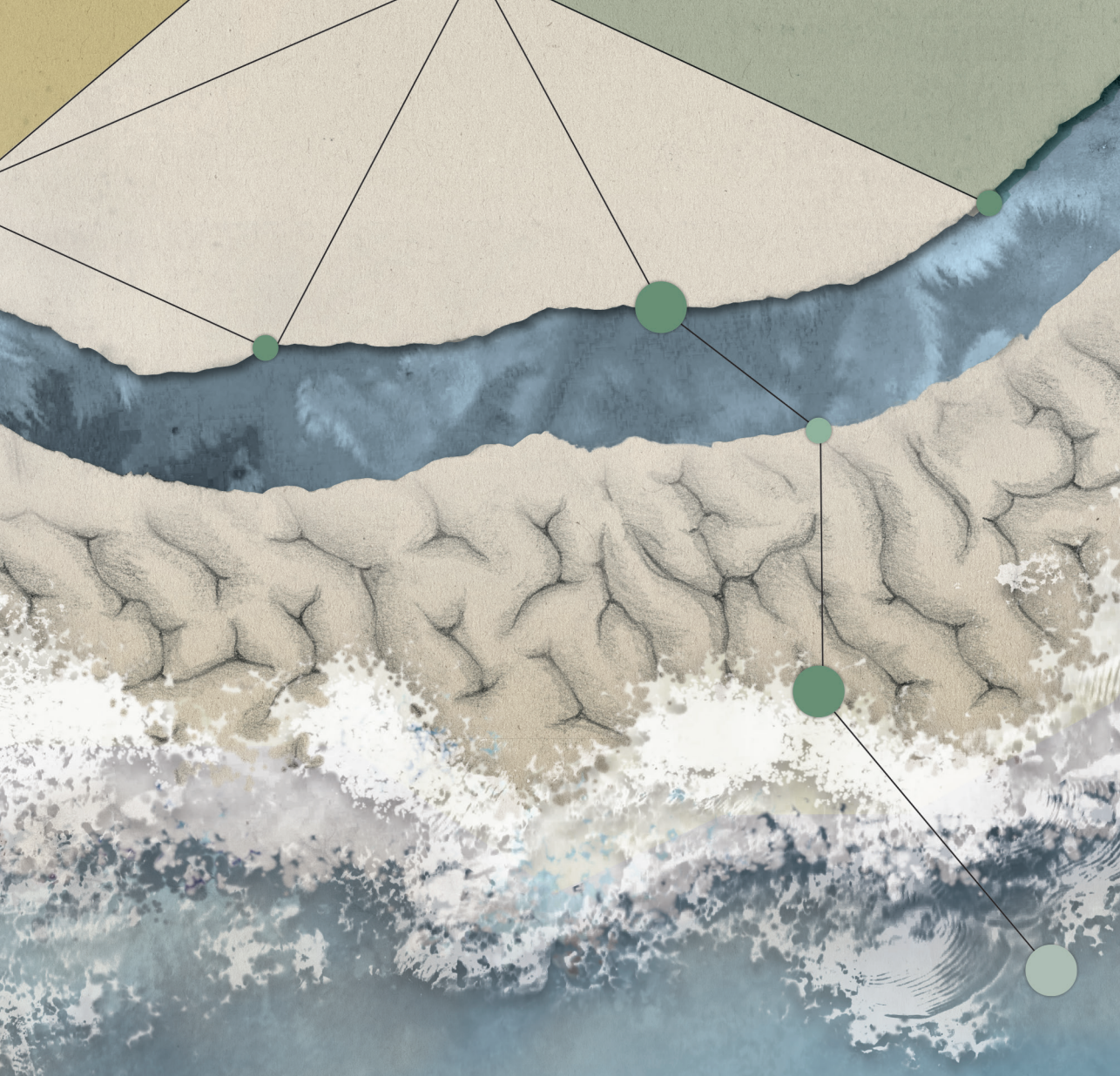

Endovascular Treatment for Ischemic Stroke

IDENTIFYING FACTORS TO IMPROVE OUTCOME AND ALTERNATIVE METHODS TO EVALUATE TREATMENT EFFECT

NOOR SAMUELS

ENDOVASCULAR TREATMENT FOR ISCHEMIC STROKE

Identifying factors to improve outcome and alternative methods to evaluate treatment effect

Noor Samuels

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ENDOVASCULAR TREATMENT FOR ISCHEMIC STROKE

Identifying factors to improve outcome and alternative methods to evaluate treatment effect

Endovasculaire behandeling van het herseninfarct

Identificatie van factoren ter verbetering van uitkomst en alternatieve methoden ter evaluatie van het behandeleffect

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Content

CHAPTER 1

General introduction

Ischemic stroke

Ischemic stroke is the rapid development of disturbance in cerebral function attributed to a sudden interruption in cerebral blood flow. Often, interruption in regional blood supply occurs from an occlusion of an artery by a thrombus (Figure 1.1). This sudden decrease in cerebral blood flow to a specific cerebral territory leads to low oxygen and glucose levels in this region, and within seconds to irreversible neuronal damage ('*ischemic core*'). Cerebral infarction is a gradual process as after the sudden onset of arterial occlusion still some residual cerebral blood flow persists to the area distal from the occlusion through collateral vessels. The brain area at risk suffers from hypoxia, but the damage is not irreversible yet ('*ischemic penumbra*'). This hypo-perfused area is functionally impaired brain tissue, and could therefore contribute to the neurological deficit of the patient, but is still viable if cerebral blood flow is restored in time.[1-4] Treatment in the acute phase of ischemic stroke is focused at restoring cerebral blood flow and saving the ischemic penumbra.

Annually, approximately 14.000.000 people suffer from an ischemic stroke worldwide.[5] In the Netherlands, this accounts for almost 30,000 patients admitted to the hospital every year.[6] Approximately 24 to 46% of all ischemic strokes are caused by an intracranial occlusion of a large artery.[7,8]

Acute treatment of ischemic stroke

In the acute phase of ischemic stroke, the two main reperfusion therapies targeted at opening the occluded vessel are intravenous thrombolysis (IVT) and endovascular thrombectomy (EVT).

Since 1995, IVT with recombinant tissue plasminogen activator (rt-PA) to dissolve the occluding thrombus, is standard care within 3 hours from stroke symptom

onset and, in selected patients, treatment benefit exists beyond this time window.[9-12] However, reperfusion based on IVT is less effective in patients with a proximal occlusion in the anterior circulation.[13,14]

In 2015, 5 randomized controlled trials showed that EVT, in addition to IVT, was highly beneficial in patients with ischemic stroke due to a large vessel occlusion in the anterior circulation (defined as the internal carotid artery, internal carotid artery tandem, and M1 and M2 segment of the middle cerebral artery) when started within 6 hours after symptom onset.[15-19] In a pooled analysis of individual patient data from the 5 EVT trials, an additional 19.5% of patients were functionally independent (modified Rankin Scale score 0-2, Table 1.1) following EVT compared to usual care alone with a number needed to treat of 2.6 to achieve improvement of at least one level on the modified Rankin Scale.[20] Recently, this time-window has been extended to up to 24 hours after symptom onset for a selected subset of patients based on ischemic core/penumbra mismatch derived from CT-perfusion.[21,22] The objective of EVT is to restore CBF as soon and complete as possible via mechanical removal of the thrombus, by using a stent-retrieval or aspiration-only. Basically, a catheter is guided towards the proximal cerebral vasculature (e.g. internal carotid artery) through which a stent-retriever is brought up to the occlusion site, passed through the thrombus, followed by deployment and finally retrieval of the thrombus in combination with the use of an aspiration technique.

Treatment effects of both IVT and EVT are strongly time-dependent, and increased onset to treatment times are associated with lower changes of good functional outcomes. On average, the probability of achieving functional independence decreases with 3-5% for every hour delay between symptom onset and start of EVT.[23,24]

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 sever 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

Periprocedural factors influencing outcome after ischemic stroke:
The implementation of EVT as a standard therapy for ischemic stroke due to large vessel occlusion within 6 hours after onset, dramatically changed the organization of stroke care pathways, including the demand for anesthesia resources. There is a broad

variation in preferred anesthetic technique and hemodynamic management during EVT, and a lack of consensus on the target blood pressure (BP).[25]

Anesthetic management

Anesthetic support during EVT is common, with general anesthesia (GA) and conscious sedation (CS) being the preferred anesthetic approaches during EVT by more than 70% of the stroke treating physcians.[25,26] The aim of the anesthetic support during EVT is to reduce patient motion, increase patient comfort by reducing pain, facilitate fast treatment and minimize the risk of complications. The choice of anesthetic strategy during EVT depends on several factors such as patients' condition, preference of the treating physician and local practices of the hospital.[27] Performing EVT under GA might increase procedural safety by limiting the risk of aspiration and mechanical complications due to patient movement. Main arguments in favor of CS during EVT are rapid initiation of EVT, monitoring neurologic status during the procedure and better hemodynamic stability.[28] More recently, several EVT centers routinely perform EVT under local anesthesia (LA) at the puncture site only, to reduce treatment delay and further limit the risk of hypotension due to anesthetic agents.[29-32] A meta-analysis on data from seven clinical trials reported that EVT under GA was associated with worse outcomes compared to EVT under non-GA (composite of CS or LA).[33] Hemodynamic fluctuations during GA might explain differences in outcome. Studies including LA as a separate anesthetic strategy are lacking.

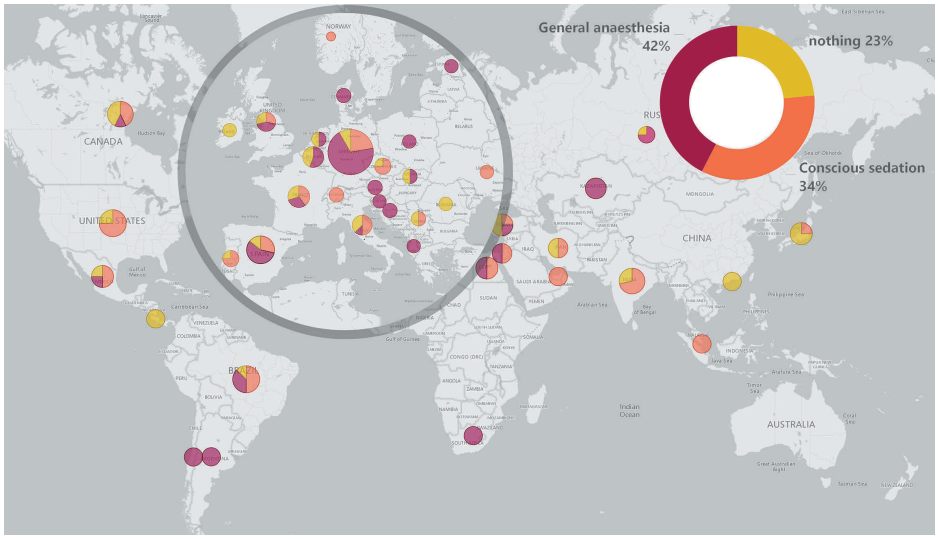

Figure 1.2. Preferred anesthetic approach during endovascular treatment overall and by country based on a survey. Red indicates general anesthesia, orange indicates conscious sedation and yellow indicates that neither is used by default. Circle sizes are proportional to the number of respondents of each country. Please note that Europe has been magnified in this illustration. Reprinted with permission from the BMJ publishing group LTD.[26]

Hemodynamic management

The majority of patients suffering from an acute ischemic stroke present with high BP in the acute phase.[34] Because ischemic stroke affects the cerebral blood flow, adequate hemodynamic management is of importance to prevent hypoperfusion of the penumbra and therefore infarct progression. The current guidelines for early management of patients with acute ischemic stroke recommend to treat first systolic blood pressure (SBP) above 185/110 mmHg prior to reperfusion therapy without differentiating between patients treated with intravenous thrombolytics (IVT) alone and patients eligible for endovascular thrombectomy (EVT).[35,36] This might lead to delay of EVT in patients with SBP levels above this threshold. As the effect of EVT strongly declines over time, withholding EVT for reasons of blood pressure management might be deleterious regarding patients' outcome after stroke. Furthermore, the use of periprocedural anesthetic agents could increase the risk of hypotension prior to reperfusion due to hemodynamic instability. Thereafter, in the subacute period after EVT, BP is often increased, taking a few days to return to baseline levels.[37-39] Information on associations between BP prior to EVT, during EVT and in the early hours following EVT and clinical outcomes like symptomatic intracranial hemorrhage (sICH) and neurologic deficit, could provide further insight in the potential of BP as a therapeutic target to improve outcomes.

Alternative approaches to evaluate ischemic stroke treatment effects

Despite the great progress in treating patients with ischemic stroke over the past years, still a large proportion of patients does not recover despite EVT. To further optimize outcomes of patients after EVT, there is need for innovative approaches for study design to accelerate research on new therapeutic strategies. Identification of periprocedural factors that explain variation in outcome after EVT might provide insight in new therapeutic strategies. For optimal evaluation of the effect of these new therapeutic interventions appropriate trial endpoints need to be selected, a decisive and challenging step in the design of a clinical trial. Selecting study endpoints does depend on both the onset and course of the disease, as well as the expected treatment mechanism and treatment effect under study. The primary outcome in the EVT trials was the modified Rankin Scale (mRS), an ordinal scale ranging from 0 (no symptoms) to 6 (death), measuring the degree of disability during daily life activities (Table 1.1) assessed at 3 months after randomization.[40] A secondary outcome in these trials was the degree of neurologic deficit according to the National Institutes of Health Stroke Scale (NIHSS), ranging from 0 (no neurologic deficit) to 42 (severe neurologic deficit) assessed at 24-48 hours and 5-7 days after randomization.[41] To efficiently evaluate ischemic stroke treatments, selection of a primary study outcome requires a trade-off between treatment specific early endpoints and more long-term patient-oriented outcomes. To accelerate the evaluation of effects of new stroke treatments, alternative trial outcomes, for example early imaging assessment, could improve the efficiency of stroke trials.

Another approach to further accelerate stroke research, is the use of synthetic cohorts of stroke patients, which are accurate representatives of real-world stroke patients. Since the introduction of General Data Protection Regulation, several issues concerning patient privacy have been highlighted including for example protection from the identification of an individual's data within large data samples [4]. As a result of this legislation, the possibility to share and use real individual-level patient data for research is limited. A promising way forward is the use of synthetic data as an alternative to individual patient data, to assist in methodological developments and in the design of trials without patient privacy concerns.[42,43] Synthetic patient data also have the potential to enable *in silico* (computer simulation) model development at a quicker pace. Despite several methods available for generating synthetic cohorts of patients, there is lack on how to assess the accuracy of these methods.[44] Since the concept of synthetic patient cohorts might be complicated for clinically oriented researchers, further evaluation of the concept, applications and methods is needed.

Aims and outline of this thesis

The overall aim of this thesis is to increase the benefit of endovascular treatment for ischemic stroke by identifying risk factors for poor outcome and improve the understanding of endovascular treatment effect.
Specific research questions are:

1. Which factors influence outcome after EVT for ischemic stroke?
1a. How do anesthetic and hemodynamic factors influence outcome after EVT?
1b. Which pre-procedural, procedural and post-procedural factors explain outcome variation after EVT?

2. What are future directions for EVT research?
2a. How to decide on efficient early (trial) endpoints?
2b. What is the potential of synthetic patient cohorts for future EVT research?

Data sources
The analyses in this thesis were performed with clinical and imaging data from the following sources:

MR CLEAN trial (The Multicenter Randomized Clinical trial of Endovascular treatment of Acute ischemic stroke in the Netherlands) randomized patients with ischemic stroke due to a proximal large vessel occlusion between EVT and versus usual care alone who present within 6 hours after stroke onset. Patients were included in the trial between December 2010 and March 2014[15,45]

MR CLEAN Registry containing data on all consecutive patients treated with EVT for ischemic stroke due to large vessel occlusion between March 2014 until November

2017 in the Netherlands. The overall purpose of this nationwide Registry is to monitor the outcome and safety of EVT in clinical practice.[46]

HERMES collaboration (The Highly effective Reperfusion Using Multiple Endovascular Devices) combined data from seven international randomized controlled trials, including the MR CLEAN trial. Patients were included in the trials between 2010 and 2015.[15-19,47,48]

Outline of this thesis

Part I of this thesis focusses on the identification of preprocedural, procedural and postprocedural factors that influence outcome after EVT. **Chapter 2** describes the role of blood pressure prior to EVT on the effect of EVT. **Chapter 3** aims to assess the influence of anesthetic management during EVT on outcome. Related to this topic, **Chapter 3.1** contains a letter discussing the effect of anesthesia on outcome. In **Chapter 4**, the influence of hemodynamic management on the effect of anesthesia during EVT is evaluated. In line with this, **Chapter 4.1** discusses the importance of distinguishing anesthesia type for the evaluation of procedural hemodynamics. In **Chapter 5,** the role of hemodynamics following EVT on outcome is assessed. In **Chapter 6,** the importance of predictors for poor outcome despite successful EVT is assessed.

Part II of this thesis focusses on the relation between early imaging and clinical outcomes and the potential role of synthetic data cohorts in future EVT research. **Chapter 7** explores the role of follow-up infarct volume on effect of EVT on early neurologic deficit. In **Chapter 8**, the concept, methods and applications of synthetic stroke data cohorts, are described.

Chapter 9 consists of a discussion of the results and provides recommendations for future research and clinical practice.

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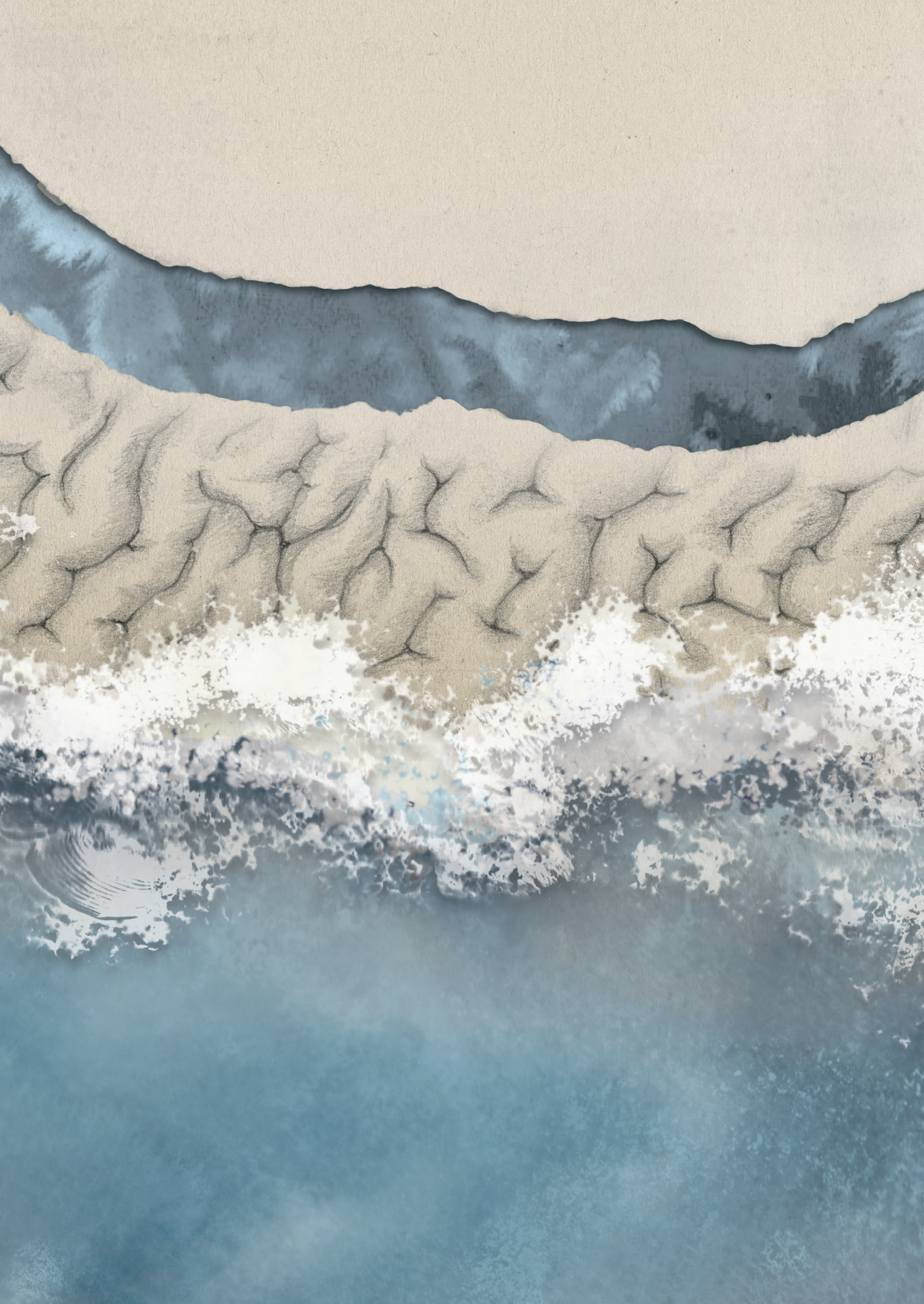

PART I

Factors influencing outcome after endovascular treatment

CHAPTER 3

Conscious sedation or local anesthesia during endovascular treatment for acute ischemic stroke

Neurology, 2018

Noor Samuels, Rob A. van de Graaf, Maxim J.H.L. Mulder, Ismail Eralp, Adriaan C.G.M. van Es, Diederik W.J. Dippel, Aad van der Lugt, Bart J. Emmer, for the Multicenter Randomized Clinical Trial of Endovascular Treatment of Acute Ischemic Stroke in the Netherlands (MR CLEAN) Registry Investigators.

Abstract

Objective: The aim of this study was to investigate the effect of conscious sedation (CS) on functional outcome and complication rates after intra-arterial treatment (IAT) for acute ischemic stroke (AIS), compared to the use of local anesthesia (LA) at the puncture site only.

Methods: Patients undergoing IAT for AIS with CS or LA in the Erasmus University Medical Center, from March 2014 until June 2016 were included for analysis. The primary outcome was the score on the ordinal modified Rankin Scale (mRS). We compared CS to LA, by ordinal logistic regression with covariate adjustment using propensity scoring.

Results: In 146 AIS patients treated with IAT, use of CS was associated with a shift towards worse mRS scores (OR 0.4 [95% CI 0.2 to 0.7]) compared to LA. Mortality after 90 days was higher in the CS group compared to the LA group (OR 2.3 [95% CI 1.0 to 5.2]). No differences between groups were noted with regard to procedure duration (d=8 minutes, β=6.3 [95% CI -7.4 to 20.0]) and occurrence of procedure-related complications (OR 1.3 [95% CI 0.6 to 2.7]).

Conclusion: CS was associated with poor functional outcome and increased mortality rates, compared to LA. Furthermore, CS did not reduce duration of intervention or interventional complications. CS during IAT for AIS is of no benefit if LA is considered safe.

Classification of evidence: This study provides Class II evidence, because of non-random allocation, that for patients with AIS undergoing IAT, LA rather than CS improves functional outcome.

Introduction

Anesthetic support is commonly used during intra-arterial treatment (IAT) procedures for large vessel occlusions in acute ischemic stroke (AIS).[1] The aim of anesthetic support during IAT is to reduce patient motion, increase patient comfort, facilitate fast treatment and minimize the risk of complications. There are different options for the anesthetic management during IAT; general anesthesia (GA), conscious sedation (CS) or local anesthesia (LA) at the puncture site only. CS is often considered as the ideal compromise during IAT by preserving patient cooperation, comfort, procedural speed compared to LA and reducing medication levels compared to GA. Although CS has become common practice during IAT, the effect on outcome is unknown.[2] Post-hoc analysis of the Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke (MR CLEAN) data showed that GA had a negative influence on treatment effect of the intra-arterial procedure in AIS patients in comparison to non-GA (composite of LA and CS).[3] This was also confirmed in the HERMES collaboration.[4] On the other hand, recently published trials showed no advantage of CS on neurological improvement after IAT compared to GA.[5,6] We do not know of studies comparing GA or CS with LA at the groin puncture site only. Until now, it is unknown whether the use of CS during IAT has any positive influence on outcome, complications and procedure times in AIS patients with a large intracranial vessel occlusion, when compared to LA. The aim of this study is to assess the effect of CS on functional outcome and occurrence of complications compared to LA.

Methods

Classification of evidence

We seek to answer the following research question: Does CS in patients with AIS caused by a large intracranial vessel occlusion of the anterior circulation improves functional outcome in comparison to LA? Class II level of evidence is assigned to this question.

Data source and study population

Patients who were enrolled in the MR CLEAN Registry were studied. The MR CLEAN Registry is a prospectively collected database containing all patients who underwent IAT for IAS in the Netherlands. The Registry started after the final MR CLEAN trial. All patients undergoing IAT (defined as at least entry into the angiography suite and arterial puncture) for acute ischemic stroke in the anterior and posterior circulation have been registered in the MR CLEAN Registry. For the current study we restricted our analysis to patients treated in the Erasmus MC in Rotterdam from the start of the MR CLEAN Registry in March 2014 until June 2016. As our center was the only participating center in which the use of CS during IAT was standard care for a defined time period, we restricted our analysis to single center data to minimize selection

bias. We additionally applied the following inclusion criteria: arterial puncture within 6.5 hours of symptom onset; age of 18 years and older; intracranial proximal arterial occlusion in the anterior circulation (intracranial carotid artery (ICA/ICA-T) or middle (M1/M2) or anterior (A1/A2) cerebral artery), demonstrated by computed tomographic angiography (CTA), magnetic resonance angiography (MRA) or digital subtraction angiography (DSA). We excluded patients with pre-stroke modified Rankin Scale (mRS) score higher than 2 points, when GA was performed as first line of defense, or when type of anesthesia was not documented. Study results are reported in accordance with the "Strengthening the reporting of observational studies in epidemiology (STROBE)" statement.[7]

Anesthetic procedure

The protocol in our institution stated that, if anesthetic support was available, CS should be started at the beginning of the IAT procedure. When CS could not be initiated due to unavailability of the attending anesthesiologist, the intervention team would go ahead and an attempt would be made to perform IAT directly under LA. When, during the procedure it became apparent that IAT was not possible due to restlessness of the patient, the anesthesiology department would be requested to perform CS. The choice of anesthetic agents used for CS was left to the discretion of the anesthesiologist. Medication strategy was based on either propofol or remifentanil. Administered propofol doses ranged from 2-6 mg/kg/hour and remifentanil doses from 1-4 mcg/kg/hour.

Study outcomes

The primary outcome was the mRS score (a 7-point scale ranging from 0 'no symptoms' to 6 'dead') at 90 days after IAT. Secondary outcomes included a score of 2 or less on the mRS indicating good functional outcome, death within 7, 30 and 90 days post-intervention and National Institute of Health Stroke Scale (NIHSS) score indicating neurological deficit on a 0-42 scale at 24-48 hours post-intervention.[8,9] A higher NIHSS score indicates a more severe deficit. Procedure-related outcome measures included modified thrombolysis in cerebral infarction (mTICI) score on DSA, total procedure time and procedure related complications. The mTICI score ranges from 0 (no antegrade reperfusion of the occluded vascular territory) to 3 (complete antegrade reperfusion of the occluded vascular territory). For eTICI, grade 2C (slow flow in a few distal cortical vessels or presence of small distal cortical emboli, corresponding to 90-99% reperfusion) was added to the original mTICI score.[10] Procedure-related complications included vessel perforation, vessel dissection, new clot, distal thrombus, vasospasm, hemorrhage and other. Procedure-related complications and eTICI score were assessed by core lab. Serious adverse events included symptomatic intracranial hemorrhage, progression of ischemic stroke, new ischemic stroke, pneumonia, other infections, cardiac ischemia, extra cranial hemorrhage, allergic reactions and other adverse events. Investigators who assessed primary and secondary outcomes,

procedure-related outcome and procedure-related complications were not aware of the type of anesthetic support during the procedure.

Statistical methodology and procedures

Based on the intention-to-treat principle patients converted from LA to CS during the IAT procedure were included in the LA group. In case the anesthesia team was not available just before starting the IAT procedure and the IAT procedure seemed unsafe under LA (due to excessive movement) the anesthesia team was called immediately without starting the procedure to increase procedural safety. If the decision for anesthesia in the form of CS was made before groin puncture, the patient was included in the CS group. For variables with missing values in less than 5% of patients, we used single imputation by mean for continuous variables and by mode for categorical variables. Normality assessment of data was performed both visually and by means of the Kolmogorov-Smirnov test. One-way ANOVA was used for parametric and Kruskal-Wallis test for non-parametric testing. Both categorical and dichotomous variables were tested using crosstabs and were shown as percentages.

Possible selection bias was addressed by performing adjustment for covariates by propensity score for both primary and secondary outcomes. Variables related to anesthetic management and outcome were selected based on clinical experience and previous literature. The saturated propensity model included the variables: age, sex, previous stroke, diabetes mellitus, atrial fibrillation, hypertension, history of myocardial infarction, peripheral artery disease, pre-stroke mRS score, NIHSS at baseline, aphasia score, pre-interventional eTICI score and time from stroke onset to groin puncture. For each case a propensity score was calculated using the propensity model. This propensity score, yielding the probability for a patient to receive anesthetic management in the form of CS given the baseline characteristics, was then incorporated in a regression model. Propensity score adjustment was performed by means of a logistic regression model for binary outcomes. The propensity score was then used in an ordinal logistic regression model to adjust the estimate of the effect of CS on the mRS score. This effect is expressed as an adjusted common odds ratio (acOR) with 95% CI, as the mRS is an ordered categorical outcome. A p-value of <0.05 was considered significant in all applied tests. All statistical analyses were performed with Stata 14.0 software (StataCorp, College Station, TX, USA).

Standard Protocol Approvals, Registrations, and Patient Consents

The MR CLEAN Registry was reviewed and approved by the medical ethics committee and research board of the Erasmus MC, University Medical Center, Rotterdam, the Netherlands (MEC-2014-235). This approval extends to all participating centers in The Netherlands. Study candidates received verbal and written explanation of the study and had the opportunity to opt out. Coded data were obtained and stored at Erasmus MC, and scientific analyses were approved and supervised by a central

writing committee. The MR CLEAN Registry study protocol is available on https://www.mrclean-trial.org/docs/latestprotocol.pdf.

Results

Patient characteristics

Between March 2014 and June 2016, 205 patients underwent IAT at the Erasmus MC. A total of 146 patients met the inclusion criteria (Figure 3.1). 60 patients (41%) received CS and 86 patients (59%) LA at the groin puncture site only during IAT. Patients treated with IAT under CS had less often a history of previous stroke than patients treated without CS (1.7% vs. 14.0%; p = 0.01) (Table 3.1).

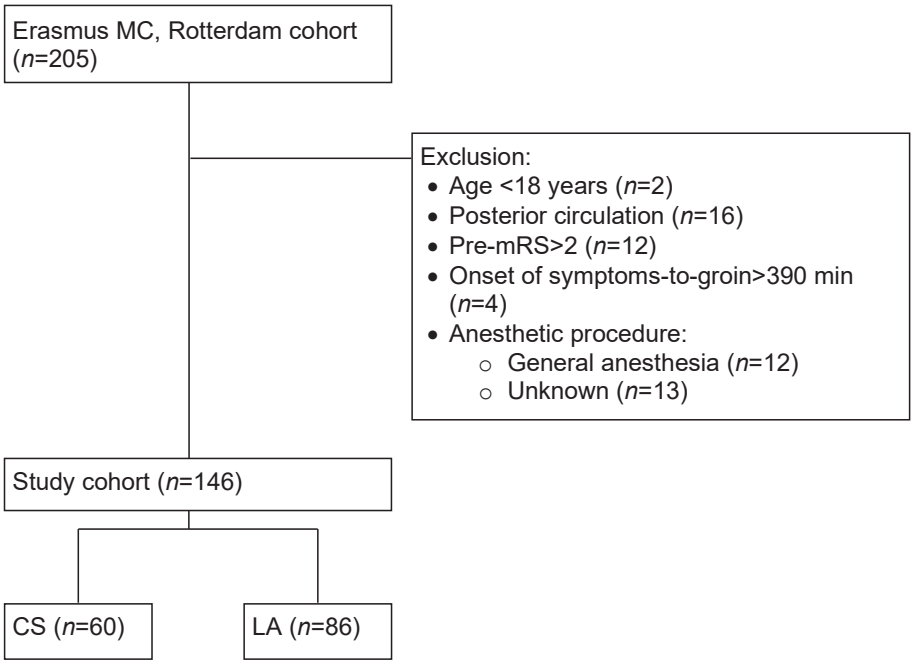

Figure 3.1. Flowchart of patients included from Erasmus MC in MR CLEAN Registry from March 2014 until June 2016

Abbreviations: CS, conscious sedation; Erasmus MC, Erasmus Medical Center; GA, general anesthesia; IAT, intra-arterial treatment; LA, local anesthesia; MR CLEAN, Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands; mRS, modified Rankin Scale

Table 3.1. Baseline characteristics

	CS (n=60)	**LA (n=86)**	**P-value**
Patient characteristics			
Age, mean (SD)	65.9 (14.2)	69.2 (13.5)	0.16
Male sex, n (%)	32 (53.3%)	51 (59.3%)	0.47
NIHSS, median (IQR)	15 (9.0-19)	14 (10-18)	0.46
Hemisphere, n (%)			
Left	22 (44.9%)	30 (39.5%)	0.55
Right	27 (55.1%)	46 (60.5%)	0.55
Systolic BP, mean (SD)	152.7 (27.0)	151.3 (24.0)	0.74
Diastolic BP, mean (SD)	81.7 (16.7)	82.7 (15.6)	0.72
IVT, n (%)	48 (80.0%)	65 (75.6%)	0.53
Medical history			
Previous stroke, n (%)	1 (1.7%)	12 (14.0%)	0.01
Atrial fibrillation, n (%)	9 (15.0%)	16 (18.6%)	0.57
Hypertension, n (%)	28 (47.5%)	48 (55.8%)	0.32
Diabetes mellitus, n (%)	10 (16.7%)	14 (16.3%)	0.95
Myocardial infarction, n (%)	6 (10.0%)	11 (12.8%)	0.61
Peripheral arterial disease, n (%)	1 (1.7%)	8 (9.3%)	0.06
Pre-stroke mRS, median (IQR)			0.96
0	52 (92.9%)	78 (92.9%)	
1	1 (1.8%)	2 (2.4%)	
2	3 (5.4%)	4 (4.8%)	
Imaging			
Occluded segment, n (%)			
M1	31 (64.6%)	31 (54.4%)	0.29
M2	12 (25.0%)	19 (33.3%)	0.35
ICA	2 (4.2%)	3 (5.3%)	0.79
ICA-T	3 (6.3%)	4 (7.0%)	0.88
Reperfusion before intervention (eTICI), n (%)			0.16
0	45 (79.0%)	62 (80.5%)	
1	9 (15.8%)	6 (7.8%)	
2A	0 (0%)	4 (5.2%)	
2B	2 (3.5%)	1 (1.3%)	
2C/3	1 (1.8%)	4 (5.2%)	

Table 3.1. Continued.

	CS (n=60)	**LA (n=86)**	**P-value**
ASPECTS, median (IQR)	8 (7-10)	9 (8-10)	0.05
Workflow			
Time from stroke onset to IVT, min, median (IQR)	70 (55-111)	72 (55-87)	0.89
Time from stroke onset to admission ER*, min, median (IQR)	166 (126-210)	138 (101-189)	0.06
Time from admission ER* to groin puncture, min, median (IQR)	55 (35-79)	54 (37-72)	0.98
Time from stroke onset to groin puncture, min, median (IQR)	224.5 (166-282.5)	195 (167-245)	0.08

Continuous data are presented as mean (SD) for normal distributed data or as median (IQR) for skewed data.
Abbreviations: ASPECTS, Alberta Stroke Program Early Computed Tomography Score; BP, blood pressure; CS, conscious sedation; ER, emergency room; eTICI, modified thrombolysis in cerebral infarction including a 2C grade; GCS, Glasgow Coma Scale; ICA, internal carotid artery; ICA-T, internal carotid artery terminus; IVT, intravenous thrombolysis; IQR, interquartile range; LA, local anesthesia at the groin puncture site; M(*segment*), middle cerebral artery; NIHSS, National Institutes of Health Stroke Scale; SD, standard deviation
Captions: * Intervention center, Erasmus MC, Rotterdam

Logistics
Time from stroke onset to admission at the emergency room (ER) of the Erasmus MC (intervention center) did not differ between both groups. Admission time was 166 minutes in the patients receiving CS versus 138 minutes for patients receiving LA, but this was not different (p = 0.06). Time from admission at the ER of the intervention center to groin puncture did not differ between groups (55 vs. 54 minutes, p = 0.98).

Outcome
Patients who underwent CS were more likely to have poor mRS scores at 90 days compared to LA (adjusted common odds ratio (acOR) 0.4 [95% CI 0.2 to 0.7]). Good functional outcome (mRS score ≤ 2) at 90 days was less often seen in patients who underwent CS compared to LA (OR 0.4 [95% CI 0.2 to 0.8]). Mortality within 30 days post IAT was higher in the CS group compared to the LA group (17/60 vs. 10/86, OR 2.6 [95% CI 1.0 to 6.4]). Also mortality within 90 days post IAT was higher in the CS group, 35% (21/60) vs. 16% (14/86) in the LA group (OR 2.3 [95% CI 1.0 to 5.2]).

Table 3.2. Effect of CS in patients undergoing IAT for AIS after propensity score adjustment

	CS (n=60)	LA (n=86)	Effect para-meter	Adjusted value* (95% CI)
Primary outcome				
mRS at 90 days, median (IQR)	4 (3-6)	3 (2-4)	acOR	0.4 (0.2 to 0.7)
Secondary outcomes, clinical				
mRS ≤ 2 at 90 days, n (%)	13 (22%)	40 (47%)	OR	0.4 (0.2 to 0.8)
Mortality at 7 days, n (%)	9 (15%)	6 (7%)	OR	1.8 (0.6 to 5.6)
Mortality at 30 days, n (%)	17 (28%)	10 (12%)	OR	2.6 (1.0 to 6.4)
Mortality at 90 days, n (%)	21 (35%)	14 (16%)	OR	2.3 (1.0 to 5.2)
NIHSS 24-48h, median (IQR)	12 (7-19)	6 (4-14)	β	5.9 (-0.9 to 12.6)
Secondary outcome, radiologic				
Reperfusion after intervention (eTICI ≥ 2B), n (%)	38 (63%)	67 (78%)	OR	0.5 (0.2 to 1.0)
Reperfusion after intervention (eTICI ≥ 2C), n (%)	23 (38%)	53 (62%)	OR	0.4 (0.2 to 0.8)
Secondary outcomes, time difference				
Time from stroke onset to reperfusion, min, median (IQR)	284 (237-347)	256 (225-297)	β	10.7 (-14.0 to 35.3)
Duration procedure, min, mean (SD)	77 (40)	69 (38)	β	6.3 (-7.4 to 20.0)
Secondary outcomes, safety parameters and serious adverse events				
Procedure-related complications, n (%)	23 (38%)	25 (29%)	OR	1.3 (0.6 to 2.7)
Serious adverse events, n (%)				
Symptomatic ICH	3 (5%)	3 (3%)	OR	1.7 (0.3 to 10.2)
ECH	2 (3%)	1 (1%)	OR	2.4 (0.2 to 29.1)
Progression of stroke	9 (15%)	8 (9%)	OR	1.3 (0.5 to 3.7)

Table 3.2. Continued.

	CS (n=60)	LA (n=86)	Effect para-meter	Adjusted value* (95% CI)
New ischemic stroke	2 (3%)	3 (3%)	OR	0.8 (0.1 to 5.6)
Cardiac ischemia	0	1 (1%)	OR	-
Pneumonia	12 (20%)	9 (10%)	OR	2.1 (0.8 to 5.8)
Allergic reaction	0	0	OR	-
Other infections	2 (3%)	0	OR	-
Other	10 (17%)	9 (10%)	OR	1.4 (0.5 to 3.7)

Abbreviations: acOR, adjusted common odds ratio; CS, conscious sedation; ECH, extracranial hemorrhage; eTICI, modified thrombolysis in cerebral infarction including a 2C grade; ICH, intracranial hemorrhage; LA, local anesthesia at the groin puncture site; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio.

*Captions: *Values of conscious sedation versus local anesthesia, adjusted by propensity score*

Variables in the propensity score model: age, sex, previous stroke, diabetes mellitus, atrial fibrillation, hypertension, history of myocardial infarction, peripheral artery disease, pre-stroke mRS score, NIHSS at baseline, aphasia score, pre-interventional eTICI score, time from stroke onset to groin puncture

The NIHSS at 24-48 hours post IAT was 12 in the patients receiving CS and 6 in the patients receiving LA, but not different (β 5.75 [IQR -0.9 to 12.6]). Successful recanalization (eTICI ≥ 2B) was achieved in 72% (105/146) of all patients, without difference between the CS and LA group (OR 0.5 [95% CI 0.2 to 1.0]). Successful recanalization at the eTICI ≥ 2C level on DSA was less often seen in the CS group (OR 0.4 [95% CI 0.2 to 0.8]). There was no difference in time stroke onset to reperfusion between the CS group and the LA group (284 vs. 256 minutes, β 10.7 [95% CI -14.0 to 35.3]). Also, total procedure time, procedure-related complications and serious adverse events did not differ between groups (Table 3.2). Conversion of anesthetic management was reported in four patients; twice from LA to CS, once from LA to GA and once from CS to GA.

Discussion

In this cohort study, CS during IAT was associated with poor functional outcome and higher mortality compared to LA. Reperfusion rates, procedure duration, procedure-related complications and serious adverse events did not differ between the two groups. Therefore, our results suggest that functional outcome is less influenced by LA than by CS as an anesthetic approach during IAT, bearing in mind that due to patient movement and need for procedural comfort the use of CS is sometimes inevitable.

Studies on anesthetic approaches during IAT focused only on GA compared to other types of anesthetic support (i.e. CS or non-GA) with contrasting results.[4-6,11] Some suggested mechanisms present in both GA and CS may lead to worse outcome in comparison to LA.[12,13] Delay in treatment initiation is considered an important disadvantage of GA, with effect on functional outcome.[14] As 'time is brain' one single hour of delay leads to a 6% decrease in good functional outcome.[15] However, time from admission at the ER of the intervention center to groin puncture did not differ between patients who underwent IAT with CS compared to LA. In addition, patients undergoing CS have an increased risk of pulmonary aspiration as they usually have not fasted before an IAT procedure.[16] Other mechanisms potentially contributing to poor functional outcome after IAT may include the detrimental effect of peri-procedural hypotension or the possible effects of anesthetic agents on the brain itself (i.e. direct neurotoxic).[13,17-19]

Time from stroke onset to admission at the ER of the intervention center was 28 minutes longer in the CS group, although not different from the LA group. This delay contributed to the longer time from stroke onset to reperfusion seen in the CS group. Notably, the net effect of CS on outcome remained, even with incorporating time from stroke onset to groin puncture in the propensity score. Time from admission at the ER of the intervention center to groin puncture was similar between patients who underwent IAT with CS or LA. Consequently, we were not able to detect a delay in the CS group regarding initiation of anesthetic management. Successful recanalization on eTICI ≥ 2C level was less often seen in the CS group. CS did not result in lower

complication rates; contrary to common belief that CS increases the safety of the procedure. Nonetheless, because of our relatively small sample size these findings need to be confirmed in a larger prospective randomized study. Concerning our intention-to-treat principle for minimization of selection bias the occurrence of conversion could not have influenced the results in favor of the LA group.

This study does have several limitations. In this single center study, patients were not randomized between CS and LA. Nevertheless, its observational design has the advantage that we observe the procedures in everyday practice, and the propensity score adjustment was performed to adjust for potential confounders between groups. Furthermore, results could have been confounded by variables not accounted for in the propensity model ("unmeasured confounding").[20] Confounding by indication might have been introduced, apart from protocol-based anesthetic management (CS), as the condition of the patient also influences the choice made by the intervention team. We tried to prevent this by saturating the propensity model. Regarding the baseline characteristics included in the propensity model, previous stroke and time from onset of stroke until groin puncture were distributed in disadvantage of CS. Another limitation is the lack of data on blood pressure during the IAT procedure. The generalizability of the results reported in this study is also limited by the lack of research on this topic and heterogeneity of IAT management between centers. Nevertheless, CS appears to influence outcome after IAT, which could be of relevance to physicians in the decision-making process for the most appropriate anesthetic management during IAT. Based on our results, a randomized trial evaluating outcome after IAT with LA, CS or GA seems justified.

We found that CS is associated with poor functional outcome and higher mortality in patients who underwent IAT for acute ischemic stroke. Furthermore, CS did not reduce duration of intervention or procedure-related complications and did not increase reperfusion rates. Our results suggest that functional outcome is less influenced by LA than by CS as an anesthetic approach during IAT.

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CHAPTER 3.1

The ongoing debate on anesthetic strategies during endovascular treatment: can local anesthesia solve the puzzle?

International Journal of Stroke, 2019
Letter regarding article by Rabinstein et al, "Factors that may contribute to poor outcome despite good reperfusion after acute endovascular stroke therapy."

Noor Samuels, Rob A. van de Graaf, Aad van der Lugt, Adriaan C.G.M. van Es, Diederik W.J. Dippel, Bart J. Emmer

Letter to the Editor

Dear Editor,

We read the review by Rabinstein et al. with interest. The authors discussed factors related to poor functional outcomes despite good reperfusion in acute ischemic stroke patients treated with endovascular thrombectomy (EVT).[1] On the subject of anesthetic techniques during the intervention, the authors conclude that equipoise exists between conscious sedation (CS) and general anesthesia (GA) and large multicenter randomized trials are needed to determine whether or not CS and GA are equally safe and effective.

We think that focusing solely on CS and GA does not do justice to a simple and potentially safer anesthetic strategy: local anesthesia at the groin puncture site only (LA). The review mentioned the well-known trials (GOLIATH, SIESTA, ANSTROKE) that randomized between CS or GA during EVT and showed contrasting results.[2-4] In the HERMES meta-analysis non-GA was superior to GA. However, the non-GA group was defined as the composite of local anesthesia (LA) at the groin puncture site only and CS.[5] Therefore, the better functional outcomes in the non-GA arm might well be the result of patients receiving LA only. Recently, we compared the effect of LA only during EVT to CS and we reported better functional outcomes in patients receiving LA.[6] Several mechanisms, present in both GA and CS (e.g. blood pressure drops, impaired airway reflexes), could explain poorer outcomes in the CS group. We think that these results should be taken into account when considering what is the optimal anesthetic approach during EVT. In our opinion, future trials should consider LA as one of the initial anesthetic strategies during EVT.

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CHAPTER 4

Blood pressure during endovascular treatment under conscious sedation or local anesthesia

Neurology, 2021

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Abstract

Objective: To evaluate the role of blood pressure as mediator of the effect of conscious sedation (CS) compared to local anesthesia (LA) on functional outcome after EVT.

Methods: Patients treated in MR CLEAN Registry centers with CS or LA as preferred anesthetic approach during EVT for ischemic stroke were analyzed. First, we evaluated the effect of CS on area under the threshold (AUT), relative difference between baseline and lowest procedural mean arterial pressure (ΔLMAP) and procedural blood pressure trend, compared to LA. Second, we assessed the association between blood pressure and functional outcome (modified Rankin Scale, mRS) with multivariable regression. Lastly, we evaluated whether blood pressure explained the effect of CS on mRS.

Results: In 440 patients with available blood pressure data, patients treated under CS (n=262) had larger AUTs (median 228 versus 23 mmHg*min), larger ΔLMAP (median 16% versus 6%) and a more negative blood pressure trend (-0.22 versus -0.08 mmHg/min) compared to LA (n=178). Larger ΔLMAP and AUTs were associated with worse mRS (adjusted common OR (acOR) per 10%-drop 0.87, 95%CI0.78-0.97, and acOR per 300mmHg*min 0.89, 95%CI0.82-0.97). Patients treated under CS had worse mRS compared to LA (acOR 0.59, 95%CI0.40-0.87) and this association remained when adjusting for ΔLMAP and AUT (acOR 0.62, 95%CI0.42-0.92).

Conclusions: Large blood pressure drops are associated with worse functional outcome. However, blood pressure drops do not explain the worse outcomes in the CS group.

Introduction

Post-hoc analyses of the MR CLEAN trial and HERMES collaboration showed that general anesthesia (GA) is associated with worse clinical outcomes than non-GA. In these studies, non-GA was the composite of conscious sedation (CS) and local anesthesia at the groin puncture site only (LA).[1,2] Furthermore, among patients managed without GA, CS seemed to be associated with worse functional outcome compared to LA.[3,4]

Previous studies in patients receiving GA during EVT reported worse outcomes in patients who experienced blood pressure drops during the procedure.[5-9] The administration of anesthetic and analgesic agents may cause gradual or sudden declines in blood pressure. This potentially impairs penumbra perfusion before recanalization.[10-12] Considering that hypotension leads to worse outcomes in GA, hypotension might also contribute to worse outcomes in patients treated under CS or LA. Until now, there is limited data on blood pressure parameters during EVT among patient treated under CS or LA.[13,14]

In the present study, we explored the effect of CS on procedural blood pressure and functional outcome, using patients under LA as control. In addition, we evaluated whether blood pressure drops explain differences in functional outcome between anesthetic regimes.

Methods

Study population

We used data from the MR CLEAN Registry, which is a prospective, multicenter, observational study including all patients who underwent EVT for ischemic stroke due to a large vessel occlusion in the Netherlands from March 2014 until November 2017. Detailed information on the description of variables and the methods of MR CLEAN Registry have been reported previously.[15] First, centers were excluded if they were non-MR CLEAN trial centers, did not perform EVT under CS or LA as the preferred anesthetic approach, or did not record periprocedural blood pressure as part of protocol care. Second, patients were excluded when they were less than 18 years old, had an occlusion in the posterior circulation or were treated after 6.5 hours of stroke onset. Third, we excluded patients who had no available blood pressure data or were treated under GA as the initial anesthetic strategy during EVT in one of the centers with CS or LA as the preferred anesthetic approach.

To address the risk of bias through selective hemodynamic monitoring and blood pressure data storage in patients at higher risk for hemodynamic instability, we additionally evaluated baseline characteristics of patients treated under CS and LA with and without blood pressure data. Procedural blood pressure values and administered medication were collected retrospectively from patients' records.

Study results are reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.[16]

Standard protocol approvals, registrations, and patients consents
The MR CLEAN Registry was approved by the medical ethics committee of the Erasmus University MC, Rotterdam, the Netherlands (MEC-2014-235). The institutional review board of each participating center approved the research protocol. At UMC Utrecht, additional approval to participate in the study was obtained from the local research board and ethics committee. The necessity of written informed consent was waived.

Anesthetic management
To limit the risk of confounding by indication, only patients treated in centers that perform EVT under either CS or LA as the preferred anesthetic approach were selected. CS was defined as the administration of any sedative with or without analgesics (e.g. propofol, remifentanil) from 10 minutes before groin puncture until the time of recanalization, not requiring intubation. LA was defined as the use of a local anesthetic (e.g. lidocaine) at the puncture site, without the use of any systemic analgesics or sedatives. Patients converted to GA during the procedure, defined as endotracheal intubation, were analyzed according to the initial anesthetic strategy to limit confounding by indication. The choice of anesthetic agents was at the discretion of the attending anesthesiologist or trained nurse. Anesthetic reports of all patients were reviewed for type, dosages and time of administered anesthetic and vasoactive agents.

Hemodynamic management
Standard hemodynamic monitoring included oxygen saturation, heart rate, non-invasive blood pressure and temperature. Invasive blood pressure monitoring was performed on individual basis as determined by the anesthesiologist. The frequency of blood pressure measurements depends on the local monitoring protocol. Systolic blood pressure, diastolic blood pressure and mean arterial pressure (MAP) values, recorded between 10 minutes before groin puncture and time of recanalization, were retrieved from the patients' procedural anesthesia reports. Since there is no consensus on which blood pressure derived measures are most relevant and what should be avoided (e.g. drops, variability) we focused on three predefined orthogonal definitions that capture different elements of blood pressure drops and variability[17]: [I] area under the threshold (AUT, with MAP on admission as the threshold determined per patient) in mmHg*minute, reflecting both the depth and duration of the relative hypotensive episode; [II] the relative difference between the MAP on admission and the lowest MAP during the EVT procedure, expressed as percentage drop in MAP (ΔLMAP), to account for shorter, larger blood pressure drops; [III] the blood pressure trend during the procedure, defined as the slope for each patient derived from a multilevel linear

regression model with "time-since-start procedure" as a predictor, with a random slope to estimate patient specific trends in blood pressure measurements, for the continuous outcome systolic blood pressure including a random effect for patient to account for within patient variability (Figure 4.1).[7,8,18-20] Hemodynamic intervention was defined as the administration of any inotropes or vasopressors (e.g. ephedrine, phenylephrine) to increase blood pressure or the use of sympathicolytics (e.g. labetalol, clonidine) to lower blood pressure. Blood pressure was regulated according to institutional practices, in general, systolic blood pressure was maintained between 140 and 185 mmHg with a diastolic blood pressure below 105 mmHg based on anesthetic critical care recommendations.[21]

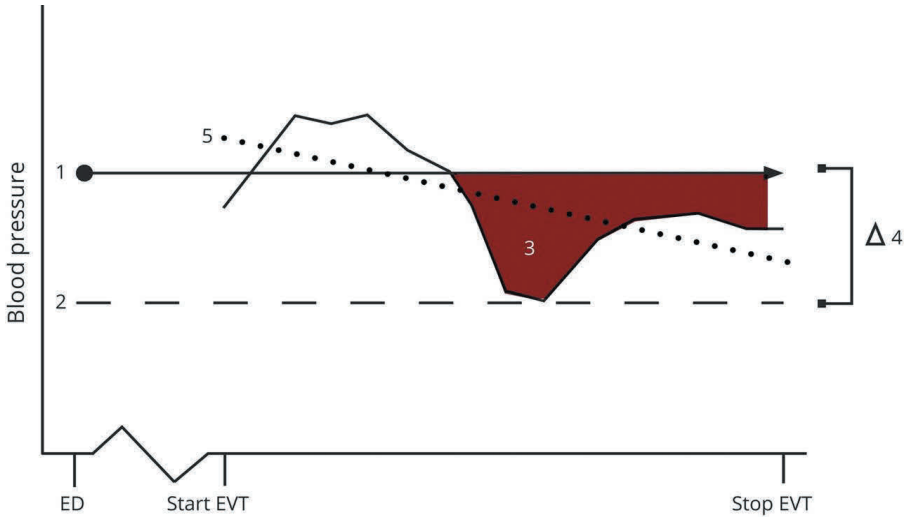

Figure 4.1. Schematic illustration procedural blood pressure parameters.
Summary: 1. mean arterial pressure (MAP) value on admission; 2. Lowest MAP; 3. Area under the threshold (AUT); 4. Relative difference between baseline MAP and lowest MAP (ΔLMAP); 5. Average trend (slope). *Abbreviations*: ED, emergency department; EVT, endovascular treatment.

Outcome measures

The primary outcome measure was score on the modified Rankin Scale (mRS). This is a 7-point scale ranging from 0 "no symptoms" to 6 "death", assessed at 90 days after EVT.[22] Secondary outcomes included functional independence (mRS ≤ 2), mortality within 90 days post EVT, National Institutes of Health Stroke Scale (NIHSS) score indicating neurologic deficit at 24-48 hours after EVT.[23] Procedure-related outcomes included occurrence of hemodynamic intervention, reperfusion grade, duration of the EVT procedure, and occurrence of procedure-related complications (i.e. vessel perforation, vessel dissection, new thrombus, distal thrombus, hemorrhage, and

vasospasm). The reperfusion grade was assessed by the extended thrombolysis in cerebral infarction (eTICI) score on digital subtraction angiography (DSA) which ranges from 0 "no reperfusion or anterograde flow beyond site of occlusion" to 3 "complete reperfusion".[24] Serious adverse events included symptomatic intracranial hemorrhage (sICH, neurologic deterioration of ≥4 points on the NIHSS, and a compatible hemorrhage on imaging assessed by an independent core laboratory according to the Heidelberg criteria)[25], extracranial hemorrhage, neurologic deterioration (increase of ³ 4 points on the NIHSS), new ischemic stroke (imaging of new brain tissue infarction with any degree of corresponding neurologic deficit), and pneumonia. Procedure-related complications and eTICI scores were assessed by an independent core laboratory. Investigators who assessed primary and secondary outcomes were not aware of the type of anesthetic management during EVT.

Statistical methods

Baseline characteristics of patients who underwent EVT under CS were compared with patients who received LA during the EVT procedure with a χ^2 test for categorical variables, independent samples *t*-test for normally distributed continuous variables, and Kruskal-Wallis test for non-normally distributed continuous variables. Missing data were imputed using multiple imputations by chained equations based on relevant covariates.[26]

We tested three associations according to a four-step approach: [I] We evaluated the effect of anesthetic modality on the predefined blood pressure parameters (i.e. AUT, ΔLMAP and trend) and hemodynamic interventions during EVT with multivariable linear regression. We adjusted for age, sex, hypertension, diabetes mellitus, atrial fibrillation, history of myocardial infarction, previous stroke, systolic blood pressure on admission, baseline NIHSS, pre-stroke mRS score and treatment center; [II] We assessed the association between the predefined blood pressure parameters and functional outcome. This association was evaluated for all blood pressure parameters separately with ordinal logistic regression adjusted for age, sex, previous stroke, diabetes mellitus, atrial fibrillation, hypertension, history of myocardial infarction, pre-stroke mRS, baseline NIHSS, treatment with intravenous thrombolysis, ASPECTS at baseline, collateral score, time from stroke onset to recanalization, and treatment center; [III] We evaluated the effect of anesthetic modality on functional outcome using an ordinal logistic regression analysis. We adjusted for the following prognostic factors to account for potential imbalances between both anesthetic modalities: age, sex, previous stroke, diabetes mellitus, atrial fibrillation, hypertension, history of myocardial infarction, pre-stroke mRS score, baseline NIHSS, treatment with intravenous thrombolysis, ASPECTS at baseline, collateral score, time from stroke onset to recanalization, and treatment center; [IV] To evaluate whether procedural blood pressure explained the association between anesthetic modality and functional outcome, we additionally adjusted for the predefined blood pressure parameters that were associated with functional outcome based on multivariable analyses. We

repeated step III for secondary outcomes (i.e. functional independence, mortality, early NIHSS, successful reperfusion, duration of procedure, serious adverse events, and procedure-related complications) using the appropriate regression analysis. Step IV was repeated for the secondary outcomes: functional independence, mortality, early NIHSS, and successful reperfusion.

To assess the association between predefined continuous blood pressure parameters and outcome we compared a model containing restricted cubic splines for blood pressure with a model including a linear blood pressure term, based on the log likelihood ratio. Odds ratios for the association between blood pressure and outcome were reported per 300mmHg*minutes for AUT or per 10% drop for DLMAP.[7]

The association between anesthetic approach and functional outcome could possibly be confounded by conversion from LA to CS later on during the EVT procedure as patients who did worse during the procedure received CS later on, and therefore were likely to have worse functional outcome. For that reason, we performed a sensitivity analysis to compare patients receiving CS from the start (<15 min from start EVT) to patients that received LA from the beginning (this group is a composite of LA only and CS administration later on during the procedure, >15 min from EVT start). No correction for multiple testing was performed. Statistical analyses were performed with R 3.5.0 software (R foundation for Statistical Computing, Vienna, Austria).

Data Availability

Data cannot be made available, as no patient approval has been obtained for sharing coded data. However, R syntax and output files of the analyses will be made available on request.

Results

From the 17 participating centers in the MR CLEAN Registry only 4 centers collected blood pressure data systematically according to protocol and reported LA or CS as the preferred anesthetic approach at start of the EVT (Figure 4.2).

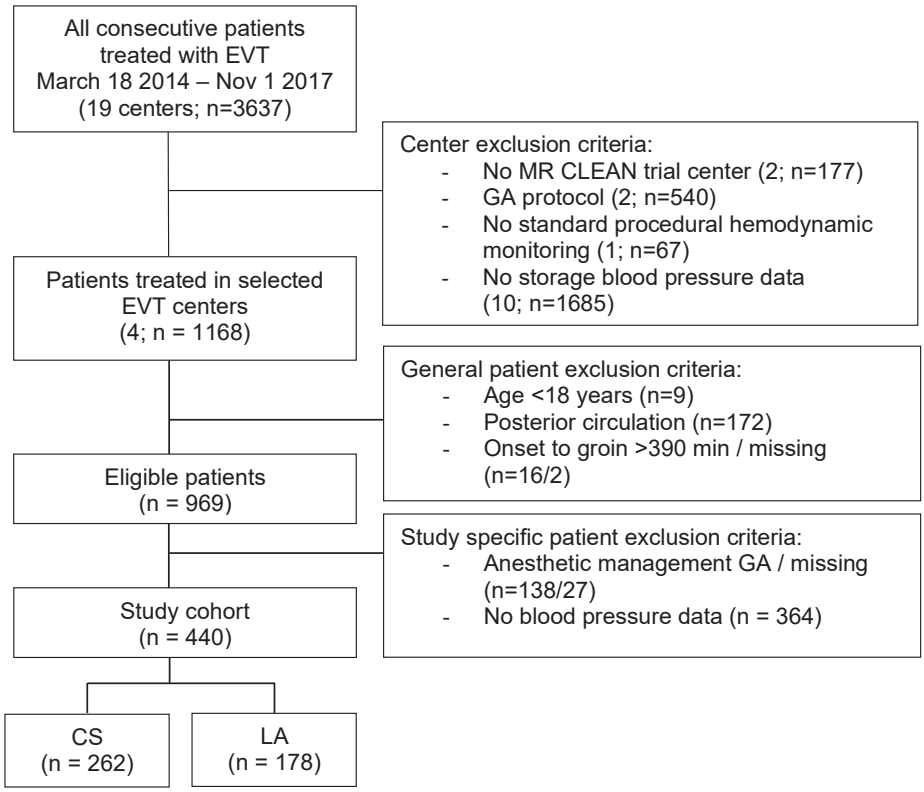

Figure 4.2. Flowchart of patient selection.
Abbreviations: GA, general anesthesia; LA, local anesthesia; min, minutes; CS, conscious sedation.

Study population

Of the 969 eligible patients treated in one of the 4 centers with consistent periprocedural anesthetic management, we included 440 patients with available blood pressure data, who underwent EVT for acute ischemic stroke due to large vessel occlusion, of whom 262/440 (60%) received CS and 178/440 (40%) received LA as procedural anesthetic strategy. Patients treated under CS were less often functionally dependent at presentation (pre-stroke mRS >2; 10/256, 3.8% versus 18/176, 10%) but had a history of previous stroke (44/261, 17% versus 12/178, 6.7%) more often. Mean diastolic blood pressure on admission was lower for patients receiving LA (81, standard deviation [SD] 15 versus 84, SD 16 mmHg; Table 4.1). We did not find substantial differences in baseline characteristics between patients treated under LA with available blood pressure data (n=178) and without blood pressure data (n=326). Also, no differences between patients treated under CS with available blood pressure data (n=262) compared to patients treated under CS without blood pressure data (n=38) were found.

Table 4.1. Baseline characteristics

	CS (n=262)	LA (n=178)	Missing
Patient characteristics			
Age, y, mean (SD)	68 (15)	69 (15)	
Male sex, n (%)	128 (49)	103 (58)	
NIHSS, median [IQR]	16 [11-19]	15 [11-19]	
Left hemisphere, n (%)	118 (45)	97 (55)	
Systolic BP, mean (SD)	149 (25)	148 (24)	
Diastolic BP, mean (SD)	84 (16)	81 (15)	
IVT, n (%)	203 (77)	135 (76)	
Center, n (%)			
1, preferred approach CS[a]	134 (70)	58 (30)	
2, preferred approach LA	2 (13)	13 (87)	
3, preferred approach LA	16 (57)	12 (43)	
4, preferred approach CS	110 (55)	95 (45)	
Medical history, n (%)			
Previous stroke	44 (17)	12 (6.7)	1/0
Atrial fibrillation	58 (22)	40 (22)	4/0
Hypertension	124 (49)	94 (53)	8/5
Diabetes mellitus	42 (16)	28 (16)	3/1
Myocardial infarction	29 (11)	24 (14)	6/1
Pre-stroke mRS			6/2
0	182 (72)	133 (76)	
1	35 (14)	18 (10)	
2	29 (11)	7 (4.0)	
>2	10 (3.9)	18 (10)	
Imaging			
Occluded segment, n (%)			7/9
M1	157 (62)	108 (64)	
M2	27 (11)	26 (16)	
ICA	16 (6.3)	5 (3.0)	
ICA-T	55 (22)	30 (18)	
ASPECTS, median [IQR]	9 [8-10]	9 [8-10]	6/9
Collaterals			9/14
Absent	14 (5.5)	9 (5.5)	
filling <50% of occluded area	97 (38)	63 (38)	

Table 4.1. Continued.

	CS (n=262)	LA (n=178)	Missing
≥50% but less <100%	99 (39)	65 (40)	
100% of occluded area	43 (17)	27 (16)	
Workflow, min, median [IQR]			
Time from admission ER to groin puncture	41 [28-69]	44 [30-73]	12/7
Time from stroke onset to groin puncture	195 [155-260]	191 [155-244]	

Abbreviations: ASPECTS, Alberta Stroke Program Early Computed Tomography Score; BP, blood pressure; CS, conscious sedation; ED, emergency room; eTICI, extended thrombolysis in cerebral infarction; ICA, internal carotid artery; ICA-T, internal carotid artery terminus; IVT, intravenous thrombolysis; LA, local anesthesia; M(*segment*), middle cerebral artery; min, minutes; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale. Continuous data are presented as mean (standard deviation, SD) for normal distributed data or as median [interquartile range, IQR] for skewed data.
Captions: [a]Preferred approach changed in 2017 to LA.

Procedural management

Average procedural systolic, diastolic and mean arterial blood pressures were lower for patients who were treated under CS (Figure 4.3, Table 4.2). AUT and ΔLMAP were larger in the CS group, (median AUT 228 mmHg*min, [interquartile range (IQR) 16-790] versus 23 mmHg*min, [0-200]) and (median ΔLMAP 16%, [5-31] versus 6%, [0-16]). Procedural systolic blood pressure trend was more negative in patients treated under CS compared to LA (-0.22 mmHg, SD 0.39 versus -0.08 mmHg, SD 0.27). Blood pressure elevating medications were administered more often in the CS group than the LA group, 59/262 (23%) versus 6/178 (3.4%). Blood pressure lowering medication was administered in 15/262 (5.7%) of patients in the CS group and in 7/178 (3.9%) of the patients in the LA group. Analgesics were used in 223/262 (85%) patients in the CS group, of which remifentanil was administered most often 116/262 (44%). Sedatives were administered in 142/262 (54%) patients, of which propofol was used most frequently 127/262 (48%) (Table 4.2). Conversion to GA requiring intubation occurred in 3 patients in the CS group and in 3 patients in the LA group.

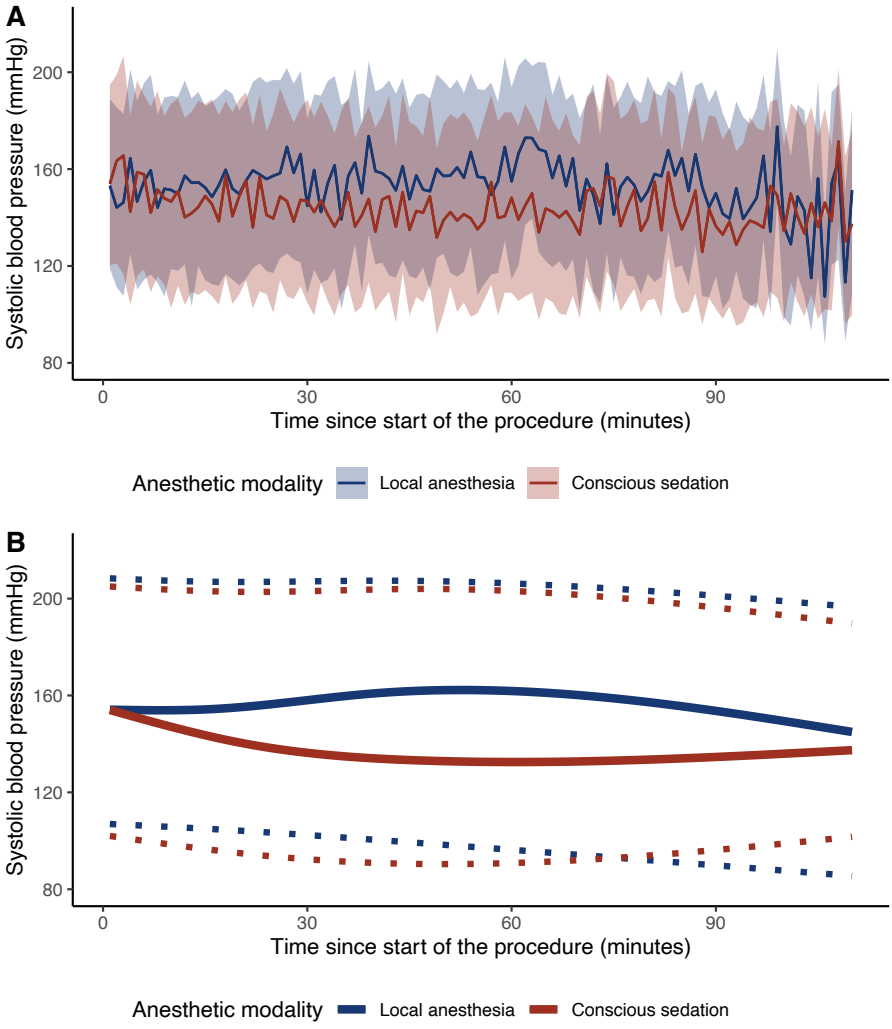

Figure 4.3. Procedural blood pressure for patients treated under conscious sedation or local anesthesia.
Summary: **A.** Non-smoothed mean systolic blood pressure curves for both anesthetic modalities with 95% tolerance interval (band). **B.** Smoothed mean systolic blood pressure curves during EVT procedure for both anesthetic modalities (continuous line) with 95% tolerance interval (dotted line). *Abbreviations*: min, minutes; mmHg, millimeter of mercury.

Table 4.2. Procedural anesthetic and hemodynamic data

	CS (n=262)	LA (n=178)
Medication, n (%)a		
Muscle relaxant		
Rocuronium	3 (1.1)	2 (1.1)
Inotropes/vasopressors	59 (23)	6 (3.4)
Atropine	17 (6.5)	1 (0.6)
Ephedrine	16 (6.1)	3 (1.7)
Epinephrine	2 (0.8)	0
Isoprenaline	2 (0.8)	0
Norepinephrine	20 (7.6)	3 (1.7)
Phenylephrine	24 (9.2)	2 (1.1)
Sympatholytics	*15 (5.7)*	*7 (3.9)*
Clonidine	1 (0.4)	4 (2.2)
Ketanserine	0	1 (0.6)
Labetalol	8 (3.1)	2 (1.1)
Nimodipine	6 (2.3)	0
Urapidil	0	1 (0.6)
Analgesics	223 (84)	-
Alfentanil	49 (19)	-
Fentanyl	11 (4.2)	-
Morfine	1 (0.4)	-
Remifentanil	116 (44)	-
Sufentanil	46 (18)	-
Sedatives	142 (53)	
Esketamine	12 (4.6)	-
Midazolam	8 (3.1)	-
Propofol	127 (48)	-
Blood pressure values, mmHg		
SBP, median [IQR]	141 [123-164]	155 [135-173]
DBP, median [IQR]	76 [67-84]	80 [70-92]
MAP, median [IQR]	100 [89-115]	107 [94-121]
ΔLMAP, median [IQR][b]	16 [5.2-31]	6.0 [0-16]
AUT, median [IQR][c]	228 [16-790]	23 [0-200]
Trend SBP, mean (SD)[d]	-0.22 (0.39)	-0.08 (0.27)

Abbreviations: AUT, area under threshold; CS, conscious sedation; DBP, diastolic blood pressure; IQR, interquartile range; DLMAP, relative difference baseline MAP and lowest procedural MAP; MAP, mean arterial pressure; SBP, systolic blood pressure; SD, standard deviation. *Captions:*
[a] Percentages may add up to more than 100 owing to combined administration of medication.
[b] Percentage drop form baseline MAP; [c] mmHg*minute; [d] Beta coefficient.

I. Association between anesthetic management and procedural blood pressure
CS was associated with larger AUTs (adjusted beta [ab] 368, [95% CI 242 to 494]) and larger ΔLMAP (ab 8.1, [95% CI 4.9 to 11.4]) compared to LA based on multivariable linear regression. Furthermore, CS was associated with a more decreasing procedural systolic blood pressure trend (ab -0.14, [95% CI -0.21 to -0.07]).

II. Association between procedural blood pressure and outcome
Both ΔLMAP (acOR 0.89 per 10% drop from baseline, [95% CI 0.80-0.99]) and AUT (acOR 0.89 per 300mmHg*min, [95% CI 0.82-0.96]) were associated with a shift towards worse functional outcome in multivariable analysis. Procedural blood pressure trend was not associated with functional outcome (acOR 0.85 per mmHg per minute, [95% CI 0.51-1.43]).

III. Association between anesthetic management and outcome
Patients undergoing EVT for acute ischemic stroke under CS were more likely to have poor mRS scores at 90 days compared to LA (acOR 0.59, [95% CI 0.40-0.87]; Table 4.3, column B, Figure 4.4). The sensitivity analysis, comparing patients receiving CS from the beginning of the procedure (n = 51) to patients receiving LA from the beginning of the procedure (n = 389), (acOR 0.49, [95% CI 0.26-0.91]), obtained similar results to the primary analysis comparing CS administration at any time point during the procedure to LA. Functional independence at 90 days was less often seen in patients who underwent CS compared to LA (aOR 0.49, [95% CI 0.30-0.83]). There were no differences in all-cause mortality (aOR 1.78, [95% CI 0.96-3.02]), NIHSS at 24-48 hours post-EVT (ab 1.13 [95% CI -0.38 to 2.64]) and successful reperfusion grades (aOR 1.01, [95% CI 0.66-1.65]) between groups. Procedure duration was almost 20 minutes longer in the CS group compared to the LA group (median 70 [44-90] versus 51 [33-74] minutes). The occurrence of procedure-related complications did not differ between patients treated under CS and LA (9/262, 3% versus 5/178, 4%; aOR 1.45, [95% CI 0.89-2.31]).

IV. Effect of blood pressure on the association between anesthetic management and outcome
Additional adjustment for ΔLMAP and AUT, did not explain the association between anesthetic modality and functional outcome (acOR 0.62, [95% CI 0.42-0.92]; Table 4.3, column C). Also, ΔLMAP and AUT did not explain the association between anesthetic modality and any of the secondary outcomes.

Table 4.3. Effect of CS versus LA on outcomes, unadjusted (model A), adjusted for potential confounding variables (model B), and with additional adjustment for blood pressure (model C).

			A	*B*	*C*
	CS (n=262)	**LA (n=178)**	**Unadjusted effect CS vs LA (c)OR (95% CI)**	**Adjusted effect CS vs LA a(c)OR (95% CI)**	**Adjusted effect, including ΔLMAP[a] and AUT[b], CS vs LA a(c)OR (95% CI)**
Primary outcome, median [IQR]					
mRS at 90 d	4 [2-6]	3 [1-4]	0.56 (0.40 to 0.79)	0.59 (0.40 to 0.87)	0.62 (0.42 to 0.92)
Secondary outcomes, clinical					
mRS ≤2 at 90 d, n (%)	80 (34)	82 (50)	0.53 (0.36 to 0.78)	0.49 (0.30 to 0.83)	0.53 (0.30 to 0.85)
Mortality at 90 d, n (%)	70 (29)	33 (20)	1.51 (0.95 to 2.37)	1.78 (0.96 to 3.02)	1.70 (0.95 to 3.18)
NIHSS 24–48 h, median [IQR]	10 [4-16]	8 [3-15]	1.68 (0.05 to 3.31)[c]	1.13 (-0.38 to 2.64)[c]	0.88 (-0.67 to 2.43)[c]
Secondary outcome, radiological, n (%)					
Successful reperfusion after intervention (eTICI ≥ 2B)	175 (69)	122 (70)	0.96 (0.64 to 1.46)	1.01 (0.66 to 1.65)	1.11 (0.70 to 1.81)
Secondary outcomes, workflow, median [IQR]					
Duration of procedure	70 [44-90]	51 [33-74]	15.9 (9.49 to 22.2)[c]	14.3 (8.17 to 20.50)[c,d]	
Secondary outcomes, safety measures, n (%)					
Procedure-related complications	9 (4)	5 (3)	1.57 (1.01 to 2.45)	1.45 (0.89 to 2.31)	
Symptomatic ICH	13 (5.0)	4 (2.3)	2.27 (0.79 to 8.17)	2.74 (0.87 to 10.4)	
ECH	5 (1.9)	7 (3.9)	0.48 (0.14 to 1.51)	0.52 (0.13 to 1.98)	
Neurologic deterioration	18 (6.9)	8 (4.5)	1.57 (0.69 to 3.90)	1.49 (0.57 to 4.14)	
New ischemic stroke	7 (2.7)	2 (1.1)	2.42 (0.58 to 16.3)	4.80 (0.84 to 20.1)	

Table 4.3. Continued.

			A	*B*	*C*
	CS (n=262)	**LA (n=178)**	**Unadjusted effect CS vs LA (c)OR (95% CI)**	**Adjusted effect CS vs LA a(c)OR (95% CI)**	**Adjusted effect, including ΔLMAP[a] and AUT[b], CS vs LA a(c)OR (95% CI)**
Pneumonia	28 (11)	16 (9.0)	1.21 (0.64 to 2.36)	1.04 (0.50 to 2.23)	

Abbreviations: acOR, adjusted common odds ratio; CI, confidence interval; CS, conscious sedation; ECH, extracranial hemorrhage; eTICI, extended thrombolysis in cerebral infarction; ICH, intracranial hemorrhage; IQR, interquartile range; LA, local anesthesia; ΔLMAP, relative difference baseline mean arterial pressure (MAP) and lowest procedural MAP; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; SD, standard deviation.

A. univariable regression analyses. B. multivariable regression analyses (adjusted for age, sex, baseline NIHSS, pre-stroke mRS, history of stroke, hypertension, diabetes mellitus, atrial fibrillation, myocardial infarction, intravenous thrombolysis, ASPECT score at baseline, time between stroke onset and recanalization, center); C. multivariable regression analyses (adjusted for the same variables as in step 2 with an additional adjustment for DLMAP and AUT to evaluate if hypotension explains the effect of CS on outcome, i.e. reduces the effect estimate).

Captions: [a] per 10% drop; [b] per 300mmHg*minutes; [c] reported effect measure is b coefficient; [d] adjustment for time between stroke onset and groin puncture instead of time between stroke onset and recanalization.

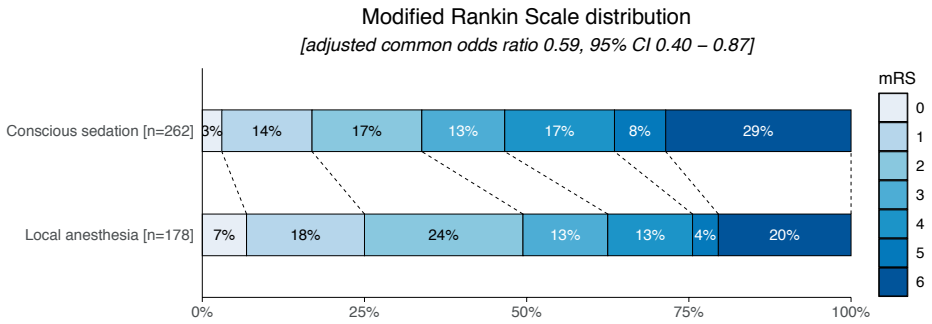

Figure 4.4. Primary outcome on the modified Rankin Scale by preferred anesthetic method. *Abbreviations*: mRS, modified Rankin Scale.

Discussion

In this study, we evaluated the effect of CS on procedural hypotension, blood pressure trend and hemodynamic interventions compared to LA. Second, we assessed if there was an association between the three predefined blood pressure measures and outcomes. Third, we evaluated the effect of CS on functional outcome compared to LA, and finally we explored if the effect of anesthetic management on outcomes, could be explained by procedural hypotension or blood pressure trend. We found that CS was associated with more blood pressure drops and that these blood pressure drops were related to worse outcomes. However, the blood pressure drops did not explain the effect of CS on functional outcome compared to LA.

Similar to previous studies, we found that patients treated under CS had lower average procedural blood pressure and more blood pressure drops compared to patients treated under LA. Consequently, more hemodynamic interventions were required to increase blood pressure in patients treated under CS.[7,13,27]

A drop in MAP from baseline and larger AUT were independently associated with worse functional outcome. Similar, previous studies reported worse functional outcomes in patients with a drop in MAP from baseline of ≥10% who received CS or GA during the procedure.[14,19,28] A recent study found that larger AUTs were associated with worse functional outcome in patients receiving GA as well as in patients receiving monitored anesthesia care (MAC), which is a composite of CS and LA.[7] In our study, blood pressure drops were relatively mild, especially in the LA group, compared to what has been observed in patients treated under GA (median AUT in our LA group of 23 mmHg*min [0-200] versus 984 mmHg*min [227-1968] in patients treated under GA and median ΔLMAP in our LA group of 6% [0-16] versus 39% [23-49] in patients treated under GA).[7,8,28] The small hemodynamic variability observed in patients treated under LA, underlines the importance of including LA as a treatment arm besides CS and GA in future RCTs focusing on optimal anesthetic and hemodynamic management during EVT.

In this study, patients treated under CS had worse functional outcome compared to patients treated under LA. Hypotension and procedural blood pressure trend did not explain the negative association of CS with functional outcome in our study. Since, there were no large differences in baseline characteristics between patients treated under CS and LA, including neurologic deficit according to the NIHSS at baseline, adjustments for potential covariates did not reduce the effect of CS on outcome compared to LA. Therefore, the effect of CS on functional outcome might be caused by confounders not accounted for in the analyses. The decision to perform EVT under CS is likely to be made by the treating interventionalist and anesthesiologist based on clinical parameters not reflected by the NIHSS score, for example patient agitation and motion. Furthermore, the NIHSS performed in an acute and time-restrained clinical situation might less well comprise mild to moderate neglect, disorientation and aphasia, which could be the determinants of the anesthetic approach. Previous trials reported equivalent functional outcome among patients treated under GA or CS, which is likely due to the strict hemodynamic regimes as part of the anesthetic protocols.[29-31] A pooled analysis of these RCTs suggested that worse outcome after EVT might be associated with blood pressure variability instead of the anesthetic strategy itself. However, conclusions of this study were restricted to the association between blood pressure variability and neurologic outcomes, stratified by anesthetic modality.[28]

In several EVT capable centers with CS or LA as the preferred anesthetic approach during EVT, the involvement of anesthesiologist is limited to patients who are hemodynamic unstable or require GA. Since these results suggest that blood pressure drops and hemodynamic interventions are seen during both CS and LA, hemodynamic monitoring and rapid treatment of hemodynamic instability during EVT should not be restricted to patients treated under GA only.

Limitations

Our study has several limitations. First, due to the retrospective observational design of this study, results could have been confounded by variables not adjusted for in the analyses.

Patients that are more affected at presentation are more likely to get CS and hemodynamic monitoring, meaning residual confounding is present in this cohort. To limit the risk of confounding by indication, we performed a sensitivity analysis for patients who received sedatives or analgesics from the beginning of the procedure. In the sensitivity analysis among patients who received CS from the beginning of the EVT procedure compared to patients receiving LA from the beginning, a similar effect of CS on outcome was found. This suggests that conversion from LA to CS was not directly related to patient's status at baseline and confounding by indication might be less likely. Furthermore, despite we selected centers reporting either CS or LA as the preferred approach we observed that a significant number of patients received the non-preferred initial anesthetic approach. Since we selected centers with

CS or LA as preferred anesthetic approach and standard hemodynamic monitoring, the generalizability of our findings to patients treated under different anesthetic or hemodynamic regimes is limited.

Second, there is no consensus on how to quantify procedural hypotension and blood pressure variability. A different quantification of procedural hemodynamics could alter the effect of anesthetics on outcome. Lastly, as heterogeneity in anesthetic approach definitions exist, comparability is difficult since sedation is a continuum ranging from minimal to deep sedation, with a concomitant variety in physiological effects (e.g. arterial hypotension, bradycardia, respiratory depression).

Conclusions

Hemodynamic interventions to maintain hemodynamic stability are common during EVT under CS and LA. In a cohort of patients treated with EVT under strict blood pressure management, decreases in blood pressure are small and do not explain the differences in functional outcome between patients treated under CS and LA. As blood pressure drops by means of ΔLMAP and AUT are independently associated with worse functional outcome, we advocate to monitor and avoid blood pressure drops (i.e. ensure hemodynamic stability) during EVT. Further randomized controlled trials are needed to determine if hemodynamic interventions improve patient outcomes.

References

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CHAPTER 4.1

Letter by Samuels et al Regarding Article, "Decreases in Blood Pressure During Thrombectomy Are Associated With Larger Infarct Volumes and Worse Functional Outcome"

Stroke, 2019

Noor Samuels, Rob A. van de Graaf, Diederik W.J. Dippel

To the Editor:

Petersen et al. evaluated the role of hypotension during endovascular treatment (EVT) and its associations with infarct progression and functional outcome. The authors found that blood pressure reduction before recanalization is associated with larger infarct volumes and worse functional outcomes.[1] The results of their observational study address the importance of blood pressure monitoring and management during EVT. We consider this an interesting study that addresses topical questions. Nevertheless, we do have some comments.

The authors solely evaluated blood pressure data from patients who underwent EVT receiving anesthesia, either in the form of conscious sedation (CS) (65%) or general anesthesia (GA) (35%). Patients receiving local anesthesia at the groin puncture site only (LA) were not mentioned in this study. It is already known that intraprocedural hypotensive episodes are associated with worse outcomes for both CS and GA, possibly attributed to the administered agents (e.g. propofol) which secondarily induce blood pressure reductions.[2,3] For this reason LA could be a safer anesthetic strategy with respect to hemodynamic stability. Moreover, in the HERMES meta-analysis non-GA was associated with better outcomes than GA. However, this non-GA group was defined as the composite of LA and CS.[4] The better functional outcomes in the non-GA arm might thus well be the result of patients receiving LA only. Recently, we compared the effect of LA only during EVT to CS and found that patients receiving LA reported better functional outcomes.[5] Therefore, LA deserves more attention in comparable analyses.

This is an observational study. Readers may be tempted to reason that reversal or prevention of the blood pressure drop will result in an effect on outcome of the same magnitude but in opposite direction as observed in this study. This is not likely to be true, because vasopressors are often needed to treat blood pressure drops and a detrimental effect of prolonged vasoconstriction in acute ischemic stroke has been suggested. More data on hemodynamic interventions during EVT is needed to understand the underlying pathway causing the poor outcomes in patients with blood pressure drops.

In conclusion, it remains important to avoid hypotension during EVT in patients receiving CS or GA. Since the association between anesthetic management and functional outcome could partially be explained by intraprocedural hypotension, we propose that future trials consider LA as a treatment arm besides CS and GA, with strict monitoring of blood pressure and hemodynamic interventions.

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CHAPTER 5

Blood pressure in the first 6 hours following endovascular treatment for ischemic stroke is associated with outcome

Stroke, 2021

Noor Samuels, Rob A. van de Graaf, Carlijn A.L. van den Berg, Simone M. Uniken Venema, Kujtesa Bala, Pieter Jan van Doormaal, Wouter van der Steen, Elbert Witvoet, Jelis Boiten, Heleen den Hertog, Wouter J. Schonewille, Jeannette Hofmeijer, Floris Schreuder, Tobien A.H.C.M.L Schreuder, H. Bart van der Worp, Yvo B.W.E.M. Roos, Charles B.L.M. Majoie, James F. Burke, Adriaan C.G.M. van Es, Aad van der Lugt, Bob Roozenbeek, Hester F. Lingsma, Diederik W.J. Dippel, on behalf of the MR CLEAN Registry investigators

Abstract

Background and Purpose: Optimal blood pressure management in the acute phase of ischemic stroke remains an unresolved issue. It is uncertain whether guidelines for blood pressure management during and after intravenous alteplase can be extrapolated to endovascular treatment (EVT) for stroke due to large artery occlusion in the anterior circulation. We evaluated the associations between systolic blood pressure (SBP) in the first 6 hours following EVT and functional outcome as well as symptomatic intracranial hemorrhage (sICH).

Methods: Patients of 8 MR CLEAN Registry centers, with available data on SBP in the 6 hours following EVT, were analyzed. We evaluated maximum, minimum and mean SBP. Study outcomes were functional outcome (modified Rankin Scale) at 90 days and sICH. We used multivariable ordinal and binary regression analysis to adjust for important prognostic factors and studied possible effect modification by successful reperfusion.

Results: Post-EVT SBP data were available for 1161/1796 patients. Higher maximum SBP (per 10mmHg increments) was associated with worse functional outcome (adjusted common odds ratio [acOR] 0.93, 95% confidence interval, [CI] 0.88-0.98) and a higher rate of sICH (aOR 1.17, 95% CI 1.02-1.36). The association between minimum SBP and functional outcome was non-linear with an inflection point at 124mmHg. Minimum SBP lower and higher than the inflection point were associated with worse functional outcomes (acOR 0.85 per 10mmHg decrements, 95% CI 0.76-0.95 and acOR 0.81 per 10mmHg increments, 95%CI 0.71-0.92). No association between mean SBP and functional outcome was observed. Successful reperfusion did not modify the relation of SBP with any of the outcomes.

Conclusions: Maximum SBP in the first 6 hours following EVT is positively associated with worse functional outcome and an increased risk of sICH. Both lower and higher minimum SBP are associated with worse outcomes. A randomized trial to evaluate whether modifying post-intervention SBP results in better outcomes after EVT for ischemic stroke seems justified.

Introduction

In the first 24 hours after stroke, blood pressure is often increased, even after EVT, and it takes a few days to return to baseline levels.[1,2] It has been demonstrated that admission blood pressure is strongly associated with functional outcome after EVT.[3-5] Since blood pressure is an important factor affecting cerebral perfusion, it is likely that blood pressure within the first hours following EVT has an impact on infarct size and thereby functional outcome.[6,7] Two observational studies found an association between systolic blood pressure (SBP) peaks in the 24 hours following stroke and increased risks of symptomatic intracranial hemorrhage (sICH) and functional dependency.[2,8] However, these studies did not relate timing of blood pressure measurement to the occurrence of sICH, so reverse causality could be present and the target blood pressure level in the first few hours after EVT remains unclear. As blood pressure can be readily managed with medication, optimizing post-EVT blood pressure is a feasible strategy to improve functional outcomes. We aimed to evaluate the associations of SBP in the first 6 hours following EVT with functional outcome and the occurrence of sICH.

Methods

Study protocol and data availability

We used data from the MR CLEAN Registry (Multicenter Randomized Clinical Trial of Endovascular Treatment of Acute Ischemic Stroke), a prospective, observational cohort, including all consecutive patients treated with EVT for acute ischemic stroke in the Netherlands between March 2014 and 2017. Detailed information on the description of variables and the methods of MR CLEAN Registry have been reported previously.[9] Data cannot be made available, as no patient approval has been obtained for sharing coded data. However, R syntax and output files of the analyses will be made available on request.

Study population

Patients were included for this analysis if they had been treated in a MR CLEAN Registry center that provided blood pressure data of the first 24 hours after EVT and were aged 18 years or older; had a proximal intracranial occlusion in the anterior circulation (intracranial carotid artery [ICA/ICA-T], middle cerebral artery [M1/M2], anterior cerebral artery [A1/A2]) confirmed on computed tomography angiography (CTA); had a groin puncture within 6.5 hours after symptom onset; and had at least one available blood pressure value within the first 6 hours following EVT.

Blood pressure measures

We collected SBP values, recorded between the end of the EVT-procedure (defined as time of reperfusion or last contrast bolus) and 24 hours after EVT or until discharge from the intervention center. To limit the risk of confounding by indication based on

missing blood pressure data due to early transfer of patients in good condition, we restricted our primary analysis to the first 6 hours following EVT. The predefined blood pressure measures of interest included I) maximum SBP (reflecting peak in blood pressure course); II) minimum SBP (reflecting drops in blood pressure), and III) mean SBP. If more than one SBP measurement was available, maximum and minimum SBP were calculated based on the average of the two highest or lowest SBP values in the 6 hours following EVT, to limit the risk of measurement error. When only one SBP value was available, there was no difference between maximum, minimum and mean SBP. Additionally, we performed a sensitivity analysis to evaluate the association between the predefined blood pressure measures in the first 24 hours following EVT and outcomes. Since the majority of sICH and extracranial hemorrhage occur within 24 hours following EVT, we did not evaluate the association between blood pressure and these outcomes, to avoid reverse causality. Details on BP protocols of the included centers are described in supplemental table 5.1.

Outcome measures

The primary outcome measure was functional outcome according to the modified Rankin Scale (mRS), which is a 7-point scale ranging from 0 "no symptoms" to 6 "death", assessed at 90 days after EVT.[10] Secondary outcome measures included functional independence (mRS ≤ 2), mortality within 90 days after EVT, National Institutes of Health Stroke Scale (NIHSS) score indicating neurologic deficit at 24-48 hours after EVT, extracranial hemorrhage (requiring surgery or blood transfusion), and new ischemic stroke (new neurologic deficit confirmed with imaging) within 90 days from stroke onset. Furthermore, any occurrence of symptomatic intracranial hemorrhage (sICH; neurologic deterioration of ≥ 4 points on the NIHSS and a compatible hemorrhage on noncontrast CT (NCCT) assessed by an independent core laboratory according to the Heidelberg criteria) was included as a secondary outcome measure.[11,12]

Statistical analysis

Baseline characteristics of the study population are tabulated by three subgroups according to maximum SBP tertiles. Continuous variables are expressed as means (standard deviations, SD) or medians (interquartile ranges, IQR), where applicable. Categorical variables are expressed as numbers of patients and percentages.

We evaluated linearity of the associations between the postprocedural SBP parameters and outcomes by comparing model fit of a regression model with a linear SBP term to a regression model with a SBP term with a restricted cubic spline transformation with 3 knots. We performed multivariable ordinal logistic regression, binary logistic regression or linear regression analyses, as appropriate with adjustment for the following potential confounders: age, sex, NIHSS score on admission, pre-stroke mRS score, medical history of hypertension, stroke, diabetes mellitus, atrial fibrillation, myocardial infarction, treatment with intravenous thrombolysis (IVT),

SBP on admission, location of occlusion, Alberta Stroke Program Early CT Score (ASPECTS) on NCCT[13], collateral score on CTA according to a 4-point scale (0 = absent collaterals [0% filling of the vascular territory downstream of the occlusion], 1 = poor collaterals [>0% and <50% filling], 2 = moderate collaterals [≥50% and <100% filling], and 3 = excellent collaterals [100% filling])[14], the use of general anesthesia during EVT, time from stroke onset to reperfusion or last contrast bolus, extended Thrombolysis in Cerebral Infarction (eTICI) score at the end of the EVT procedure[15], number of blood pressure measurements in the 6 hours following EVT, and intervention center. For the outcome sICH, we aimed to reduce the possibility that results were hampered by reverse causality (i.e. blood pressure measurements collected during or after occurrence of sICH) by excluding patients in whom sICH occurred within 6 hours following EVT. The associations of blood pressure parameters with outcomes were presented per 10 mmHg change in blood pressure.

We assessed whether the relation between postprocedural blood pressure and outcomes was modified by the extent of reperfusion. We fitted a similar multivariable regression model as described above including an interaction term for SBP parameter*successful reperfusion, a dichotomized term for extent of reperfusion (unsuccessful, eTICI score < 2B versus successful, eTICI score ≥ 2B).[15] For all regression analyses, missing data were imputed using multiple imputations by chained equations based on relevant covariates and outcomes.[16] All analyses were performed using R software (Version 3.6.1, R foundation for Statistical Computing, Vienna, Austria) with the packages: *tableone*, *mice*, *Hmisc, ggplot* and *rms*.

Medical ethics committee statement

The medical ethics committee of the Erasmus University MC, Rotterdam, the Netherlands evaluated the study protocol of the MR CLEAN Registry and granted permission to carry out the study as a registry (MEC-2014-235).

Results

Study population

Of 1796 patients treated with EVT during the study period in the 8 participating centers, 1161 (65%) were included in the current analysis (Figure 5.1). The median available number of SBP measurements in the first 6 hours following EVT was 7 (IQR 4 to 11). For 86/1161 patients only one SBP value in the first 6 hours was available. The mean SBP in the first 6 hours following EVT was 150 mmHg (SD 25). Baseline characteristics of the study population are shown according to maximum SBP tertiles (Table 5.1). Patients with a higher maximum SBP in the first 6 hours following EVT were on average older and were more likely to have a history of atrial fibrillation, diabetes mellitus, hypertension, distal occlusion, and poorer collateral scores.

Table 5.1. Baseline characteristics of all patients shown according to tertiles of maximum SBP during first 6 hours following EVT.

	Maximum SBP < 140 mmHg (n = 364)	**Maximum SBP 140 - 170 mmHg (n = 466)**	**Maximum SBP >170 mmHg (n = 331)**	**Missing**
Patient characteristics				
Age, mean (SD)	65 (15)	71 (13)	74 (12)	
Male sex, n (%)	190 (52)	242 (52)	166 (50)	
NIHSS, median [IQR]	16 [11-19]	15 [10-19]	17 [12-20]	2/3/3
Left hemisphere, n (%)	200 (55)	228 (49)	174 (53)	0/0/1
SBP, mean (SD)	134 (20)	150 (22)	162 (24)	10/3/3
DBP, mean (SD)	77 (14)	83 (16)	87 (16)	10/5/5
IVT, n (%)	275 (76)	368 (79)	251 (76)	2/1/0
Medical history, n (%)				
Previous stroke	54 (15)	84 (18)	62 (19)	2/5/5
Atrial fibrillation	87 (24)	118 (26)	91 (28)	3/7/8
Hypertension	151 (42)	237 (53)	199 (61)	7/20/7
Diabetes mellitus	44 (12)	79 (17)	66 (20)	2/4/5
Myocardial infarction	50 (14)	67 (15)	52 (16)	3/9/11
Peripheral arterial disease	49 (14)	41 (8.9)	31 (9.7)	4/7/11
Pre-stroke mRS				8/8/12
0	261 (73)	332 (73)	220 (69)	
1	37 (10)	51 (11)	43 (14)	
2	18 (5.1)	28 (6.1)	24 (7.5)	
≥ 3	40 (11)	47 (10)	32 (10)	
Medication, n (%)				
Antihypertensive	170 (48)	249 (55)	199 (61)	6/14/6
Statin	133 (37)	170 (37)	118 (37)	7/12/12
Antiplatelet	111 (31)	133 (29)	114 (35)	4/7/9
DOAC	19 (5.3)	15 (3.3)	8 (2.4)	4/7/4
Coumarin	11 (3.1)	11 (2.4)	4 (1.2)	5/8/7
Imaging, n (%)				
Occluded segment				9/16/15
ICA	14 (3.9)	23 (5.1)	17 (5.4)	
ICA-T	69 (19)	79 (18)	69 (22)	
M1	236 (67)	275 (61)	172 (54)	
M2	32 (9.0)	71 (16)	57 (18)	
Other †	4 (1.1)	2 (0.4)	1 (0.3)	
ASPECTS subgroups				5/17/18
0 - 4	16 (4.5)	18 (4.0)	10 (3.2)	

Table 5.1. Continued.

	Maximum SBP < 140 mmHg (n = 364)	**Maximum SBP 140 - 170 mmHg (n = 466)**	**Maximum SBP >170 mmHg (n = 331)**	**Missing**
5 - 7	67 (19)	72 (16)	67 (21)	
8 - 10	276 (77)	359 (80)	236 (75)	
Collateral score				15/25/21
Absent	8 (2.3)	21 (4.8)	23 (7.4)	
filling <50% of occluded area	122 (35)	148 (34)	145 (47)	
filling ≥50% but less <100%	143 (41)	198 (45)	97 (31)	
filling 100% of occluded area	76 (22)	74 (17)	45 (15)	
Workflow				
Transfers from primary stroke center, n (%)	208 (57)	308 (66)	213 (64)	1/0/0
Time from stroke onset to groin puncture, min,median [IQR]	190 [150-240]	190 [150-240]	192 [153-250]	
Procedure				
General anesthesia, n (%)	22 (6.5)	23 (5.3)	23 (7.4)	26/30/20
Duration procedure, min, median [IQR]	60 [38-86]	55 [36-80]	61 [42-80]	49/41/23
Reperfusion grade after intervention, (eTICI), n (%)				8/15/13
0	38 (11)	67 (15)	56 (18)	
1	6 (1.7)	17 (3.8)	5 (1.6)	
2A	71 (20)	81 (18)	57 (18)	
2B	92 (26)	98 (22)	66 (21)	
2C	36 (10)	42 (9.3)	35 (11)	
3	113 (32)	146 (32)	99 (31)	

Continuous data are presented as mean (SD) for normal distributed data or as median [IQR] for skewed data. Categorical data are presented as numbers (percentage).
SBP tertiles are for data inspection only, analysis is based on the full range of SBP measures.
Abbreviations: ASPECTS, Alberta Stroke Program Early Computed Tomography Score; DBP, diastolic blood pressure; DOAC, direct oral anticoagulant; eTICI, extended thrombolysis in cerebral infarction; ICA-(T), internal carotid artery (terminus); IQR, interquartile range; IVT, intravenous thrombolysis; M(*segment*), middle cerebral artery; min, minutes; mRS, modified Rankin Scale; n, number; NIHSS, National Institutes of Health Stroke Scale; SD, standard deviation; SBP, systolic blood pressure; y, year. *Captions:* *Tertiles of maximum SBP were rounded to tens. †A1/A2/M3 occlusion.

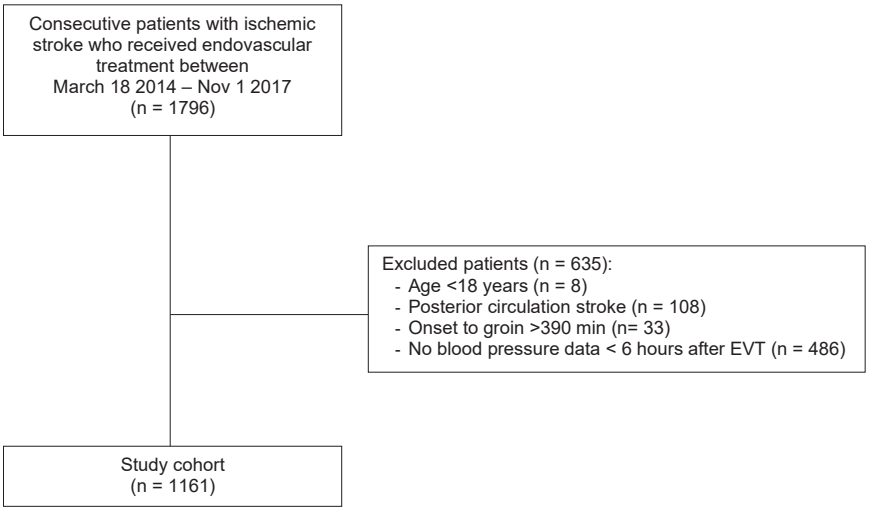

Figure 5.1. Flowchart of patient inclusion.
Abbreviations: EVT; endovascular treatment; min, minutes; n, number

Association of maximum systolic blood pressure with outcomes
The association between maximum SBP and functional outcome at 90 days (shift towards better mRS score) was linear (Figure 5.2A, LR test p=0.14 for maximum SBP). Patients with higher maximum SBP in the 6 hours following EVT were more likely to have worse functional outcomes compared to patients with lower maximum SBP (acOR 0.93 per 10mmHg, 95% CI 0.88 to 0.98, Table 5.2). Higher maximum SBP was associated with a larger neurologic deficit (measured with the NIHSS) at 24-48 hours after EVT (ab 0.31, 95% CI 0.14 to 0.49), increased risk of sICH (aOR 1.17, 95% CI 1.02 to 1.36), but not with an increased risk of death (aOR 1.02, 95% CI 0.95 to 1.08, Table 5.2). In the sensitivity analysis of SBP measures during the first 24 hours, we observed a similar association between higher maximum SBP and worse functional outcome (acOR 0.90 per 10mmHg, 95% CI 0.85 to 0.94, supplemental table 5.2).

Association of minimum systolic blood pressure with outcomes
The association between minimum SBP and functional outcome was non-linear (Figure 5.2B) based on multivariable model fit comparing a linear SBP term to a model allowing 3 knots for SBP (LR test p<0.01 for minimum SBP). Due to the non-linearity of this association, we obtained effect estimates for lower minimum and higher minimum SBP separately (inflection point at around 124 mmHg). Minimum SBP below 124 mmHg and minimum SBP above 124 mmHg were both associated with worse functional outcome (acOR per 10 mmHg decrement 0.85, 95% CI 0.76 to 0.95 for minimum SBP < 124 mmHg and 0.81 per 10 mmHg increment, 95% CI 0.71 to 0.92 for minimum SBP ≥ 124 mmHg). Also, minimum SBP lower than 124 mmHg and minimum SBP higher

than 124 mmHg were associated with higher mortality rates and a more frequent occurrence of extracranial hemorrhage. Minimum SBP higher than 124 mmHg was associated with more neurologic deficit at 24-48 hours, which was not observed for lower minimum SBP (supplemental table 5.3).

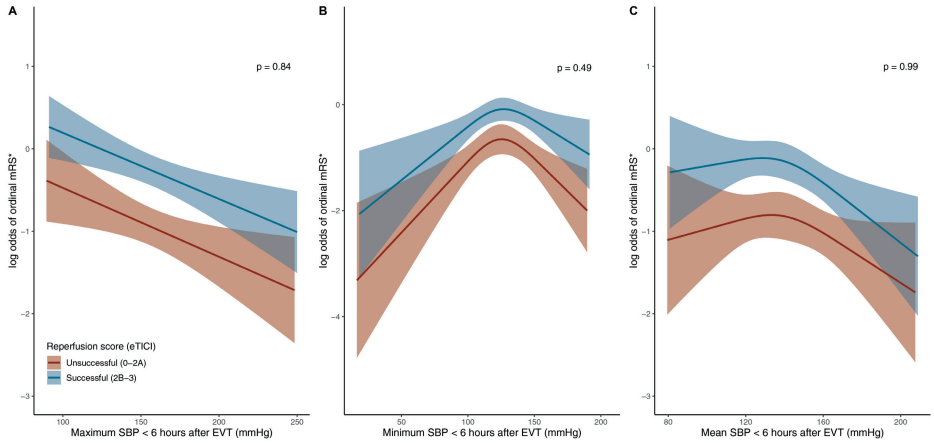

Figure 5.2. Relationship of systolic blood pressure and shift toward better functional outcome.
Summary: The models are fitted with a linear function for maximum SBP and restricted cubic spline function with 3 knots for minimum SBP and mean SBP parameters. All models include the following variables: age, NIHSS at baseline, ASPECTS at baseline, history of hypertension, time between stroke onset to reperfusion, and an interaction term for SBP parameter*reperfusion grade. The graphs depict the log odds for a shift towards better mRS score (*ordinal mRS) with 95% confidence intervals, for each level of maximum SBP (A), minimum SBP (B), and mean SBP (C) in the first 6 hours following EVT for successful and unsuccessful reperfusion, with corresponding p-value for interaction. The ranges of the x-axes correspond to the lowest and highest SBP value in the data.
Abbreviations: eTICI, extended Thrombolysis in Cerebral Infarction; EVT, endovascular treatment; mRS, modified Rankin Scale; SBP, systolic blood pressure.

Association of mean systolic blood pressure with outcomes

The associations between mean SBP and functional outcome was also non-linear (Figure 5.2C) based on multivariable model fit comparing a linear SBP term to a model allowing 3 knots for SBP (LR test p<0.01 for mean SBP). Therefore, we obtained effect estimates for lower mean SBP and higher mean SBP separately (inflection point at around 138 mmHg). Mean SBP below 138 mmHg was associated with higher likelihood of extracranial hemorrhage (aOR 1.66 per 10 mmHg decrement, 95% CI 1.07 to 2.51). We did not observe an association between mean SBP higher than 138 mmHg and any of the outcomes (supplemental table 5.4). The distribution of outcomes according to maximum, minimum and mean SBP tertiles is shown in supplemental figure 5.1 and supplemental table 5.5.

We did not find an interaction between extend of reperfusion and the relation of SBP with functional outcome (p-value for interaction: maximum SBP = 0.84; minimum SBP = 0.49 and mean SBP = 0.99, Figure 5.2) or any of the secondary outcomes (supplemental figure 5.2). We observed a decline in maximum SBP from baseline during the 6 hours following EVT for both reperfusion categories, with higher maximum SBPs among patients with unsuccessful reperfusion at the end of EVT procedure compared to patients with successful reperfusion (supplemental figure 5.3).

Table 5.2. Associations between continuous maximum SBP within first 6 hours following EVT and outcomes shown per 10mmHg increment in SBP.

	n= 1161	**(c)OR / b-coefficient**	**a(c)OR / ab-coefficient***
Primary outcome			
mRS at 90 days, median [IQR]	3 [1-6]	0.85 (0.85 to 0.92)	0.93 (0.88 to 0.98)
Secondary outcomes, clinical			
mRS ≤2 at 90 days, n (%)	474 (44)	0.89 (0.85 to 0.92)	0.92 (0.86 to 0.98)
NIHSS 24–48 hours, median [IQR]	9 [4-16]	0.51 (0.34 to 0.69)†	0.31 (0.14 to 0.49)†
Mortality at 90 days, n (%)	278 (26)	1.11 (1.05 to 1.16)	1.02 (0.95 to 1.08)
Symptomatic intracranial hemorrhage, n (%)	56 (4.8)	1.19 (1.07 to 1.33)‡	1.17 (1.02 to 1.36)‡
Extracranial hemorrhage, n (%)	23 (2.0)	1.05 (0.90 to 1.21)	1.00 (0.84 to 1.19)
New ischemic stroke, n (%)	19 (1.6)	0.89 (0.75 to 1.06)	0.90 (0.74 to 1.13)

Abbreviations: ab, adjusted beta-coefficient; a(c)OR, adjusted (common) odds ratio; CI, confidence interval; IQR, interquartile range; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; n, number; SBP, systolic blood pressure. Captions: *Variables in the model: maximum SBP, age, sex, history of stroke, diabetes mellitus, hypertension, atrial fibrillation, myocardial infarction, pre-stroke mRS, intravenous thrombolysis, SBP on hospital admission, NIHSS at baseline, collateral score, ASPECTS at baseline, occlusion location, general anesthesia, eTICI after EVT, time from stroke onset to reperfusion, number of blood pressure measurements, and intervention center.
Captions: †Reported effect measure is b-coefficient. ‡Patients with sICH ≤6 hours following EVT were excluded (n=17).

Discussion

Increased maximum SBP in the first 6 hours following EVT was associated with worse functional outcome, a greater risk of sICH and more severe early neurologic deficits. Minimum SBP lower and higher than the inflection point of 124 mmHg were associated with worse functional outcome. A mean SBP lower than 138 mmHg was associated with an increased risk of extracranial hemorrhage. None of the associations between blood pressure and outcomes were modified by successful reperfusion at the end of the EVT procedure.

Our results are in line with previous studies reporting that higher maximum SBPs in the 24 hours following EVT are associated with worse clinical outcomes.[2,8,17-19] The explanation for the worse outcome observed in patients with higher maximum SBP is likely to be multifactorial, including disruption of the blood-brain barrier, hemorrhagic transformation, elevated serum cathecholamine levels, and larger infarcts.[20] The association between higher blood pressure and worse outcomes following EVT has been observed up to 3 days after treatment, stressing the importance of patient monitoring and support following EVT.[21] In contrast with our findings, no association between maximum SBP after EVT and risk of sICH was observed in a subgroup analysis of a recent meta-analysis including 791 patients.[19]

We observed a non-linear association between minimum SBP and functional outcome, with an inflection point at 124 mmHg during the first 6 hours following EVT. Previous studies evaluating minimum SBP did not find an association with functional outcome. However, these studies were small, no test for non-linearity was performed, and functional outcome was assessed dichotomously.[18,22] Only one other study reported that an increase in minimum SBP was associated with an increased likelihood of functional independence.[17] Low SBP in the (sub)acute phase of ischemic stroke might be associated with impaired cerebral perfusion, infarct expansion or complications like impending sepsis.[22,23]

We observed a small decrease of maximum SBP following EVT in patients with successful compared to unsuccessful reperfusion, similar to previous findings.[1] It has been hypothesized that optimal blood pressure regime varies with the reperfusion status (i.e. successful or unsuccessful). For example, higher SBP might be associated with hemorrhagic transformation given complete reperfusion.[24,25] On the other hand, maintaining hypertension might be of benefit in patients with unsuccessful reperfusion to optimize collateral blood flow and maintain cerebral perfusion pressure.[7,17,26] Several studies reported modification of the effect of blood pressure on outcome by reperfusion status.[18,22] However, in our large study cohort, we did not observe different associations between SBP and functional outcome for patients with successful and unsuccessful reperfusion, which was also observed by another cohort study.[2] This might partially be explained by the fact that high SBP is a marker of tissue damage rather than reperfusion success. Therefore, successful reperfusion should probably be regarded as a confounder of the association between blood pressure and outcome, and not only as an effect modifier.

Given the clear association between blood pressure and outcome after EVT, the lack of evidence on optimal blood pressure management, the variation in hemodynamic management among EVT centers, and the possibility of a modifiable effect of blood pressure on outcome, a clinical trial seems justified.[27] Currently, the BEST-II trial (NCT04116112) aims to evaluate the safety of lower SBP in patients treated with EVT in whom successful reperfusion is achieved. In this trial, patients will be randomly assigned to one of the following SBP targets: ≤180 mmHg, <160 mmHg, and <140

mmHg. Intravenous antihypertensive treatment will be started after reperfusion to maintain SBP below the assigned target for 24 hours.[28]

Furthermore, the BP TARGET trial (NCT03160677) aims to determine whether strict SBP control (intervention arm: SBP between 110 and 129 mmHg) versus standard SBP control (control arm: SBP between 130 and 185 mmHg) during 24 hours following EVT in patients with successful reperfusion will reduce the risk of any intracranial hemorrhage.[29,30] Besides, the ongoing MR ASAP trial (Multicentre Randomised trial of Acute Stroke treatment in the Ambulance with Nitroglycerin Patch) aims to assess the effect of transdermal glyceryl trinitrate started within 3 hours of symptom onset in the pre-hospital setting on functional outcome in patients with ischemic stroke or intracerebral haemorrhage. This intervention is suggested to improve outcome after stroke by an increase in the intracranial collateral flow and a reduction of the blood pressure.[31] Although these further studies on hemodynamic management in stroke patients are warranted, one of the major challenges of hemodynamic management remains to extrapolate population-based data to determine the target blood pressure for an individual stroke patient.

Limitations

Our study has several limitations. First, due to the retrospective observational design, results could have been confounded by variables not adjusted for in the analyses, so residual confounding might be present. Second, our observed associations do not prove causality between SBP and outcome measures. SBP could have been measured during the asymptomatic phase preceding sICH. Hence, definitive inferences on effects of SBP treatment are not possible. Furthermore, as we did not have data on individual SBP targets or information on administration of either a vasopressor or an antihypertensive agent after EVT, we do not know how well SBP was managed. Besides, as data on follow-up infarct volumes were not available systematically, we could not evaluate if patients with higher SBP were more likely to have larger infarcts.

Conclusions

Patients with higher maximum SBP in the 6 hours following EVT are more likely to have worse functional outcome or sICH compared to patients with lower maximum SBP. Lower as well as higher minimum SBP are associated with worse functional outcome. Randomized trials are needed to evaluate whether modifying SBP post EVT improves outcome.

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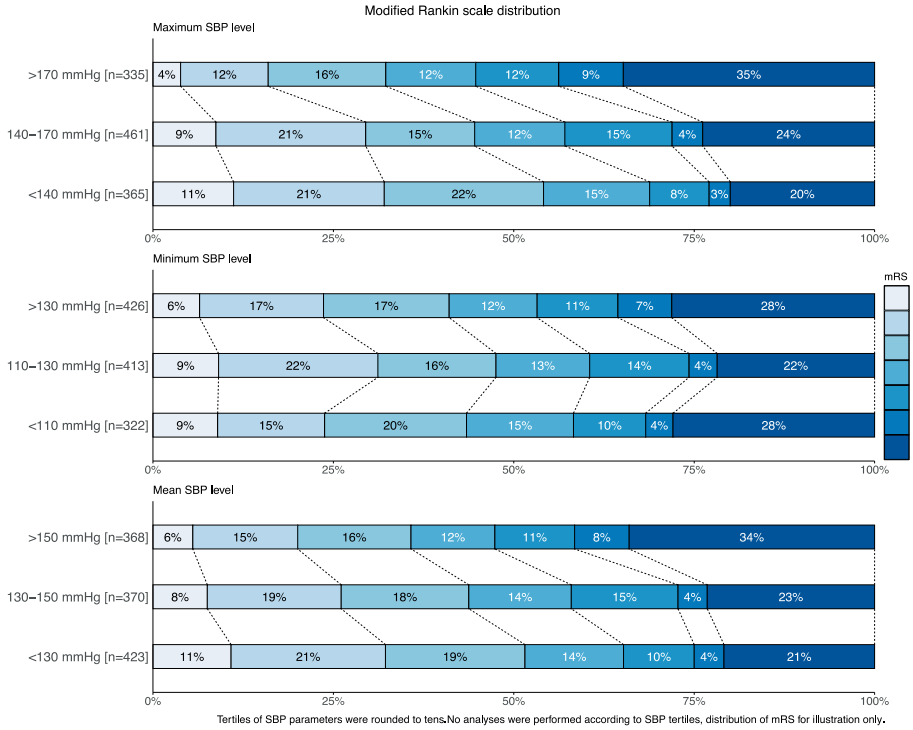
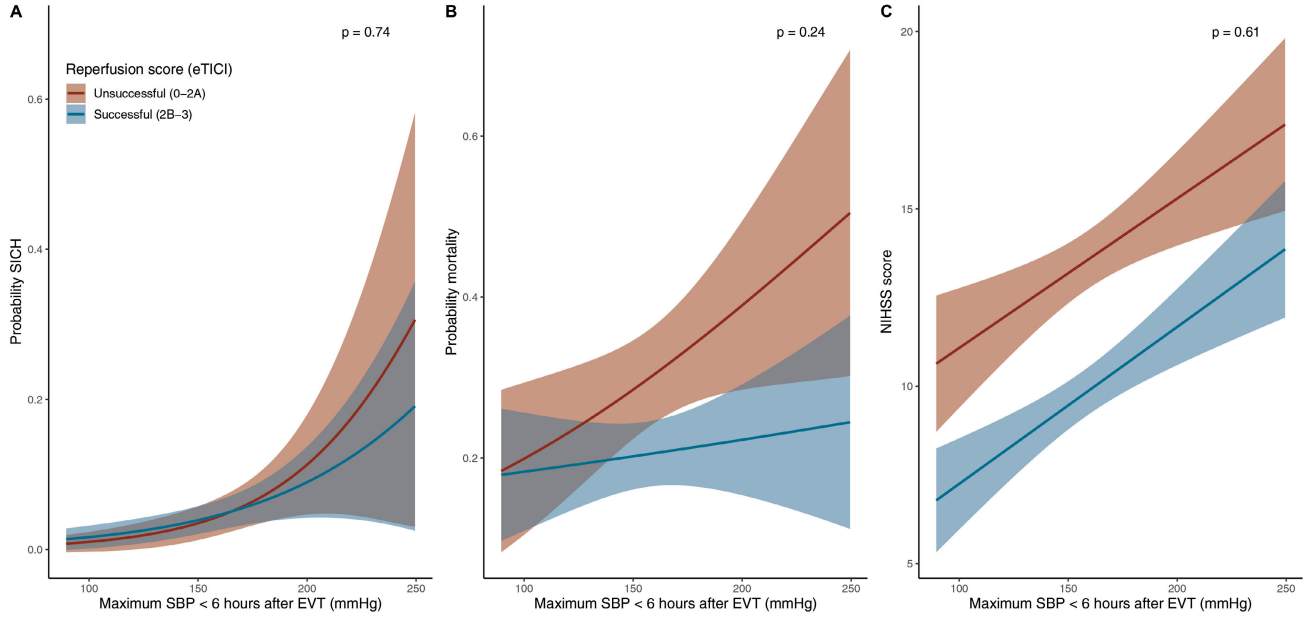
Supplemental material



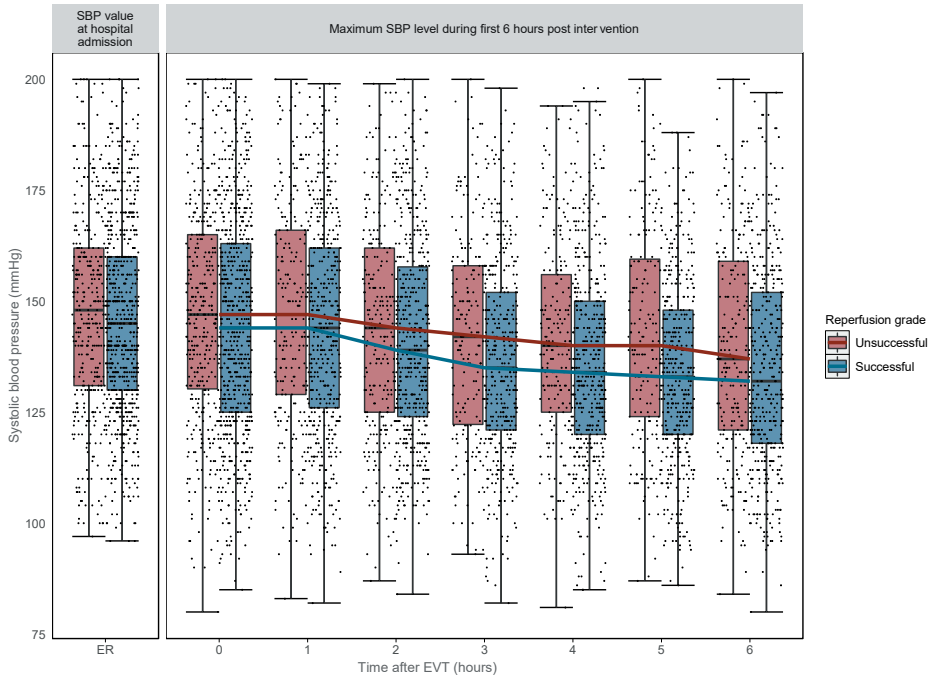
Supplemental figure 5.1. Distribution of modified Rankin scale according to tertiles of maximum, minimum and mean SBP during the first 6 hours following EVT. SBP tertiles are used for data inspection only, analysis is based on the fulle range of SBP measures.
Abbreviations: EVT, endovascular treatment; mRS, modified Rankin Scale; n, number; SBP, systolic blood pressure.



Supplemental figure 5.2. Relationship of maximum SBP with probability of sICH, probability of mortality at 90 days and NIHSS at 24-48 hours following EVT.

Summary: The models include the following variables: maximum SBP, age, NIHSS at baseline, ASPECTS at baseline, history of hypertension, time between stroke onset to reperfusion, and an interaction term for maximum SBP*reperfusion grade. The figures depict the probability of symptomatic intracranial hemorrhage (A), the probability of mortality (B) and NIHSS score at 24-48 hours after EVT (C) with 95% confidence intervals, for each level of maximum SBP in the first 6 hours following EVT for successful and unsuccessful reperfusion separately and a p-value for interaction (maximum SBP*reperfusion grade).

Abbreviations: eTICI, extended Thrombolysis in Cerebral Infarction; EVT, endovascular treatment; mRS, modified Rankin Scale; NIHSS, National Institute of Health Stroke score; SBP, systolic blood pressure; sICH, symptomatic intracranial hemorrhage.



Supplemental figure 5.3. Maximum SBP course in the first 6 hours following EVT for patients with successful reperfusion versus patient with unsuccessful reperfusion.
Summary: Black dots represent individual SBP measurements. The boxplots indicate the interquartile ranges around the median which are reflected by the red (unsuccessful reperfusion) and blue (successful reperfusion) lines.
Abbreviations: EVT, endovascular treatment; SBP, systolic blood pressure.

Supplemental table 5.1. Overview of protocols for blood pressure management in the 8 included centers

Center	Periprocedural blood pressure targets* (SBP/DBP)	Frequency of blood pressure measurements during 24 hours following EVT†	First and second preferred agent to treat arterial hypertension during first 24 hours after EVT‡
1	<185/110 mmHg	0-6: hourly 6-24 hours: 2-hourly NB IVT first hour every 15 minutes	Labetalol, nicardipine
2	<185/110 mmHg	0-24: hourly	Labetalol
3	<185/110 mmHg	0-2 hours: 15 minutes 2-10 hours: 2-hourly 10-24 hours: 4-hourly	Labetalol, nicardipine
4	<185/110 mmHg	0-2 hours: 15 minutes 2-6 hours: 30 minutes 6-24 hours: hourly	Labetalol
5	<185/110 mmHg	0-2 hours: 15 minutes 2-6 hours: 30 minutes 6-24 hours: hourly	Labetalol, nicardipine
6	<185/110 mmHg	0-2 hours: 15 minutes 2-8 hours: 30 minutes 8-24 hours: hourly	Nifedipine, labetalol
7	<185/110 mmHg	0-2 hours: 15 minutes 2-6 hours: 30 minutes 6-24 hours: hourly	Labetalol, perindopril/ nifedipine
8	<185/110 mmHg	0-2 hours: 15 minutes 2-8 hours: 30 minutes 8-24 hours: hourly	Labetalol, clonidine

Abbreviations: DBP, diastolic blood pressure; EVT, endovascular treatment; SBP, systolic blood pressure.
*Non-invasive blood pressure monitoring. † Preprocedural, procedural, and up to 24 hours post-procedural SBP targets. ‡Might be different from the preferred agents for lowering blood pressure prior to intravenous alteplase administration or EVT.

Supplemental table 5.2. Associations between continuous maximum SBP within first 24 hours following EVT and outcomes shown per 10mmHg increment in SBP *(full cohort, n= 1161).*

	(c)OR / b-coefficient (95% CI)	**a(c)OR / ab-coefficient (95% CI)***
Primary outcome		
mRS at 90 days	0.85 (0.82 to 0.89)	0.90 (0.85 to 0.94)
Secondary outcomes		
mRS ≤2 at 90 days	0.85 (0.82 to 0.90)	0.89 (0.83 to 0.95)
NIHSS 24–48 hours	0.77 (0.58 to 0.95) †	0.51 (0.31 to 0.70) †
Mortality at 90 days	1.15 (1.10 to 1.21)	1.06 (0.99 to 1.14)
New ischemic stroke	0.89 (0.74 to 1.06)	0.92 (0.73 to 1.18)

Abbreviations: ab, adjusted beta-coefficient; a(c)OR, adjusted (common) odds ratio; CI, confidence interval; EVT, endovascular treatment; IQR, interquartile range; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; SD, standard deviation; SBP, systolic blood pressure. *Captions:* *Variables in the model: maximum SBP, age, sex, history of stroke, diabetes mellitus, hypertension, atrial fibrillation, myocardial infarction, pre-stroke mRS, intravenous thrombolysis, SBP on hospital admission, NIHSS at baseline, collateral score, ASPECTS at baseline, occlusion location, general anesthesia, eTICI score, time between stroke onset to reperfusion, number of blood pressure measurements, and intervention center. †Reported effect measure is b-coefficient.

Supplemental table 5.3. Associations between continuous minimum SBP within first 6 hours following EVT and outcomes.

	Minimum SBP < 124mmHg per 10mmHg decrement in SBP		**Minimum SBP ≥ 124mmHg per 10mmHg increment in SBP**	
	(c)OR/ b-coefficient, (95% CI)*	**a(c)OR/ ab-coefficient, (95% CI)*†**	**(c)OR/b-coefficient, (95% CI)***	**a(c)OR/ab-coefficient, (95% CI)*†**
Primary outcome				
mRS at 90 days	0.86 (0.78 to 0.95)	0.85 (0.76 to 0.95)	0.76 (0.67 to 0.86)	0.81 (0.71 to 0.92)
Secondary outcomes				
mRS ≤2 at 90 days	0.88 (0.79 to 0.99)	0.90 (0.78 to 1.04)	0.79 (0.67 to 0.90)	0.89 (0.73 to 1.04)
NIHSS 24–48 hours	0.74 (-0.26 to 1.23)‡	0.41 (-0.02 to 0.84)‡	1.44 (0.83 to 2.05)‡	0.76 (0.23 to 1.28)‡
Mortality at 90 days	1.20 (1.06 to 1.34)	1.22 (1.04 to 1.40)	1.33 (1.15 to 1.54)	1.23 (1.01 to 1.45)
Symptomatic intracranial hemorrhage ∫	1.11 (0.80 to 1.43)	1.17 (0.83 to 1.57)	1.32 (0.93 to 1.79)	1.34 (0.91 to 1.90)
Extracranial hemorrhage	1.61 (1.26 to 2.05)	1.71 (1.27 to 2.30)	1.78 (1.24 to 2.50)	1.80 (1.21 to 2.67)
New ischemic stroke	1.30 (0.92 to 1.71)	1.38 (0.91 to 1.93)	1.30 (0.79 to 1.93)	1.35 (0.78 to 2.19)

Abbreviations: ab, adjusted beta-coefficient; a(c)OR, adjusted (common) odds ratio; CI, confidence interval; EVT, endovascular treatment; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; SBP, systolic blood pressure. *Captions*: *regression models include a restricted cubic spline function with 3 knots for the continuous minimum SBP term. †Variables in the model: minimum SBP, age, sex, history of stroke, diabetes mellitus, hypertension, atrial fibrillation, myocardial infarction, pre-stroke mRS, intravenous thrombolysis, SBP on hospital admission, NIHSS at baseline, collateral score, ASPECTS at baseline, occlusion location, general anesthesia, eTICI after EVT, time from stroke onset to reperfusion, number of blood pressure measurements, and intervention center. ‡Reported effect measure is b-coefficient. ∫Patients with sICH ≤6 hours following EVT were excluded (n=17).

Supplemental table 5.4. Associations between continuous mean SBP within first 6 hours following EVT and outcomes.

	Mean SBP< 138mmHg per 10mmHg decrement		Mean SBP ≥ 138mmHg per 10mmHg increment	
	(c)OR/ b-coefficient, (95% CI)*	a(c)OR/ ab-coefficient, (95% CI)*†	(c)OR/b-coefficient, (95% CI)*	a(c)OR/ab-coefficient, (95% CI)*†
Primary outcome				
mRS at 90 days	1.01 (0.90 to 1.13)	0.97 (0.86 to 1.10)	0.83 (0.72 to 0.96)	0.88 (0.76 to 1.03)
Secondary outcomes				
mRS ≤2 at 90 days	1.05 (0.92 to 1.18)	1.06 (0.88 to 1.23)	0.90 (0.74 to 1.03)	1.01 (0.78 to 1.19)
NIHSS 24–48 hours	0 (-0.54 to 0.55)‡	-0.07 (-0.56 to 0.41)‡	0.86 (0.16 to 1.56)‡	0.40 (-0.20 to 0.99)‡
Mortality at 90 days	1.04 (0.90 to 1.21)	1.13 (0.95 to 1.36)	1.26 (1.06 to 1.51)	1.20 (0.97 to 1.49)
Symptomatic intracranial hemorrhage ∫	0.94 (0.61 to 1.35)	1.06 (0.66 to 1.56)	1.18 (0.75 to 1.77)	1.29 (0.79 to 1.99)
Extracranial hemorrhage	1.50 (1.02 to 2.10)	1.66 (1.07 to 2.51)	1.61 (0.98 to 2.52)	1.55 (0.90 to 2.58)
New ischemic stroke	1.49 (0.99 to 2.16)	1.66 (0.98 to 2.52)	1.53 (0.86 to 2.52)	1.73 (0.88 to 3.11)

Abbreviations: ab, adjusted beta-coefficient; a(c)OR, adjusted (common) odds ratio; CI, confidence interval; EVT, endovascular treatment; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; SBP, systolic blood pressure. *Captions*: *regression models include a restricted cubic spline function with 3 knots for the continuous mean SBP term. *Captions:* †Variables in the model: mean SBP, age, sex, history of stroke, diabetes mellitus, hypertension, atrial fibrillation, myocardial infarction, pre-stroke mRS, intravenous thrombolysis, SBP on hospital admission, NIHSS at baseline, collateral score, ASPECTS at baseline, occlusion location, general anesthesia, eTICI after EVT, time from stroke onset to reperfusion, number of blood pressure measurements, and intervention center. ‡Reported effect measure is b-coefficient. ∫Patients with symptomatic intracranial hemorrhage ≤6 hours following EVT were excluded (n=17).

Supplemental table 5.5. Outcomes shown according to tertiles of SBP during first 6 hours following EVT.

	Maximum SBP < 140 mmHg (n = 365)	**Maximum SBP 140 - 170 mmHg (n = 461)**	**Maximum SBP >170 mmHg (n = 335)**	**Missing**
Outcome measures				
mRS ≤2 at 90 days, n (%)	184 (54)	189 (45)	101 (32)	25/37/22
NIHSS 24–48 hours, median [IQR]	8 [3 to 14]	10 [4 to 16]	12 [5 to 18]	18/23/21
Mortality at 90 days, n (%)	68 (20)	101 (24)	109 (35)	25/37/22
Symptomatic intracranial hemorrhage, n (%)	12 (3.3)	13 (2.8)	31 (9.3)	
Extracranial hemorrhage, n (%)	6 (1.6)	11 (2.4)	6 (1.8)	
New ischemic stroke, n (%)	7 (1.9)	8 (1.7)	4 (1.2)	
	Minimum SBP < 110 mmHg (n = 322)	**Minimum SBP 110 - 130 mmHg (n = 413)**	**Minimum SBP >130 mmHg (n = 426)**	**Missing**
mRS ≤2 at 90 days, n (%)	126 (43)	183 (48)	165 (41)	32/28/24
NIHSS 24–48 hours, median [IQR]	10 [4 to 16]	9 [3 to 15]	11 [4 to 17]	14/18/30
Mortality at 90 days, n (%)	81 (28)	84 (22)	113 (28)	32/28/24
Symptomatic intracranial hemorrhage, n (%)	16 (5)	10 (2.4)	30 (7.0)	
Extracranial hemorrhage, n (%)	13 (4.0)	3 (0.7)	7 (1.6)	
New ischemic stroke, n (%)	8 (2.5)	4 (1.0)	7 (1.6)	
	Mean SBP < 130 mmHg (n = 423)	**Mean SBP 130 - 150 mmHg (n = 370)**	**Mean SBP >150 mmHg (n = 368)**	**Missing**
mRS ≤2 at 90 days, n (%)	200 (52)	151 (44)	123 (36)	35/25/24

Supplemental table 5.5 Continued

	Maximum SBP < 140 mmHg (n = 365)	**Maximum SBP 140 - 170 mmHg (n = 461)**	**Maximum SBP >170 mmHg (n = 335)**	**Missing**
Outcome measures				
NIHSS 24–48 hours, median [IQR]	8 [3 to 15]	9 [4 to 16]	12 [5 to 18]	23/15/24
Mortality at 90 days, n (%)	81 (21)	80 (23)	117 (34)	35/25/24
Symptomatic intracranial hemorrhage, n (%)	11 (2.6)	13 (3.5)	32 (8.7)	
Extracranial hemorrhage, n (%)	13 (3.1)	3 (0.8)	7 (1.9)	
New ischemic stroke, n (%)	8 (1.9)	7 (1.9)	4 (1.1)	

Abbreviations: IQR, interquartile range; min, minutes; mRS, modified Rankin Scale; n, number; NIHSS, National Institutes of Health Stroke Scale; SD, standard deviation; SBP, systolic blood pressure

Captions: *Tertiles of SBP were rounded to tens. Continuous data are presented as mean (SD) for normal distributed data or as median [IQR] for skewed data. Categorical data are presented as numbers (percentage).

CHAPTER 6

Predictors of worse outcome despite successful endovascular thrombectomy for ischemic stroke: results from the MR CLEAN Registry

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Abstract

Background: Approximately one-third of ischemic stroke patients treated with endovascular treatment (EVT) do not recover to functional independence, despite rapid and successful recanalization. We aimed to quantify the importance of predictors of poor functional outcome despite successful reperfusion.

Methods: We analyzed patients from the MR CLEAN Registry between March 2014 and November 2017, with successful reperfusion (extended-thrombolysis-in-cerebral-infarction [eTICI≥2B). First, predictors were selected based on expert opinion and were clustered according to acquisition over time (i.e. *baseline patient factors, imaging factors, treatment factors and post-procedural factors*). Second, several models were constructed to predict 90-day functional outcome (modified Rankin Scale [mRS]). The relative importance of individual predictors in the most extensive model was expressed by the proportion of unique added Chi^2 to the model of that individual predictor.

Results: Of 3180 patients, 1913 (60%) patients had successful reperfusion. Of these 1913 patients, 1046 (55%) were functionally dependent at 90 days (mRS>2). The most important predictors for mRS were baseline patient factors (i.e., pre-stroke mRS, added Chi^2 0.16; NIHSS at baseline, added Chi^2 0.12; age, added Chi^2 0.10) and post-procedural factors (i.e., symptomatic intracranial hemorrhage[sICH], added Chi^2 0.12; pneumonia, added Chi^2 0.09). Probability of functional independence for a typical stroke patient with sICH was 54% (95%CI 36%-72%) lower compared to no sICH, and 21% (95%CI 4%-38%) for pneumonia compared to no pneumonia.

Conclusion: Baseline patient factors and post-procedural adverse events are important predictors of poor functional outcome in successfully reperfused patients with ischemic stroke. This implies that prevention of post-procedural adverse events has the greatest potential to further improve outcomes in these patients.

Introduction

Approximately 50% of the patients with ischemic stroke caused by a proximal large vessel occlusion in the anterior circulation do not recover to functional independence, even when successful reperfusion is achieved by endovascular treatment (EVT).[1] Factors such as age, NIHSS at baseline, and ASPECTS are associated with poor outcome after successful reperfusion.[2-5] Better understanding of the key determinants of poor recovery despite successful reperfusion after EVT, could guide researchers and physicians in the development of new treatments to further improve outcomes. Therefore, we aimed to quantify the importance of predictors for poor functional outcome despite successful reperfusion.

Methods

Study design

We used data from the MR CLEAN Registry, which is a national, prospective, open, multicenter, observational monitoring study for stroke intervention centers that perform EVT in the Netherlands. The complete methods and description of variables of the MR CLEAN Registry have been described elsewhere.[6] For the present study, we selected patients who were registered between March 2014 and November 2017 and adhered to the following criteria: age of 18 years or older; presence of a proximal intracranial occlusion in the anterior circulation confirmed on CT angiography (intracranial carotid artery [ICA/ICA-T], middle cerebral artery [M1/M2], anterior cerebral artery [A1/A2]), groin puncture within 6.5 hours after symptom onset; treatment in a center that participated in the MR CLEAN trial, and successful post interventional macrovascular reperfusion status (extended thrombolysis in cerebral infarction [eTICI≥2B) assessed by an independent core laboratory. The current observational study was guided by the STROBE statement.[7]

Measures and outcomes

We constructed multivariable ordinal regression models to predict functional outcome measured with the modified Rankin Scale at 90 days. We selected candidate predictors based on expert opinion and availability.[2-5,8] In the selection, priority was given to causal and modifiable factors. The predictors were clustered in four groups according to the time of acquisition: *baseline patient factors*, *imaging factors*, *treatment factors*, and *post-procedural factors* (i.e. adverse events). We successively added each group of predictors to a basic model only including baseline patient factors. This resulted in four multivariable ordinal regression models of increasing extensiveness. The most extensive model was used to quantify the relative importance of the individual predictors. Finally, we evaluated the overall explained variance of the most extensive model.

Subsequently, we repeated these analyses [1] for the subgroup with excellent reperfusion (eTICI≥2C) and [2] using a modified NIHSS score at 24-48 hours as the outcome. A modification of the NIHSS score at 24-48 hours was necessary to also include patients who died within 48 hours, by assigning them the maximum NIHSS score of 42. This early modified NIHSS scale may be a better representation of direct stroke-related factors associated with outcome after EVT as opposed to the mRS and less inflicted by patients who died early.[9]

Statistical methods

Any mRS score assessed within 30 days of symptom onset was considered invalid and treated as missing. For the purpose of unbiased estimation of associations of outcome with baseline characteristics, we replaced missing outcome and predictor values by values derived from multiple imputation by chained equations with 5 imputations.[10,11] After constructing ordinal logistic or linear regression models as appropriate, quantification measures were derived. Nagelkerke's pseudo-R^2 for the mRS (ordinal outcome) and R^2 for the modified NIHSS at 24-48 hours (continuous outcome) were applied to quantify the explained variance in outcome by the models. This derived (pseudo-)R^2 reflects the explained variance in outcome of the models by the included predictors, ideally aiming to achieve a highest possible score of 1 representing complete variance explanation. Subsequently, the strength of relationship between an individual predictor in the model and the outcome was quantified by the proportion of unique added value in that particular model using the Wald Chi^2 test, with penalization for degrees of freedom. Further explanation on this approach is provided in the supplemental text 6.1. For the most important modifiable predictors associated with functional outcome, we calculated the absolute difference in predicted probability for good functional outcome (mRS≤2) for a typical stroke patient.

To account for non-linearity of the associations between continuous parameters and outcome, the variables age and systolic blood pressure were handled using restricted cubic splines with 3 knots based on prior knowledge.[8,12] The modified NIHSS at 24-48 hours was log transformed, after adding 1 point to all NIHSS scores, to best satisfy the linear model (normal distribution of residuals and homoscedasticity).[9] Confidence intervals for individual predictor importance were calculated using bootstrapping with 10,000 iterations. All statistical analyses were performed with R version 3.5.0 (R foundation for Statistical Computing, Vienna, Austria).

Results

Study population

In total, 3180 patients were analyzed. Successful reperfusion was observed in 1913/3180 (60%) and excellent reperfusion in 1218/3180 (38%) patients (Figure 6.1). Characteristics of patients with successful and excellent reperfusion, along with clustering of predictors according to the four predefined groups, are presented in Table 6.1 (and per

reperfusion grade in supplemental table 6.2). Within 90 days following EVT, 900/1913 (51%) patients remained functionally dependent or died (mRS>2) given successful reperfusion was achieved. This was similar for patients with excellent reperfusion with 554/1218 (49%) being dependent or death at 90 days. Given successful reperfusion, 78/1913 (4%) of the patients died within 48 hours and once excellent reperfusion was achieved 46/1218 (4%) patients died within 48 hours. Median modified NIHSS score at 24-48 hours was 8 [IQR 3, 15] for successful reperfusion and 7 [IQR 3, 14] for excellent reperfusion.

Table 6.1. *Cohort characteristics and predictor clustering*

	eTICI≥2B, n=1913	**Missing**	**eTICI≥2C, n=1218**	**Missing**
Patient factors				
Age	69 (14)	0	70 (14)	0
Male sex	1010 (53)	0	651 (53)	0
NIHSS on admission	16 [11, 19]	1.5	16 [11, 20]	1.6
Ischemia in left hemisphere	1019 (54)	0.6	637 (53)	0.5
Systolic blood pressure on admission	148.7 (24)	3.2	149 (24)	2.9
INR on admission	1.2 (0.4)	19	1.2 (0.4)	18
Glucose level on admission	7.4 (2.6)	11	7.4 (2.5)	11
Previous stroke	309 (16)	0.8	197 (16)	0.7
Atrial fibrillation	427 (23)	1.3	286 (24)	1.3
Hypertension	967 (52)	2.2	626 (52)	1.7
Diabetes mellitus	310 (16)	0.7	209 (17)	0.5
Pre-stroke mRS (%)		2.3		2.1
0 - No symptoms	1280 (69)		823 (69)	
1 - Minor symptoms, no limitations	247 (13)		161 (14)	
2 - Slight disability, no help needed	135 (7.2)		90 (7.5)	
>2	207 (11)		119 (10)	
Prior antiplatelet therapy	601 (32)	1.4	397 (33)	1.0
Time from symptom onset to admission ER (intervention center)	133 [65, 185]	4.9	133 [65, 183]	4.3
Imaging factors				
Occluded segment		3.8		3.4
Intracranial ICA	81 (4.4)		51 (4.3)	
ICA-T	366 (20)		239 (20)	
M1	1118 (61)		730 (62)	
M2	262 (14)		149 (13)	

Table 6.1. Continued.

	eTICI≥2B, n=1913	Missing	eTICI≥2C, n=1218	Missing
Other (e.g., M3, ACA)	14 (0.8)		8 (0.7)	
ASPECTS	9 [8, 10]	2.9	9 [8, 10]	2.2
Collaterals		6.1		5.9
Grade 0 - Absent collaterals	101 (5.6)		63 (5.5)	
Grade 1 - Occluded area filling <50%	649 (36)		408 (36)	
Grade 2 - Occluded area filling ≥50% but <100%	708 (39)		452 (39)	
Grade 3 - Occluded area filling 100%	338 (19)		223 (20)	
Treatment factors				
Treatment with intravenous alteplase	1472 (77)	0.4	925 (76)	0.4
Time from admission ER (intervention center) to groin puncture	58 [35, 87]	8.9	58 [35, 84]	8.2
Duration procedure	50 [35, 73]	7.4	50 [35, 70]	5.5
General anesthetic management	528 (29)	5.1	363 (31)	4.0
Periprocedural heparin use	548 (29)	0	373 (31)	0
Reperfusion grade after intervention or spontaneous		0		0
eTICI 2B	695 (36)		NA	NA
eTICI 2C	332 (17)		332 (27)	0
eTICI 3	886 (46)		886 (73)	0
First pass success	719 (47)	20	539 (51)	13
*Post-procedural factors**				
New ischemic stroke	30 (1.6)	0	17 (1.4)	0
Symptomatic intracranial hemorrhage	88 (4.6)	0	54 (4.4)	0
Pneumonia	177 (9.3)	0	108 (8.9)	0

Summary: Cohort characteristics of patients with successful (eTICI≥2B) and with excellent reperfusion (eTICI≥2C). Continuous data are presented as mean (SD) for normal distributed data or as median [IQR] for skewed data. Categorical data are presented as numbers (%).
Abbreviations: ACA, anterior cerebral artery; APT, antiplatelet therapy; ASPECTS, Alberta stroke program early computed tomography score; DOAC, direct oral anticoagulant; ER, emergency room; eTICI, extended thrombolysis in cerebral infarction including a 2C grade; ICA (T), internal carotid artery (terminus); INR, international normalized ratio; M(*segment*), middle cerebral artery; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale
Captions: *For the model with the modified NIHSS at 24-48 hour as outcome, post-procedural factors in the model were restricted to occurrence within 24 hours, which was only recorded for sICH (so new ischemic stroke and pneumonia were excluded).

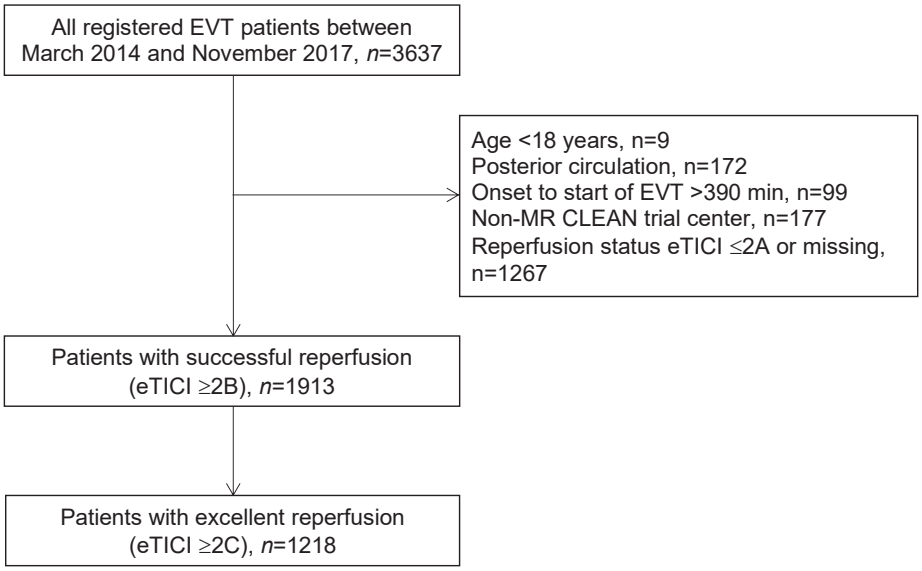

Figure 6.1. Flowchart

Variable importance

The basic model including *patient factors* already explained the largest proportion in variance (Figure 6.2). Successive addition of the other grouped factors based on clustering on acquisition over time (i.e. *imaging factors, treatment factors,* and *post-procedural factors*) increased the explained variance by the models, but these were relatively less important than the contribution of *patient factors*. The four most extensive models, including all independent variables, explained between 42% and 47% of the variation in outcome prediction among patients with reperfusion after EVT. In patients with successful reperfusion (eTICI≥2B) the 5 most important individual predictors of functional outcome at 90 days were pre-stroke mRS (added Chi^2: 0.16), NIHSS at baseline (added Chi^2: 0.12), sICH (added Chi^2: 0.12), age (added Chi^2: 0.10), and pneumonia (added Chi^2: 0.09; Figure 6.3A). The five individual predictors with the highest added Chi^2 were similar in patients with excellent reperfusion (eTICI≥2C), although the order of importance and the quantity of added Chi^2 differed: pre-stroke mRS (added Chi^2: 0.19), pneumonia (added Chi^2: 0.12), sICH (added Chi^2: 0.11), NIHSS at baseline (added Chi^2: 0.10), and age (added Chi^2: 0.09; Figure 6.3C). The most important predictors of the modified NIHSS at 24-48 hours as outcome were NIHSS on admission (added Chi^2: 0.26), sICH that occurred within 24 hours (added Chi^2: 0.07), collaterals (added Chi^2: 0.06), duration of the procedure (added Chi^2: 0.03), and ASPECTS on admission (added Chi^2: 0.02; Figure 6.3B). In patients with excellent reperfusion, the order of importance of added Chi^2 of the 4 most important predictors was similar to those with successful reperfusion, only the 5th most important predictor differed: NIHSS at baseline (added Chi^2: 0.28), sICH that occurred within 24 hours

(added Chi²: 0.08), collaterals (added Chi²: 0.05), duration of the procedure (added Chi²: 0.02), and glucose (added Chi²: 0.02; Figure 6.3D).

Probability of good functional outcome (mRS≤2) for a typical stroke patient with sICH was 54% (95% CI 36%-72%) lower compared to a patient without sICH, and 21% (95% CI 4%-38%) for pneumonia compared to no pneumonia.

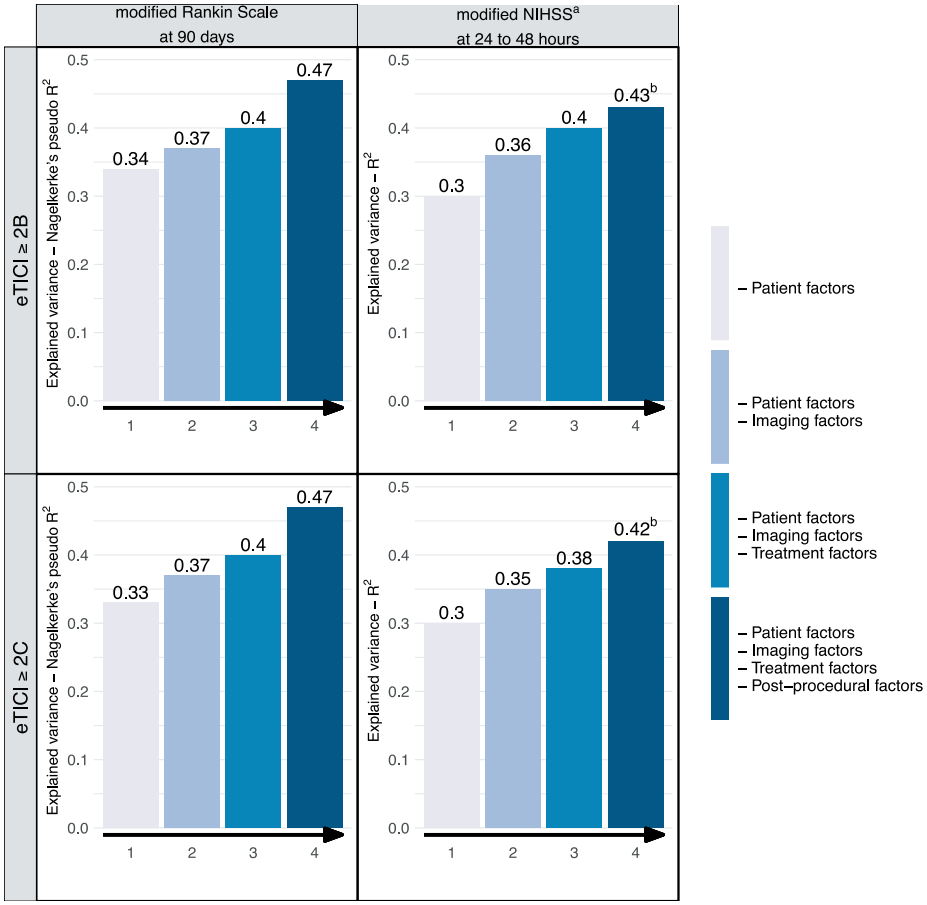

Figure 6.2. Performance of models with increasing extensiveness; in patients with successful reperfusion defined as an eTICI≥2B (A, B) and excellent reperfusion defined as an eTICI≥2C (C, D), predicting mRS at 90 days (A, C) and modified NIHSS at 24 to 48 hours (B, D);
Abbreviations: eTICI, extended thrombolysis in cerebral infarction; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale;
Captions: [a]Death within 48 hours was assigned the maximum score of 42. [b]For the model with the modified NIHSS at 24 to 48 hours as outcome, post-procedural factors in the model were restricted to occurrence within 24 hours, which was only recorded for sICH (resulting in exclusion of new ischemic stroke and pneumonia for these analyses).

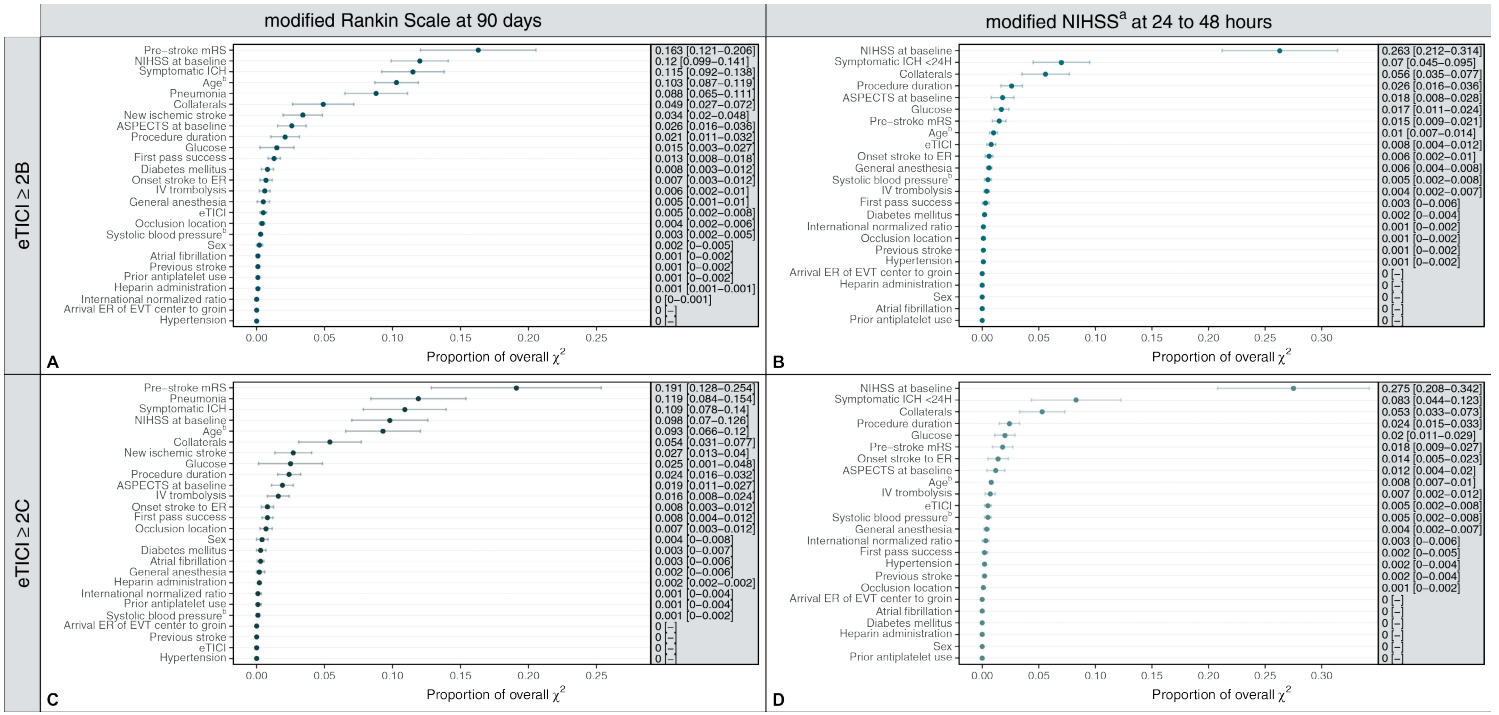

Figure 6.3. Individual penalized variable importance within the most extensive models; in patients with successful reperfusion defined as an eTICI≥2B (A, B) and excellent reperfusion defined as an eTICI>2C (C, D), predicting mRS at 90 days (A, C) and modified NIHSS at 24 to 48 hours (B, D). Confidence intervals for individual predictor importance were calculated using bootstrapping with 10,000 iterations;
Abbreviation: ASPECTS, Alberta stroke program early computed tomography score; ER, emergency room; eTICI, extended thrombolysis in cerebral infarction; EVT, endovascular treatment; IV, intravenous; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale.
Captions: [a]Death within 48 hours was assigned the maximum score of 42, [b]Were handled using 3 restricted cubic spines

Discussion

In this study in which we evaluated the importance of predictors according to their acquisition over time, we found that baseline patient factors and post-procedural adverse events are the most important predictors of poor functional outcome in ischemic stroke patients with successful reperfusion after EVT. It is conceivable that prevention of post-procedural adverse events (i.e. sICH, pneumonia) has the greatest potential to further improve outcomes.

Strategies currently investigated that could be of benefit in prevention of post-procedural adverse events are (I) direct EVT without preceding intravenous alteplase to reduce sICH (MR CLEAN-NO IV [ISRCTN80619088], DIRECT MT [NCT03469206], SKIP [UMIN000021488], SWIFT-DIRECT [NCT03192332], DIRECT-SAFE [NCT03494920], DEVT [ChiCTR-IOR-17013568]), (II) strict blood pressure control to reduce the risk of intracranial hemorrhage (BP TARGET [NCT03160677]) and (III) pharmacological strategies reducing complications like pneumonia (PRECIOUS [ISRCTN82217627]).

Comparing the most important predictors for the group with successful and those with excellent reperfusion this resulted only in minor differences, assuming that predictor importance seems relatively constant with regard to the level of reperfusion. Results of this study should not be used to determine for which reperfusion grade one should strive as this was not our aim. The observation that pre-stroke mRS was a strong predictor in explaining outcomes after 90 days confirms the hypothesis that most patients with poor outcomes at 90 days already have poor outcomes at baseline and vice versa. Yet, as no perfect prediction was observed, other factors contribute to the prediction of outcomes at 90 days. We observed that the time from stroke onset to admission at the emergency room of the intervention hospital and time from admission at the emergency room of the intervention hospital to groin puncture, were relatively less important compared to duration of the procedure.

Possibly, the importance of pre-interventional time intervals was negated by the achievement of successful reperfusion as our analyses were inherent to this selection criterion. The relative importance of duration of the procedure could reflect the difficulty of the procedure, for example caused by agitation of the patient, tortuosity of the vessels, or performance of multiple attempts, which is associated with poor functional outcomes.[13]

Six earlier studies also found that the non-modifiable patient factor baseline NIHSS was a very important predictor of poor functional outcome despite reperfusion.[3-5,14-16] In five of these studies, age was found to be an important predictor for poor functional outcome.[3-5,15,16] Two studies found that EVT without prior IV alteplase administration was associated with poor outcome.[4,14] Lower (diffusion weighted imaging [DWI]) ASPECTS on admission was found to be related to poor outcome in two studies.[5,16] Factors such as collateral status, blood glucose, occlusion location, diabetes mellitus,

neutrophil-to-lymphocyte ratio, delayed EVT, mTICI 2B (versus mTICI 3), procedural complications, and higher number of passes (≥3) were mentioned in only one study to be associated with poor functional outcome.[4,5,14-15] Besides, our results confirm the suggestion of an opinion review that unfavorable non-modifiable patient factors (reflecting limited "brain reserve") are the most notable factors explaining why patients do not recover despite reperfusion.[17] Remarkably, none of these studies evaluated the influence of post-procedural factors, such as sICH, pneumonia and new ischemic stroke (i.e. imaging of new brain infarction with corresponding clinical neurologic deficit within 90 days), which based on our results are very important in explaining why some patients with successful reperfusion recover well and others do not. It should be kept in mind that the identified factor is not necessarily causal in explaining the detrimental outcomes. For example, it is possible that the occurrence of pneumonia is associated with other conditions like heart failure and sepsis followed by hemodynamic instability and hypoperfusion requiring ICU admission which actually explains why these patients do worse.

The variance in outcome explained by the models varied between 42% and 47%. Still, a substantial part of the variability in outcome after successful reperfusion is unexplained. Therefore, we do advocate to incentivize the identification of new predictors as well as to optimize determination of current predictors. Considering the identification of new predictors additional information on quantification of perfusion at the microvascular level, preferably at an early stage, could be a useful new approach to improve outcome prediction. Current visual scoring techniques are unable to evaluate vessels less than 90 micron in diameter.[18] Yet, it is believed that microvascular dysfunction (vasculature <90 micron in diameter) following reperfusion could contribute to poor functional outcomes despite macrovascular reperfusion.[19]

Regarding optimization of predictor determination, our current models could be optimized even more by improving both pre-interventional as well as post-interventional quantification of brain tissue status with more advanced neuro-imaging techniques as MRI or CT perfusion instead of CT.

As no baseline MRI-DWI or CT perfusion data (e.g. information on pre-interventional perfusion status such as CBF and core volume) were available in this observational registry, our analyses were limited to ASPECTS evaluation, which is probably a less accurate measure of the infarct core. Also, in-depth information on for example periprocedural device technique used (e.g. use of balloon protection, assisted aspiration), periprocedural blood pressure course and malignant brain edema, could be of additional value to further improve outcome explanation. Furthermore, addition of the follow-up infarct volume might have improved the model's performance further.[20-22] However, this assessment was not available in our dataset. Besides, as we only documented the occurrence of pneumonia, not the occurrence of other infections, this could have limited our study. Nevertheless, pneumonia accounts for at least half of all stroke related infections, and is by far the strongest prognostic factor among the stroke associated infections.[23,24] Another limitation is the possibility

of information bias introduction as factors were selected for the model based on prior knowledge. Furthermore, it should be considered that the chosen outcome of the modified NIHSS (including death) should be interpreted with caution as it is not known whether assigning patients who died before 24-48 hours NIHSS assessment the maximum NIHSS score of 42, is the most optimal strategy for the evaluation of early stroke-related outcome after EVT. However, this outcome is a strong mediator of the mRS at 90 days and might be seen as a more essential evaluation of neurological deficit and directly stroke-related outcome measure, which is less inflicted by early death.[9] Finally, although we did not detect a large influence of the included modifiable factors use of antithrombotic medication (e.g. antiplatelets, heparin) or anesthesia type on poor functional outcome despite reperfusion, it should be kept in mind that these treatments were not assigned systematically and confounding by indication may have occurred. Foremost, to improve outcomes further we suggest to evaluate the effect of modifiable factors in randomized studies as well as to incentivize identification of additional modifiable predictors. As these treatments are modifiable this warrants further randomized study.

Conclusion

Both patient and post-procedural factors are important predictors of outcome in successfully reperfused patients with ischemic stroke. This implies that prevention of post-procedural adverse events has the greatest potential to further improve clinical outcomes in these patients.

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Supplemental material

Supplemental text 6.1. Additional method explanation
In the evaluation of the added Chi^2 of the individual parameters, the sum of all individual Chi^2 proportions can be below or above 1 and quantification measures should be interpreted in context of the model. For example, if all independent variables are perfectly identical (collinear), the model can have good performance, but proportion Chi^2 for all independent variables will be zero, because any single predictor has zero additional explanatory value. On the other hand, if all independent variables together explain the dependent variable perfectly, proportion Chi^2 for each predictor will be 1, because whatever is unexplained by all other predictors can perfectly be explained by the remaining variable.

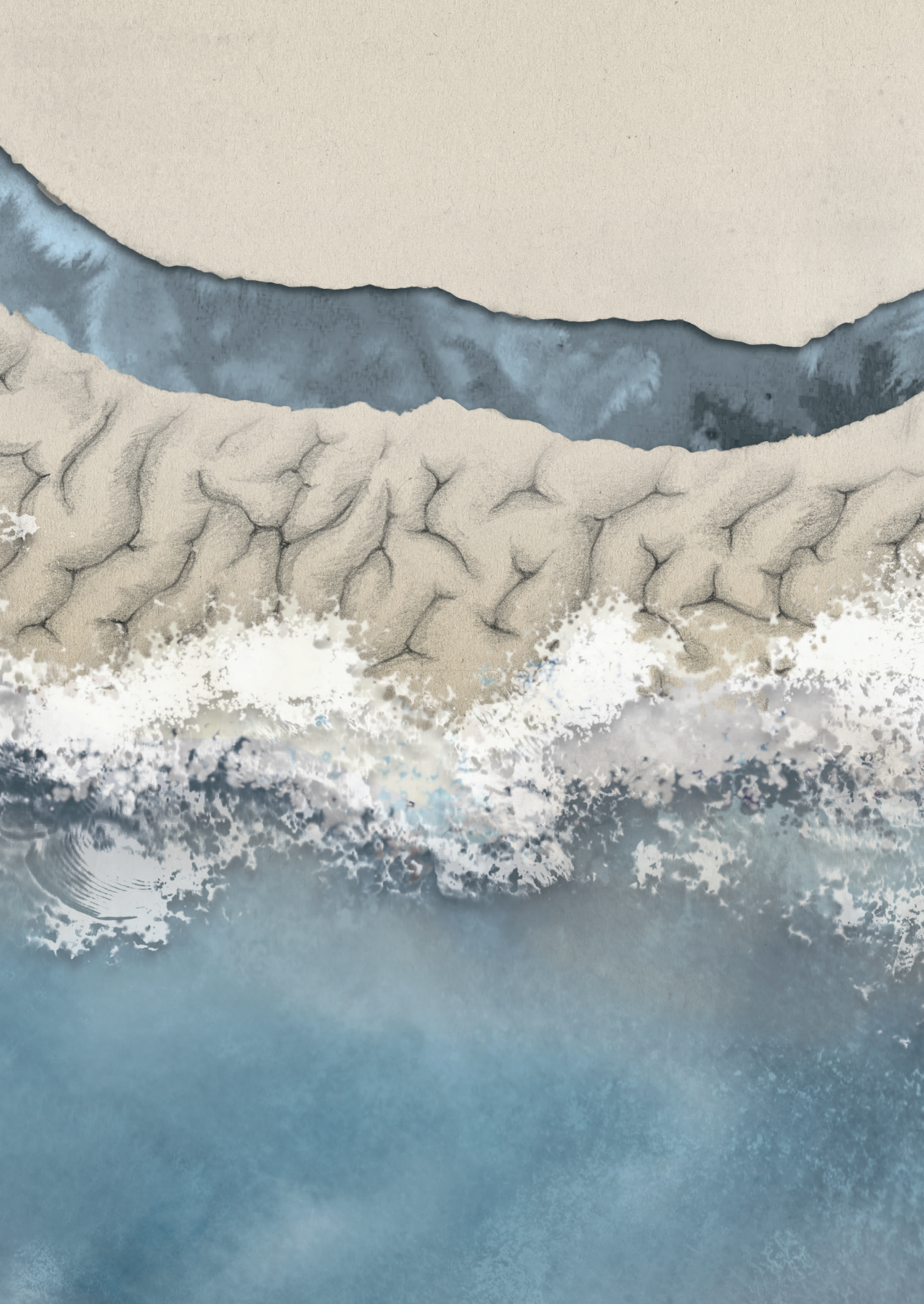
Supplemental table 6.2. Cohort characteristics and predictor clustering

	eTICI 2B, n=695	eTICI 2C, n=332	eTICI 3, n=886	Missing
Patient factors				
Age	69 (15)	69 (14)	70 (14)	0
Male sex	359 (52)	184 (55)	467 (53)	0
NIHSS on admission	15 [10, 19]	16 [11, 20]	16 [11, 20]	1.5
Ischemia in left hemisphere	382 (55)	177 (53)	460 (52)	0.6
Systolic blood pressure on admission	149 (25)	151 (25)	148 (24)	3.2
INR on admission	1.1 (0.4)	1.2 (0.4)	1.2 (0.4)	18
Glucose level on admission	7.4 (2.7)	7.4 (2.4)	7.4 (2.6)	11
Previous stroke	112 (16)	58 (18)	139 (16)	0.8
Atrial fibrillation	141 (21)	87 (26)	199 (23)	1.3
Hypertension	341 (51)	171 (52)	455 (52)	2.2
Diabetes mellitus	101 (15)	63 (19)	146 (17)	0.7
Pre-stroke mRS (%)				2.3
0 - No symptoms	457 (68)	229 (71)	594 (68)	
1 - Minor symptoms, no limitations	86 (13)	39 (12)	122 (14)	
2 - Slight disability, no help needed	45 (6.7)	30 (9.2)	60 (6.9)	
>2	88 (13)	27 (8.3)	92 (11)	
Prior antiplatelet therapy	204 (30)	112 (34)	285 (33)	1.4
Time from symptom onset to admission ER (intervention center)	133 [65, 186]	135 [60, 189]	130 [68, 181]	4.9
Imaging factors				
Occluded segment				3.8
Intracranial ICA	30 (4.5)	15 (4.7)	36 (4.2)	
ICA-T	127 (19)	73 (23)	166 (19)	

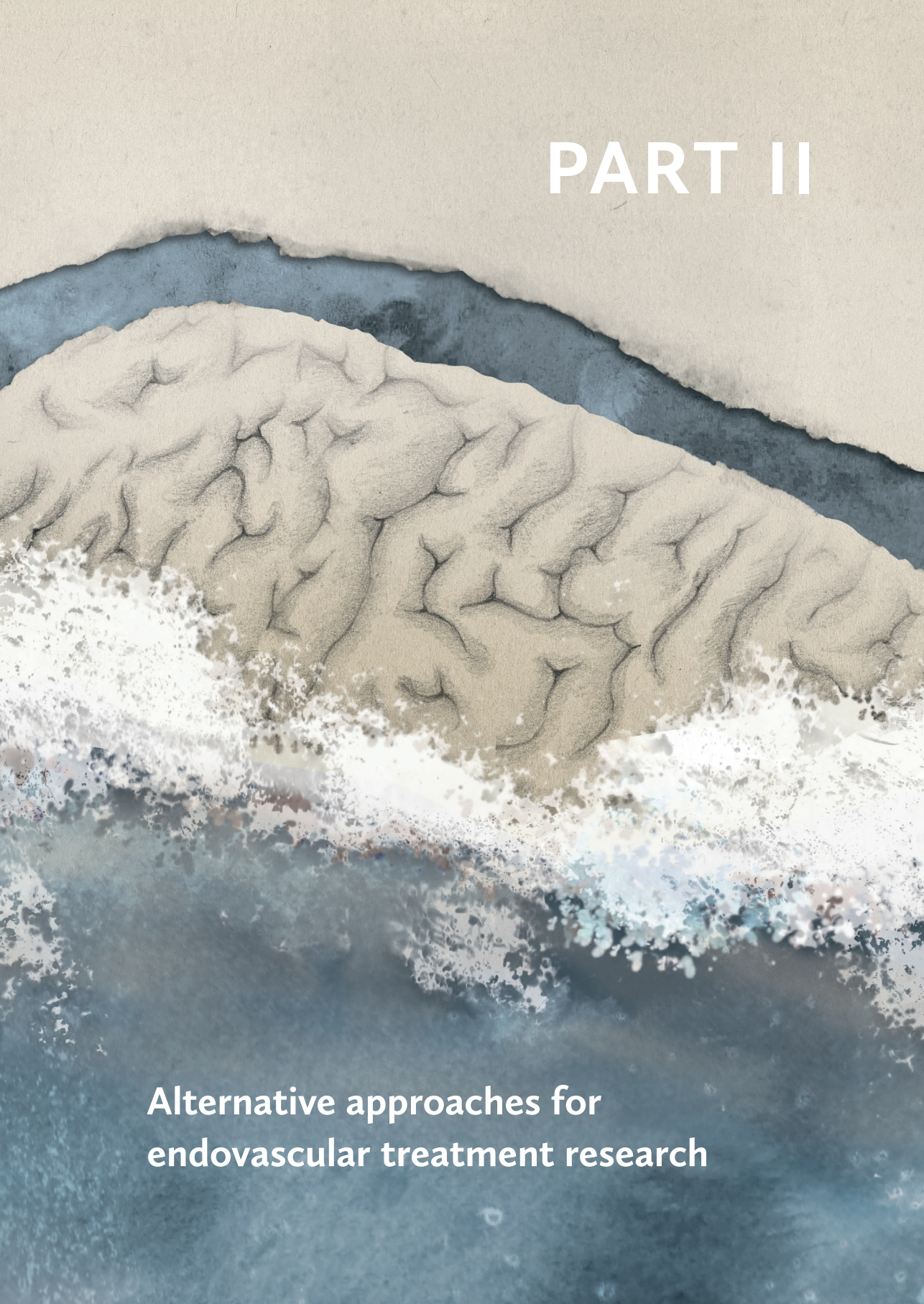
Supplemental table 6.2 Continued

	eTICI 2B, n=695	eTICI 2C, n=332	eTICI 3, n=886	Missing
M1	388 (58)	194 (61)	536 (63)	
M2	113 (17)	37 (12)	112 (13)	
Other (e.g., M3, ACA)	6 (0.9)	0 (0)	8 (0.9)	
ASPECTS	9 [7, 10]	9 [8, 10]	9 [8, 10]	2.9
Collaterals				6.1
Grade 0 - Absent collaterals	38 (5.8)	21 (6.7)	42 (5)	
Grade 1 - Occluded area filling <50%	241 (37)	115 (37)	293 (35)	
Grade 2 - Occluded area filling ≥50% but <100%	256 (39)	129 (41)	323 (39)	
Grade 3 - Occluded area filling 100%	115 (18)	47 (15)	176 (21)	
Treatment factors				
Treatment with intravenous alteplase	547 (78.9)	243 (73)	682 (77)	0.4
Time from admission ER (intervention center) to groin puncture	58 [35, 93]	60 [38, 86]	57 [35, 83]	8.9
Duration procedure	53 [35, 75]	56 [40, 79]	46 [32, 70]	7.4
General anesthetic management	165 (26)	115 (37)	248 (29)	5
Periprocedural heparin use	175 (25)	115 (35)	258 (29)	0
First pass success	180 (39)	128 (45)	411 (53)	20
*Post-procedural factors**				
New ischemic stroke	13 (1.9)	3 (0.9)	14 (1.6)	0
Symptomatic intracranial hemorrhage	34 (4.9)	16 (4.8)	38 (4.3)	0
Pneumonia	69 (9.9)	32 (9.6)	76 (8.6)	0

Summary: Cohort characteristics of patients with successful (eTICI≥2B) and with excellent reperfusion (eTICI≥2C). Continuous data are presented as mean (SD) for normal distributed data or as median [IQR] for skewed data. Categorical data are presented as numbers (%).
Abbreviations: ACA, anterior cerebral artery; APT, antiplatelet therapy; ASPECTS, Alberta stroke program early computed tomography score; DOAC, direct oral anticoagulant; ER, emergency room; eTICI, extended thrombolysis in cerebral infarction including a 2C grade; ICA (T), internal carotid artery (terminus); INR, international normalized ratio; M(*segment*), middle cerebral artery; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale
Captions: *For the model with the modified NIHSS at 24-48 hour as outcome, post-procedural factors in the model were restricted to occurrence within 24 hours, which was only recorded for sICH (so new ischemic stroke and pneumonia were excluded).



PART II



Alternative approaches for endovascular treatment research

CHAPTER 9

General discussion

The overall aim of this thesis was to increase the benefit of endovascular treatment for ischemic stroke by identifying risk factors for poor outcome and to improve the understanding of endovascular treatment effect.

Specific research questions were:
- *How do anesthetic and hemodynamic factors influence outcome after EVT?*
- *Which pre-procedural, procedural and post-procedural factors explain outcome variation after EVT?*
- *How to decide on efficient early study endpoints?*
- *What is the potential of synthetic patient cohorts for future EVT research?*

We found that patients treated under conscious sedation had worse outcomes compared to patients treated under local anesthesia (LA). If possible, LA should be the first line anesthetic approach during EVT. Blood pressure did not explain the differences in outcomes between anesthetic modalities. However, low and high blood pressure on hospital admission, low procedural blood pressure and low and high blood pressure in the first 6 hours after EVT, were independently associated with worse outcomes. Therefore, we advocate to avoid procedural hypotension and maintain normotensive blood pressure levels in the first six hours after EVT. The effect of EVT was not influenced by admission blood pressure, so EVT should not be delayed or withheld based on blood pressure. Proof of an effect of blood pressure management should be provided by randomized clinical trials.

Regarding outcome variation after EVT we found that baseline patient factors age, pre-stroke level of functional dependence and neurologic deficit, as well as the post-procedural adverse events symptomatic intracranial hemorrhage and pneumonia, were important predictors of poor functional outcome in successfully reperfused patients with ischemic stroke. Prevention of postprocedural adverse events has the greatest potential to further improve outcomes in these patients.

For optimal evaluation of the effect of a medical intervention, clinical trials should include endpoints that are both sensitive to detect treatment effects as well as be clinically relevant and important to the patient. Therefore, careful selection of a trial endpoint is important as it is expected to result in more efficient clinical trial design. Better understanding of stroke treatment effects is needed to optimally select alternative study endpoints, like infarct volume as an early imaging outcome for specific stroke interventions. A reduced infarct volume after ischemic stroke explained one third of the effect of EVT on early postprocedural neurologic deficit. Therefore, early imaging endpoints remains relevant to assess the differences in ischemic stroke treatment strategies.

There are several statistical methods to generate realistic cohorts of synthetic stroke patients. Synthetic stroke cohorts have the potential to further improve the design of stroke trials and accelerate data driven innovations.

Factors influencing outcome after endovascular treatment

In Chapter 2, we found that there was a beneficial effect of EVT on clinical outcome across the whole range of systolic blood pressure (SBP) on hospital admission, indicating that the effect of EVT is not modified by admission SBP. This is in line with the post-hoc analysis of the MR CLEAN, in which the number of patients with BP >185/110 mmHg treated with EVT was considered too low to recommend performing EVT in patients with admission BP above this threshold.[1,2] By pooling a large number of individual patient data of seven randomized controlled trials, we improved the statistical power to accurately assess the influence of admission SBP on effect of EVT. Based on our findings, the American Heart Association/American Stroke Association (AHA/ASA) guidelines for acute ischemic stroke management, recommending to maintain systolic blood pressure (SBP) below 185/110 mmHg prior to reperfusion therapy in patients eligible for endovascular thrombectomy (EVT), deserve revision.[3] Firstly, because these BP thresholds have been arbitrarily adopted from the early IVT trials.[4,5] Secondly, because this could lead to significant delay in start of EVT in patients with SBP levels above the threshold and as the effect of EVT strongly declines over time, this might be deleterious regarding patients' outcome after stroke.[6]

Further, we found that there is a wide variation in procedural modifiable factors such as anesthetic and hemodynamic management among EVT centers.[7] Conscious sedation (CS) is the most commonly used anesthetic modality during EVT in both Europe and the USA mainly because it is assumed to be the ideal compromise between general anesthesia (GA) and local anesthesia at the puncture site only.[7,8] Recently, multiple Dutch EVT centers started performing EVT routinely under local anesthesia at puncture site only (LA), instead of CS, with the idea to avoid treatment delays and anesthesia induced hypotension. We observed that in these centers LA was associated with better functional outcome compared to CS (Chapters 3 and 4). A potential explanation for the differences in outcome between these two anesthetic modalities, is anesthesia induced hypotension prior to reperfusion. Despite CS was associated with more hypotensive episodes during EVT compared to LA, procedural blood pressure did not modify the association between anesthesia type and outcome after EVT (Chapter 4). Nevertheless, the presence of hypotensive episodes during EVT was associated with worse outcomes irrespective of anesthetic modality, which was also observed by others.[9-11] This attributes to the idea that hypotension prior to reperfusion does negatively affect collateral flow to the hypoperfused penumbra that is highly depending on cerebral perfusion pressure.[12]

Currently, blood pressure targets during periprocedural and postprocedural management are mostly empirically chosen and rather fixed in any individual stroke patient. This practice finds its origin in the concept of cerebral autoregulation, which refers to a modulating mechanism that controls cerebral blood flow (CBF) during changes in cerebral perfusion pressure (CPP).[13,14] Yet, it is known that cerebral autoregulation might be impaired in patients with ischemic stroke and therefore, the current practice of applying a fixed blood pressure threshold in an individual

stroke patient is risky, and tighter blood pressure control might be mandatory.[14-16] The Society for Neuroscience in Anesthesiology and Critical Care addresses the importance of targeted anesthetic and hemodynamic management during EVT, but acknowledges the wide variation in anesthetic and hemodynamic management across EVT centers.[17,18] This emphasizes the need for stroke specific recommendations on periprocedural management and the value of multidisciplinary stroke care teams including the presence of an anesthesiologist with the objective to ensure rapid and safe EVT.[8]

In addition to the associations of pre- and intraprocedural hemodynamic parameters with outcomes after EVT, blood pressure control should not be restricted to the acute period of ischemic stroke. We observed strong associations of SBP in the subacute period after EVT with neurologic deficit, symptomatic intracranial hemorrhage (sICH) and functional outcome (Chapter 5). Again, this underlines the importance of patient monitoring and support in the first hours following EVT. Based on our findings, we advocate that ideally, normotensive SBP levels should be maintained during the first six hours following EVT. Due to the lack of evidence regarding optimal blood pressure targets for patients treated with EVT, the variation in hemodynamic management among EVT centers and the fact that blood pressure is modifiable, a randomized clinical trial is justified.[19] Ideally, different procedural and postprocedural blood pressure regimens should be compared with at least one arm with strict hemodynamic control avoiding hypotensive episodes during the procedure and avoiding both episodes of very high and low blood pressure in the first hours following EVT.

Several studies suggested that the association between postprocedural blood pressure and functional outcome is modified by reperfusion grade.[20,21] Although we did not observe this in our study, the effect of blood pressure on lesion volume and consequently clinical outcomes, might be different for patient with and without successful reperfusion following EVT. For example, higher SBP might be associated with hemorrhagic transformation given complete reperfusion.[22,23] On the other hand, maintaining hypertension might be of benefit in patients with unsuccessful reperfusion to optimize collateral blood flow and maintain cerebral perfusion pressure.[24-26] Therefore, future trials evaluating the effect of different postoperative BP regimes in patients treated with EVT might consider to stratify for reperfusion grade. The BP TARGET Trial was the first randomized controlled trial, designed to compare the effect of two SBP target regimes during the first 24 hours after EVT, on any intracranial hemorrhage (ICH), including sICH, in patients with successful reperfusion. In this trial, patients were randomized to either an intensive SBP target (100-129 mmHg) or a standard care systolic blood pressure target (130-185 mmHg).[27] Despite the associations between postprocedural blood pressure and outcomes described in observational studies, no effect of BP reduction on the occurrence of sICH was observed in this trial.[28] Given the prognostic value of SBP on outcomes observed in our study, the estimated treatment effect in BP TARGET Trial might be explained by lack of adherence to the blood pressure target and the relatively substantial unintended crossover, with each

group spending approximately a third of the 24 hour study duration in the SBP target range of the other treatment group. Another potential explanation might be that no other potentially more impactful dynamic blood pressure parameters were evaluated, such as blood pressure change (e.g. from baseline to end of the study) and blood pressure variability (e.g. standard deviation).[29]

To better understand the importance of modifiable factors such as anesthesia type and admission blood pressure as predictors for outcome after EVT, we quantified the relative importance of both modifiable and non-modifiable factors in predicting neurologic deficit and functional outcome (Chapter 6). Non-modifiable patient factors such as pre-stroke mRS, age and NIHSS at baseline were the most important predictors of 90-day functional outcome in patients with successful reperfusion based on an extensive multivariable analysis including baseline patient factors, imaging factors, treatment factors, and post-procedural factors. Besides, we observed that postprocedural adverse events, like sICH and pneumonia, were substantial contributors to poor outcome. This suggests that prevention of these post-procedural adverse events would further improve functional outcomes in patients with successful reperfusion. In this study, we did not observe that variation in outcome after successful reperfusion was clearly explained by modifiable factors such as anesthesia type and admission blood pressure. In this observational cohort, the influence of these parameters might be confounded by other factors, like stroke severity. This underpins the complexity of stroke as a disease with wide variations in the age at onset, etiology, comorbidities, and adequacy of collateral circulation. Several studies also focused on the question why some patients with successful reperfusion following EVT reach functional independence and others do not.[30-35] Both non-modifiable factors NIHSS on admission and age were the most important predictors of poor outcome in most of these studies. In line with this, poor outcomes despite reperfusion are suggested to be explained by a combination of unfavorable non-modifiable patient factors reflecting limited "brain reserve".[36] This suggested concept of "brain reserve" addresses the complexity of brain function in relation to the ischemic injury, as described in Chapter 7. None of these studies included postprocedural adverse events such as sICH and pneumonia in their models. Further in-depth evaluation of causal factors related to these post-procedural adverse events is warranted to be able to prevent them to improve patient outcomes.

Alternative approaches for endovascular treatment research

Follow-up infarct volume within 1 week after EVT explained 34% of the effect of EVT on early neurologic deficit according to the NIHSS at 1 week after randomization, which is a larger explained proportion compared to the 12% of the effect of EVT on functional outcome measured with mRS.[37,38] From a pathophysiological point of view, differences in clinical outcomes between patients treated with EVT versus without EVT are likely to be explained by differences in infarct volume. This seems very "simple" to assess; however, the concept of brain tissue viability is much more complex as

neurologic functioning could not be captured by one single dimension like infarct size, but is more likely to be an interplay between infarct size, location and 'brain reserve'.[39]

Since, imaging is the only way to objectively quantify tissue damage in alive patients, development of new imaging techniques for accurate, reliable assessment of brain tissue viability is of importance to further improve both stroke research and clinical practice. Improved understanding of the complex relation between brain tissue status and clinical outcomes could support the selection of optimal study outcomes to detect differences in targeted stroke interventions. Besides, more accurate quantification of brain tissue viability using imaging might further optimize the selection of patients for (adjunctive) therapeutic interventions (e.g. late treatment window, neuroprotective or antithrombotic agents). Five ongoing trials are evaluating if patients with low ASPECTS or large ischemic core benefit from EVT (TESLA (Thrombectomy for Emergent Salvage of Large Anterior Circulation Ischemic Stroke; NCT03805308), SELECT 2 (A Randomized Controlled Trial to Optimize Patient's Selection for Endovascular Treatment in Acute Ischemic Stroke; NCT03876457), TENSION (Efficacy and Safety of Thrombectomy in Stroke With Extended Lesion and Extended Time Window; NCT03094715), LASTE (LArge Stroke Therapy Evaluation; NCT03811769) and RESCUE-Japan LIMIT (Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy; NCT03702413)). These trials might provide further insight in the relation between imaging parameters at baseline and follow-up, as well as their impact on the effect of EVT. Although the potential benefit of more advanced imaging parameters to improve patient selection and detection of treatment effects, prediction should never be performed based on a single characteristic.[40] Therefore, we advocate to evaluate alternative imaging parameters in combination with other patient characteristics to improve prognostication and prediction in patients with ischemic stroke.

Another alternative method for future stroke research, is the use of synthetic data to facilitate the use of large cohorts of stroke patients for research. In other medical fields, such as cardiology, oncology and critical care medicine, there are several examples of studies using synthetic data cohorts to assist in shaping research hypothesis and accessing estimated analyses.[41-43] In chapter 8, we introduced the concept of synthetic data cohorts for stroke research and discussed potential applications. We provided an overview of 3 statistical methods, including their performance, that could be used to generate realistic cohorts of ischemic stroke patients eligible for EVT. There are more advanced methods to generate synthetic cohorts of patients, like for example deep learning algorithms, compared to the methods evaluated in our study.[44] However, the purpose of this chapter was to introduce this relatively new data concept to stroke researchers. Future studies may assess the added value of more advanced statistical methods. However, one of the challenges of the development and implementation of synthetic data cohorts is assessing the performance of the simulation models to generate the synthetic cohorts.[45] Data privacy concerns seems to be one of the biggest roadblocks on the path to innovation and more advanced

artificially intelligence applications in stroke research, as well as healthcare in general.[46] Realistic, large synthetic cohorts of stroke patients could assist researchers and clinicians in answering prognostic and predictive questions related to this disease. For now, it is too early to use synthetic stroke cohorts to evaluate stroke treatments, but recent studies suggested the potential use of synthetic datasets in early phase clinical trials to generate groups of control patients that mimic the patients receiving active therapy.[47,48] To guarantee the quality, efficient implementation and adequate usage of synthetic patients' cohorts in stroke research, close collaboration between stroke treating physicians, researchers, mathematicians, and computer scientists is warranted.

Limitations

In the first part of this thesis, we assessed the influence of modifiable periprocedural factors on outcomes after EVT in the MR CLEAN Registry, one of the largest cohorts of consecutive patients treated with EVT. Although this cohort is representative of ischemic stroke patients treated in routine clinical practice in the Netherlands, causality cannot be ascribed to these periprocedural factors, because of the observational nature of the studies. Therefore, randomized trials investigating the causal relation of periprocedural hemodynamic and anesthetic management remain warranted. Yet, despite performing randomized clinical trials, several questions regarding the influence of these modifiable factors on outcomes will remain due to restrictive inclusion- and exclusion criteria and strict trial protocols. Therefore, well-designed observational studies can serve as complementary type of research to ensure that the results of randomized clinical trials translate into actual benefits in the general stroke population.[49]

Considering our findings presented in Part II, infarct volume could be of interest as an early imaging endpoint to assess differences in stroke treatment strategies. However, therapeutic intervention induced changes in an early imaging endpoint, like infarct volume, need to be reflected in changes in clinical outcomes. At present, no imaging endpoint is able to achieve this standard. Imaging endpoints that are '*prognostic*' are not necessarily good surrogate endpoints in terms of assessing the effects of stroke treatment. However, imaging endpoints do increase our understanding of stroke treatment effect. More advanced imaging techniques to quantify brain tissue status are needed to better capture the complexity of infarcted tissue and selective neuronal loss.

Finally, several statistical methods to generate synthetic cohorts of patients have been described in literature and consensus on the optimal method is lacking. To our knowledge, we are the first who developed realistic synthetic cohorts of stroke patients based on different statistical methods. Nevertheless, no method currently exists to develop and validate realism in synthetic data in a unified way.

Recommendations for clinical practice

Endovascular treatment should never be withheld or delayed from an individual patient solely based on admission SBP considering the beneficial effect of EVT across the range of SBP levels.

Furthermore, we recommend that local anesthesia at the puncture site only should be the first line anesthetic modality, since it is fast and provides the ability to examine patients during the procedure to help guide treatment decisions, including when to stop. Obviously, for some patient conditions (e.g. respiratory distress, cardio-respiratory compromise or extreme agitation), general anesthesia is required. Procedural anesthetic management should no longer depend solely on individual or institutional preferences. Despite, LA is associated with lower risk of procedural hypotension, blood pressure variability during EVT is not restricted to CS or GA. Therefore, we suggest that anesthetic support during all EVT procedures is needed to guarantee adequate cerebral blood flow prior to reperfusion. Since patients with ischemic stroke present with a wide variation in existing cardiovascular comorbidity, hypertension, associated antihypertensive treatment and adequacy of collateral circulation, a one-size-fits-all approach for periprocedural anesthetic and hemodynamic management seems inadequate. Until results from randomized clinical trials on optimal periprocedural anesthetic modality and hemodynamic targets come available, we suggest that anesthesiologists caring for patients with ischemic stroke, who are vulnerable to changes in blood pressure, should systematically monitor vital parameters (i.e. heart rate, blood pressure, oxygen saturation) during all procedures. Furthermore, we suggest to adhere to strict blood pressure regimes, avoiding hypotensive episodes with admission blood pressure as the reference, as these were associated with worse functional outcomes irrespective of anesthetic modality.

Recommendations for research

Based on our main findings and their interpretation, several specific recommendations on future stroke research and clinical practice can be summarized.

Focusing solely on CS and GA does not do justice to a simple and potentially safer anesthetic strategy: local anesthesia at the groin puncture site only (LA). Therefore, performing a randomized trial with a separate LA arm seems justified. Furthermore, randomized controlled trials are needed to assess the effect of anesthetic modality on the risk of pneumonia due to aspiration and the role of blood pressure in the early hours after EVT on the risk of intracranial hemorrhage, in addition to their effects on functional outcome.

Finally, the prognostic value of more sophisticated imaging techniques (e.g. functional MRI, perfusion imaging) to quantify brain tissue lesion after reperfusion therapy in combination with patient factors, is needed to increase our understanding of the relation between early imaging and clinical outcomes and endovascular treatment effects.

Overall conclusions

The aim of this thesis was to identify pre-, peri- and postprocedural factors associated with outcomes after EVT and to evaluate alternative approaches for future EVT research. Optimization of periprocedural anesthetic and hemodynamic management, and prevention of post-procedural adverse events could be targets to further improve outcomes in patients with ischemic stroke. Accurate quantification of brain tissue viability could be an imaging outcome for specific stroke treatment evaluations. Finally, synthetic stroke cohorts are a new method to further improve stroke research.

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Appendices

Summary

Despite the large treatment benefit of endovascular treatment for patients with ischemic stroke due to a proximal occlusion in the anterior circulation, still a large proportion of patients do not recover to functional independence. Optimizing periprocedural anesthetic and hemodynamic management might further improve patient outcomes. Furthermore, stroke research and eventually patient outcomes could be improved by optimizing selection of endpoints for trials evaluating reperfusion therapies.

The overall aim of this thesis was to increase the benefit from endovascular treatment (EVT) for ischemic stroke by identifying risk factors for poor outcome, improve the understanding of endovascular treatment effect and evaluate alternative approaches for EVT research.

The specific research questions were:

1. Which factors influence outcome after EVT for ischemic stroke (Part I)?
1a. How do anesthetic and hemodynamic factors influence outcome after EVT?
1b. Which periprocedural factors explain outcome variation after EVT?

2. What are future directions for EVT research (Part II)?
2a. How to decide on efficient early (trial) endpoints?
2b. What is the potential of synthetic patient cohorts for future EVT research?

Part I Factors influencing outcome after endovascular treatment

In the first part of this thesis, we focused on identifying factors that influence outcome after EVT and we aimed to determine most optimal periprocedural anesthetic and hemodynamic management, both facilitators of perfusion.

Despite current guidelines for ischemic stroke treatment recommend strict thresholds for periprocedural blood pressure in patients eligible for EVT, studies evaluating the influence of blood pressure on the effect of EVT are sparse. In **Chapter 2**, we studied the influence of admission systolic blood pressure on functional outcome and on the effect of EVT using pooled individualized patient data from 7 randomized controlled trials on EVT. We found no interaction between blood pressure and effect of EVT for both clinical and imaging outcomes. This indicates that high or low blood pressure on hospital admission is not an argument to withhold or delay EVT for ischemic stroke as blood pressure does not negate the beneficial effect of EVT.
The implementation of EVT as a standard therapy for ischemic stroke due to large vessel occlusion within 6 hours after onset, dramatically changed the organization of stroke care pathways, including the demand for anesthesia resources. There is a broad variation in preferred anesthetic technique during EVT and there is no consensus on

optimal anesthetic approach in patients undergoing EVT. In **Chapter 3**, we evaluated the effect of conscious sedation on functional outcome and complication rates after EVT compared to the use of local anesthesia at the puncture site only. We found that conscious sedation was associated worse functional outcome and higher mortality rates compared to local anesthesia. Furthermore, conscious sedation did not reduce the duration of intervention or interventional-related complications. Therefore, we advocate local anesthesia should be the first-line anesthetic strategy during EVT when considered safe.

Administration of anesthetic agents has been associated with hemodynamic changes. Therefore, we evaluated if differences in outcome between patients treated under conscious sedation and local anesthesia could be explained by differences in periprocedural blood pressure course in **Chapter 4**. We found that large blood pressure drops were associated with worse functional outcome, however, blood pressure drops do not explain the worse outcomes in patients treated under conscious sedation. For this reason, it remains important to strictly monitor blood pressure and avoid hypotension during EVT, irrespective of anesthetic modality.

Since it is conceivable that optimizing cerebral perfusion via blood pressure is not restricted to the EVT procedure alone, we evaluated the associations between systolic blood pressure in the first 6 hours following EVT and functional outcome as well as symptomatic intracranial hemorrhage in **Chapter 5**. We found that higher maximum systolic blood pressure in the first 6 hours following EVT is associated with worse functional outcome and a higher rate of symptomatic intracranial hemorrhage. Minimum systolic blood pressure levels below and above 120-125 mmHg are associated with worse outcomes. A randomized trial to assess whether modifying blood pressure results in better outcomes after EVT for ischemic stroke seems justified.

To better understand the mechanisms behind poor outcome despite successful reperfusion, we quantified the importance of several modifiable and non-modifiable factors associated with poor outcome in successfully reperfused patients in **Chapter 6**. We found that baseline patient factors and post-procedural adverse events are the most important predictors of poor functional outcome. This indicates that prevention of post-procedural adverse events is important to further improve outcomes.

Part II Alternative approaches to evaluate ischemic stroke treatment effects

In the second part of this thesis, we studied alternative approaches for EVT related research. To accelerate the evaluation of effects of new stroke treatments, alternative trial outcomes could improve the efficiency of stroke trials. In **Chapter 7**, we evaluated the role of follow-up infarct volume on effect of EVT on early neurologic deficit. Larger follow-up infarct volume was associated with larger neurological deficits after treatment. A reduced infarct volume after EVT explains one third of treatment benefit in terms of neurological deficit. This indicates that the concept of brain tissue viability

is much more complex as neurologic functioning could not be captured by one single dimension like infarct size.

In **Chapter 8,** we introduced the concept of synthetic data cohorts for stroke research and discussed potential applications. We provided an overview of 3 statistical methods, including their performance, that could be used to generate realistic cohorts of ischemic stroke patients eligible for EVT. Realistic synthetic cohorts of stroke patients might enable broader access to health care data, while ensuring patients' privacy. We demonstrated that all three statistical methods generate realistic cohorts of synthetic stroke patients. Potential applications are development and validation of prediction tools, decision model analysis, and in-silico trials.

Closing message

Despite the overall treatment effect of EVT is highly effective, there are many targets to further improve patient outcomes. In this thesis, we identified factors influencing outcome after EVT and evaluated alternative approaches for study design to accelerate research on new therapeutic strategies.

Based on our findings, we recommend to perform EVT under local anesthesia instead of conscious sedation if this is considered safe. Besides, large drops in periprocedural blood pressure should be avoided as these are associated with worse outcomes. Blood pressure on hospital admission is not an argument to withhold or delay EVT for ischemic stroke as blood pressure does not negate the effect of EVT. Furthermore, prevention of post-procedural adverse events has a great potential to further improve outcomes in successfully reperfused patients.

A reduced infarct volume after EVT explains one third of treatment benefit in terms of neurological deficit. Development of new imaging techniques for accurate, reliable assessment of brain tissue viability is of importance to further improve both stroke research and clinical practice. Another future direction for EVT research is the use of cohorts of synthetic stroke patients for the development and validation of prediction tools, decision model analysis, and in-silico trials, as we demonstrated statistical methods to generate realistic cohorts of synthetic stroke patients.

Samenvatting

Ondanks het grote behandelvoordeel van de endovasculaire behandeling voor patiënten met een ischemische beroerte ten gevolge van een afsluiting van een groter bloedvat in de voorste circulatie, herstelt een groot deel van de patiënten nog steeds niet tot zelfstandig functioneren. Het optimaliseren van periprocedureel anesthesiologisch en hemodynamisch management zou de uitkomsten na een ischemische beroerte verder kunnen verbeteren. Daarnaast kan onderzoek naar de behandeling van het herseninfarct worden verbeterd door de selectie van eindpunten van studies te optimaliseren.

Het doel van dit proefschrift was om de effectiviteit van de endovasculaire behandeling voor ischemische beroerte te vergroten door risicofactoren voor een slechte uitkomst te identificeren, het behandeleffect beter te begrijpen en alternatieve methoden voor onderzoek naar de verbetering van de endovasculaire behandeling te evalueren.

De specifieke onderzoeksvragen waren:

1. Welke factoren beïnvloeden de uitkomst na endovasculaire behandeling voor een ischemische beroerte (Deel I)?

1a. *Hoe beïnvloeden anesthesiologische en hemodynamische factoren de uitkomst na endovasculaire behandeling?*

1b. Welke periprocedurele factoren verklaren variatie in uitkomsten na endovasculaire behandeling?

2. Wat zijn toekomstige richtingen voor onderzoek gericht op de verbetering van de endovasculaire behandeling (Deel II)?

2a. *Hoe te beslissen over een efficiënt vroegtijdig studie eindpunt?*

2b. Wat is het potentieel van synthetische patiëntcohorten voor toekomstig onderzoek gericht op de endovasculaire behandeling?

Deel I Factoren geassocieerd met uitkomsten na endovasculaire behandeling

In het eerste deel van dit proefschrift hebben we ons gericht op het identificeren van factoren die de uitkomst na endovasculaire behandeling beïnvloeden en hebben we verschillende anesthesiologische en hemodynamische procedures, beide facilitators van perfusie, geëvalueerd.

Ondanks dat de huidige richtlijnen voor de behandeling van ischemische beroerte strikte grenzen aanbevelen voor periprocedurele bloeddruk bij patiënten die in aanmerking komen voor endovasculaire behandeling, zijn studies die de invloed van bloeddruk op het effect van endovasculaire behandeling evalueren schaars. In

Hoofdstuk 2 hebben we de invloed van de systolische bloeddruk bij ziekenhuisopname op het effect van endovasculaire behandeling bestudeerd. We vonden geen interactie tussen bloeddruk en effect van de endovasculaire behandeling voor zowel klinische als beeldvormende uitkomsten. Dit geeft aan dat zowel hoge als lage bloeddruk bij ziekenhuisopname geen reden zijn om endovasculaire behandeling voor ischemische beroerte uit te stellen, aangezien bloeddruk het gunstige effect van endovasculaire behandeling niet tenietdoet.

De implementatie van de endovasculaire behandeling als standaardbehandeling voor ischemische beroerte ten gevolge van een afsluiting van een groter bloedvat, veranderde de organisatie van zorgpaden voor het herseninfarct drastisch, inclusief de vraag naar periprocedurele anesthesiologische ondersteuning. Er is een brede variatie in de gewenste anesthesiologische ondersteuning tijdens de endovasculaire behandeling en er is geen consensus over de optimale vorm van anesthesie voor patiënten die een endovasculaire behandeling ondergaan. In **Hoofdstuk 3** hebben we de invloed van sedatie (roesje) op klinische uitkomsten en het risico op complicaties na endovasculaire behandeling vergeleken met het gebruik van lokale verdoving ter plaatste van de punctieplaats. We vonden dat sedatie geassocieerd was met een slechtere uitkomst en hogere mortaliteit in vergelijking met lokale verdoving. Bovendien was er geen reductie van de duur van de interventie of het aantal interventie gerelateerde complicaties in patiënten behandeld onder sedatie. Daarom adviseren we lokale verdoving als primaire vorm anesthesiologisch management tijdens EVT, wanneer dit als veilig kan worden beschouwd.

Toediening van anesthetica is in verband gebracht met hemodynamische veranderingen. Daarom hebben we in **Hoofdstuk 4** onderzocht of de verschillen in uitkomst tussen patiënten behandeld onder sedatie en lokale verdoving verklaard konden worden door verschillen in periprocedureel bloeddrukverloop. We vonden dat grote bloeddrukdalingen geassocieerd waren met slechtere uitkomsten, maar bloeddrukdalingen verklaarde niet de slechtere uitkomsten bij patiënten die onder sedatie werden behandeld. Om deze reden blijft het belangrijk om bloeddruk strikt te monitoren en hypotensie tijdens de endovasculaire behandeling te vermijden, ongeacht de toegepaste anesthesietechniek.

In **Hoofdstuk 5** hebben we de associaties tussen systolische bloeddruk in de eerste 6 uur na de endovasculaire behandeling en klinische uitkomsten evenals het risico op symptomatische intracraniële bloeding geëvalueerd. We vonden dat een hogere maximale systolische bloeddruk in de eerste 6 uur geassocieerd is met een slechtere klinische uitkomst en een hoger percentage symptomatische intracraniële bloedingen. Minimale systolische bloeddrukniveaus onder en boven de 120-125 mmHg worden geassocieerd met slechtere uitkomsten. Een gerandomiseerde studie, waarin het effect van verschillende periprocedurele bloeddruk regimes op uitkomsten na endovasculaire behandeling voor een ischemische beroerte wordt onderzocht, lijkt gerechtvaardigd.

In **Hoofdstuk 6** hebben we het belang van verschillende modificeerbare en niet-modificeerbare factoren die geassocieerd zijn met een slechte uitkomst binnen

patiënten met succesvolle reperfusie gekwantificeerd. We vonden dat patiënt karakteristieken en post-procedurele bijwerkingen de belangrijkste voorspellers waren van een slechte uitkomst. Het voorkomen van post-procedurele bijwerkingen lijkt daarom een belangrijke stap ter verbetering van de uitkomsten.

Deel II Alternatieve methoden voor de evaluatie van behandelingen voor het herseninfarct.

In het tweede deel van dit proefschrift hebben we alternatieve methoden voor onderzoek naar de endovasculaire behandeling bestudeerd. Om de evaluatie van effecten van nieuwe behandelingen voor het herseninfarct te versnellen, zouden alternatieve studie eindpunten de efficiëntie van onderzoek kunnen vergoten. In **Hoofdstuk 7** evalueerden we de rol van het follow-up infarctvolume op het effect van de endovasculaire behandeling op vroegtijdige neurologische uitval. Een groter follow-up infarctvolume was geassocieerd met ernstigere neurologische uitval na de behandeling. Een verminderd infarctvolume na endovasculaire behandeling verklaart een derde van het behandeleffect in termen van neurologische uitval. Dit geeft aan dat het concept van levensvatbaarheid van het hersenweefsel complex is en dat neurologisch functioneren dus niet kan worden gevangen in één enkele parameter zoals de grootte van een infarct.

In **Hoofdstuk 8** introduceerden we het concept van synthetische datacohorten voor onderzoek naar het herseninfarct en bespraken we potentiële toepassingen. We hebben een overzicht gegeven van 3 statistische methoden die kunnen worden gebruikt om realistische cohorten van patiënten met een ischemische beroerte te genereren die in aanmerking komen voor endovasculaire behandeling. Realistische synthetische cohorten van patiënten met een herseninfarct kunnen de toegang tot grote hoeveelheden data vergemakkelijken waarbij de privacy van patiënten wordt gewaarborgd. Middels alle drie de statistische methoden was het mogelijk om realistische cohorten van synthetische patiënten met een ischemische beroerte te genereren. Mogelijke toepassingen zijn de ontwikkeling en validatie van predictiemodellen, beslismodel analyses en in-silico studies.

Conclusies

Ondanks dat de endovasculaire behandeling zeer effectief is, zijn er meerdere mogelijkheden om de uitkomsten voor de patiënt verder te verbeteren. In dit proefschrift identificeerden we factoren die uitkomsten na endovasculaire behandeling beïnvloeden en evalueerden we alternatieve methoden voor onderzoek naar de behandeling van het herseninfarct om de evaluatie van effecten van nieuwe therapeutische strategieën te optimaliseren.

Op basis van onze bevindingen raden we aan om EVT uit te voeren onder lokale verdoving in plaats van sedatie indien dit veilig wordt geacht. Bovendien moeten grote

dalingen van de periprocedurele bloeddruk worden vermeden, omdat deze gepaard gaan met slechtere uitkomsten. Bloeddrukwaarden ten tijde van ziekenhuisopname zijn geen argument om een endovasculaire behandeling voor een ischemische beroerte uit te stellen of te onthouden, aangezien bloeddruk het effect van de endovasculaire behandeling niet tenietdoet. Het voorkomen van post-procedurele bijwerkingen heeft een groot potentieel om de uitkomsten voor patiënten met succesvolle reperfusie verder te verbeteren.

Een verminderd infarctvolume na endovasculaire behandeling verklaart een derde van het behandeleffect in termen van neurologische uitval. De ontwikkeling van nieuwe beeldvormende technieken voor nauwkeurige, betrouwbare beoordeling van de status van het hersenweefsel is van belang voor de optimalisatie van zowel het onderzoek als de behandeling van het herseninfarct. Synthetische cohorten van patiënten met een herseninfarct kunnen in de toekomst een bijdrage leveren aan de ontwikkeling en validatie van predictiemodellen, beslismodel analyses en in-silico-studies, gezien de mogelijkheid tot het genereren van realistische synthetische cohorten van patiënten middels statistische methoden.

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Imaging assessment committee

Charles B.L.M. Majoie[3] (chair); Wim H. van Zwam[6]; Aad van der Lugt[2]; Geert J. Lycklama à Nijeholt[13]; Marianne A.A. van Walderveen[10]; Joseph C.J. Bot[37]; Henk A. Marquering[39]; Ludo F. Beenen[3]; Marieke E.S. Sprengers[3]; Sjoerd F.M. Jenniskens[27]; René van den Berg[3]; Olvert A. Berkhemer[1,3]; Albert J. Yoo[40].

Outcome assessment committee

Yvo B.W.E.M. Roos[4] (chair); Peter J. Koudstaal[1]; Jelis Boiten[14]; Ewoud J. van Dijk[19].

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

Trial statisticians
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INSIST Consortium
WP1 Management
Charles Majoie[1], Henk Marquering[6], Ed van Bavel[14], Alfons Hoekstra[15]

WP2 Population and morphology models
Diederik Dippel[2], Hester Lingsma[4], Aad van der Lugt[3], Noor Samuels[2,3,4], Nikki Boodt[2,3,4], Heleen van Beusekom[17], Yvo Roos[1], Simon de Meyer[5], Senna Staessens[5],

Sarah Vandelanotte[5], Henk Marquering[1,6], Praneeta Konduri[1,6], Nerea Arrarte Terreros[1,6], Charles Majoie[1]

WP3 In silico models for thrombosis and thrombolysis
Bastien Chopard[7], Franck Raynaud[7], Remy Petkantchin[7], Mikhail Panteleev[11], Alexey Shibeko[11], Karim Zouaoui Boudjeltia[16], Vanessa Blanc-Guillemaud[8]

WP4 In silico models for thrombectomy
Francesco Migliavacca[9], Gabriele Dubini[9], Giulia Luraghi[9], Jose Felix Rodriguez Matas[9], Sara Bridio[9], Patrick Mc Garry[10], Michael Gilvarry[12], Ray McCarthy[12], Kevin Moerman[10], Behrooz Fereidoonnezhad[10], Anushree Dwivedi[12], Sharon Duffy[12]

WP5 In silico models of perfusion defects and tissue damage
Stephen Payne[13], Tamas Jozsa[13], Wahbi El-Bouri[13], Ed van Bavel[14], Sissy Georgakopoulou[14], Alfons Hoekstra[15], Raymond Padmos[15]

WP6 Integration and validation
Alfons Hoekstra[15], Victor Azizi[15], Claire Miller[15], Max van der Kolk[15], Raymond Padmos[15]

WP7 Dissemination and sustainability
Henk Marquering[6]

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PhD Portfolio

Name PhD student: Noor Samuels
PhD period: Feb 2018- Feb 2021
Erasmus MC Department: Radiology and Nuclear Medicine, Neurology, Public Health

Promotor(s): Prof. dr. A. van der Lugt and Prof. dr. D.W.J. Dippel
Supervisor: Prof. dr. H.F. Lingsma

1. PhD training		
	Year	**Workload**
		(Hours/ECTS)
General research skills		
Master's degree in Clinical Epidemiology	2013-2017	
- Erasmus Summer Programme		
- Principles of Research in Medicine		0.7
- Social Epidemiology		0.7
- Methods of Clinical Research		0.7
- Clinical Decision Analysis		0.7
- Markers and Prognostic Research		0.7
- The Practice of Epidemiologic Analysis		0.7
- Core curriculum		
- Study Design		4.3
- Biostatistical Methods I: Basic Principles		5.7
- Biostatistical Methods II: Classical Regression Models		4.3
- Clinical Epidemiology		5.7
- Methodologic Topics in Epidemiologic Research		1.4
- Scientific Writing in English for Publication		2.0
- Pharmaco-epidemiology and Drug Safety		1.9
- Advanced Topics in Clinical Trials		1.9
- Advanced Analysis of Prognosis Studies		0.9
- Principles of Epidemiologic Data-analysis		0.7

- John Hopkins University (USA), Graduate Summer Institute of Epidemiology and Biostatistics		4.2
- Design and Conduct Clinical Trials		
- Epidemiology in Evidence-based Policy		
- Topics in Management of Clinical Trials		
- Clinical Trials: issues and controversies		
- Systematic reviews and meta-analyses		
- Elective courses		
- Planning and Evaluation of Screening		1.4
- Advanced Topics in Decision-making in Medicine		1.9
- Intervention Research and Clinical Trials		0.9
- Diagnostic Research		0.9
- Prognosis Research		0.9
- Maternal and Child Health		0.9
- From Problem to Solution in Public Health		3.0
- Research Seminars 1 & 2		3.0
- Women's Health		0.9
- Preventing Failed Interventions in Behavorial Research		1.4
- Clinical Research Introduction		2.8
- Cardiovascular Epidemiology		0.9
- History of Epidemiologic Ideas		0.7
- Health Economics		0.7
- Case-control Studies		0.7
- Pharmaco-epidemiology		0.7
- COEUR		
- Sex and gender in Cardiovascular Research	2018	0.5
- Aneurysmal Disease	2018	0.5
- Experimental models of stroke	2018	0.5
- Imaging for Ischemic Heart and Brain Disease	2018	0.5
- Vascular Clinical Epidemiology	2019	0.4

Other		
- Research Integrity	2018	0.3
- CPO course	2018	0.3
- BROK	2020	1.5
Presentations at national and international conferences		
- Nederlands Neurovasculair genootschap (oral presentation)	2018	1.0
- Radiologendagen, Hilversum (oral presentation)	2018	1.0
- European Stroke Organisation Congress, Gothenburg (poster presentation)	2018	1.0
- ESMINT, Nice	2018	1.0
- ESNR Annual meeting, Rotterdam (oral presentation)	2018	1.0
- European Stroke Organisation Congress, Milan (2 oral presentations)	2019	2.0
- WFITN, Naples (oral presentation)	2019	1.0
- European Radiology Congress, Vienna (virtual, oral presentation)	2020	1.0
- European Stroke Organisation Congress, Vienna (virtual, 2 oral presentations)	2020	2.0
2. Teaching activities		
Supervising Bachelor/Master theses		
- Assisted dr. T. van Walsum with supervising 4 Bachelor students from the TU Delft/EMC (Bachelor Thesis, Technical Medicine). Topic: Quantification of bloodflow on DSA.	2018	2.0
- Supervising C.A.L. van den Berg (Master thesis, Medicine)	2018-2019	3.0
Total ECTS		79.4

About the author

Noor Samuels was born in Roosendaal, the Netherlands, on July 9th 1990. After graduating from secondary school Norbertus College in Roosendaal, she started studying Medicine at Erasmus University Medical Center Rotterdam in 2010. After obtaining her Bachelor in Medicine in 2013, she enrolled in the research master Health Sciences (Clinical Epidemiology) from NIHES. She started a research project at the neonatal intensive care unit about necrotizing enterocolitis. Her passion for research was further developed there. During her internships she became interested in radiology and started a research project at the radiology department under supervision of neurointerventional radiologists dr. van Es and dr. Emmer. After finishing her research master cum laude, she simultaneously obtained her Medical Degree in 2017. She started working as a surgical resident not in training at Daniel den Hoed Hospital.

In 2018 she got the opportunity to start as a PhD-candidate at the department of Radiology under supervision of prof. dr. Aad van der Lugt, prof. dr. Diederik Dippel and prof. dr. Hester Lingsma. She worked mainly on a large European project about in silico medicine for acute treatment of ischemic stroke. She presented her work at several (inter)national conferences.

In her spare time, Noor likes to kitesurf and to ride her horse. Noor is currently working as a Radiology resident at Albert Schweitzer Hospital and continuous her research work at the Department of Radiology and Nuclear Medicine at the Erasmus MC.