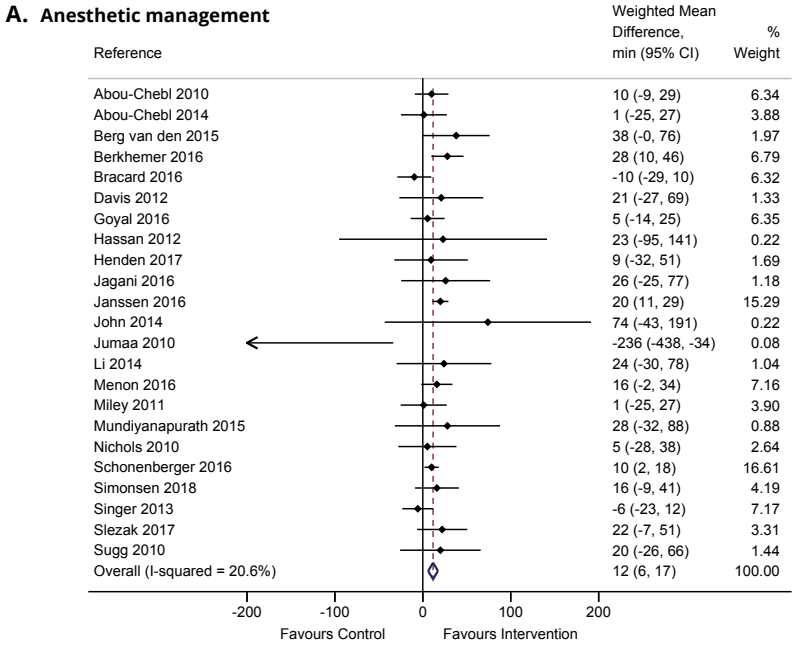
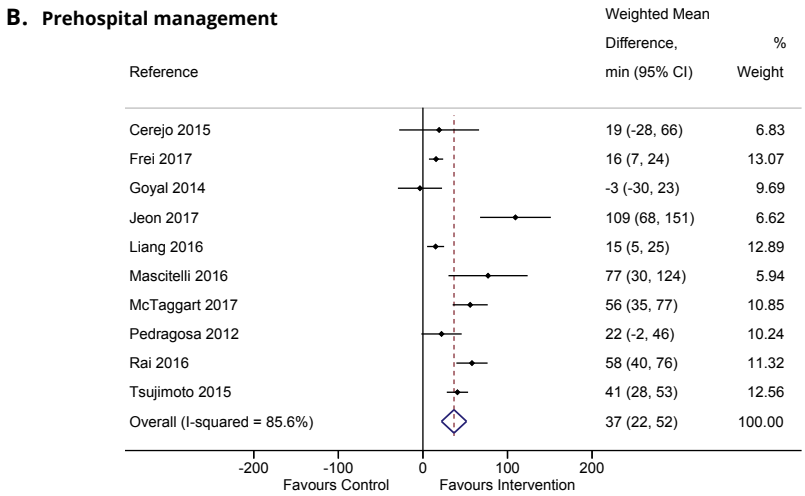
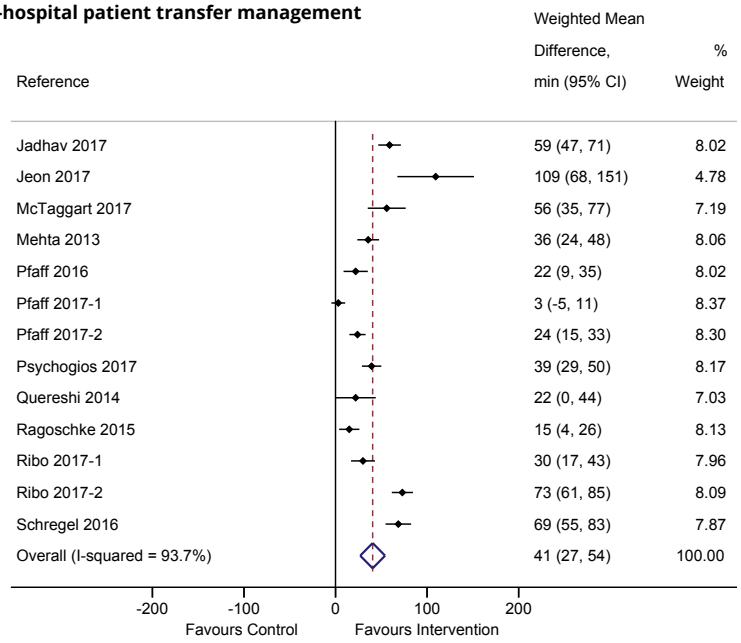
(exp stroke/ OR exp Brain Ischemia/ OR (Cerebrovascular Disorders/ AND Arterial Occlusive Diseases/) OR ((cerebrovascular ADJ3 accident*) OR cva OR stroke* OR ((brain OR cerebr* OR basilar arter*) ADJ3 (ischemi* OR ischaemi* OR occlu* OR infarct*))).ab,ti.) AND (Thrombectomy/ OR Endovascular Procedures/ OR (thrombectom* OR endovascular* OR intravascul* OR endo-vascular* OR intra-vascul* OR intraarterial* OR intra-arterial*).ab,ti.) AND (workflow/ OR Time-to-Treatment/ OR time factors/ OR (workflow* OR work-flow* OR pathway* OR ((therap* OR treat* OR puncture* OR reperfusion* OR admission OR care) ADJ6 (delay* OR time-to OR door-to OR picture-to OR arrival* OR onset*)) OR ((Streamlin* OR speed OR rapid OR optimi*) ADJ3 (treat* OR therap* OR recanal* OR reperfus* OR revascular*)) OR ((Intrahospital* OR Intra-hospital* OR prehospital* OR pre-hospital*) ADJ3 (time OR period* OR delay*)) OR (time ADJ3 (factor* OR lapse)) OR timing).ab,ti.) NOT (letter OR news OR comment OR editorial OR congresses OR abstracts).pt. AND english.la.



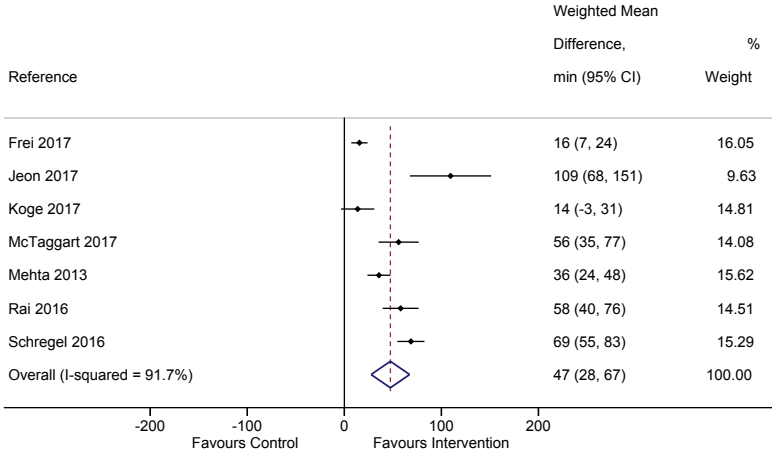


Supplementary Figure 8.1. Forest plots of weighted difference in mean time to treatment for specific intervention types, using random effect meta-analysis.

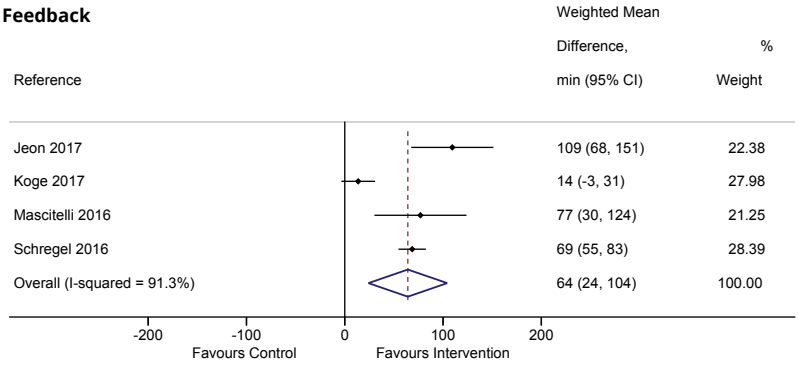
C. In-hospital patient transfer management



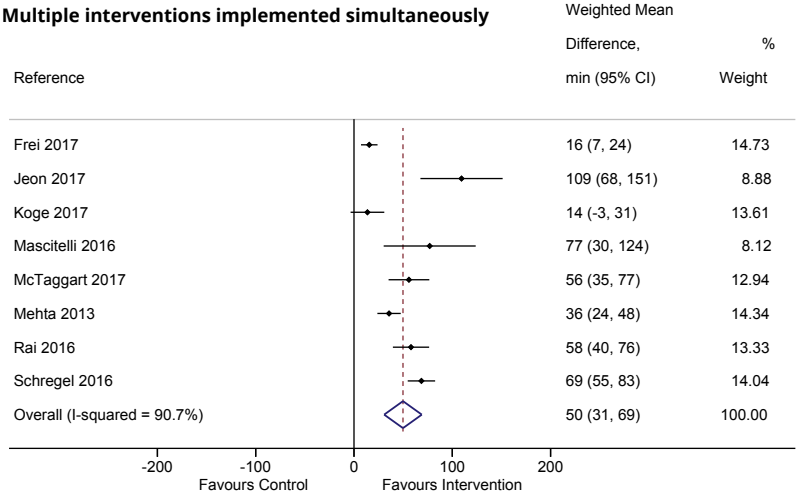
D. Teamwork



E. Feedback



F. Multiple interventions implemented simultaneously



Supplementary Table 8.1. Risk of bias for included studies on effect of workflow improvements on time to treatment.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias) (time to treatment)	Incomplete outcome data (attrition bias) (time to treatment)	Selective reporting (reporting bias)
Abou-Chebl[13]	-	-	?	+	+	?
Abou-Chebl[14]	-	-	-	+	+	?
Abou-Chebl[15]	-	-	?	+	+	?
Aghaebrahim[16]	-	-	+	+	+	+
Alotaibi[17]	-	-	?	-	+	-
van den Berg[18]	-	-	-	+	+	?
Berkhemer[19]	-	-	-	+	+	?
Bracard[2]	-	-	?	?	+	?
Cerejo[20]	-	-	+	+	+	?
Davis[21]	-	-	+	+	?	?
Eesa[22]	-	-	+	+	+	-
Frei[23]	-	-	-	?	+	+
Goyal[24]	-	-	+	+	+	?
Goyal[25]	-	-	-	+	+	?
Hassan[26]	-	-	?	+	+	?
Henden[27]	+	+	+	+	+	+
Herrmann[28]	-	-	-	-	-	+
Jadhav[29]	-	-	+	+	+	?
Jagani[30]	-	-	+	+	?	?
Janssen[31]	-	-	+	+	+	?
Jeon[32]	-	-	+	+	+	+
John[33]	-	-	+	+	+	?
Jumaa[34]	-	-	+	+	+	?
Just[35]	-	-	+	+	+	?
Kamper[36]	-	-	-	+	+	+
Koge[37]	-	-	+	+	+	+
Komatsubara[38]	-	-	+	?	+	+
Li[39]	-	-	-	+	+	?
Liang[40]	-	-	?	+	+	?
Mascitelli[41]	-	-	+	+	+	+
McTaggart[42]	-	-	+	+	+	?
Mehta[43]	-	-	-	-	+	+

Supplementary Table 8.1. Contined

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias) (time to treatment)	Incomplete outcome data (attrition bias) (time to treatment)	Selective reporting (reporting bias)
Menon[44]	-	-	?	+	+	?
Miley[45]	-	-	?	+	+	?
Mundiyanapurath[46]	-	-	-	+	+	?
Nichols[47]	-	-	?	+	+	?
Pedragosa[48]	-	-	+	+	+	?
Pfaff[49]	-	-	-	?	+	?
Pfaff[50]	-	-	-	+	+	?
Psychogios[51]	-	-	?	+	+	?
Qureshi[52]	-	-	?	+	+	?
Ragoschke[53]	-	-	-	-	+	+
Rai[54]	-	-	-	+	+	+
Ribo[55]	-	-	?	?	+	?
Schonenberger[56]	+	+	+	+	+	+
Schregel[57]	-	-	+	+	+	+
Simonsen[58]	+	+	+	+	+	+
Singer[59]	-	-	-	+	+	?
Slezak[60]	-	-	+	?	+	?
Sugg[61]	-	-	+	+	+	?
Tsujimoto[62]	-	-	-	?	+	?
Total						
Low Risk	6%	6%	45%	80%	94%	29%
Unclear risk	0%	0%	24%	14%	4%	67%
High Risk	94%	94%	31%	6%	2%	4%

Low risk is '+' in green, high risk is '-' in red, unclear risk is '?' in yellow.

Supplementary Table 8.2. Mean time to treatment for each study group and pooled weighted mean time to treatment, for specific time intervals, using random effects meta-analysis .

A. Onset to start endovascular treatment

Author	Time to treatment in minutes, mean (SD)	
	Intervention group	Control group
Abou-Chebl et al[13]	296 (172)	306 (133)
van den Berg et al[18]	231 (99)	269 (147)
Bracard et al[2]	254 (57)	244 (60)
Davis et al[21]	264 (93)	285 (115)
Goyal et al[24]	229 (49)	225 (42)
Henden et al[27]	190 (88)	199 (110)
Jagani et al[30]	256 (119)	282 (126)
Jumaa et al[34]	654 (804)	418 (291)
Li et al[39]	276 (120)	300 (138)
McTaggart et al[42]	112 (31)	168 (56)
Nichols et al[47]	232 (55)	237 (58)
Simonsen et al[58]	186 (72)	202 (71)
Slezak et al[60]	277 (126)	299 (157)
Tsujimoto et al[62]	233 (12)	273 (15)

Number of patients (intervention/control group): 1,466/1,243
Pooled weighted mean difference, minutes (95% CI): 18 (4 to 32), P=0.01

B. Door to start endovascular treatment

Author	Time to treatment in minutes, mean (SD)	
	Intervention group	Control group
Abou-Chebl et al[14]	141 (91)	142 (91)
Berkhemer et al[19]	134 (60)	162 (69)
Cerejo et al[20]	52 (24)	71 (39)
Frei et al[23]	61 (42)	76 (36)
Goyal et al[25]	97 (42)	103 (48)
Hassan et al[26]	287 (348)	310 (335)
Herrmann et al[28]	108 (58)	144 (42)
Jadhav et al[29]	22 (21)	81 (73)
Jeon et al[32]	993 (44)	202(179)
Kamper et al[36]	248 (165)	581 (823)
Liang et al[40]	43 (18)	58 (13)
Mascitelli et al[41]	104 (53)	181 (110)
Mehta et al[43]	106 (28)	142 (44)

Supplementary Table 8.2. Continued

B.

Author	Time to treatment in minutes, mean (SD)	
	Intervention group	Control group
Pedragosa et al[48]	47 (31)	69 (45)
Psychogios et al[51]	21 (6)	61 (35)
Qureshi et al[52]	158 (68)	180 (79)
Ragoschke et al[53]	106 (30)	121 (46)
Rai et al[54]	92 (37)	151 (51)
Ribo et al[55] –1	60 (29)	90 (53)
Ribo et al[55] –2	17 (8)	90 (53)
Schonenberger et al[56]	66 (20)	76 (29)
Schregel et al[57]	73 (42)	142 (93)
Singer et al[59]	92 (53)	86 (32)
Sugg et al[61]	141 (52)	161 (66)

Number of patients (intervention/control group): 1,595/2,441
Pooled weighted mean difference, minutes (95% CI): 33 (23 to 43), P<0.001

C. Imaging to start endovascular treatment

Author	Time to treatment in minutes, mean (SD)	
	Intervention group	Control group
Janssen et al[31]	59 (22)	79 (18)
Koge et al[37]	56 (24)	70 (30)
Menon et al[44]	56 (28)	72 (34)
Miley et al[45]	173 (57)	174 (66)
Pfaff et al[49]	39 (8)	61 (17)
Pfaff et al[50] –1	42 (18)	45 (12)
Pfaff et al[50] –2	45 (12)	69 (20)

Number of patients (intervention/control group): 305/198
Pooled weighted mean difference, minutes (95% CI): 15 (7 to 23), P<0.001

D. Onset to recanalization

Author	Time to treatment in minutes, mean (SD)	
	Intervention group	Control group
John et al[33]	436 (189)	510 (538)
Mundiyanapurath et al[46]	246 (90)	274 (99)

Number of patients (intervention/control group): 114/120

Supplementary Table 8.3. Efficacy and safety outcomes for workflow interventions aimed at reducing time to endovascular stroke treatment.

	Intervention group	Control group	Absolute risk difference (%)	Risk ratio (95% CI)
mRS 0–2 at 90 days	42.9% (946/2,206)	30.7% (690/2,246)	12.2	1.39 (1.15 to 1.66) P<0.001
Symptomatic intracranial hemorrhage	7.7% (183/2,368)	8.2% (154/1,883)	-0.5	0.88 (0.71 to 1.09) P=0.239
Mortality (all)	17.7% (411/2,325)	25.1% (535/2,133)	-7.4	0.74 (0.63 to 0.87) P<0.001
In-hospital mortality	15.0% (197/1,316)	24.2% (190/785)	-9.2	0.71 (0.54 to 0.94) P=0.017
Mortality at 30 days	14.4% (28/194)	19.8% (23/116)	-5.4	0.62 (0.31 to 1.24) P=0.175
Mortality at 3 months	22.8% (186/815)	26.1% (322/1,232)	-3.3	0.79 (0.64 to 0.96) P=0.019

Part III

Treat in the right place

Chapter 9

Personalized prehospital triage in acute ischemic stroke: a decision-analytic model

Stroke, 2019

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Abstract

Background and purpose

Direct transportation to a center with facilities for endovascular treatment might be beneficial for patients with acute ischemic stroke, but it can also cause harm by delay of intravenous treatment. Our aim was to determine the optimal prehospital transportation strategy for individual patients and to assess which factors influence this decision.

Methods

We constructed a decision tree model to compare outcome of ischemic stroke patients after transportation to a primary stroke center versus a more distant intervention center. The optimal strategy was estimated based on individual patient characteristics, geographical location and workflow times. In the base case scenario, the primary stroke center was located at 20 minutes and the intervention center at 45 minutes. Additional sensitivity analyses included an urban scenario (10 versus 20 minutes) and a rural scenario (30 versus 90 minutes).

Results

Direct transportation to the intervention center led to better outcomes in the base case scenario when the likelihood of large vessel occlusion (LVO) was >33%. With a high likelihood of LVO (66%, comparable with a Rapid Arterial Occlusion Evaluation score of 5 or above), the benefit of direct transportation to the intervention center was 0.10 quality-adjusted life years (=36 days in full health). In the urban scenario, direct transportation to an intervention center was beneficial when the risk of LVO was 24% or higher. In the rural scenario, this threshold was 49%. Other factors influencing the decision included door-to-needle times, door-to-groin times and the door-in-door-out time.

Conclusions

The preferred prehospital transportation strategy for suspected stroke patients depends mainly on the likelihood of LVO, driving times, and in-hospital workflow times. We constructed a robust model that combines these characteristics and can be used to personalize prehospital triage, especially in more remote areas.

Introduction

Inter-hospital transfer for endovascular treatment (EVT) of patients with acute ischemic stroke due to an intracranial large vessel occlusion (LVO) is one of the major causes of treatment delay.[1-5] Delay of EVT is associated with poor functional outcome.[6,7] Early identification of patients eligible for EVT followed by direct transportation to an endovascular-capable center might reduce transfer-related delay and thereby improve outcome. For this purpose, several prehospital stroke scales have been developed to identify patients who are at high risk of having an intracranial LVO based on their clinical symptoms. Currently, there is no evidence on superiority of one of these scales and more prospective validation in the prehospital setting is needed to reliable assess their accuracy.[8,9]

Other factors that might be of importance for the prehospital triage of suspected stroke patients include the prognosis of an individual patient and the expected benefit of EVT. Especially since the large majority of ischemic stroke patients is not eligible for EVT and only benefits from rapid treatment with intravenous thrombolytics (IVT), the harm of delaying IVT should be taken into account as well. The time-dependent effect of both treatments requires a trade-off between reducing delay of IVT by transportation to the nearest primary stroke center, and avoiding transfer-related delay of EVT by direct transportation to an intervention center.

Our aim was to determine the optimal prehospital transportation strategy for individual patients with suspected ischemic stroke and to assess which factors influence this decision.

Methods

Decision model

We constructed a decision tree model to compare outcome of patients with ischemic stroke after two different prehospital strategies: transportation to the nearest primary stroke center versus direct transportation to a more distant intervention center (Figure 9.1). The outcome of each strategy was estimated based on individual patient characteristics, geographical location and treatment times. We combined a short-run model including 3 months outcome data from randomized controlled trials and a long-run Markov model that simulated 40 annual cycles. The benefit of direct transportation to the intervention center was defined as the average amount of quality-adjusted life years (QALYs) gained by this strategy. We considered a difference of more than 0.02 QALYs (=1 week in full health) to be clinically relevant.

Our study did not need approval by an ethics committee since we did not use individual patient data. Analytic methods and study materials that support the findings of this study are available from the corresponding author upon reasonable request.

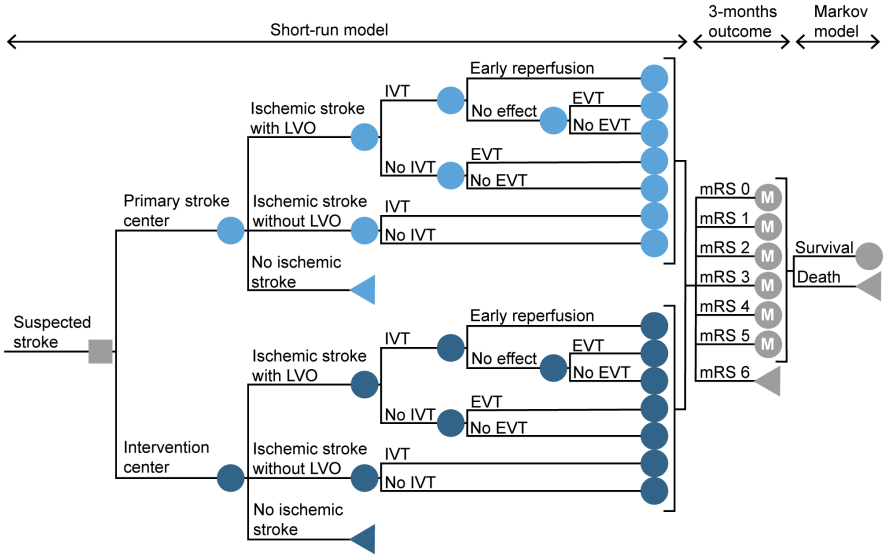

Figure 9.1. Schematic overview of the model structure. The model starts with the initial decision of transportation to the nearest primary stroke center or to the nearest intervention center. The short-run model calculates the probability of every possible pathway and the associated distribution of the modified Rankin Scale (mRS) score after 3 months. It takes into account driving times, in-hospital workflow characteristics, and time-dependent treatment effects. In each annual cycle of the following Markov model, patients can remain in the same health state or die. These probabilities are based on the age and sex dependent annual mortality rates, adjusted for previously reported death hazard rate ratios of stroke patients. The decision node is represented with a square. The circles represent chance nodes, the circles marked with an M represent Markov models and the triangles represent terminal nodes.
EVT, endovascular treatment; IVT, treatment with intravenous thrombolytics; LVO, large vessel occlusion.

Model parameters

Individual input parameters consisted of age, sex, time since onset of stroke symptoms, likelihood of LVO, driving time from scene to the primary stroke center, driving time from scene to the intervention center, and driving time between the primary stroke center and the intervention center. The base case used in our analyses was a 68-year old man with suspected stroke symptoms since one hour and an average risk of 30% to have an LVO causing the ischemic stroke. The nearest primary stroke center in the base case scenario was located at a 20 minutes drive by ambulance, while the intervention center was located at 45 minutes. Driving time between the centers was 35 minutes. Total time to treatment was calculated based on the driving times and in-hospital workflow characteristics (Tables 9.1 through 9.3). These parameters were varied in several sensitivity analyses.

Other model parameters were estimated based on previous literature and expert opinion of two neurovascular specialists (Drs Dippel and Roozenbeek, Supplementary Table 9.1). The β coefficients of treatment effect and time-dependent decline of treatment effect were

Table 9.1. Driving times used in the various analyses, in minutes.

	Base case scenario	Urban scenario	Rural scenario
From scene to primary stroke center	20	10	30
From scene to intervention center	45	20	90
From primary stroke center to intervention center	35	15	75

Table 9.2. In-hospital workflow characteristics used in the various analyses, in minutes.

	Base case analysis	Sensitivity analysis
Door-to-needle time (primary stroke center)	30	60
Door-to-needle time (intervention center)	30	30
Door-in-door-out time (primary stroke center)	60	90
Door-to-groin time (directly admitted)	80	80
Door-to-groin time (transferred)	50	50

Table 9.3. Calculations of treatment times in the model, in minutes.

Time to IVT (primary stroke center)	Time since onset of symptoms + driving time from scene to primary stroke center + door-to-needle time in primary stroke center
Time to IVT (intervention center)	Time since onset of symptoms + driving time from scene to intervention center + door-to-needle time in intervention center
Time to EVT (directly admitted)	Time since onset of symptoms + driving time from scene to intervention center + door-to-groin time for directly admitted patients
Time to EVT (transferred)	Time since onset of symptoms + driving time from scene to primary stroke center + door-in-door-out time + driving time from primary stroke center to intervention center + door-to-groin time for transferred patients

IVT, treatment with intravenous thrombolytics; EVT, endovascular treatment.

estimated with an ordinal logistic regression model using previously reported outcome distributions of treated patients and control patients in different time intervals.[6,10] The effect of the uncertainty around these estimates was assessed with a probabilistic sensitivity analysis.

Likelihood of LVO

We modeled the entire range from 0% to 100% likelihood of having an LVO as cause of the ischemic stroke, and we calculated the threshold at which direct transportation to the intervention center would be beneficial. The average prevalence of LVO ranges mostly between 20% and 40% in different populations of ischemic stroke patients,[11] but prehospital stroke scales can be used in individual patients to distinguish between lower and higher

risk. To illustrate this, we calculated the likelihood of LVO in case of a positive test (positive predictive value) and in case of a negative test (1 minus the negative predictive value) for the Los Angeles Motor Scale (LAMS), the Rapid Arterial Occlusion Evaluation (RACE), and the 3-Item Stroke Scale (3I-SS), using the pooled sensitivity and specificity rates reported in a previous meta-analysis (Table 9.4).[8] In the sensitivity analyses, we used the RACE scale as an example of low risk (14%) and high risk (66%).

Table 9.4. Likelihood of large vessel occlusion based on several prehospital stroke scales.

Stroke scale	Sensitivity*	Specificity*	Prior probability = 20%		Prior probability = 30%		Prior probability = 40%	
			PPV	1-NPV	PPV	1-NPV	PPV	1-NPV
LAMS ≥4	38%	87%	42%	15%	56%	23%	66%	32%
RACE ≥5	67%	85%	53%	9%	66%	14%	75%	21%
3I-ISS ≥4	19%	97%	61%	17%	73%	26%	81%	36%

The different prior probabilities illustrate the prevalence of large vessel occlusion in different populations of ischemic stroke patients.
*Pooled sensitivity and specificity rates as reported previously.[8]
3I-SS, 3-Item Stroke Scale; LAMS, Los Angeles Motor Scale; NPV, negative predictive value; PPV, positive predictive value; and RACE, Rapid Arterial Occlusion Evaluation.

Outcome measures

Primary outcome of the short-run model was the distribution of modified Rankin Scale (mRS) scores after 3 months. The mRS is a 7-point scale to assess functional outcome and disability, and ranges from 0 (no symptoms) to 6 (death). The outcome distributions of untreated ischemic stroke patients with and without an LVO were based on the control groups of previously reported randomized clinical trials (Supplementary Figure 9.1).[10,12] These distributions were shifted for different outcomes based on the estimated treatment effect. To do so, we first transformed the probabilities of each of the baseline mRS scores to the log-odds scale, using the formula log-odds(p)= log(p/(1-p)). We then adjusted these log-odds for the effect of IVT and EVT by adding the βcoefficient (=log odds ratio) for the treatment effect at time 0 minus the decline in treatment effect over time (Tables 9.5 and 9.6). The adjusted log-odds were then converted back to probabilities using the inverse logit function: p(log-odds) = 1/(1+exp(-log-odds)). This resulted in the adjusted mRS distributions for treated patients.

All mRS scores were considered to be separate health states with an associated utility score to calculate the average amount of QALYs per strategy. This is a commonly used measure to assess both the length and the quality of life.[13] Utility scores represent the quality of life, and range from 1 (perfect quality of life) to 0 (death), or lower for states considered worse

than death. We used previously reported utility scores for ischemic stroke patients: 0.95 for mRS 0; 0.93 for mRS 1; 0.83 for mRS 2; 0.62 for mRS 3; 0.42 for mRS 4; and 0.11 for mRS 5.[14] The average life expectancy was calculated for every mRS category with a long-run Markov model that simulated 40 annual cycles. Age and sex dependent annual mortality rates were adjusted for previously reported death hazard rate ratios of stroke patients (Supplementary Table 9.1).[15] Life years were discounted with 3% per year. We calculated the total number of QALYs by multiplying the utility scores of each mRS category with the corresponding life expectancy in years.

Model assumptions

The model was used for scenarios in which the nearest hospital is not an intervention center, since there has to be decisional uncertainty about the optimal transportation strategy. Outcome was modeled for patients with ischemic stroke only, disregarding other diagnoses. A substantial proportion of all patients suspected of ischemic stroke have an intracerebral hemorrhage, a transient ischemic attack or a stroke-mimic, but we assumed the outcome of these patients to be unrelated to the transportation strategy. Because our analyses concerned the trade-off between IVT and EVT, we did not consider patients presenting >4.5 hours after onset of symptoms.

We assumed that IVT could be given within 4.5 hours after onset of symptoms and EVT within 6 hours after onset. We modeled the decrease in treatment effect of IVT and EVT consistently over time and similar for all patients. Since large pooled analyses showed no significant interaction between age or gender and treatment effect, we did not include age or gender specific treatment effects in our model.[12,16] The relative treatment effect of IVT was not influenced by stroke severity, which implies a smaller absolute treatment effect for patients with a more severe stroke. The importance of these model assumptions was assessed in several sensitivity analyses.

Sensitivity analyses

In addition to the base case scenario, we also assessed examples of an urban scenario (10 minutes from scene to primary stroke center; 20 minutes from scene to intervention center; and 15 minutes inter-center driving time) and a more rural scenario (30, 90, and 75 minutes respectively). We used a Tornado-analysis to explore the relative importance of the model parameters, by varying each parameter at a time while the others were held constant. Additional sensitivity analyses were performed with: increased workflow times in the primary stroke center (Table 9.2); a female patient; a patient with contra-indications for IVT; an absent effect of IVT for patients with LVO; and utility weights as defined in a study of Chaisinanunkul et al.[17]

We performed a probabilistic sensitivity analysis using second-order Monte-Carlo simulations to assess decisional uncertainty around the model parameters. This involves running the

model 10,000 times and calculating the optimal transportation strategy every single time. In each simulation, the estimates of the model parameters were randomly sampled from the prespecified distribution of each parameter (β, (log)normal or triangular) (Supplementary Table 9.1). We reported the percentage of simulations in which transportation to the primary stroke center or direct transportation to the intervention center was preferred, and the median benefit of direct transportation to an intervention center with a 95% credible interval.

We constructed an online tool in which input factors and regional workflow times can be adjusted for an individual patient in a specific scenario. We used R statistical software (version 3.4.4) with the dampack package (version 0.0.0.9) and the R Shiny package (version 1.0.5).

Results

Base case analysis

Direct transportation to the intervention center was preferred for the 68-year old man in the base case scenario, with a primary stroke center located at 20 minutes and an intervention center at 45 minutes, when the likelihood of LVO was 34% or above (Figure 9.2). When the risk of having an LVO was 66%, comparable with a RACE score of 5 or more, the benefit of direct transportation to the intervention center was 0.10 QALYs (=36 days). When the risk of having an LVO was 14%, comparable with a RACE score below 5, transportation to the primary stroke center was preferred with a difference of 0.03 QALYs (=11 days).

Sensitivity analyses

In the urban scenario (10 minutes to the primary stroke center, 20 minutes to the intervention center), the threshold for direct transportation to the intervention center was lower than in the base case scenario (24%, Figure 9.2). In the rural scenario (30 minutes to the primary stroke center and 90 minutes to the intervention center), direct transportation to the intervention center was only preferred for patients with an LVO likelihood of 49% or above.

Other factors that strongly affected the decision threshold in the Tornado-analysis were the in-hospital workflow characteristics (Supplementary Figure 9.3). While remaining the other parameters of the base case constant, transportation to the primary stroke center was beneficial when the door-to-groin time for directly transported patients was above 102 minutes, the door-to-groin time for transferred patients was below 28 minutes, or the door-in-door-out time in the primary stroke center was <38 minutes. Age did not influence the preferred strategy, although it was important for the general prognosis of individual patients.

In the analysis with increased workflow times in the primary stroke center, transportation to the intervention center was more favorable (Supplementary Figure 9.4). As might be

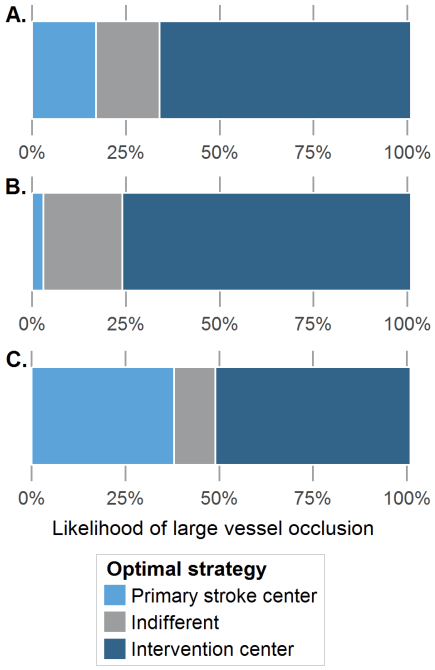

Figure 9.2. The optimal transportation strategy based on the likelihood of large vessel occlusion.
Primary stroke center: the nearest nonendovascular-capable stroke center; intervention center: the nearest endovascular-capable stroke center. A, represents the base case scenario (primary stroke center at 20 minutes and intervention center at 45 minutes); B, the urban scenario (10 and 20 minutes, respectively); and C, the rural scenario (30 and 90 minutes).

expected, we found that transportation to the primary stroke center was never preferred for a patient with contra-indications for IVT. In all other exploratory sensitivity analyses, the decision threshold remained relatively unchanged.

Probabilistic sensitivity analysis

The uncertainty around the estimates of the model parameters caused little decisional uncertainty in the probabilistic sensitivity analysis (Supplementary Table 9.2). When the risk of having an LVO in the base case scenario was high, transportation to the intervention center was associated with a clinically relevant benefit in 94% of the simulations with a median difference of 0.09 QALYs (=33 days in full health, 95% credible interval: 0.00 to 0.20). When the risk of having an LVO was low, direct transportation to the intervention center was preferred in only 6% of the simulations, with a median difference of -0.03 QALYs (95% credible interval: -0.09 to 0.03).

Online tool

The effect of simultaneous changes in individual patient characteristics and regional workflow characteristics on the optimal prehospital transportation strategy for individual patients can be further explored by using the online tool at mrpredicts.shinyapps.io/triage (Figure 9.3).

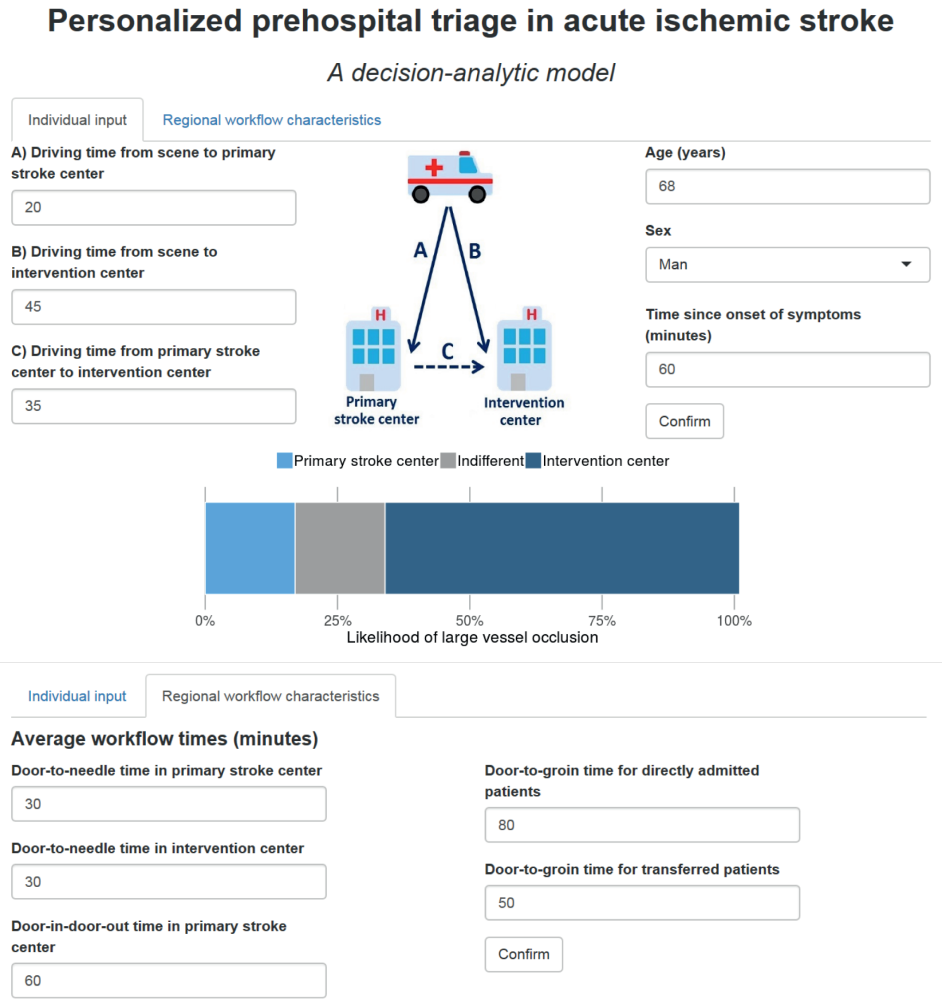

Figure 9.3. Screenshot of the online tool. This interactive tool can be used at mrpredicts.shinyapps.io/triage. It shows the effect of changes in individual patient characteristics and regional workflow times on the optimal transportation strategy based on the likelihood of large vessel occlusion.

Table 9.5. Calculations of treatment effect in the model.

Probability of receiving IVT	**If treatment is possible within 4.5 hours after onset of symptoms: 55%, otherwise: 0%**
Probability of early reperfusion	If LVO present and treated with IVT: 11%, otherwise: 0%
Probability of receiving EVT	If treatment is possible within 6 hours after onset of symptoms: 85%, otherwise 0%
Treatment effect IVT (β coefficient)*	0.56 (=odds ratio 1.75) at time 0, minus 0.0019 x time to IVT in minutes
Treatment effect EVT (β coefficient)*	1.35 (=odds ratio 3.85) at time 0, minus 0.0026 x time to EVT in minutes

*The time-dependent decrease in treatment effect is illustrated in Supplementary Figure 9.2.
IVT, treatment with intravenous thrombolytics; EVT, endovascular treatment.

Table 9.6. Calculations of treatment effect in the model.

	Primary stroke center	**Intervention center**
Outcome with large vessel occlusion (log-odds)*		
Early reperfusion after IVT	1.35 + (-0.0026 x time to IVT (primary stroke center)) + log-odds from baseline mRS distribution with LVO	1.35 + (-0.0026 x time to IVT (intervention center)) + log-odds from baseline mRS distribution with LVO
EVT (with or without prior IVT)	1.35 + (-0.0026 x time to EVT (transferred)) + log-odds from baseline mRS distribution with LVO	1.35 + (-0.0026 x time to EVT (directly admitted)) + log-odds from baseline mRS distribution with LVO
No EVT	Log-odds from baseline mRS distribution with LVO	Log-odds from baseline mRS distribution with LVO
Outcome without large vessel occlusion (log-odds)*		
IVT	0.56 + (-0.0019 x time to IVT (primary stroke center)) + log-odds from baseline mRS distribution without LVO	0.56 + (-0.0019 x time to IVT (intervention center)) + log-odds from baseline mRS distribution without LVO
No IVT	Log-odds from baseline mRS distribution without LVO	Log-odds from baseline mRS distribution without LVO

*The baseline mRS distribution with LVO and without LVO is illustrated in Supplementary Figure 9.1. The corresponding probability of a certain outcome was calculated as: 1/(1+exp(-log-odds)).
EVT, endovascular treatment; IVT, treatment with intravenous thrombolytics; LVO, large vessel occlusion; and mRS, modified Rankin Scale.

Discussion

Our decision model shows that direct transportation to an intervention center can be beneficial for patients with a high risk of having an LVO, but will likely lead to worse outcomes when the risk is low, especially in scenarios with longer driving times. Combining individual likelihood of LVO and estimated driving times on a case-by-case basis could improve prehospital triage decisions, decrease treatment delay and thereby improve functional outcome of individual patients. In-hospital workflow characteristics such as the door-in-door-out and door-to-groin times have a large effect on the optimal strategy as well. Our online tool allows individual and regional input to inform prehospital triage strategies in different settings.

No single time threshold can be given to optimize triage decisions without considering the probability of being eligible for EVT, as was described by other models.[18-21] As a measure for the likelihood of LVO, these models used previously reported cutoffs of one or multiple prehospital stroke scales. However, prospective prehospital validation is required to assess and compare the accuracy of these scales when used by emergency medical services in a broad population of suspected stroke patients.[8] The full dependence of these models on insufficiently validated prehospital stroke scales limits the validity of their results. Therefore, we did not depend our model on a specific prehospital stroke scale, but assessed the entire range from 0% to 100% likelihood of LVO. Several prehospital stroke scales may be used to estimate this likelihood, preferably after more extensive validation.

Our study also has some limitations. Decision-analytic modeling requires the use of estimated model parameters and multiple assumptions. In extensive sensitivity analyses, we found no substantial decisional uncertainty. Nevertheless, the assumptions we made about the treatment effect of IVT and EVT might have influenced our results. We used reported outcomes and effect sizes of IVT based on studies that did not assess LVO status, since randomized trials on the effect of IVT were performed before the introduction of CT angiography as standard of care for acute stroke patients. To calculate a common odds ratio for the decay in effect of IVT, we used mRS distributions at different time points provided by a pooled analysis from 2004.[10] A more recent study with a larger sample size only reported odds ratios specific for the cutoff of mRS 0-1,[16] which are not valid to use in shift-analyses of total mRS score. Although the effect of IVT tends to diminish with more proximally located occlusions,[22,23] we included a consistent relative treatment effect of IVT in the range of the National Institute of Health Stroke Scale score of 5 to 22.[16] Since the baseline outcome distribution is less favorable for patients with an LVO, the same relative treatment effect will give a smaller absolute effect in LVO stroke. The precise benefit of IVT prior to EVT is still uncertain, since the available studies are flawed by confounding by indication.[24,25] The results of ongoing randomized controlled trials comparing EVT and EVT with prior IVT have to provide more insight on this matter.

Outcome of stroke mimics, such as migraine, epilepsy and conversion disorder, were considered to be independent of time, since there are no time-dependent treatment options that would require transportation to the nearest hospital. Patients with an intracerebral hemorrhage might benefit from transportation to a specialized center, but there is currently insufficient evidence to include the effect of rapid treatment in our model. Recent studies showed that EVT can be effective in a subgroup of stroke patients presenting between 6 and 24 hours after onset.[26,27] Other factors might be important to optimize triage of these patients and our results therefore only apply to patients presenting within 6 hours. Furthermore, we did not include costs in our model. Because outcome was measured based on functional outcome, we were only able to model harm due to delayed treatment. Inconvenience of unnecessary transportations for patients and their relatives, as well as inefficient resource utilization was not integrated in the model. It is likely that unnecessary transportation to an intervention center will cause crowding at the emergency department, which might have financial consequences and a negative effect on the in-hospital workflow. It is therefore important to further explore the cost-effectiveness of different prehospital triage strategies.

We constructed a decision model that predicts the optimal strategy based on individual patient characteristics, and that can easily be adjusted for differences in geographical location or in-hospital workflow characteristics. Our online tool forms the basis of personalized prehospital triage of suspected ischemic stroke patients. Clinicians and researchers can plug in the specific characteristics of their own region into this tool to guide local prehospital triage policies. Although a fixed threshold the likelihood of LVO might be suitable for triage in urbanized regions with small distances between centers, our model showed that a higher threshold should likely be considered in more remote areas. After more extensive validation of the prehospital stroke scales, the tool can be used to combine the individual's likelihood of LVO with estimated driving and local workflow times to improve prehospital triage decisions on a case-by-case basis. Future integration with a GPS-controlled navigation application will further facilitate personalized triage based on real-time information about driving and local workflow times.

Conclusions

The preferred prehospital transportation strategy for suspected stroke patients depends mainly on the likelihood of LVO, driving times and in-hospital workflow times. We constructed a robust model that combines these characteristics and can be used to personalize prehospital triage, especially in more remote areas.

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Supplementary material

Supplementary Table 9.1. Overview of the model parameters used in the probabilistic sensitivity analysis.

Model parameter	Estimated value	SE	Distribution	Source
Treatment characteristics				
Probability of receiving IVT if presenting <4.5h with an ischemic stroke	0.55	±10%	β	Expert opinion
Effect of IVT, beta	0.56 at time 0	0.18	Normal	Hacke et al.[1] (n=2763)
Time-dependent decrease in effect of IVT, beta	-0.0019 per minute	0.001	Normal	Hacke et al.[1] (n=2763)
Probability of early reperfusion after IVT	0.11	0.008	β	Tsivgoulis et al.[2] (n=1561)
Probability of receiving EVT if presenting<6h with an LVO	0.85	±10%	β	Expert opinion
Effect of EVT, beta	1.35 at time 0	0.29	Normal	Saver et al.[3] (n=1275)
Time-dependent decrease in effect of EVT, beta	-0.0026 per minute	0.001	Normal	Saver et al.[3] (n=1275)
Outcome parameters				
Utility values				Dijkland et al.[4]
mRS scores 0	0.95	0.08	β	(n=7)
mRS scores 1	0.93	0.04	β	(n=36)
mRS scores 2	0.83	0.04	β	(n=84)
mRS scores 3	0.62	0.05	β	(n=87)
mRS scores 4	0.42	0.04	β	(n=133)
mRS scores 5	0.11	0.05	β	(n=45)
Death hazard rate ratios				Samsa et al.[5]
mRS scores 0-1	1.00	NA	NA	
mRS scores 2	1.11	1.0-1.5	Triangular	
mRS scores 3	1.27	1.2-1.4	Triangular	
mRS scores 4	1.71	1.3-2.0	Triangular	
mRS scores 5	2.37	1.5-4.0	Triangular	

EVT, endovascular treatment; IVT, treatment with intravenous thrombolytics; mRS, modified Rankin Scale; NA, not applicable; SE, standard error.

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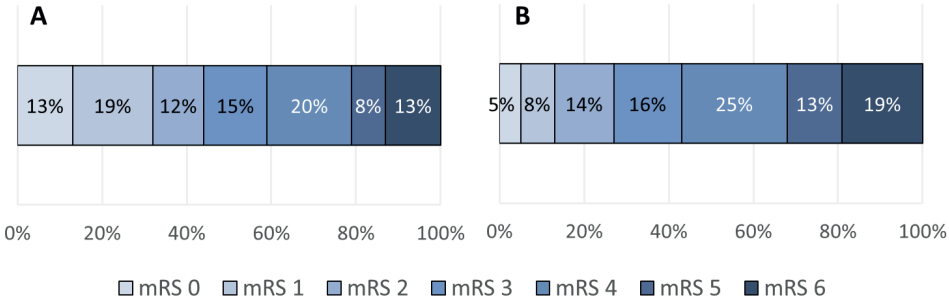
[5] J Clin Epidemiol 1999;52:259-271.

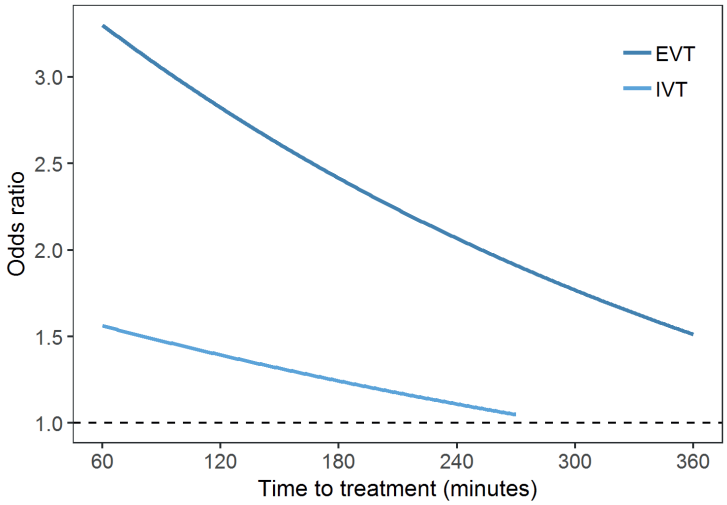
Supplementary Table 9.2. Results of the probabilistic sensitivity analysis using 10,000 Monte Carlo simulations.

Probability of large vessel occlusion	Optimal transportation strategy (percentage of simulations)			Median benefit of direct transportation to intervention center, QALYs (95% credible interval)
	Primary stroke center	Indifferent	Intervention center	
Base case scenario				
Low risk (14%)	60%	35%	6%	-0.03 (-0.09 to 0.03)
Average risk (30%)	20%	43%	37%	0.01 (-0.06 to 0.08)
High risk (66%)	1%	7%	92%	0.09 (-0.01 to 0.20)
Urban scenario				
Low risk (14%)	8%	82%	10%	0.00 (-0.03 to 0.03)
Average risk (30%)	1%	33%	66%	0.03 (-0.01 to 0.08)
High risk (66%)	<1%	4%	96%	0.09 (0.01 to 0.19)
Rural scenario				
Low risk (14%)	87%	9%	4%	-0.10 (-0.25 to 0.03)
Average risk (30%)	68%	18%	14%	-0.05 (-0.19 to 0.07)
High risk (66%)	10%	16%	74%	0.06 (-0.07 to 0.20)

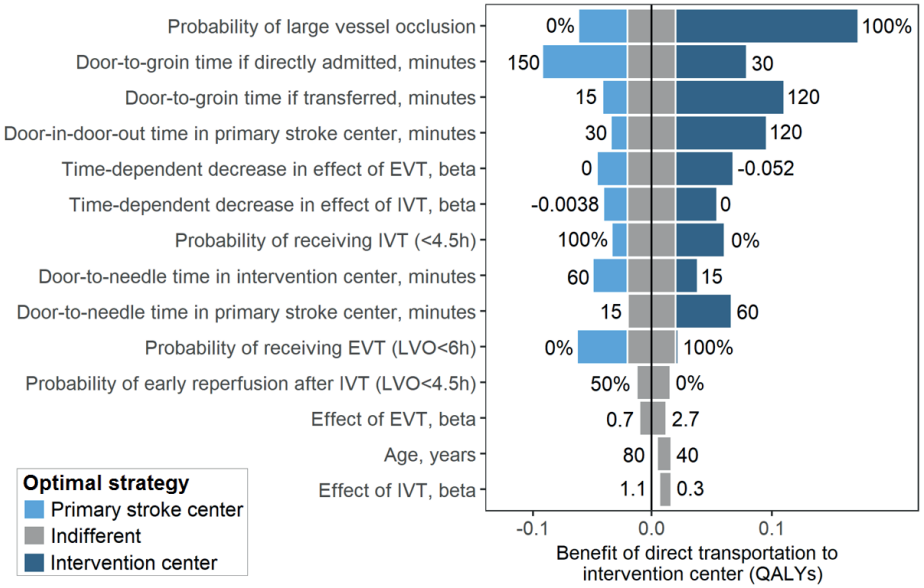
The percentage of simulations in which transportation to the primary stroke center or direct transportation to the intervention center was preferred and the median difference in expected outcome between the two strategies is shown for different scenarios and different likelihood of large vessel occlusion. The percentages may not add up to 100% due to rounding.
QALYs, quality-adjusted life years.



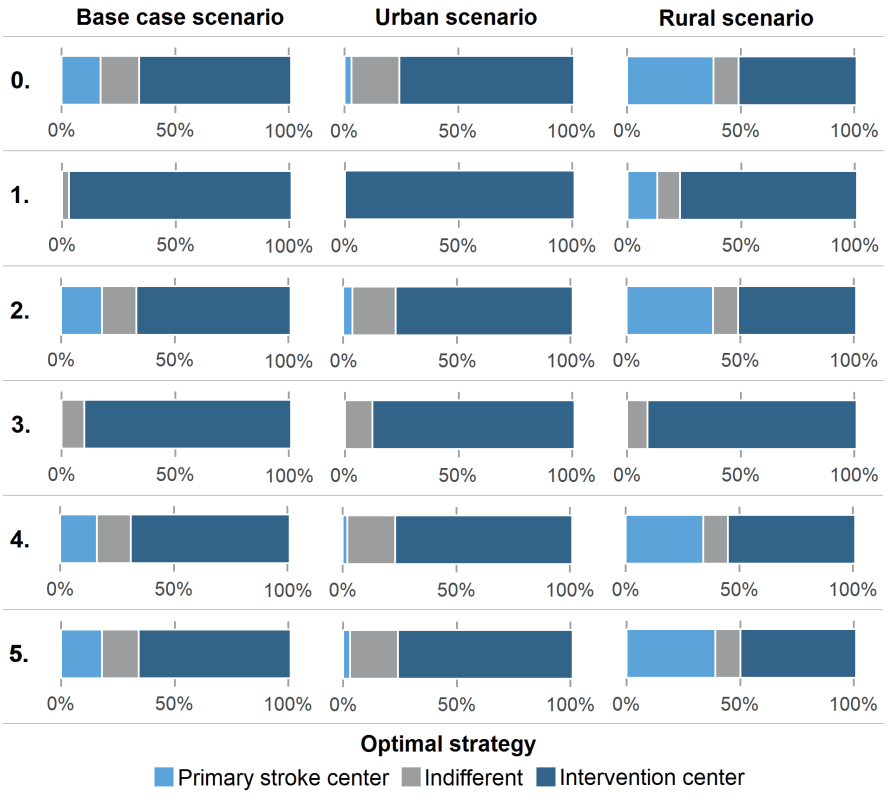
Supplementary Figure 9.1. Distribution of the baseline modified Rankin Scale (mRS) scores. Outcome for untreated ischemic stroke patients without large vessel occlusion (A) and untreated ischemic stroke patients with large vessel occlusion (B).
A. Hacke et al. placebo group, n=1384 (Lancet 2004;363:768-774).
B. Goyal et al. control group, n=644 (Lancet 2016;387:1723–1731).



Supplementary Figure 9.2. The time-dependent decrease in treatment effect as used in the model.
EVT, endovascular treatment; IVT, treatment with intravenous thrombolytics.



Supplementary Figure 9.3. Tornado-plot with the effect of changes in model parameters on the optimal transportation strategy. The bars illustrate the effect of changes in the model parameter estimates, within the indicated ranges, on the optimal transportation strategy. The bars are ordered according to their impact on the difference in outcome.
EVT, endovascular treatment; IVT, treatment with intravenous thrombolytics; LVO, large vessel occlusion.



Supplementary Figure 9.4. Results of the sensitivity analyses. The bars show the optimal transportation strategy for different likelihood of large vessel occlusion in the base case scenario (primary stroke center at 20 minutes and intervention center at 45 minutes); the urban scenario (primary stroke center at 10 minutes and intervention center at 20 minutes); and the rural scenario (primary stroke center at 30 minutes and intervention center at 90 minutes).

0. Base case analysis.
1. Sensitivity analysis with increased workflow times in primary stroke center (door-to-needle time 60 minutes and door-in-door-out time 90 minutes).
2. Sensitivity analysis with female patient.
3. Sensitivity analysis with contra-indications for treatment with intravenous thrombolytics.
4. Sensitivity analysis with absent effect of treatment with intravenous thrombolysis for patients with a large vessel occlusion.
5. Sensitivity analysis with utility weights as defined in the study of Chaisinanunkul et al (Stroke 2015;46:2238-2243).

Chapter 10

Prehospital triage strategies for the transportation of suspected stroke patients in the United States

Accepted for publication

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Abstract

Background and Purpose

Patients with large vessel occlusion (LVO) could benefit from direct transportation to an intervention center for endovascular treatment, but ischemic stroke patients without LVO need rapid IV thrombolysis in the nearest stroke center. Our aim was to evaluate prehospital triage strategies for suspected stroke patients in the United States.

Methods

We used a decision tree model and geographic information system to estimate outcome of suspected stroke patients transported by ambulance within 6 hours after symptom onset. We compared the following strategies: (1) Always to nearest center, (2) American Heart Association (AHA) algorithm (ie, directly to intervention center if a prehospital stroke scale suggests LVO and total driving time is <30 minutes, provided that the delay would not exclude from thrombolysis), (3) "modified" algorithms with additional driving time to intervention center <30 minutes, <60 minutes, or without time limit, and (4) always to intervention center. Primary outcome was the annual number of death and severe disability prevented. A strategy was preferred when no other strategy resulted in improved outcomes with an incremental "number needed to transport to intervention center" (NNTI) <100 to prevent one death or severe disability.

Results

Nationwide implementation of the AHA triage algorithm prevented death or severe disability in 692 patients per year compared to transportation to the nearest center (NNTI 28). The modified algorithm with direct transportation of LVO-suspected patients regardless of the additional driving time yielded an incremental benefit of 905 patients compared to the AHA algorithm (NNTI 34) and was preferred in the majority of states (n=32 (65%)). Tailoring policies at county-level did not further improve outcomes but slightly reduced the number of transportations to the intervention center (NNTI 31).

Conclusions

Prehospital triage strategies can greatly improve outcomes of the ischemic stroke population in the United States. The current AHA algorithm should be modified to allow more delay when directly transporting patients with suspected LVO to an intervention center.

Introduction

Patients with ischemic stroke due to a proximal intracranial large vessel occlusion (LVO) are often severely affected and are more likely to have a poor outcome than ischemic stroke patients without LVO.[1-3] Endovascular treatment (EVT) using thrombectomy devices can strongly improve outcome in patients with LVO stroke, but this effect is highly time-dependent and treatment should be started as soon as possible.[4-6]

In clinical practice, suspected stroke patients are often transported to the nearest hospital, where they will receive a diagnostic work-up and can be treated with IV thrombolytics (IVT). When an LVO is present on non-invasive imaging, patients need to be transferred to a specialized intervention center capable of providing EVT. These inter-hospital transfers are associated with treatment delay and a significantly lower chance of good outcome after EVT.[7,8] Patients with LVO could therefore benefit from direct transportation to an intervention center, while non-LVO stroke patients need rapid IVT in the nearest stroke center.[9] Numerous prehospital stroke scales have been developed to identify stroke patients with LVO in the prehospital setting based on their clinical symptoms, but none of these scales have both a high sensitivity and high specificity.[10]

Therefore, in determining the best prehospital triage strategy, the potential benefit of rapid EVT for LVO patients needs to be weighed against the harm of delaying IVT in (false-positive) non-LVO patients. Previous modeling studies showed that the harms and benefits of transportation decisions are mainly dependent on the likelihood of LVO and the geographical distribution of centers, but the optimal triage policy for suspected stroke patients is still unknown.[11-16] Currently, the Mission: Lifeline® Stroke algorithm of the American Heart Association and American Stroke Association (AHA/ASA) recommends direct transportation to an intervention center when LVO is suspected (based on a positive prehospital stroke scale), the additional driving time will not disqualify for IVT, and the total transport time from scene to nearest intervention center is less than 30 minutes.[17]

In this study, we aim to assess the effect of alternative prehospital triage strategies and to determine the optimal policy for suspected stroke patients in the United States.

Methods

We used a previously developed decision tree model for suspected stroke patients presenting to the emergency medical services within 6 hours after symptom onset.[15] We modeled the following prehospital triage strategies: (1) transportation of all patients to the nearest stroke center, (2) triage using the original AHA algorithm (to intervention center when LVO is suspected based on a positive prehospital stroke scale, the additional transport

time will not disqualify for IVT, and the total transport time from scene to nearest intervention center is <30 minutes), (3) triage using a "modified" algorithm with extended time limits for the transport of suspected LVO patients (additional driving time <30 minutes, <60 minutes, and no time limit (under the condition that IVT will not be disqualified when bypassing the nearest stroke center)), and (4) transportation of all patients to the intervention center.

This study did not use individual patient data and therefore did not need approval by an ethics committee. Analytic methods and study materials that support the findings of this study are available from the corresponding author upon reasonable request.

Input parameters

We included all 48 contiguous states and the District of Columbia. As geographic input parameters, we used the 2010 US Census tracts, which are small statistical subdivisions of counties with a population of approximately 1200 to 8000 inhabitants. The annual number of ischemic stroke patients was calculated based on the number of inhabitants per Census tract, the county-specific age distribution and the national hospitalization rates of ischemic stroke patients in 2010 for age categories 25-44, 45-64, 65-84, and 85 years and older.[18,19] We estimated that 35% of these patients presented within the 6 hour time window.[20] To assess hospital certification status, we used data from three national accreditors: The Joint Commission Quality Check Stroke Certification program, Det Norske Veritas (DNV) National Integrated Accreditation for Healthcare Organizations (NIAHO) program, and the Healthcare Facilities Accreditation Program (HFAP).[21-23] When hospitals were registered by multiple accreditors, we used the highest level of certification. Hospitals capable of delivering IVT, using telemedicine if necessary, were classified as primary stroke centers. Hospitals capable of delivering both IVT and EVT were classified as intervention centers.

As prehospital stroke scale for LVO assessment, we used the prospectively validated Rapid Arterial Occlusion Evaluation (RACE) with a sensitivity of 84% and a specificity of 60% at a cutoff at ≥5 points.[24,25] This yielded a positive predictive value of 34% and a negative predictive value of 94% at the base case prevalence of 20% LVO among suspected stroke patients. We used an average time of 90 minutes between symptom onset and departure from scene. The door-to-needle time was estimated to be 60 minutes in all primary stroke centers and 50 minutes in all intervention centers.[26] Door-in-door-out time in the primary stroke centers was considered to be 100 minutes; door-to-groin time in the intervention centers 85 minutes for directly admitted patients and 55 minutes for transferred patients.[7] Stroke scale characteristics, LVO prevalence and workflow times were varied in the sensitivity analyses to assess their effect on the preferred strategy.

Outcome measures

For each strategy, we calculated the annual number of good outcomes (defined as a modified Rankin Scale 0–2) and the additional number of non-LVO patients transported to an

intervention center (including intracranial hemorrhages and stroke mimics). The "number needed to transport to an intervention center" (NNTI) was defined as the ratio between these two measures, ie, how many non-LVO patients are transported to an intervention center to prevent death or disability in one patient.

Analyses

We used origin-destination matrix analyses to calculate driving times from all Census tract population centers (n=72,263) to the nearest primary stroke center and the nearest intervention center. The population centers defined by the Census Bureau were used as the geographic center of the population in each Census tract. Hospitals were located based on the Homeland Infrastructure Foundation-Level Data (HIFLD). Air transportation was not considered. We entered the driving times in the existing decision tree model to calculate the estimated effect of each strategy per Census tract. Differences in outcome were only modeled for ischemic stroke patients; outcomes of patients with intracranial hemorrhage or stroke mimics were considered to be unrelated to the initial transportation policy. The probability of a good outcome (defined as modified Rankin Scale 0–2) decreased with approximately 2.5% per hour for patients receiving IVT and with 5.2% per hour for patients receiving EVT.[5,9] Further details of the decision tree model have been published previously.[15]

The effect of nationwide implementation of each triage strategy was assessed with the number of poor outcomes prevented compared to transportation of all patients to the nearest stroke center, and the corresponding NNTI. We also calculated the incremental benefit of each strategy compared to the previous, more restrictive, strategy. Additionally, we assessed the best strategy for each state and each county. A strategy was preferred when no other strategy resulted in improved outcomes with an incremental NNTI <100 patients to prevent one death or severe disability. We assessed state characteristics, such as population density and local driving times, according to the preferred strategy per state. We also calculated the incremental effect of a state-level or county-level policy, when implementing the preferred strategy in each state or each county separately.

Sensitivity analyses were performed by varying the prevalence of LVO among suspected stroke patients (from 10 to 30%), the workflow times in the primary stroke center (door-to-needle time from 30 to 90 minutes and door-in-door-out time from 50 to 150 minutes), and the maximum accepted NNTI (from 25 to 400). We showed the effect of these different scenarios on the state-level and county-level distribution of preferred strategies. We also performed a sensitivity analysis using a prehospital stroke scale with a 10% absolute increase in sensitivity or specificity.

We used ESRI ArcGIS Pro (version 2.0.0) for the network analyses and visualization of the maps. R statistical software (version 3.5.1) was used for all other analyses.

Results

We found certification data for 1,644 US hospitals, of which 328 (20%) are intervention centers. In the base case scenario, nationwide implementation of the AHA algorithm prevented poor outcome (death or severe disability) in 692 patients compared to transportation of all patients to the nearest stroke center (NNTI 28). The modified algorithms yielded an incremental benefit of 490 (additional driving time <30 min for LVO-suspected patients) to 905 (no time limit for LVO-suspected patients) poor outcomes prevented, with an NNTI varying between 28 and 34 compared to the AHA algorithm. Nationwide transportation of all suspected stroke patients to an intervention center was inferior to an universally applied algorithm without time limit, but could still be beneficial compared to transporting all patients to the nearest stroke center in several states (n=20 (41%)) and counties (n=1,346 (43%), Table 10.1).

The modified triage algorithm without time limit was preferred in the majority of states (n=32 (65%)), Figure 10.1A). Transportation of all patients to the nearest stroke center was optimal in Idaho, Montana, and Wyoming, sparsely populated states without certified intervention centers, while the current AHA algorithm was only preferred in the District of Columbia, where the average driving time to an intervention center is very short (14 minutes). Using a modified algorithm with an additional driving time of <30 minutes was favored in rural states with very large between-center distances, while a longer delay was accepted in states with shorter driving times (Table 10.2). On county-level, liberal triage strategies were less often beneficial compared to standard transportation to the nearest stroke center (Figure 10.1B). The county-specific policy was slightly more efficient but did not improve outcome compared to the nationwide application of an algorithm without time limit (1,600 versus 1,597 poor outcomes prevented, NNTI 31 versus 32). Applying the optimal policy on Census tract level did not further increase the number of poor outcomes prevented, but slightly reduced the number of unnecessary transportations (NNTI 30).

The incremental NNTI of triage strategies when using the RACE scale with a cutoff at ≥5 points varied between 28 and 60 (Figure 10.2A). Improving the specificity of the prehospital stroke scale with 10% decreased the number of non-LVO strokes transported to the intervention center, resulting in an incremental NNTI between 19 and 33 (Figure 10.2B). A 10% improvement in sensitivity led to better outcomes with an incremental NNTI between 25 and 47 (Figure 10.2C). Further sensitivity analyses showed that more restrictive triage strategies (ie, always to nearest stroke center or using the AHA algorithm) were preferred in scenarios with lower LVO prevalence, shorter workflow times in the primary stroke center, and when applying a maximum NNTI of 25 (Figure 10.3).

Table 10.1. The effect of prehospital triage strategies in the base case scenario.

			Modified triage algorithm			
	Always to nearest stroke center	AHA triage algorithm (total driving time <30 min)	Additional driving time <30 min	Additional driving time <60 min	No time limit	Always to intervention center
Nationwide policy						
Annual number of poor outcomes prevented	0 (ref)	692	1,182	1,494	1,597	1,504
Incremental good outcomes*	NA	692	490	312	103	-93
Additional number of non-LVO patients transported to intervention center	0 (ref)	19,499	33,308	44,254	50,457	163,756
Incremental transportations*	NA	19,499	13,809	10,946	6,203	113,299
NNTI	NA	28	28	29	32	109
Incremental NNTI*	NA	28	28	35	60	NA
State-level policy						
States with benefit†, n (%)	0 (ref)	42 (86%)	46 (94%)	45 (92%)	45 (92%)	20 (41%)
NNTI in states with benefit, median (IQR)	NA	28 (28–28)	28 (27–29)	29 (29–31)	32 (30–35)	83 (80–89)
County-level policy						
Counties with benefit†, n (%)	0 (ref)	432 (14%)	1,497 (48%)	1,904 (61%)	2,069 (67%)	1,346 (43%)
NNTI in counties with benefit, median (IQR)	NA	27 (26–29)	27 (24–29)	29 (26–33)	30 (27–36)	73 (66–82)

*Compared to the previous, more restrictive, strategy.
†Benefit is defined as an increase in good outcomes compared to transportation to the nearest stroke center, with a maximum "number needed to transport to the intervention center" (NNTI) of 100 patients without large vessel occlusion (LVO) to prevent one death or severe disability.

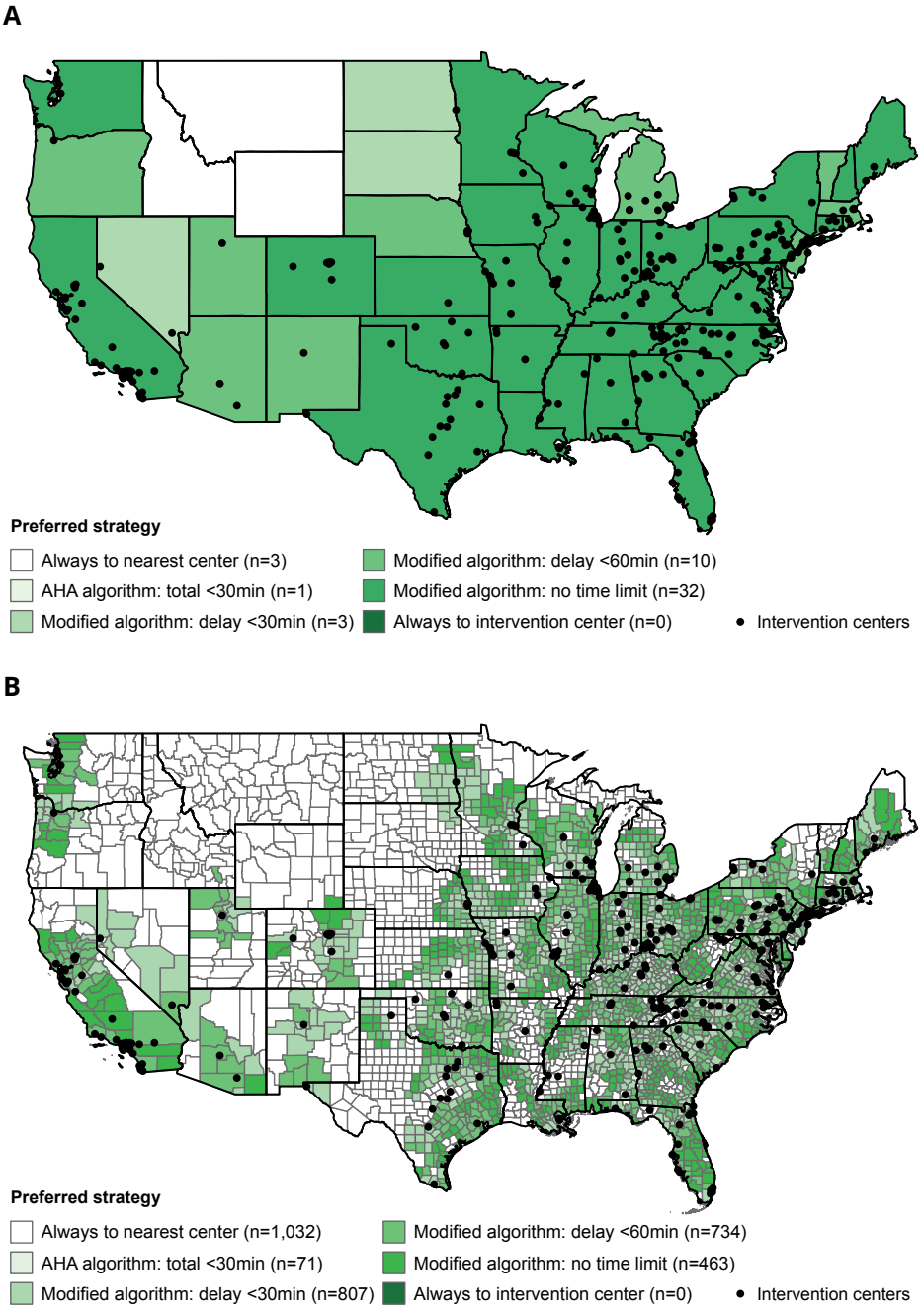

Figure 10.1. The preferred prehospital triage strategies in the base case scenario, on state-level (A; n=49) and county-level (B; n=3,107).

Table 10.2. State characteristics according to the preferred prehospital triage strategy in the base case scenario.

			Modified triage algorithm		
	Always to nearest stroke center	**AHA triage algorithm (total driving time <30 min)**	**Additional driving time <30 min**	**Additional driving time <60 min**	**No time limit**
Number of states	3	1*	3	10	32
Population density per mi^2 land area	7 (7–14)	11,377	11 (11–19)	65 (39–704)	131 (74–236)
Total number of stroke centers per 10,000 mi^2 land area	0.03 (0.02–0.03)	82	0.08 (0.06–0.1)	0.2 (0.1–0.9)	0.7 (0.3–1.4)
Percentage of stroke centers that are intervention centers	0% (0%–0%)	60%	7% (3%–0%)	15% (10%–22%)	16% (10%–19%)
Average driving time to nearest primary stroke center, in minutes	90 (76–104)	11	61 (43–69)	30 (26–40)	29 (20–34)
Average driving time to nearest intervention center, in minutes	280 (261–379)	14	163 (99–201)	53 (37–87)	49 (39–67)
Average driving time between primary stroke center and nearest intervention center, in minutes	250 (230–352)	13	128 (75–167)	38 (29–69)	43 (34–59)

*District of Columbia.
All characteristics are expressed as median (IQR). A strategy was considered the preferred strategy if no other strategy resulted in improved outcomes with an incremental "number needed to transport to intervention center" of <100 patients without large vessel occlusion to prevent one death or severe disability.

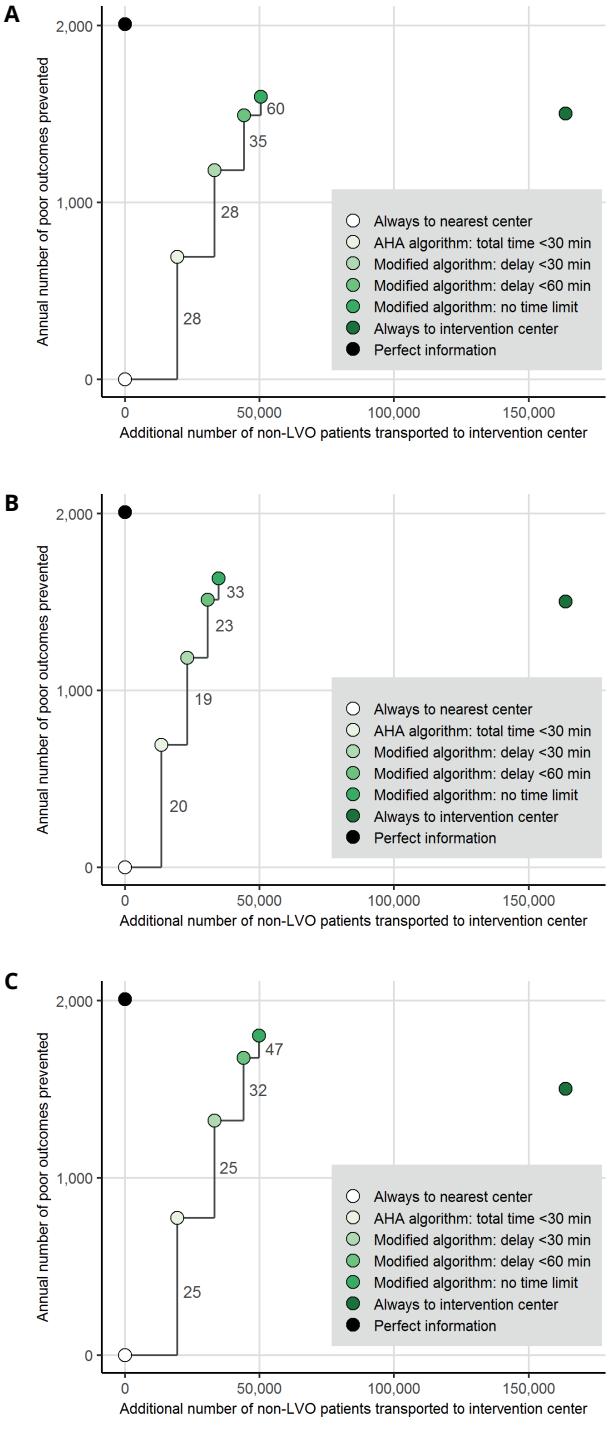

Figure 10.2. The effect of nationwide implementation of prehospital triage strategies.
The annual number of poor outcomes prevented, the additional number of patients without large vessel occlusion (LVO) transported to an intervention center and the corresponding "number needed to transport to intervention center" (NNTI) to prevent death or disability in one patient, in scenarios with different prehospital stroke scale characteristics. In A, the Rapid Arterial Occlusion Evaluation (RACE) was used with a sensitivity of 84% and a specificity of 60% at a cutoff at ≥5 points; B, shows a 10% absolute increase in specificity (ie, sensitivity 84% and specificity 70%); C, a 10% absolute increase in sensitivity (ie, sensitivity 94% and specificity 60%).

Figure 10.3. Results of the sensitivity analyses.
The state-level and county-level distribution of preferred prehospital triage strategies with changing prevalence of large vessel occlusion, workflow times in the primary stroke center, and maximum accepted "number needed to transport to intervention center" to prevent one death or severe disability.
*In this scenario, the door-to-needle time in the intervention center was also adjusted to 30 minutes.

Discussion

Our major finding is that, as a nationwide policy, the AHA triage algorithm is suboptimal when compared to strategies that permit direct transport of patients with suspected LVO to an intervention center even when leading to delays of 30 minutes or beyond. The current AHA policy is only preferred for the District of Columbia, where driving times are very short, or in scenarios with a low prevalence of LVO, very efficient workflow in the primary stroke centers or a low number of additional non-LVO patients accepted in the intervention centers. An algorithm without time limit for the transportation of LVO-suspected patients would be optimal in the majority of states and could greatly improve outcomes of the ischemic stroke population. Tailoring triage policies at county-level does not increase good outcome compared to the best nationwide strategy, but slightly improves triage efficacy by reducing the number of unnecessary transportations to the intervention center.

We assessed the effect of triage strategies on functional outcome of the ischemic stroke population, thereby assuming that optimizing patient outcomes is the driving force of these decisions. However, an increasing number of patients may lead to problems with resources and crowding in the intervention centers. We therefore used the NNTI to weight the effect of triage strategies on outcome against the number of additional non-LVO stroke patients transported to an intervention center. We defined an NNTI of <100 to prevent one death or severe disability as a reasonable limit in our base case. More restrictive triage strategies were only preferred when the maximum NNTI became <25. Improving the specificity of the prehospital stroke scale, either by choosing a higher cutoff or using another instrument, would also lower the number of unnecessary transportations without any increase in poor outcomes. Other criteria should also be taken into consideration when determining the optimal policy in a region. Transportation to an intervention center further away from their hometown can be inconvenient for patients and their relatives. Emergency medical services will be affected by the triage strategy: although less inter-hospital transfers will be needed, more patients will be transported directly to an intervention center further away, potentially outside the region. The shift of patient volume will also have economic consequences for primary stroke centers that will receive and treat less stroke patients. These centers need to be stimulated to improve their in-hospital workflow, because direct transportation to an intervention center becomes less favorable when the door-to-needle and door-in-door-out times in the primary stroke centers decrease.

Several limitations of this study need to be considered. First, not all centers in the US that are capable of IVT and/or EVT are officially certified, so we may have underestimated the number of centers. A higher number of centers might make transportation of patients to the intervention center more favorable. Second, “thrombectomy-capable” centers were treated in a similar way as comprehensive stroke centers, although it is unclear whether these centers are able to maintain the same level of experience and high standards of care.[27]

Third, we assumed that outcomes of non-LVO stroke patients are similar after transportation to a primary stroke center or intervention center. Fourth, we only considered the effect on the most severely affected patients (modified Rankin Scale score ≥2), without taking into account the full shift on the modified Rankin Scale. This might have underestimated the absolute effect of triage strategies, although the pattern of the contrasts between different strategies would probably remain similar. Fifth, our analyses only apply to patients that are presented within 6 hours after symptom onset. Recent studies showed that EVT can also be effective in a subgroup of imaging-selected patients presenting between 6 and 24 hours, but triage of these patients is affected by many other factors and needs further evaluation.[28,29] Finally, a formal cost-effectiveness analysis was beyond the scope of this study.

Little evidence is available from clinical studies on triage strategies.[30] An ongoing randomized clinical trial in Catalonia, Spain, might provide real-world evidence for a triage strategy based on the RACE score.[31] However, these results will only be directly applicable to regions with similar population density, between-center distances and in-hospital workflow times. Modeling studies can be used to translate these results to other regions with different geographical features, while clinical data is needed to optimize the estimates of (time-dependent) treatment efficacy, performance of prehospital stroke scales and model assumptions. A recent modeling study compared the effect of different triage policies on population level for a large region in Germany and showed that in certain regions direct transportation to an intervention center may yield better outcomes than the drip-and-ship approach.[32,33] Another mathematical study of this group showed that the current guidelines might be too conservative and suggested an additional delay to IVT of <30 minutes in urban areas and <50 minutes for rural regions.[34] Our study was the first to evaluate nationwide triage strategies for the US and confirmed the beneficial effect of increasing the accepted delay for bypassing the primary stroke center.

Adjustment of the current recommendations from the AHA/ASA are warranted to improve outcomes of the ischemic stroke population. Direct transportation of LVO-suspected patients within the 6 hour time-window should be permitted when leading to delays of 30 minutes or more, but only when this will not disqualify IVT. Regional policies can be further optimized based on local geographic circumstances and organization of stroke care, for example by using a more specific stroke scale or cut point when driving times are long or resources are scarce. Air transportation or the use of mobile stroke units could be of great importance for local triage systems in rural areas. The additional benefit of a GPS-controlled application to calculate the preferred strategy based on the exact location of the ambulance (ie, on Census tract level) seems limited, unless local driving times and workflow times fluctuate strongly. In the future, with increasing population density and increasing numbers of intervention centers expected, direct transportation to the intervention center may become more beneficial.

Conclusions

Implementation of prehospital triage strategies can greatly improve outcomes of the ischemic stroke population in the United States. The current AHA triage algorithm should be modified to allow more delay when directly transporting suspected LVO patients to an intervention center.

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Chapter 11

Prehospital triage of patients with suspected stroke symptoms (PRESTO): protocol of a prospective observational study

BMJ Open, 2019

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Abstract

Introduction

The efficacy of both intravenous treatment (IVT) and endovascular treatment (EVT) for patients with acute ischemic stroke strongly declines over time. Only a subset of patients with ischemic stroke caused by an intracranial large vessel occlusion (LVO) in the anterior circulation can benefit from EVT. Several prehospital stroke scales were developed to identify patients that are likely to have an LVO, which could allow for direct transportation of EVT eligible patients to an endovascular-capable center without delaying IVT for the other patients. We aim to prospectively validate these prehospital stroke scales simultaneously to assess their accuracy in predicting LVO in the prehospital setting.

Methods and analysis

Prehospital triage of patients with suspected stroke symptoms (PRESTO) is a prospective multicenter observational cohort study in the southwest of the Netherlands including adult patients with suspected stroke in the ambulance. The paramedic will assess a combination of items from five prehospital stroke scales, without changing the normal workflow. Primary outcome is the clinical diagnosis of ischemic stroke with an intracranial LVO in the anterior circulation. Additional hospital data concerning the diagnosis and provided treatment will be collected by chart review. Logistic regression analysis will be performed and performance of the prehospital stroke scales will be expressed as sensitivity, specificity and area under the receiver operator curve (AUC).

Ethics and dissemination

The Institutional Review Board of the Erasmus MC University Medical Center has reviewed the study protocol and confirmed that the Dutch Medical Research Involving Human Subjects Act (WMO) is not applicable. The findings of this study will be disseminated widely through peer-reviewed publications and conference presentations. The best performing scale, or the simplest scale in case of clinical equipoise, will be integrated in a decision model with other clinical characteristics and real-life driving times to improve prehospital triage of suspected stroke patients.

Trial registration number NTR7595 (www.trialregister.nl)

Box 11.1 Strengths and limitations of this study.

- *Prospective simultaneous validation of several prehospital stroke scales allows for direct comparison of their accuracy.*
- *In contrast to previous studies based on in-hospital assessment by experienced physicians, assessment of the prehospital stroke scales will be performed by paramedics in daily clinical practice.*
- *The results of this study will provide unique insight in the characteristics of an unselected group of patients with suspected stroke in the prehospital setting.*
- *The best performing scale will be integrated in a prehospital decision tool with other clinical characteristics and real-life driving times to select those patients that benefit from direct transportation to an endovascular-capable center.*
- *Performance will be measured with the area under the receiver operator curve (AUC), which does not always relate directly to the clinical usefulness of these scales.*

Introduction

Rapid treatment with intravenous thrombolytics (IVT) is effective for patients with an ischemic stroke of less than 4.5 hours after onset.[1,2] However, the effect of IVT is limited for ischemic stroke caused by an intracranial large vessel occlusion (LVO) in the anterior circulation, which accounts for approximately 30% of the patients.[3] These patients can benefit from endovascular treatment (EVT), preferably started within 6 hours after onset of symptoms, but this treatment can only be performed in specialized intervention centers.[4] The effect of both treatments strongly declines over time.[5-7] In current clinical practice, most suspected stroke patients are transported by ambulance to the nearest hospital for immediate treatment with IVT. Patients can subsequently be transferred to an endovascular-capable center, if eligible for EVT. This is one of the main causes of treatment delay and is associated with worse functional outcomes after EVT.[8,9]

Several prehospital stroke scales were developed to identify patients that are likely to have an LVO, which could allow for direct transportation of EVT eligible patients to an endovascular-capable center without delaying IVT for the other patients.[10,11] Most of these scales were derived from the National Institute of Health Stroke Severity (NIHSS) score and external validation was often attempted by retrospective assessment of the items based on the NIHSS score completed by the treating physician at the emergency department.[12-14] The results of existing prehospital validation studies are limited due to small sample sizes, selected populations or the exclusion of stroke mimics.[15-18] Further prospective validation

is therefore required to assess and compare the accuracy of these scales when used by emergency medical services (EMS) personnel in a broad population of suspected stroke patients under circumstances that reflect usual care.

Objective

The primary objective of this study is to prospectively validate several prehospital stroke scales simultaneously to assess their accuracy in predicting the likelihood of ischemic stroke caused by an intracranial LVO in the prehospital setting.

Methods and analysis

Study design

Prehospital triage of patients with suspected stroke symptoms (PRESTO) is a prospective multicenter observational cohort study. Patients will be recruited in the ambulance and a combination of items from different prehospital stroke scales will be assessed by the paramedic. The normal workflow will not be affected and there is no intervention. Additional hospital data will be collected by chart review. Routinely performed neuro-imaging will be collected and centrally assessed. Follow-up will only be performed in patients with a final diagnosis of ischemic stroke.

Study population

We will include patients in the southwest of the Netherlands, a region with approximately 2 million inhabitants. Participating paramedics have ample experience with the initial management of patients with acute neurological deficits and they received additional training before the start of the study with regards to the study procedures and the use of the prehospital stroke scales. Additional to the prior training, an instruction video is available for all paramedics. Also, during the duration of the study, regular visits are paid to all ambulance stations to provide feedback and address uncertainty or questions of the paramedics. All adult patients with acute neurologic deficit, defined as at least 1 point on the Face-Arm-Speech-Test (FAST), and a suspected diagnosis of stroke by the paramedic, will be included. Patients with a blood glucose level below 2.5 mmol/L will be excluded.

Prehospital stroke scales

We choose five well known prehospital stroke scales to validate: the Los Angeles Motor Scale (LAMS),[19,20] the Rapid Arterial oCclusion Evaluation (RACE),[18] the Cincinnati Stroke Triage Assessment Tool (C-STAT),[21] the Prehospital Acute Stroke Severity scale (PASS),22 and the Gaze-Face-Arm-Speech-Test (G-FAST).[23] These scales have many similarities in the items that are being used, but there are differences in the scoring systems and the degree of complexity of these scores. In the PRESTO study, we will assess a combination of the items used in these five scales (Table 11.1).

Table 11.1. Overview of the items and corresponding scores used in the prehospital stroke scales.

	LAMS	RACE	C-STAT	PASS	G-FAST	Items collected in this study
Answering questions (age and current month)						
Correctly answers both questions			0	0		0
Correctly answers one question			1*	1		1
Does not correctly answer either question						
Following commands ('close your eyes, 'make a fist')						
Correctly performs both tasks		0†	0			0
Correctly performs one task		1†	1*			1
Does not correctly perform either task		2†				2
Head and gaze deviation						
Normal; able to follow pen or finger to both sides		0	0	0	0	0
Gaze palsy or deviation (total or partial)		1	2	1	1	1
Facial palsy						
Normal and symmetrical movement	0	0			0	0
Mild palsy (flattened nasolabial fold or minor asymmetry in smile)		1			1	1
Moderate to severe palsy	1	2				2
Grip strength						
Normal grip strength	0					0
Weak grip strength	1					1
No grip possible	2					2
Motor function arm						
Normal	0	0	0	0	0	0
Drift (minimal drift with closed eyes)	1					
Mild palsy (arm drifts down within 10 seconds)		1	1	1	1	1
Severe palsy (not able to lift arm)	2	2				2
Motor function leg						
Normal		0				0
Drift (minimal drift with closed eyes)						
Mild palsy (leg drifts down within 5 seconds)		1				1
Severe palsy (not able to lift leg)		2				2
Language						
Normal speech					0	0
Speech problems (dysarthria, language abnormality, or unable to speak)					1	1
Agnosia						
Patient recognises his/her arm and the impairment		0‡				0‡
Does not recognises his/her arm or the impairment		1‡				1‡
Does not recognises his/her arm nor the impairment		2‡				2‡

*1 point if the patient answers at least one question incorrect and does not follow at least one command. †Only scored if right hemiparesis. ‡Only scored if left hemiparesis.

Data collection

Eligible patients presenting with suspected stroke symptoms will be recruited in the ambulance. The items from the prehospital stroke scales will be assessed by the paramedic and entered in a web-based database (LimeSurvey GmbH/Carsten Schmitz, www.limesurvey.org). The paramedic will also enter the transportation number (to link with EMS data and hospital data), the time of symptom onset or last known well (according to patient or bystander), the side of the hemiparesis (if applicable), and the presence of a known neurological deficit on the symptomatic side. Data concerning demographics, vital functions, general neurological examination and transportation times will be collected from the EMS databases.

After arrival in the hospital, patients will receive the usual care. A non-contrast CT scan and additional imaging (eg, CT angiography (CTA), digital subtraction angiography (DSA) and/or CT perfusion) can be performed as part of the regular workup of a suspected stroke. No additional imaging will be performed in the context of this study. Clinical data concerning the medical history, medication use, laboratory results, physical examination, and diagnosis will be collected by chart review. All diagnostic neuro-imaging data and radiology reports will be collected. If applicable, we will also collect information on the given treatment and corresponding treatment times (eg, the door-to-needle time, the door-to-groin time, the imaging-to-treatment time, and the door-in-door-out time of transferred patients).

Follow-up will only be collected for patients with a final diagnosis of ischemic stroke. We will use the outcome registration of the hospitals to collect length of hospital stay, discharge destination, and the modified Rankin Scale (mRS) score after 90 days.

Outcome measures

Primary outcome will be the clinical diagnosis of ischemic stroke with an intracranial LVO in the anterior circulation, defined as an occlusion of the internal carotid artery, the middle cerebral artery segment M1 or M2, or the anterior cerebral artery segment A1 or A2 (assessed on CTA or DSA). Secondary outcome measures include the presence of an LVO in the posterior circulation (vertebral artery or basilar artery); the final diagnosis at hospital discharge; the given treatment (IVT, EVT, or both) and corresponding treatment times; and the functional outcome, measured with the 90-day mRS.

Sample size calculation

At least 100 events (ie, intracranial LVOs) are required for the external validation of predictive models.[24,25] The annual incidence of suspected ischemic stroke within 6 hours after onset of symptoms is estimated to be 50 per 100,000 people, based on an earlier cohort study.[14] In the catchment area of the participating EMS (approximately 2 million inhabitants), this would imply 1,000 patients every year presenting with stroke symptoms within the 6-hour time window. Of these 1,000 patients, approximately 15% are assumed

to have an ischemic stroke due to an LVO; 31% an ischemic stroke without the presence of an LVO; 9% a transient ischemic attack (TIA); 10% an intracerebral hemorrhage; and 35% a stroke mimic.[14] To reach the required number of 100 stroke patients with an LVO, we will have to include at least (number of cases / prevalence = 100 / 0.15) 667 patients with stroke symptoms of less than 6 hours. To allow for a 5% loss of follow up, we will aim for a sample size of 700 patients.

After inclusion of the first 500 patients, we will perform an interim analysis to calculate the percentage of LVO in our study population. If necessary, the required sample size will be adjusted based on this information. Although patients presenting after 6 hours will be included in the study, they will not count for the required sample size.

Data analysis plan

After completion of the last inclusion, the data will be checked and the database will be locked for statistical analyses. We will report the absolute numbers and percentages of patients based on the final diagnosis (eg, ischemic stroke, hemorrhagic stroke, TIA or stroke mimic) and, if applicable, the location of the intracranial LVO. For ischemic stroke patients, we will report the given treatment (IVT, EVT, or both) and corresponding treatment times, the number of inter-hospital transfers, and the functional outcome after 90 days. Missing values will be imputed with simple imputation based on the mean or mode (if less than 5% missing) or multiple imputation based on relevant covariates and outcome (if more than 5% missing).

The different prehospital stroke scales will be reconstructed based on the items assessed in the ambulance (Table 11.1). We will validate the prehospital stroke scales for patients presented within 6 hours after symptom onset using a logistic regression model with the presence of an LVO in the anterior circulation as outcome measure. We will analyze the scores both continuously and dichotomised, based on the previously reported cut points in the original studies. Sensitivity and specificity of all cut points will be reported separately. The global performance of the prehospital stroke scales will be expressed as the area under the receiver operator curve (AUC).

Prespecified sensitivity analyses will be performed for patients that presented more than 6 hours after symptom onset, for the separate occlusion locations, and for the presence of an LVO in the posterior circulation. We will also assess the original outcome definitions as defined in each prehospital stroke scale instead of our own primary outcome and we will analyse the correlation between the prehospital stroke scales and the NIHSS assessed at the emergency department. Additional analyses will be performed to predict the probability of treatment with EVT based on the prehospital stroke scales and relevant factors in the medical history, medication use or vital signs.

Patient and public involvement

Patients and public were not involved in the development of the research questions or the design of this study. All study participants and every interested person in the public will have the possibility to read regular project updates on the project website (www.presto-studie.nl).

Duration and current status of the study

The study was registered in The Netherlands Trial Register on November 11, 2018 under number NTR7595 (www.trialregister.nl). The study started on August 13, 2018 in the region Zuid-Holland Zuid and on September 1, 2018 in the region Rotterdam-Rijnmond. Recruitment of patients is ongoing and at the time of submission, April, 2019, 665 patients have been included in the study within 6 hours of symptom onset. In anticipation of a formal interim analysis, first raw data analysis shows a prevalence of 8% LVO in our study population. Based on this information, we increased our sample size to 1250 patients. With the current inclusion rate, we expect to reach the required sample size of 1250 patients by September 2019.

Ethics and dissemination

Ethical aspects and informed consent

This study will be conducted in accordance with the principles of Good Clinical Practice, the Dutch Agreement on Medical Treatment Act (WGBO), and the European General Data Protection Regulation (GDPR). The Institutional Review Board of the Erasmus MC University Medical Center has reviewed the study protocol and confirmed that the Dutch Medical Research Involving Human Subjects Act (WMO) is not applicable.

Acquiring informed consent can be very challenging in the prehospital inclusion of suspected stroke patients. Many patients suffer from a language deficit, anosognosia, or other cognitive symptoms that impede an informed consent procedure, and often there is no (legal) representative of the patient present in the prehospital setting. Furthermore, an adequate informed consent procedure takes time, which is not available in the prehospital setting. Sometimes a deferred consent procedure can be used, but in the context of the WGBO this should be done by the treating physician. Since our unselected population of patients, including many stroke mimics, will spread towards different directions after presentation in the hospital, a disproportionate number of health care providers from a variety of specialisms (eg, neurologists, emergency physicians, internists, cardiologists) should be involved in the research to enable a deferred consent procedure.

The extent of the effort by a large number of health care providers needed to obtain permission from the participating patients is disproportionate to the relatively limited sensitivity of the collected and linked personal data and the related limited intrusion to the

personal privacy. We will therefore use an opt-out procedure in this study. The including paramedic will provide a leaflet with information about the study to the patient or their relatives. In this leaflet, we will explain that some routinely collected data can be collected from the EMS databases and the hospital charts for further analysis. Patients or their relatives are offered the opportunity to object to the use of these data in this study. When a patient or relative objects to study participation, all data will be destroyed and the patient will be excluded from the study.

Dissemination plan

The main study results will be disseminated via publication in an international peer-reviewed journal and presentation at international conferences for stroke and emergency medicine experts. Representatives of the EMS providers and participating hospitals will be given the opportunity to comment on the manuscript and to participate as co-author, following the recommendations of the International Committee of Journal Editors (ICMJE). We plan to disseminate the results of the planned secondary analyses in one or more separate papers.

The best performing scale, or the simplest scale in case of clinical equipoise, will be integrated in a decision model with other clinical characteristics and real-life driving times.[26] This model can be implemented in an online tool to improve prehospital triage of patients with suspected stroke symptoms without harming those patients that benefit from rapid IVT in the nearest hospital. Patients eligible for EVT will be directly transported to an endovascular-capable center, which will lead to an increased number of treated patients, reduced treatment times and improved patient outcomes. Moreover, avoiding unnecessary inter-hospital transfers will lead to more efficient use of EMS resources.

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Chapter 12

General discussion

The overall aim of this thesis was to increase the benefit of endovascular treatment for ischemic stroke by optimizing prediction of outcome and treatment effect, reducing treatment delay, and improving prehospital triage strategies. In this final chapter, I present the main findings, followed by recommendations for clinical practice and future research.

Treat the right patient

Endovascular treatment (EVT) greatly improves the overall functional outcome of patients with ischemic stroke due to a proximal, intracranial large vessel occlusion (LVO) in the anterior circulation.[1] However, to maximize the effect and reduce potential harms or costs, it is important to identify those patients who are likely to benefit and those who are not. Although subgroup analyses are valuable to explore potential differences in the relative treatment effect, they are insufficient for individual treatment decisions.[2] Patients are placed in a specific subgroup based on a single feature, such as old age or poor collateral score, without taking into account the large variation between individual patients. Also, subgroup analyses are mostly underpowered and prone to false-negative and false-positive results.[3,4] Therefore, we developed the MR PREDICTS decision tool which combines the effect of multiple clinical and imaging characteristics on outcome and treatment effect simultaneously (Chapters 2 and 3). Included in the model were age, baseline National Institute of Health Stroke Severity (NIHSS) score, systolic blood pressure, history of ischemic stroke, history of diabetes mellitus, degree of pre-stroke disability, prior intravenous treatment with alteplase (IVT), Alberta Stroke Program Early Computed Tomography Score (ASPECTS), location of the occlusion, collateral score, and time from onset to start of treatment, defined as groin puncture. We found large differences in the predicted benefit between individual patients, but almost no harm was predicted. Even in subgroups were previous subgroup analyses showed absence of treatment effect (ie, patients with no collaterals or poor ASPECTS), the model identified a substantial proportion of patients who would benefit.

External validation of MR PREDICTS with data from the HERMES trials and the MR CLEAN Registry showed reasonable to good model performance for the prediction of outcome (Chapter 4). However, prediction of treatment benefit, defined as the difference between the probability of functional independence with and without EVT, is more complex. The observed treatment benefit in HERMES was systematically larger than predicted, especially in the quintile of patients with the lowest predicted benefit. This might be explained by the strict selection of patients who were included in the HERMES trials; patients with unfavorable imaging characteristics were only randomized when a large treatment effect was expected based on other characteristics. Patient selection in the MR CLEAN Registry was less strict, but treatment benefit could not be assessed directly due to the lack of a control group. However, patients with small predicted treatment benefit had low rates of functional independence at 3 months, irrespective of their reperfusion status after the intervention, which might suggest absence of treatment benefit.

Box 12.1 Overview of the main findings per research question

Can we reliably and accurately predict outcome and treatment benefit of endovascular treatment for individual patients?
We developed and validated a prediction model (MR PREDICTS) that combines multiple baseline clinical and radiological characteristics to predict outcome with and without endovascular treatment. This model performed reasonably well in several validation cohorts and can support clinical judgement in distinguishing between patients who are likely to benefit from endovascular treatment and those who are not. Individual outcome predictions can be improved one day after the intervention using our post-procedural model (MR PREDICTS@24H), which showed excellent discriminative ability.

What are the main causes of prehospital and in-hospital delay of endovascular treatment?
Inter-hospital transfer proved to be the main determinant of treatment delay and a significant cause of poor outcomes even in the Netherlands, where the between-center distances are relatively small. In-hospital workflow processes in the emergency department and the angiosuite should be streamlined to ensure rapid treatment.

How do workflow improvements effect treatment delay and outcome?
Workflow interventions aimed at reducing any delay in the time between symptom onset and treatment, lead to a higher chance of good functional outcome for individual patients, especially when multiple interventions are combined. Effective interventions concern prehospital triage and transportation, in-hospital patient transfers, parallel workflow processes, anesthetic management, teamwork, and feedback on target times.

Which factors should influence the decision to transport individual patients directly to an intervention center?
Prehospital triage decisions should be based on the individual likelihood of large vessel occlusion, transportation times to the nearest primary stroke center and nearest intervention center, and in-hospital workflow characteristics such as the door-in-door-out time and door-to-groin time.

What is the optimal prehospital triage strategy for suspected stroke patients?
The use of a prehospital stroke scale to directly transport patients with suspected large vessel occlusion to an intervention center can improve outcomes, but the optimal triage strategy depends on geographic and organizational characteristics. We constructed a decision model that can be used to inform personalized triage decisions and to evaluate triage policies for specific regions.

Outcome predictions are more accurate when taking into account post-procedural variables such as the degree of reperfusion achieved and the National Institute of Health Stroke Scale (NIHSS) score after 24 hours. We used data available within one day after the intervention to develop MR PREDICTS@24H, a simple tool that combines nine variables to predict functional outcome following EVT (Chapter 5). The severity of stroke symptoms after one day, measured with the NIHSS, was the strongest predictor for functional outcome after 3 months. External validation with MR CLEAN Registry data showed excellent discriminative performance, but suboptimal calibration. The model was therefore updated with a separate intercept to reflect the baseline risk of the population treated in clinical practice. Although this model does not affect the decision to provide EVT, it may guide physicians in personalizing a patients' treatment and rehabilitation plan based on the probability of full recovery.

Several other pre-procedural models for the prediction of functional outcome following EVT exist, with c-statistics ranging between 0.60 and 0.80, but none of these predict outcome with and without EVT to assess the absolute treatment effect.[5] The most frequently used predictors are age, baseline NIHSS score, and some kind of imaging characteristic. The addition of collateral score improves the predictive performance of existing models, which strengthens the hypothesis that collateral blood flow is a major predictor of outcome and treatment effect.[6] Two models found potential subgroups of patients with small treatment benefit, based on a poor outcome irrespective of the reperfusion status, but these results need further validation in larger samples.[7,8] Of the previously published post-procedural models, only three were externally validated and these are all developed with data from the period before the proven effectiveness of EVT.[9-11]

Overall, MR PREDICTS and MR PREDICTS@24H showed large variations in anticipated outcome and treatment benefit of individual patients based on multiple characteristics. Both models were developed and validated using recent high-quality datasets of patients treated within 6 hours after stroke onset. The updated models are available online to aid patient selection and outcome prediction in daily clinical practice (www.mrpredicts.com).

Treatment benefit in perspective

With a number needed to treat of 2.6 to reduce disability with one level on the modified Rankin Scale (mRS), EVT ranks among the most effective treatments in the medical field.[1] However, it is important to realize that the total benefit on population-level is not only affected by the size of the treatment effect, but also to a large extent by the number of eligible patients. Treatments with a small effect for the individual patient, might have a large effect on the whole population when applicable to a larger proportion of patients. Organized stroke unit care by a multidisciplinary team, for example, has a small absolute treatment benefit, but leads to a high increase in the number of patients achieving functional independence. EVT has the largest effect on individual patients, but the effect size on

Table 12.1 An illustration of the annual effect of ischemic stroke interventions in the Netherlands, based on 29,082 hospitalizations in 2018.[12]

	Target population	Estimated number of eligible patients (% of total)	Percentage of patients achieving functional independence (mRS 0-2)	Absolute risk difference	Additional number of patients achieving functional independence (% of total)
Stroke unit care	All ischemic stroke patients admitted to the hospital	29,082 (100%)	Treatment 49.6% Control 39.8%[13]	9.8% (NNT = 10)	2,850 (9.8%)
IV treatment with alteplase	Patients with ischemic stroke presenting within 4.5 hours after onset of symptoms or last seen well	5,917[12] (20.3%)	Treatment 45.9% Control 39.5%[14]	6.4% (NNT = 16)	333 (1.1%)
Endovascular treatment	Patients with ischemic stroke due to an intracranial LVO in the anterior circulation, presenting within 6 hours after onset of treatment or last seen well	1,906[12] (6.6%)	Treatment 46.0% Control 26.5%[1]	19.5% (NNT = 5)	372 (1.3%)
Decompressive hemicraniectomy	Ischemic stroke patients under 60 years with malignant middle cerebral artery infarction	87 (0.3%[15])	Treatment 26.7% Control 13.9%[16] (mRS 0-3)	12.8% (NNT = 8)	11 (0.04%)
Early antiplatelet therapy	All ischemic stroke patients presenting within 2 weeks after stroke onset	29,082 (100%)	Treatment 54.3% Control 53.0%[17]	1.3% (NNT = 79)	378 (1.3%)

IV, intravenous; LVO, large vessel occlusion; mRS, modified Rankin Scale; NNT, number needed to treat.

population-level is comparable to the effect of IVT or early treatment with antiplatelet agents (Table 12.1).

Strict selection of patients with a high expected treatment benefit, for example based on favorable imaging characteristics, will increase the treatment effect found in a study, but decreases the total number of patients treated in clinical practice and thereby the overall impact on the stroke population.[18] A clear example is the large treatment effect that was shown in the recent randomized controlled trials (RCTs) on EVT for patients presenting between 6 and 24 hours since symptom onset or last seen will.[19-21] The reported absolute risk difference of 28-36% for achieving functional independence suggests an enormous effect of treatment in the late time window, but the overall impact is limited due to the small percentage of eligible patients.[22,23] Further studies on late treatment should therefore focus on expanding the number of treatable patients. Within the 6 hour time window, benefit of EVT is considerable within all subgroups. MR PREDICTS should not be used to select patients with the highest expected benefit, but only to identify patients for whom treatment would likely be futile. Referral of these patients to an intervention center is costly for the health system and unnecessarily inconvenient for their families.

Treat at the right time

Time is brain and rapid initiation of EVT is of great importance to maximize outcomes of ischemic stroke patients with intracranial LVO.[24,25] Any delay between onset of symptoms and achieving reperfusion directly translates to a decreased chance of a favorable outcome. Early recognition of stroke symptoms and public awareness of the importance of rapid treatment are necessary to avoid patient delay in seeking medical attention.[26-28] In-hospital determinants of delay in the MR CLEAN trial were presentation during off-hours and the use of general anesthesia (Chapter 6), which was confirmed in several studies.[29-33] Analyses of treatment delay in two other RCTs, Endovascular Treatment for Small Core and Proximal Occlusion Ischemic Stroke (ESCAPE) and Solitaire With the Intention for Thrombectomy as Primary Endovascular Treatment (SWIFT PRIME), did not find a significant association with off-hour treatment, but these trials were focused on improving workflow and participating centers were trained in the delivery of fast care and logistics.[34,35] Prior IVT was not associated with treatment delay, which is likely explained by the streamlined protocols for the administration of alteplase while preparing for CT angiography and transferring the patient to the angiosuite, without waiting for a clinical response.

The most significant modifiable source of delay in the delivery of EVT is the transportation from a primary stroke center to an intervention center.[34-37] In the MR CLEAN trial, 44% of all patients were transferred, and time from onset to treatment was increased with more than one hour in these patients (Chapter 6). The total delay that occurred in the primary stroke center was much larger, but part of this delay was compensated by a faster work-up in the intervention center. Similar results were found for transferred patients in the MR CLEAN

Registry, reflecting current clinical practice (Chapter 7). The probability of achieving functional independence decreases with 8.5% when a patient was first presented in a primary stroke center. In addition, there are probably also patients who were not transferred to an intervention center because the time window for EVT does not allow for the transfer time. On the other hand, patients without LVO may have benefited from early admission to a primary stroke center by receiving IVT as early as possible, but these patients were not included in the Registry.

Although transferred patients arrive later after stroke onset at the intervention center, they are treated more quickly after arrival than directly admitted patients (Chapters 6 and 7). This finding is probably explained by the fact that part of the diagnostic work-up and treatment, including IVT, is already performed in the primary stroke center. Also, pre-notification allows for the interventional team to prepare in advance. The short door-to-groin time of transferred patients suggests that in-hospital workflow times can also be improved for directly admitted patients by streamlining processes on the emergency department and in the angiosuite.

Workflow improvements

In a systematic review and meta-analysis, we showed that interventions in the workflow of EVT lead to better clinical outcomes, and that this effect increases when multiple interventions are combined (Chapter 8). Strategies that reduced transfer-related delay include requiring the emergency medical services to wait at the primary stroke center until the decision of EVT eligibility has been made, improving cloud-based image sharing with the intervention center, and transporting transfer patients directly to the angiosuite. In regions with very large between-center distances, the additional use of air ambulance services for inter-hospital transportation should also be considered. Another possibility would be to bypass the primary stroke center by using a mobile stroke unit. This is an ambulance with a CT scanner and a specialized team on board, allowing in-ambulance initiation and administration of IVT and direct transportation to the intervention center.[38-41] Despite its potential advantages, the clinical benefit and cost-effectiveness of this strategy are unclear and warrant further research.[42]

Interventions that reduced in-hospital delay were focused on pre-notification by the emergency medical services, direct activation of the entire stroke team, rapid acquisition of brain imaging, and provision of feedback on workflow times to the entire team. Parallel workflow processes for the administration of IVT without delaying EVT might be improved by the use of novel thrombolytic agents such as IV tenecteplase, that do not depend on a 60-minute infusion duration.[43,44] The 24/7 in-house presence of a vascular neurologist and an interventional team could further improve treatment times during off-hours, but this might be limited by the low number of stroke patients currently eligible for EVT.[45] It has also been suggested that increased experience, reflected in higher volumes of patients treated

with EVT, leads to shorter treatment times.[46] Centralization of stroke care could increase the experience of stroke teams and neuro-interventional teams, but should be weighed against the harm of longer transportation times that will emerge. Finally, procedural factors also affect the time between groin puncture and reperfusion, but this is beyond the scope of this thesis.

The significant effect of workflow interventions on time to treatment is consistent with previous studies related to IVT. Studies that successfully reduced treatment times used a combination of several interventions, a multidisciplinary approach, intensive training, and frequent evaluation. After implementation of a national quality improvement initiative and education program by the American Heart Association/American Stroke Association (AHA/ASA), the percentage of patients treated within 60 minutes increased from 29.6% to 53.3% in participating centers.[47] A Dutch multicenter study proved cost-effectiveness of an intensive implementation program to increase the proportion of patients treated with IVT, although it was lacking power to show an effect on functional outcome.[48,49] Reported factors of delay in patients with door-to-needle times of >60 minutes include delayed diagnosis, inability to determine eligibility, and difficulties in the management of comorbidities.[50] A dedicated center in Helsinki systematically implemented multiple interventions over a period of more than 10 years and was able to reduce the median door-to-needle time to 20 minutes.[51] In 2018, the median door-to-needle time in the Netherlands was 24 minutes (IQR 18–34) and the proportion of patients receiving IVT is currently among the highest of Europe.[12,52]

Target times

Specified target times can be used to improve workflow and compare between centers, but what times are reasonable to achieve in clinical practice? Many different time metrics are proposed in the literature, but one should always keep in mind that the total time interval from symptom onset to reperfusion is relevant for patients.

The door-in-door-out time reflects the total workflow in the primary stroke center from arrival at the emergency department until departure to an intervention center. A recent study suggested a median target time of <45 minutes, which was the top 15th percentile of

Table 12.2 Proposed target times and real-world time metrics of Dutch intervention centers, in minutes.

	Target times		Time metrics in the Netherlands		
	AHA/ASA[56]	This thesis	MR CLEAN trial	MR CLEAN Registry	Dutch Acute Stroke Audit 2018[12]
Door-to-groin time transferred patients	60	25	96 (75–120)	47 (31–70)	26 (17–39)
Door-to-groin time directly admitted patients	90	60	170 (142–205)	104 (80–135)	69 (54–93)

their own door-in-door-out times.[53] This target might be too ambitious, considering the median door-in-door-out time of 88 minutes (IQR 68 to 117) in the MR CLEAN Registry and approximately 100 minutes in another large registry in the United States.[37] The so called picture-to-puncture time, defined as the time from first imaging to groin puncture, describes the total workflow for transferred patients in both centers, with a proposed target time of <90 minutes.[54,55] Since this measure includes the driving time between the centers, which is a non-modifiable part of the workflow that depends on the local distribution of hospitals, it should only be used to describe regional workflow characteristics.

For the workflow in the intervention center, the HERMES collaborators proposed a median door-to-groin time of <75 minutes, which was achieved in only 11.5% of the patients treated in the MR CLEAN trial (Chapter 6). It seems more appropriate to determine specific target times for patients that arrive directly at the intervention center and patients that are referred from a primary stroke center, as proposed by the AHA/ASA Target: Stroke Phase III initiative (Table 12.2).

As a last remark, I would like to emphasize that these target times might not be sufficient to ensure rapid treatment of the majority of stroke patients by focusing on the median. By its definition, only 50% of the ischemic stroke population is treated within a median target time, while significant delay may occur in the other 50%. It is therefore always important to assess the interquartile range, and maybe even the 90th percentile, when evaluating treatment times.[57]

Treat in the right place

Prehospital triage of suspected stroke patients involves the trade-off between allowing rapid IVT in the nearest hospital versus avoiding transfer-related delay by direct transportation to an intervention center. We constructed a robust decision tree model to predict the optimal strategy based on individual and regional characteristics (Chapter 9). Factors that influence optimal triage decisions are the likelihood of LVO, estimated driving times to the primary stroke center and the intervention center, and local in-hospital workflow times. This finding is consistent with the results of other (mathematical) models, which used fixed values for the probability of LVO.[58-62] Our model is based on the entire range from 0% to 100% likelihood of LVO, and can therefore be used with different prehospital stroke scales as input. It can also be used to assess which differences in sensitivity or specificity between different stroke scales would be clinically relevant.

In Chapter 10, the decision model was combined with a geographic information system analysis to estimate the effect of nationwide, state-level, and county-level implementation of several prehospital triage strategies in the US. We evaluated the current AHA Mission: Lifeline® Stroke algorithm, which recommends direct transportation of suspected LVO patients (based on any positive prehospital stroke scale) to an intervention center when the

additional driving time will not disqualify for IVT and the total driving time from scene to the nearest intervention center is less than 30 minutes.[63] The results showed that nationwide implementation of this AHA algorithm prevents death or severe disability in 692 patients per year compared to transportation of all patients to the nearest center, but is suboptimal compared to strategies that allow to bypass the primary stroke center even when leading to delays of 30 minutes or beyond. The current AHA algorithm is only preferred in scenarios with very short driving times, a low prevalence of LVO, very efficient workflow times in the primary stroke centers, or a low number of additional patients without LVO accepted in the intervention centers. A modified algorithm without a time limit for the transportation of LVO-suspected patients would be optimal in the majority of states and could greatly improve outcomes of the ischemic stroke population in the United States.

There is no randomized data available to support these findings, and although clinical data showed better outcomes for patients directly transported to an intervention center, these studies did not take into account the negative effect of bypassing the primary stroke center for patients without LVO.[64] An ongoing RCT in Catalonia, Spain, will be the first to directly compare standard transportation to the nearest hospital to prehospital triage with the Rapid Arterial Occlusion Evaluation (RACE) score.[65] This study might provide real-world evidence for the use of a prehospital stroke scale, but the results will only be applicable to regions with similar population density, geographic distribution of hospitals and in-hospital workflow times. Modeling studies will therefore always be required to translate trial results to regions with other geographic and organizational characteristics.

Prehospital stroke scales

Because the likelihood of LVO is one of the main drivers of triage decisions, early prehospital identification of patients at risk of having an LVO in the ambulance is of utmost importance. Numerous prehospital stroke scales have been proposed, but none of these scales predict LVO with both a high sensitivity and a high specificity.[66,67] Most validation studies used retrospective reconstruction of the scores with data from the in-hospital assessment by experienced physicians, which is not representative of clinical practice. The RACE score was prospectively validated in a prehospital setting and showed a sensitivity of 84% and a specificity of 60% at a cutoff at ≥5 points.[68] The prevalence of LVO among suspected stroke patients was 20%, resulting in a positive predictive value of 34%. When transporting all patients with a positive RACE score to an intervention center, there will be two non-LVO patients (false positives) for every patient with LVO stroke (true positives).

Further prospective, prehospital validation of prehospital stroke scales is needed to compare their accuracy. Choosing the optimal prehospital stroke scale for triage of suspected stroke patients depends on the false positives (ie, patients without LVO that are transported to an intervention center) and false negatives (ie, patients with LVO that are transported to the primary stroke center). These numbers are based on the sensitivity and specificity of a scale,

but also on the prevalence of LVO in the local population. Previous studies reported a prevalence among ischemic stroke patients ranging from 7% to 60%.[69] Most physicians will prefer a scale with a high sensitivity to increase the number of patients with LVO stroke directly transported to an intervention center. However, the specificity of a score reflects the number of false positives, which is a very relevant measure when financial resources or the capacity of intervention centers are limited.

We designed the PRESTO study to prospectively evaluate and compare several prehospital stroke scales used by emergency medical services in a broad population of suspected stroke patients (Chapter 11). The simultaneous in-field validation of several prehospital stroke scales allows for direct comparison of their accuracy in an unselected population. Patient inclusion was finished in September 2019 and the final results of this study, including core lab assessed imaging data, are expected soon.

Strengths and limitations

The main analyses in this thesis were performed with data from the MR CLEAN trial, which is considered to have the broadest inclusion criteria of the recent trials, and the MR CLEAN Registry, one of the largest cohorts of consecutive patients treated with EVT. Both cohorts are representative of patients treated in routine clinical practice without mandatory clinical or imaging-based selection criteria, which makes them especially suitable for the development of clinical prediction models. Patient outcomes in MR CLEAN and the Registry were less favorable than in the HERMES cohort, but this might be explained by the strict selection criteria, the inclusion of high-quality centers with ample experience, and the fast workflow times of the studies included in HERMES, which may not correspond to real-life clinical practice. On the other hand, the relatively small sample size of the MR CLEAN trial (n=500) limits generalizability, especially for small subgroups (eg, patients with M2 occlusions or low ASPECTS). The Registry, although larger in sample size, is limited by the lack of a control group and the high number of missing values, including missing outcomes.

Experienced clinicians are able to consider multiple factors when predicting outcome of individual patients with ischemic stroke, but several cognitive biases may occur and physicians' predictive accuracy showed to be suboptimal compared to prediction models that combine the information of large datasets.[70-73] Well developed and externally validated models can be used to aid the clinician when making treatment decisions or rehabilitation plans. MR PREDICTS showed modest predictive ability, especially in the clinical trial population, but the main predictor effects were comparable in the different cohorts, and the model was updated using data from daily clinical practice. The effect of MR PREDICTS on patient selection will be limited, due to the substantial treatment effect and small potential harm of EVT. More difficult treatment decision arise when patients present after 6 hours of symptom onset, but there is currently insufficient data to develop an accurate model for late window patients.

The analyses of treatment delay and prehospital transportation times were performed with data from the Netherlands, which is a small, densely populated country compared to other Western regions. The average transfer time in our study was less than 30 minutes, which limits the generalizability of our results to other regions. It is likely that the negative effect of inter-hospital transfer is even larger in countries with large between-center distances. Therefore, we used the wide variety of geographical areas in the United States to further evaluate triage strategies.

The driving force of our prehospital model was to optimize patient outcomes, but the effect of triage strategies extends far beyond functional outcome alone. Unnecessary transportations to a more distant intervention center are inconvenient for patients and their relatives, and may lead to problems with resources and crowding at the intervention centers. This can be reduced by choosing a higher cut point or a more specific prehospital stroke scale. The shift of patient volume will also have economic consequences for the primary stroke centers that will receive and treat less stroke patients. This will create a substantial incentive for these centers to improve their workflow times, which makes transportation to a primary stroke center less harmful.

Comparison with acute myocardial infarction

The current developments in the field of vascular neurology have many similarities with previous developments in cardiology due to the large similarity between ischemic stroke and myocardial infarction (MI). During MI, the blood flow in a coronary artery is suddenly blocked, causing ischemia of the heart muscle. An electrocardiogram, which records the electrical activity of the heart, is used to identify patients with an ST elevation MI, which indicates salvageable tissue in distress. These patients benefit from direct restoration of the blood flow by a percutaneous coronary intervention (PCI), while patients without ST elevation are initially treated with medication.

Treatment of MI is time-critical, just like ischemic stroke treatment, and delayed initiation of PCI is associated with increased mortality.[74] In 1999, the American Heart Association recommended a door-to-balloon time of <90 minutes to increase the chance of good outcome.[75,76] This target time was achieved in only half of the American patients in 2005, which increased to 76% of the patients in 2008 due to the efforts of a national quality campaign implementing several workflow interventions.[77] A study on specific strategies showed a significant effect of rapid activation and availability of the catheterization laboratory, 24/7 availability of an attending cardiologist, and the provision of real-time feedback to the entire team.[78] Early emergency department activation of the catheterization team can reduce door-to-balloon times with >30 minutes.[79,80]

As in ischemic stroke, the transfer of patients from a non-intervention center to an intervention center is associated with significant delay. Several strategies to improve workflow of the emergency medical services, emergency department and in-hospital care

Table 12.3 Potential interventions to reduce delay between symptom onset and start of treatment.

Time metric	Prehospital targets	In-hospital targets
Symptom onset to EMS notification	• Increasing public awareness • Training family doctors	
Scene to first hospital	• Improving stroke recognition of EMS staff	
Scene to intervention center	• Bypassing the primary stroke center when the likelihood of LVO is high • Use of mobile stroke unit to identify patients with LVO	
Door-to-imaging	• Prehospital notification • Direct EMS transfer to CT scanner	• Direct activation of the stroke team
Door-in-door-out	• Enlisting EMS crew to remain at primary stroke center until the definitive treatment decision is made	• Rapid imaging acquisition • Parallel treatment with IV alteplase • Direct contact with intervention center • Initiation of transfers without awaiting approval of the intervention center in patients clearly meeting well-defined criteria • Providing time targets with frequent feedback to the entire team
Transfer time	• Air transportation	
Door-to-groin puncture (general)		• Rapid imaging acquisition • Parallel treatment with IV alteplase • Extending the on-site presence of stroke team members during off-hours • Early activation of the interventional team • More experienced teams • Providing time targets with frequent feedback to the entire team
Door-to-groin puncture (transferred patients)	• Direct EMS transfer to the angiosuite	• Electronic transmission of CT images • Early activation of the interventional team
Angiosuite to groin puncture		• Protocols to preselect devices • Ready-to-use equipment tray • Early consultation of the anesthetist • Avoiding general anesthesia if possible

CT, computed tomography; EMS, emergency medical services; IV, intravenous; LVO, large vessel occlusion.

were independently associated with decreased door-in-door-out times, but the prehospital processes were the most important factor.[81] Despite the similarities between the treatment of MI and stroke, the prehospital triage of MI patients is less complex. MI patients that should receive rapid treatment with PCI are easily identified in the ambulance using an electrocardiogram. This enables direct transportation of these patients to a PCI center, while the triage of suspected stroke patients is complicated by the fact that the diagnosis can only be confirmed with a CT angiography in the hospital. Our efforts should therefore be aimed on identifying eligible EVT patients in the prehospital setting, for example using prehospital stroke scales or a mobile stroke unit.

Recommendations for clinical practice

The MR PREDICTS decision tool and MR PREDICTS@24H are online available for use in clinical practice (www.mrpredicts.com), and emphasize the importance of taking various factors into account when making treatment decisions. EVT should never be withheld based on a single characteristic, and patients directly presenting at the intervention center within 6 hours after symptom onset should be treated as soon as possible, considering the large treatment effect and the small potential harm. I suggest that the decision tool may be particularly relevant when patients have to be transferred to an intervention center and there is doubt whether EVT will be beneficial. Transferring patients with low expected benefit causes unnecessary health care costs and inconvenience for patients and their families. Clinical judgement remains important, especially when there are rare, but strongly predictive characteristics not captured by the model, for example an abnormal anatomy of the circle of Willis or fluctuations in the course of symptoms.

Further reorganization of acute stroke care should be aimed on structuring workflow processes to ensure rapid treatment independent of the time or day of presentation. Multiple interventions can be combined to maximize the potential effect (Table 12.3). Ambitious but feasible time targets should be determined to motivate hospital staff and policy makers to improve in-hospital workflow. These time metrics should be monitored in every hospital and reported back to the stroke team regularly. At this moment, I would suggest that primary stroke centers in the Netherlands aim for a median door-in-door-out time of <45 minutes, which will only be possible when the ambulance waits at the emergency department until the result of CT angiography. Intervention centers should strive for a door-to-groin time of <60 minutes for directly admitted patients and <25 minutes for transferred patients.

Prehospital triage of suspected stroke patients is essential to reduce the number of inter-hospital transfers. I would recommend to extend the current AHA triage algorithm for prehospital triage in the US and allow more delay when bypassing a primary stroke center. No universal time threshold can be given, because this strongly depends on geographic circumstances and organization of stroke care, but it seems beneficial to allow at least 30-45

minutes additional driving time for suspected LVO patients. Regional protocols should be further optimized based on local driving times, financial resources, and capacity of the intervention centers. The online tool, based on the decision model described in Chapter 9, can be used to inform these decisions.

Currently, there is insufficient evidence to recommend one prehospital stroke scale over another, but one should at least use a scale that was prospectively validated in the prehospital setting (eg, RACE or the Cincinnati Prehospital Stroke Severity Scale (CPSSS)), and that is easy to use for emergency medical services.[68,82] The choice for a prehospital stroke scale should not depend on sensitivity alone, because adequate specificity is required to limit the number of patients unnecessarily transported to an intervention center. Assessment of the individual likelihood of LVO based on a continuous scale instead of one fixed threshold, may further improve the effectiveness of prehospital triage.

Recommendations for future research

Despite the huge impact of EVT on clinical outcome, still more than half of the treated patients are deceased or disabled at 3 months after stroke.[1] This emphasizes the devastating effect of the disease and warrants innovations for further improvement of the current treatment options.

Patient selection is especially important for patients presenting more than 6 hours after onset of symptoms or last seen well, because EVT might be futile or even harmful in many of these patients. However, the currently available trial data only includes a strictly selected patient population and is therefore insufficient to use for predictive modeling. Large databases of patients treated in the late time window are required to develop a robust model that can aid patient selection. Results of the ongoing MR CLEAN LATE trial (ISRCTN19922220), which assesses the use of more liberal selection criteria without restrictions on infarct core size, might be useful in identifying which late window patients benefit from treatment.

Machine learning methods, or artificial intelligence, are increasingly popular in the medical field and are suggested to improve personalized predictions by discovering data patterns and associations through automated algorithms.[83,84] However, these algorithms require very large datasets for which clinical data sources are often not sufficient.[85] The relatively small number of variables available might explain why machine learning methods did not outperform conventional logistic regression in the MR CLEAN Registry.[86] Also, machine learning models do not provide further insight in the underlying pathophysiological mechanisms and cannot be adjusted for the use in different settings or populations. Therefore, I believe that machine learning is mostly valuable for pattern recognition tasks, for example for the automatic interpretation of neuroimaging. Prediction modeling should focus on the development of simple, robust models and adequate external validation of existing models.

It is important to acknowledge that patients with a poor prognosis might still benefit from treatment, and therefore MR PREDICTS estimates outcome with and without EVT. However, evaluation of treatment benefit brings a number of challenges. In Chapter 4, I used the c-for-benefit to evaluate the discriminative performance of the predicted treatment benefit. While the traditional c-statistic assesses whether a model can discriminate between patients with a low risk versus high risk of the outcome, this novel measure focuses on the whether the model can separate patients who are very likely to benefit from treatment and those who are not.[87] Because the real treatment benefit of a patient cannot be observed, the c-for-benefit uses the outcomes of patient pairs that were matched on predicted benefit but discordant for treatment assignment. This method needs further evaluation and new benchmark values should to be defined to guide the interpretation of this promising measure.

A large number of prehospital stroke scales have been developed, and researchers should now focus on thorough validation of these scales in the prehospital setting, rather than the development of new scales. The future results of the PRESTO study will allow direct comparison of several prehospital stroke scales to improve triage decisions. Further decision modeling combined with geographic information systems can provide guidance for triage decisions in different settings. It can also be used to determine in which regions the implementation of a mobile stroke unit could be beneficial. Integration of a decision model with a GPS-controlled navigation application will facilitate personalized triage based on real-time information about driving times and in-hospital workflow times.

Final remarks

Although the overall effect of EVT is overwhelming, there are many targets to further improve outcome of individual patients. In this thesis, I developed and validated prediction models to predict outcome and treatment benefit; identified determinants of treatment delay and interventions to improve workflow; and applied decision-analyses to evaluate and optimize prehospital triage strategies.

The MR PREDICTS decision tool is the only model that estimates individual benefit of EVT and thereby improves patient selection. It performed reasonably well in a an international trial population and a large cohort of patients treated in daily clinical practice. Treatment benefit is substantial in the vast majority of patients, but absence of treatment effect is suggested in a small number of patients with multiple unfavorable characteristics. Rapid initiation of EVT is essential to improve patient outcomes, and requires the implementation of various prehospital and in-hospital workflow interventions. Inter-hospital transfer is the main determinant of treatment delay and should be avoided by transporting suspected stroke patients directly to an intervention center, but the optimal triage strategy varies based on regional characteristics. The future results of the PRESTO study will provide more information on the real-world performance of prehospital stroke scales, allowing further improvement of prehospital decision-making.

Box 12.2 Overview of the main recommendations.

Treat the right patient

Endovascular treatment should never be withheld from an individual patient based on a single characteristic. The MR PREDICTS decision tool can be used to evaluate the effect of multiple patient and imaging characteristics simultaneously, when there is uncertainty about the treatment indication or when patients need to be transferred to an intervention center. Patient selection is particularly important for patients presenting more than 6 hours after symptom onset, but large databases of not strictly selected patients are required to develop a robust model for the late time window.

Treat at the right time

Rapid initiation of endovascular treatment is essential to improve patient outcomes, and requires the implementation of various prehospital and in-hospital workflow interventions. Acute stroke care should be reorganized to reduce any delay between stroke onset and start of treatment. Every effort is needed to streamline workflow processes, improve team work and communication, and reduce the number of inter-hospital transfers. Door-in-door-out times and door-to-groin times should be monitored and reported back to the stroke team regularly.

Treat in the right place

A validated prehospital stroke scale should be used to identify patients that benefit from direct transportation to an intervention center. The choice of a specific prehospital stroke scale and the maximum allowed delay when bypassing the primary stroke center depends on local geographic characteristics, resources and preferences. Decision modeling will therefore be needed to translate results of clinical studies on prehospital triage to different settings and regions.

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Appendices

Summary

The effect of endovascular treatment (EVT) for ischemic stroke due to a proximal, intracranial large vessel occlusion (LVO) varies between individual patients. Treatment benefit, defined as the difference between the chance of a good outcome with and without treatment, is affected by differences in clinical characteristics at baseline. For example, the treatment effect strongly declines over time because a larger part of the brain tissue is already irreversibly damaged. Early initiation of EVT is therefore associated with better functional outcome, and time to treatment should be reduced to improve chances of good recovery. A possibility to reduce delay is to directly transport patients with suspected LVO to an intervention center capable of performing EVT, instead of bringing them to a primary stroke center for the first evaluation. However, this strategy might be harmful for stroke patients without LVO, who only benefit from rapid treatment with intravenous thrombolytics in the nearest hospital. The likelihood of LVO in suspected stroke patients can be assessed in the ambulance using a prehospital stroke scale, but the optimal triage strategy requires a trade-off between the harm of delaying intravenous thrombolytics versus the potential benefit of rapid EVT.

The overall aim of this thesis was to increase the benefit of EVT by optimizing prediction of outcome and treatment effect (**Part I**), reducing treatment delay (**Part II**), and improving prehospital triage strategies (**Part III**).

The specific research questions were:

1. Which are the right patients to treat?
   a. Can we reliably and accurately predict outcome and treatment benefit of EVT for individual patients?
2. How can we treat patients at the right time?
   a. What are the main causes of prehospital and in-hospital delay of EVT?
   b. How do workflow improvements effect treatment delay and outcome?
3. How to direct patients to the right place?
   a. Which factors should influence the decision to transport individual patients directly to an intervention center?
   b. What is the optimal prehospital triage strategy for suspected stroke patients?

Part I – Treat the right patient

The first part of this thesis concerns the development and external validation of a prediction model for functional outcome and treatment benefit of individual patients (MR PREDICTS), and a post-procedural model to improve outcome prediction for patients treated with EVT at one day after the intervention (MR PREDICTS@24H).

Chapters 2 and 3 describe the development of the MR PREDICTS decision tool with data from the MR CLEAN trial. Eleven baseline patient and imaging characteristics were included in the model, together with three interaction terms to account for differential relative treatment effects. An external validation with data from the IMS III trial showed a moderate ability of the model to distinguish between patients with low and high likelihood of a good outcome. Predicted treatment benefit varied substantially between individual patients, and clinically relevant benefit was predicted for some patients from subgroups in which no effect of EVT was expected, such as those with no or poor collaterals.

In **Chapter 4**, we performed external validation of MR PREDICTS with data from multiple international trials within the HERMES collaboration, including patients from different healthcare systems and countries. Based on these results, the model was updated and validated again in the MR CLEAN Registry, representing daily clinical practice in the Netherlands. The model performed reasonably well in both cohorts. Median predicted treatment benefit of routinely treated patients in the Registry was 10.6% (IQR 6.4% to 14.5%). A small group of patients in the Registry with low predicted treatment benefit had poor outcomes irrespective of reperfusion status, suggesting potential absence of treatment benefit.

MR PREDICTS@24H was developed with data from the HERMES collaboration, as described in **Chapter 5**. This prognostic model includes nine pre- and post-procedural characteristics, of which the National Institute of Health Stroke Severity scale at 24 hours after EVT was the most predictive of functional outcome at 3 months. External validation with data from the MR CLEAN Registry showed excellent discriminative performance, although the observed probability of survival was lower than predicted. This was resolved by providing separate intercepts that reflect the differences in outcome between the trial population and the broad group of routinely treated patients.

Part II – Treat at the right time

Chapter 6 describes the effect of workflow characteristics on the time intervals in the MR CLEAN trial. Patients admitted during off-hours had an average delay of 23 minutes before the start of EVT, and patients treated under general anesthesia were treated 19 minutes

later from arrival at the emergency department. Prior administration of intravenous thrombolytics was not related with any significant treatment delay. Most importantly, almost half of the patients (44%) were transferred from a primary stroke center, and those patients received EVT on average 65 minutes later than patients directly admitted to an intervention center.

To further explore the effect of inter-hospital transfer on time to treatment and functional outcome after EVT in daily clinical practice, we performed an analysis with data from the MR CLEAN Registry (**Chapter 6)**. More than half of the routinely treated patients (54%) were transferred from a primary stroke center and these patients had an average delay of 57 minutes between first presentation and start of EVT. The negative impact of this delay on functional outcome of transferred patients was reflected in an absolute decrease of 8.5% in the probability of achieving functional independence after 3 months.

Chapter 7 consists of a systematic review and meta-analysis on the effect of workflow improvements for EVT, including 51 studies on different types of workflow interventions. The most frequently reported interventions were aimed at using local anesthesia or conscious sedation instead of general anesthesia, reducing in-hospital patient transfers, and optimizing the prehospital workflow. The mean time to treatment was 26 minutes shorter for patients in the intervention group, and simultaneous implementation of multiple interventions even reduced treatment delay with 50 minutes.

Part III – Treat in the right place

Because inter-hospital transfer is the most important factor of modifiable treatment delay, we constructed a decision tree model to determine the optimal prehospital transportation strategy of suspected stroke patients (**Chapter 8**). This model combines the likelihood of LVO in an individual patient with local driving times and in-hospital workflow times. Direct transportation to an intervention center was beneficial for patients with a high risk of having an LVO, especially in scenarios with short between-center distances. The optimal triage decision was also affected by the in-hospital workflow characteristics of both the primary stroke center (door-to-needle time and door-in-door-out time) and the intervention center (door-to-groin time).

In **Chapter 9**, our decision model was integrated in a geographic information system analysis to assess the effect of prehospital triage strategies for the United States. Evaluation of the current triage algorithm of the American Heart Association showed that this strategy is suboptimal for most states and counties. Modified versions of this algorithm, allowing for more time delay when bypassing a primary stroke center, showed large improvement of outcomes of the ischemic stroke population.

These triage strategies rely on prehospital stroke scales to assess the likelihood of LVO in suspected stroke patients, but prospective, prehospital validation of these scales is lacking. Therefore, I present the study protocol of PRESTO (prehospital triage of patients with suspected stroke symptoms) in **Chapter 10**. This prospective, multicenter, observational cohort study will evaluate the performance of several prehospital stroke scales based on the initial assessment in the ambulance. The results of this study will provide a unique insight in the characteristics of an unselected group of patients with suspected stroke in the prehospital setting.

Discussion

Although the overall effect of EVT is overwhelming, there are many targets to further improve outcome of individual patients. In this thesis, I developed and validated prediction models to predict outcome and treatment benefit; identified determinants of treatment delay and interventions to improve workflow; and applied decision-analyses to evaluate and optimize prehospital triage strategies.

Based on my findings, I recommend to never withheld EVT from an individual patient based on a single characteristic. The vast majority of patients will benefit when treated within 6 hours after stroke onset, but the MR PREDICTS decision tool can be used to evaluate the effect of multiple patient and imaging characteristics when there is uncertainty about the treatment indication or when patients need to be transferred to an intervention center. Patient selection is particularly important for patients presenting more than 6 hours after symptom onset, but large databases of not strictly selected patients are required to develop a robust model for the late time window.

Rapid initiation of EVT is essential to improve patient outcomes, and requires the implementation of various prehospital and in-hospital workflow interventions. Acute stroke care should be reorganized to reduce any delay between stroke onset and start of EVT. Every effort is needed to streamline workflow processes, improve team work and communication, and reduce the number of inter-hospital transfers. Ambitious target times should be set for the door-in-door-out time in the primary stroke center and the door-to-groin time in the intervention center. These time metrics should be monitored and reported back to the stroke team regularly.

To improve prehospital triage, a validated prehospital stroke scale should be used to identify patients that benefit from direct transportation to an intervention center. The choice of a specific prehospital stroke scale and the maximum allowed delay when bypassing the primary stroke center depends on local geographic characteristics, resources and preferences. The future results of the PRESTO study will provide more information on the

real-world performance of prehospital stroke scales, allowing further improvement of prehospital decision-making. However, decision modeling will always be needed to translate results of clinical studies to different settings and regions.

Samenvatting

Patiënten met een herseninfarct op basis van een proximale intracraniële occlusie in de voorste circulatie kunnen baat hebben bij intra-arteriële therapie waarbij het stolsel wordt verwijderd (trombectomie). De winst van deze behandeling, gedefinieerd als het verschil tussen de kans op een goed resultaat met en zonder behandeling, varieert tussen individuele patiënten en wordt beïnvloed door verschillen in klinische factoren. Zo neemt het effect van intra-arteriële therapie sterk af in de eerste uren na het ontstaan van de symptomen, doordat met het verstrijken van de tijd een groter deel van het hersenweefsel onomkeerbaar beschadigd raakt. Een snelle start van de behandeling wordt geassocieerd met een betere functionele uitkomst. De tijd tussen het ontstaan van de symptomen en het starten van intra-arteriële therapie moet daarom zoveel mogelijk worden gereduceerd om de kans op goed herstel te vergroten.

Een mogelijkheid om vertraging te voorkomen is om patiënten rechtstreeks naar een interventiecentrum te brengen waar intra-arteriële therapie kan worden uitgevoerd, in plaats van naar een primair stroke centrum voor de initiële opvang. Deze triage strategie kan echter schadelijk zijn voor patiënten met een herseninfarct zonder intracraniële occlusie, aangezien die patiënten alleen profiteren van snelle intraveneuze trombolyse in het dichtstbijzijnde ziekenhuis. Bij patiënten met de verdenking op een herseninfarct moet daarom worden ingeschat hoe waarschijnlijk het is dat zij een intracraniële occlusie hebben. Dit kan in de ambulance worden gedaan met behulp van een prehospitale stroke score. Optimale prehospitale triage vereist echter een afweging tussen de schade die kan ontstaan door het uitstellen van intraveneuze trombolyse versus het potentiële voordeel van snelle intra-arteriële therapie.

Het algemene doel van dit proefschrift was om de winst van intra-arteriële therapie voor patiënten met een herseninfarct te vergroten door voorspellingen van uitkomst en behandeleffect te optimaliseren (**Deel I**), vertraging van de behandeling te verminderen (**Deel II**) en prehospitale triage strategieën te verbeteren (**Deel III**).

De specifieke onderzoeksvragen waren:
1. Welke patiënten moeten worden behandeld?
   a. Kunnen we uitkomsten en de winst van intra-arteriële therapie voor individuele patiënten betrouwbaar en nauwkeurig voorspellen?
2. Hoe kunnen we patiënten op het juiste moment behandelen?
   a. Wat zijn de belangrijkste oorzaken van vertraging in de prehospitale setting en in het ziekenhuis?
   b. Hoe beïnvloeden workflow interventies de tijd tot behandeling en de uitkomsten van behandelde patiënten?

3. Hoe kunnen we patiënten naar de juiste plaats leiden?
   a. Welke factoren zouden van invloed moeten zijn op de beslissing om individuele patiënten rechtstreeks naar een interventiecentrum te vervoeren?
   b. Wat is de optimale prehospitale triage strategie voor patiënten met de verdenking op een herseninfarct?

Deel I - Behandel de juiste patiënt

Het eerste deel van dit proefschrift betreft de ontwikkeling en externe validatie van een predictiemodel voor functionele uitkomst en behandelwinst voor individuele patiënten (MR PREDICTS), en een post-procedureel model om de voorspelling van uitkomsten te verbeteren één dag na de interventie (MR PREDICTS@24H).

Hoofdstukken 2 en 3 beschrijven de ontwikkeling van het MR PREDICTS model met gegevens van de MR CLEAN studie. Elf patiëntkarakteristieken en radiologische kenmerken werden in het model opgenomen, samen met drie interactietermen om rekening te houden met differentiële relatieve behandeleffecten. Een externe validatie met gegevens van de IMS III studie toonde een redelijk voorspellend vermogen van het model in het onderscheiden van patiënten met een lage en een hoge kans op een goede uitkomst. De voorspelde winst van de behandeling varieerde aanzienlijk tussen individuele patiënten. Er werd ook baat van de behandeling voorspeld voor sommige patiënten uit subgroepen waarin eerder geen effect van intra-arteriële therapie werd verwacht, zoals patiënten met een zeer slechte collaterale bloedvoorziening.

In **Hoofdstuk 4** heb ik een externe validatie van MR PREDICTS uitgevoerd met behulp van zes internationale, gerandomiseerde studies die zijn aangesloten bij de HERMES collaboration. Op basis van deze resultaten is het model geactualiseerd en opnieuw gevalideerd in de MR CLEAN Registry, een database waarin alle patiënten zijn opgenomen die in de dagelijkse praktijk in Nederland worden behandeld. Het model presteerde redelijk goed in beide cohorten. Voor de routinematig behandelde patiënten in de Registry werd een absolute toename van 10.6% voorspeld in de kans op goed functioneel herstel (interkwartiel range 6.4% tot 14.5%). Bij een kleine groep patiënten in de Registry werd geen baat van de behandeling voorspeld en een slechte uitkomst waargenomen ongeacht de reperfusiestatus, wat duidt op een mogelijk afwezig behandeleffect.

MR PREDICTS@24H is ontwikkeld met gegevens van de HERMES collaboration, zoals beschreven in **Hoofdstuk 5**. Dit prognostische model omvat 9 pre- en post-procedurele kenmerken, waarvan de National Institute of Health Stroke Severity score afgenomen 24 uur na de interventie de belangrijkste voorspellende factor was van de functionele uitkomst na 3 maanden. Externe validatie met data van de MR CLEAN Registry toonde een uitstekend

discriminerend vermogen, maar de waargenomen overlevingskans in dit cohort was lager dan voorspeld. Dit werd opgelost door twee afzonderlijke intercepts te presenteren die het verschil in uitkomst weerspiegelen tussen de studiepopulatie en de brede groep van patiënten die in de dagelijkse praktijk behandeld wordt.

Deel II - Behandel op het juiste moment

Hoofdstuk 6 beschrijft het effect van workflow factoren op de tijd tot behandeling in de MR CLEAN studie. Patiënten die buiten kantooruren werden opgenomen zijn gemiddeld 23 minuten later behandeld dan patiënten binnen kantooruren, en patiënten onder algehele narcose zijn gemiddeld 19 minuten later behandeld. Het toedienen van intraveneuze trombolyse was niet gerelateerd aan enige significante vertraging van de behandeling. De belangrijkste bevinding was dat bijna de helft van de patiënten (44%) werd overgeplaatst vanuit een primair stroke centrum. Deze overgeplaatste patiënten werden gemiddeld 65 minuten later behandeld dan patiënten die rechtstreeks werden opgenomen in een interventiecentrum.

Om het effect van overplaatsingen tussen ziekenhuizen op de tijd tot behandeling en functionele uitkomst na intra-arteriële therapie in de dagelijkse klinische praktijk te onderzoeken, heb ik ook een analyse uitgevoerd met data van de MR CLEAN Registry (**Hoofdstuk 6**). Meer dan de helft van de routinematig behandelde patiënten in Nederland (54%) werd overgebracht vanuit een primair stroke centrum en deze patiënten hadden een gemiddelde vertraging van 57 minuten tussen de eerste presentatie en het starten van de intra-arteriële therapie. Het negatieve effect hiervan kwam tot uiting in een absolute afname van 8.5% in de kans op goed functioneel herstel na 3 maanden.

Hoofdstuk 7 bestaat uit een systematische review en meta-analyse naar het effect van workflow interventies, waarin 51 studies van verschillende type interventies geïncludeerd werden. De meest frequent gerapporteerde interventies waren gericht op het gebruik van lokale anesthesie of sedatie in plaats van algehele narcose, het verminderen van overplaatsingen van patiënten en het optimaliseren van de prehospitale workflow. De gemiddelde tijd tot de behandeling was 26 minuten korter voor patiënten in de interventiegroep en gelijktijdige implementatie van meerdere interventies verkortte de tijd tot behandeling zelfs met 50 minuten.

Deel III - Behandel op de juiste plaats

Omdat overplaatsingen tussen ziekenhuizen de belangrijkste factor zijn in de vertraging van intra-arteriële therapie, heb ik een besliskundig model opgesteld om de optimale

prehospitale strategie te bepalen voor patiënten waarbij een herseninfarct vermoed wordt (**Hoofdstuk 8**). Dit model combineert de waarschijnlijkheid van een intracraniële occlusie bij een individuele patiënt met lokale reistijden en doorlooptijden in de regionale ziekenhuizen. Direct vervoer naar een interventiecentrum was gunstig voor patiënten waarbij een intracraniële occlusie waarschijnlijk is, vooral in scenario's met korte afstanden tussen de verschillende centra. De optimale triage strategie werd ook beïnvloed door de doorlooptijden in het primaire stroke centrum (deur-tot-naald tijd en deur-in-deur-uit tijd) en het interventiecentrum (deur-tot-lies tijd).

In **Hoofdstuk 9** werd dit besliskundige model geïntegreerd in een geografisch informatiesysteem om het effect van prehospitale triage strategieën in de Verenigde Staten te beoordelen. Het huidige triage algoritme van de American Heart Association bleek onvoldoende effectief te zijn in de meerderheid van de staten en provincies. Aangepaste versies van dit algoritme, die meer vertraging toestaan bij het vervoer naar een interventiecentrum, hadden een groot positief effect op de uitkomsten van de Amerikaanse patiëntenpopulatie.

Prehospitale stroke scores worden gebruikt om de waarschijnlijkheid van een intracraniële occlusie te beoordelen in de ambulance, maar prospectieve, prehospitale validatie van deze scores ontbreekt. Daarom presenteer ik in **Hoofdstuk 10** het studieprotocol van PRESTO (prehospitale triage van patiënten met de verdenking op een herseninfarct). Deze prospectieve, multicenter, observationele cohortstudie zal het voorspellend vermogen van verschillende prehospitale stroke scores evalueren op basis van de initiële beoordeling in de ambulance. De resultaten van deze studie zullen tevens inzicht bieden in de ongeselecteerde groep van patiënten met de verdenking op een herseninfarct.

Discussie

Hoewel het algehele effect van intra-arteriële therapie overweldigend is, zijn er veel mogelijkheden om de uitkomsten van individuele patiënten met een herseninfarct verder te verbeteren. In dit proefschrift heb ik predictiemodellen ontwikkeld en gevalideerd om functionele uitkomst en behandelwinst te voorspellen; determinanten die leiden tot vertraging van de behandeling en interventies om de workflow te verbeteren geïdentificeerd; en besliskundige analyses toegepast om prehospitale triage strategieën te evalueren en te optimaliseren.

Op basis van mijn bevindingen raad ik aan om nooit een individuele patiënt intra-arteriële therapie te onthouden op basis van één enkele eigenschap. Het MR PREDICTS model kan worden gebruikt om het effect van meerdere patiëntkarakteristieken en radiologische kenmerken tegelijkertijd te evalueren, wanneer er onzekerheid bestaat over de

behandelindicatie of wanneer patiënten moeten worden overgeplaatst naar een interventiecentrum. Patiëntselectie is vooral belangrijk voor patiënten die zich meer dan 6 uur na het begin van de symptomen presenteren, maar er zijn grote databases met niet strikt geselecteerde patiënten nodig om een robuust model voor het late tijdvenster te ontwikkelen.

Een snelle start van intra-arteriële therapie is essentieel om de uitkomsten van patiënten te verbeteren en vereist implementatie van verschillende workflow interventies in de prehospitale setting en in het ziekenhuis. De acute beroertezorg moet worden gereorganiseerd om de vertraging tussen het begin van een herseninfarct en de start van de behandeling te verminderen. Er moet alles aan gedaan worden om de logistieke processen te stroomlijnen, samenwerking en communicatie te verbeteren en het aantal overplaatsingen tussen ziekenhuizen te verminderen. Het is raadzaam om de doorstroomtijden te monitoren en regelmatig aan het stroke team te rapporteren.

Om de prehospitale triage te verbeteren, moet een gevalideerde prehospitale stroke score worden gebruikt om patiënten te identificeren die baat hebben bij direct transport naar een interventiecentrum. De keuze voor een specifieke prehospitale stroke score en de maximaal toegestane vertraging wanneer wordt omgereden naar een interventiecentrum hangt af van geografische kenmerken, beschikbare capaciteit van de ziekenhuizen en lokale voorkeuren. De toekomstige resultaten van de PRESTO studie zullen naar verwachting meer informatie verschaffen over de werkelijke prestaties van prehospitale stroke scores, zodat de besluitvorming kan worden geoptimaliseerd. Besliskundige modellen zullen echter altijd nodig zijn om de resultaten van klinische studies te vertalen naar verschillende regionale omstandigheden.

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In life, it's not where you go, it's who you travel with
Charles M. Schulz

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List of publications

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Letters to the editor

- Chalos V, **Venema E**, Lingsma HF, Dippel DWJ. Letter to the Editor Regarding "Predicting Clinical Outcome After Mechanical Thrombectomy: The GADIS (Gender, Age, Diabetes Mellitus History, Infarct Volume, and Sex) Score". *World Neurosurg.* 2020;138:587–8.

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- **Venema E**, Mulder M, Lingsma HF. Letter by Venema et al Regarding Article, "Validating a Predictive Model of Acute Advanced Imaging Biomarkers in Ischemic Stroke". *Stroke*. 2017;48:e225.

- **Venema E**, Lingsma HF, Dippel DW. Letter by Venema et al Regarding Article, "Analysis of Workflow and Time to Treatment on Thrombectomy Outcome in the Endovascular Treatment for Small Core and Proximal Occlusion Ischemic Stroke (ESCAPE) Randomized, Controlled Trial". *Circulation*. 2016;134:e404–e405.

*equal contribution

PhD portfolio

Name:	Esmee Venema
Erasmus MC Department:	Public Health & Neurology
Research School:	Netherlands Institute for Health Sciences (NIHES)
PhD period:	November 2015 – November 2019
Promotors:	Prof.dr. E.W. Steyerberg & prof.dr. D.W.J. Dippel
Copromotors:	Dr. H.F. Lingsma & dr. B. Roozenbeek

	Year	Workload (ECTS)
1. PhD training		
General academic courses		
Master of Science – Clinical Epidemiology	2016-2017	39
Biomedical English Writing and Communication	2017	4.0
Research Integrity	2017	0.3
Basiscursus Regelgeving en Organisatie voor Klinisch onderzoekers (BROK)	2019	1.0
Presentations at (inter)national conferences		
European Stroke Organisation Conference; Barcelona (two oral presentations)	2016	2.0
European Stroke Organisation Conference; Prague (oral and poster presentation)	2017	1.5
1st Translational Cardiovascular Research Meeting; Utrecht (poster presentation)	2017	0.5
39th Annual meeting of the Society for Medical Decision Making; Pittsburgh (poster presentation)	2017	0.5
Dutch Society for Neurology Science Days; Nunspeet (oral presentation)	2017	1.0
European Stroke Organisation Conference; Gothenburg (oral presentation)	2018	1.0
European Meeting of the Society for Medical Decision Making; Leiden (oral and poster presentation)	2018	1.5
Dutch Emergency Medicine Conference; Egmond aan Zee (two oral presentations)	2018	2.0
40th Annual meeting of the Society for Medical Decision Making; Montreal (oral and poster presentation)	2018	1.5
Seminars and workshops		
Various seminars and research meetings of the department of Public Health, the department of Neurology, the MR CLEAN Registry and the CONTRAST consortium	2016-2019	4.0

European Stroke Organisation Stroke Summer School; Larissa, Greece	2017	1.0
Sensitivity Analysis and Value of Information Analysis Using Regression Metamodeling in R	2017	0.2
2. Teaching activities		
General teaching activities		
Revising bachelor essays	2016	0.5
Supervising community projects of bachelor students	2016-2019	2.0
Lecturing 'VO Choices in healthcare'	2017-2018	0.5
Developing R assignments NIHES Biostatistical Methods I (CC02)	2018	0.2
Teaching-assistant NIHES Clinical Epidemiology (CE02)	2018	0.2
Supervising research master students		
Eveline Wiegers	2017-2018	2.0
Charlie Sewalt	2017-2018	2.0
Femke Kremers	2019	1.0
3. Other activities		
Member of the organizing committee of the Erasmus MC PhD day and Career Event	2016	1.0
Secretary of the Promeras PhD students association	2016-2017	1.5
Member of the Junior Representatives committee, department of Public Health	2016-2017	0.5
Training paramedics to use prehospital stroke scales (ambulance regions Rotterdam-Rijnmond, Zuid-Holland Zuid, and Zeeland)	2018	2.5
Visiting researcher at the Predictive Analytics and Comparative Effectiveness (PACE) Center, Boston, USA	2018	2.0
Peer reviews for several journals (European Journal of Neurology, Journal of NeuroInterventional Surgery, European Stroke Journal, Intensive Care Medicine)	2018-2019	0.6
4. Awards		
Netherlands Institute for Health Sciences (NIHES) award for the best paper written in the academic year 2016-2017	2017	
Dutch Emergency Medicine Conference award for the best abstract presentation	2018	
Lee B. Lusted Student Award for outstanding presentation of research at the Society for Medical Decision Making meeting	2018	
Total ECTS		**77.5**

About the author

Esmee Venema was born on March 1st, 1988 in Rotterdam, the Netherlands. After finishing secondary school at the Dalton Lyceum in Barendrecht, she returned to Rotterdam to study medicine at the Erasmus Medical Center. As part of her study, she conducted a research project on the effect of intravenous thrombolytic therapy given prior to endovascular treatment of ischemic stroke in the MR CLEAN pre-trial (under supervision of professor Diederik Dippel). In 2013, she finished her clinical rotations after working for 3 months at the St. Carolus hospital in Tanzania. She obtained her medical degree cum laude and started working as resident at the Emergency Department of the Bravis hospital in Bergen op Zoom. It is there that she discovered a great passion for acute care and emergency medicine.

In 2015, she was given the opportunity to start a PhD on personalized treatment of ischemic stroke at the Department of Public Health and the Department of Neurology in the Erasmus Medical Center, under supervision of professor Ewout Steyerberg and professor Diederik Dippel. She combined her PhD trajectory with a Master of Science in Clinical Epidemiology, which she finished in 2017, and was secretary of the Promeras PhD students association. In 2018, she worked for 2 months under the supervision of professor David Kent at the Predictive Analytics and Comparative Effectiveness Center of Tufts Medical Center in Boston (USA), a collaboration that continues to this day. She designed and coordinated the PRESTO study, a prospective multicenter study for the in-field validation of prehospital stroke scales. She returned to her clinical work in 2019. Currently, she works at the Emergency Department of the Albert Schweitzer hospital in Dordrecht and is pursuing a career as emergency physician and researcher. She lives in Rotterdam, together with her boyfriend Romero.