IMPROVING OUTCOMES BY BETTER REPERFUSION AFTER ENDOVASCULAR TREATMENT FOR ACUTE ISCHEMIC STROKE

ROB VAN DE GRAAF

Improving outcomes by better reperfusion after endovascular treatment for acute ischemic stroke

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Verbeteren van uitkomsten door betere reperfusie na endovasculaire behandeling van patiënten met een acuut herseninfarct.

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Contents

CHAPTER I

General introduction

Ischemic Stroke – the problem

Annually, approximately 32,000 patients suffer from an ischemic stroke in the Netherlands.[1] Ischemic stroke occurs mainly in situations when the regional blood supply by an artery is insufficient, most often due to blockage of the artery by a clot. In about 10% of patients with ischemic stroke, accounting for ±4,000 patients in the Netherlands yearly, symptoms are caused by an intracranial occlusion of a large supplying artery in the anterior circulation (i.e., intracranial carotid artery [ICA], middle cerebral artery [MCA], anterior cerebral artery [ACA]). In this group of patients, the combined 3-month risk of death or permanent disability is about 75% when not treated.[2]

Over the past decades the main evidence-based improvements in treatment, resulting in reduction of death and dependency after ischemic stroke, were 1) antithrombotic agents (before 90's), 2) intravenous recombinant tissue plasminogen activator [rtPA] (early 90's) and more recent, 3) endovascular treatment [EVT] (since 2015) for large vessel occlusion ischemic stroke. [3-7] The main goal of rtPA and EVT is facilitation of early clot lysis or mechanical clot removal resulting in preservation of brain tissue and thus physiological function.

Every year, over 1500 patients in the Netherlands presenting with an occlusion of a major supplying artery receive EVT with or without prior rtPA, reducing the percentage of patients being dead or dependent at 90 days from 75% without EVT to 54% with EVT.[2] This accounts for approximately 375 patients being saved from death or being dependent in daily life in the Netherlands annually. Despite the substantial beneficial effect of current EVT on patient functional outcomes, still 54% of patients do not recover to functional independence.

Macrovascular and microvascular reperfusion

Procedural success of EVT strategies is scored using visual evaluation by digital subtraction angiography (DSA), which displays the vessel status at the clot location and the distal vessel bed. Current evaluation using these techniques is restricted to the larger vessels with a spatial resolution of >200 micrometer in diameter.[8] The smallest vessels remain thus hidden for evaluation after EVT. Although macrovascular distal vessel bed reperfusion may intuitively be linked to reperfusion in the microvasculature (diameter <200 micrometer) the underlying pathophysiology of reperfusion in these two vessel beds is different. Animal studies demonstrated that successful reperfusion not necessarily means microvascular reperfusion. For example, it has been demonstrated already more than 50 years ago that restoration of blood flow after 5 minutes of focal ischemia in a rabbit brain did not result in complete reperfusion of brain tissue.[9] As a result localized areas of brain ischemia were observed. The authors were the first to refer to this phenomenon as "no-reflow" phenomenon, which was later renamed by others to "incomplete microvascular reperfusion".[10] Some underlying processes causing this incomplete microvascular reperfusion after focal ischemia are 1) microthrombi formation, 2) neutrophil extracellular traps (NETs) and 3) pericyte

contraction. The dimensions of a typical capillary bed in the brain in which these microcirculatory disturbances occur are typically in the order of <100 micrometer.[11] As the microcirculatory processes seem to differ fundamentally from the mechanical blockage at macrovascular vessel it is conceivable that other treatments than clot lysis or removal are required. These treatments should focus on the biological principle causing the impaired reperfusion by reduction of microthrombi formation, or dismantling neutrophil extracellular traps.

Prerequisites for reperfusion optimisation

Other important determinants of brain perfusion that could contribute to poor outcomes despite procedural success on DSA are periprocedural anesthetic management and blood pressure control.[12]

The aim of anesthetic support during EVT is to promote stable vital functions, reduce patient motion, facilitate fast treatment, and minimize the risk of complications. There are different options for anesthetic support during EVT; general anesthesia (GA), conscious sedation (CS), or local anesthesia (LA) at the puncture site only.

A post-hoc analysis of the Highly Effective Reperfusion evaluated in Multiple Endovascular Stroke trials (HERMES) collaboration showed that GA had a negative influence on treatment effect of the EVT in acute ischemic stroke patients in comparison to non-GA (composite of LA and CS).[13] On the other hand, subsequent randomized trials showed no clear advantage of one anesthetic strategy over the other when comparing CS and GA.[14,15] In depth evaluation of LA are lacking.

Parallel to this topic, the interest in the course of periprocedural blood pressure grows.[16-18] Since blood pressure is an important factor affecting cerebral perfusion, it is likely that blood pressure plays an important role in recovery after EVT. Shifting attention to LA and periprocedural blood pressure course could contribute to optimization of perfusion pressure in patients with acute ischemic stroke.

Aims

The overall aim of the research described in this thesis was to assess which factors aimed at improvement of reperfusion contribute to better outcomes of patients undergoing EVT for acute ischemic stroke.

The specific aims are:

- to identify the most important modifiable and non-modifiable factors associated with poor outcome after EVT despite good macrovascular reperfusion (**Part I**).
- to assess whether adjunctive antithrombotic treatment to EVT is safe and could improve functional outcome (**Part I**).
- to assess the most optimal periprocedural approach regarding anesthetic and hemodynamic management, associated with functional outcome (**Part II).**

Cohorts used for the performed studies

The **MR CLEAN Registry** is a post-trial Registry of the Multicenter Randomized Clinical trial of Intra-arterial treatment for acute ischemic stroke in the Netherlands (MR CLEAN trial) which was developed to monitor implementation and safety of EVT.[19] The MR CLEAN Registry is a multicenter registry, covering the Netherlands, in which data of all patients who underwent EVT for acute ischemic stroke caused by intracranial large vessel occlusion have been registered consecutively, between March 2014 until November 2017. The main results of the first 1488 patients (containing data until June 2016) have been published.[20]

The **MR CLEAN-MED** trial; is a randomized trial which aimed to enroll 1,500 patients with a clinical diagnosis of acute ischemic stroke due to a large vessel occlusion who undergo EVT. This trial is aimed to answer the question whether additive treatment during EVT by means of acetylsalicylic acid and/or unfractionated heparin improves outcomes by improving microvascular reperfusion. The first patient in this trial was enrolled in January 2018.

Outline of this thesis

In **Part I**, I described the results of a study evaluating the key drivers of poor outcome in patients with successful macrovascular reperfusion after EVT by the development of various prognostic models with data from the MR CLEAN Registry (**Chapter 2**). I evaluated the safety and efficacy of antithrombotic use during EVT. Firstly, by a systematic review of literature (**Chapter 3**) and secondly by three observational studies within the MR CLEAN Registry assessing the effect of prior use of acetylsalicylic acid (**Chapter 4**), prior use of oral anticoagulants (**Chapter 5**), and periprocedural use of heparin (**Chapter 6**). Furthermore, the design (**Chapter 7**) and preliminary results (**Chapter 8**) of the multicenter randomized controlled trial MR CLEAN-MED were presented.

In **Part II**, I focused on the most optimal periprocedural anesthetic and hemodynamic management, evaluated with data from the MR CLEAN Registry. Firstly, the effect of local anesthesia at the puncture site only versus conscious sedation on functional outcome was evaluated (**Chapter 9**). Secondly, I explored the difference in functional outcome between anesthetic managements further by evaluating the role of periprocedural blood pressure trends (**Chapter 10**). Finally, I assessed the influence of early postprocedural blood pressure trends following 6 hours after EVT (**Chapter 11**).

Finally, implications, methodological considerations and future perspectives are presented in the General Discussion.

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PART I

Microvascular reperfusion and antithrombotic treatment

CHAPTER II

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 2.1. 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 2.1). Characteristics of patients with successful and excellent reperfusion, along with clustering of predictors according to the four predefined groups, are presented in Table 2.1 (and per

reperfusion grade in supplemental table 2.2). 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 2.1. *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)	
Other (e.g., M3, ACA)	14 (0.8)		8 (0.7)	

Table 2.1. Continued.

	eTICI≥2B, n=1913	**Missing**	**eTICI≥2C, n=1218**	**Missing**
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).

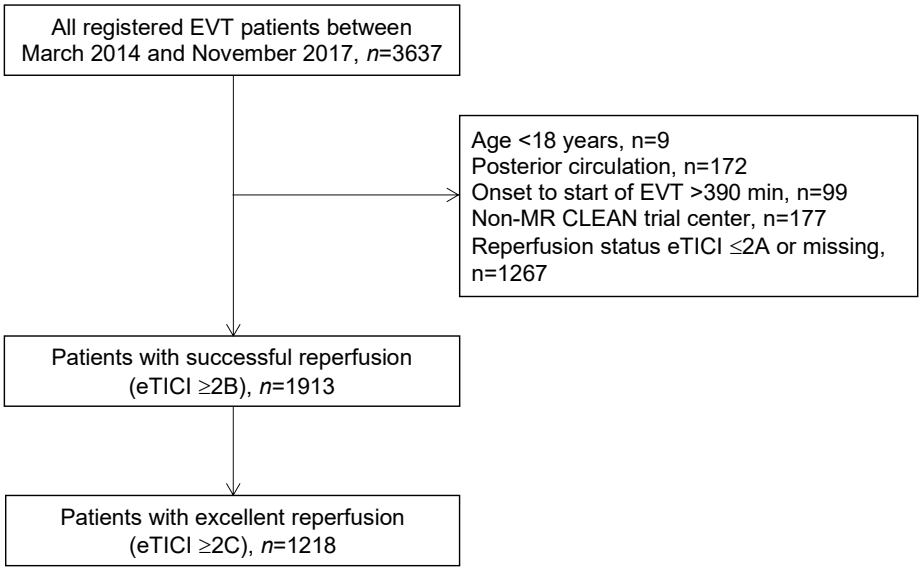

Figure 2.1. Flowchart

Variable importance

The basic model including *patient factors* already explained the largest proportion in variance (Figure 2.2). 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 2.3A). 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 2.3C). 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 2.3B). 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 2.3D).

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.

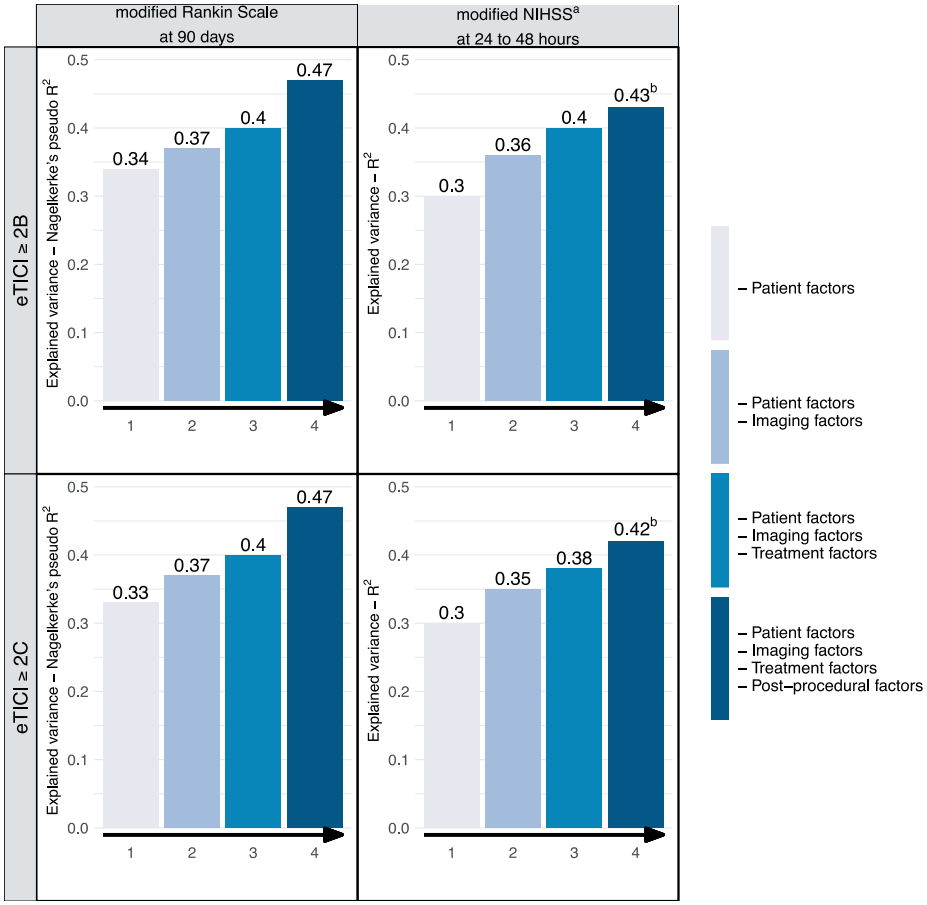

Figure 2.2. Performance of models with increasing extensiveness; in patients with successful reperfusion defined as an eTICI≥2B (A, B) and excellent reperfusion defined as an eTICI≥2C (C, D), predicting mRS at 90 days (A, C) and modified NIHSS at 24 to 48 hours (B, D);
Abbreviations: eTICI, extended 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).

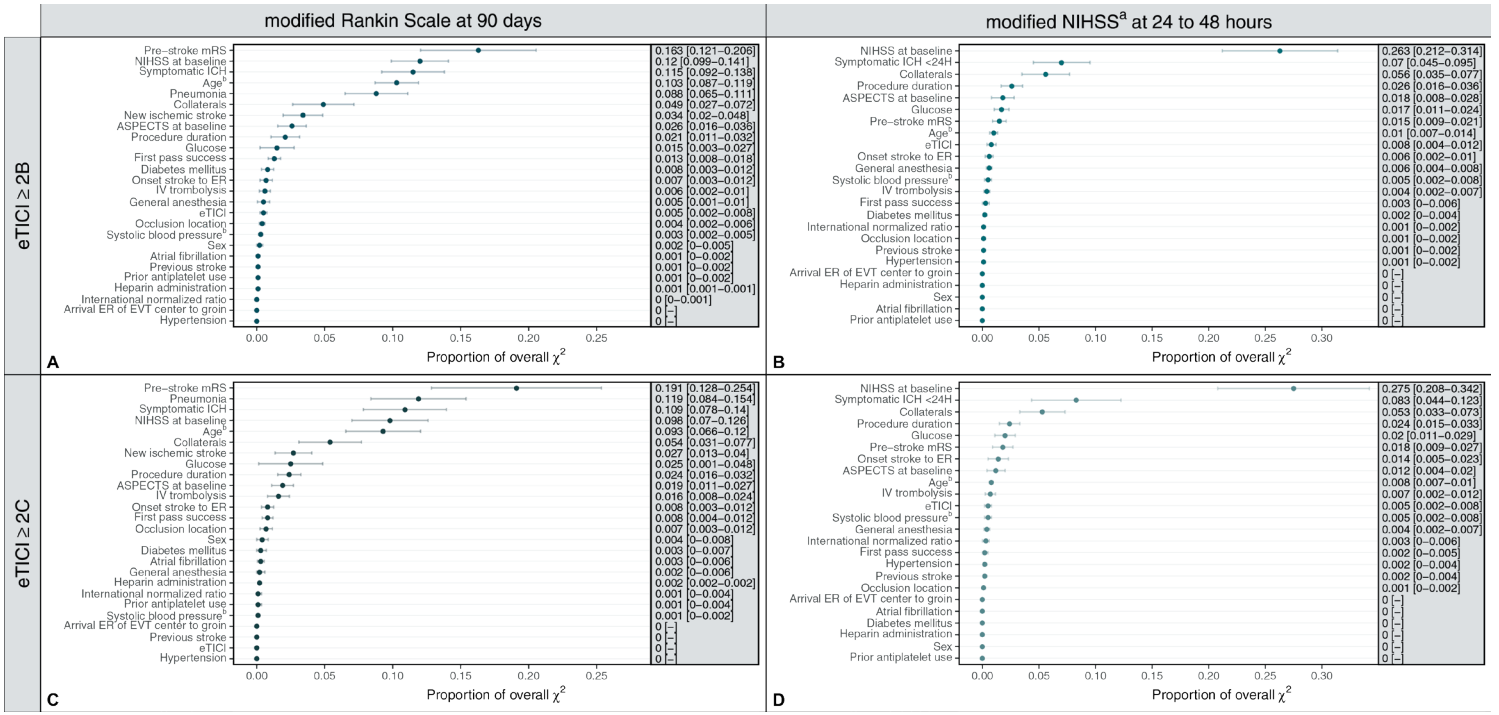

Figure 2.3. Individual penalized variable importance within the most extensive models; in patients with successful reperfusion defined as an eTICI≥2B (A, B) and excellent reperfusion defined as an eTICI>2C (C, D), predicting mRS at 90 days (A, C) and modified NIHSS at 24 to 48 hours (B, D). Confidence 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 2.1. 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 2.2. 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

Supplemental table 2.2 Continued

	eTICI 2B, n=695	eTICI 2C, n=332	eTICI 3, n=886	Missing
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)	
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).

CHAPTER III

Periprocedural anti-thrombotic treatment during acute mechanical thrombectomy for ischemic stroke: a systematic review

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Abstract

Background: More than one-third of the patients with ischemic stroke caused by an intracranial large vessel occlusion do not recover to functional independence despite fast and successful recanalization by acute mechanical thrombectomy (MT). This may partially be explained by incomplete microvascular reperfusion. Some antithrombotics, e.g., antiplatelet agents and heparin, may be able to restore microvascular reperfusion. However, antithrombotics may also increase the risk of symptomatic intracranial hemorrhage (sICH). The aim of this review was to assess the potential safety and functional outcome of periprocedural antiplatelet or heparin use during acute MT for ischemic stroke.

Methods: We systematically *searched PubMed, Embase, Medline, Web of Science,* and *Cochrane* for studies investigating the safety and functional outcome of periprocedural antiplatelet or heparin treatment during acute MT for ischemic stroke. The primary outcome was the risk for sICH. Secondary outcomes were functional independence after 3–6 months (modified Rankin Scale 0–2) and mortality within 6 months.

Results: 837 studies were identified through the search, of which 19 studies were included. The sICH risks of the periprocedural use of antiplatelets ranged from 6 to 17%, and for heparin from 5 to 12%. Two of four studies reporting relative effects of the use of antithrombotics are pointing toward an increased risk of sICH. Among patients treated with antiplatelet agents, functional independence varied from 23 to 60% and mortality from 18 to 33%. For heparin, this was, respectively, 19–54% and 19–33%. The three studies presenting relative effects of antiplatelets on functional independence showed neutral effects. Both studies reporting relative effects of heparin on functional independence found it to increase this chance.

Conclusion: Randomized controlled trials investigating the effect of periprocedural antithrombotic treatment in MT are lacking. Some observational studies report a slight increase in sICH risk, which may be acceptable because they also suggest a beneficial effect on functional outcome. Therefore, randomized controlled trials are warranted to address the question whether the potentially higher risk of sICH could be outweighed by improved functional outcome.

Background

The introduction of endovascular treatment by means of acute mechanical thrombectomy (MT) has been a major change in the emergent treatment of ischemic stroke caused by an intracranial large vessel occlusion. An individual patient data meta-analysis of randomized trials showed that this approach is highly effective[1]. In that meta-analysis, MT significantly improved functional outcome at 90 days, with a number needed to treat of 2.6 to reduce disability by one level on the modified Rankin Scale (mRS). Still, approximately one-third of the patients do not recover to functional independence despite fast and complete recanalization by MT[2,3]. This could partially be attributable to microvascular dysfunction also known as incomplete microvascular reperfusion (IMR). The concept of IMR stems from observations in the non-human primate of focal "no-reflow" following focal ischemia—caused by adhesion of polymorphonuclear leukocytes[4-6], and/or platelet-fibrin occlusions[7] within the downstream microvasculature – that could be prevented by anti-leukocyte or anti-thrombotic strategies. More recently, this concept has been described again[8]. Antiplatelet agents in experimental systems have shown to prevent the microvascular occlusive events in both non-human primate and mouse models and to improve outcome[9,10]. Also heparin may be of additional value to MT, by preventing microthrombus formation and microvascular obstruction and potentially restore microvascular reperfusion. It has been suggested that microvascular obstructions could arise from neutrophil extracellular trap (NET) formation[11]. NET formation can be dissolved by heparin, but not by tissue plasminogen activator (tPA) [12,13]. As antiplatelet agents and heparin seem promising in their ability to restore microvascular function, these drugs might contribute to the recovery of patients with ischemic stroke undergoing acute MT. A direct test of this hypothesis in humans has not yet taken place. An important disadvantage of both antiplatelet and heparin use in the setting of focal cerebral ischemia is the increased risk of intracranial hemorrhage. Symptomatic intracranial hemorrhage (sICH) leads to severe handicap or death in almost all patients[14]. A randomized trial—in which patients with an ischemic stroke were either assigned to intravenous (IV) antiplatelet agents within 90 min after starting treatment with IV recombinant tPA or to no antiplatelet agents—was stopped before the intended conclusion due to non-superior outcomes and a higher risk of sICH in the group that received antiplatelet agents[15]. Although the absolute sICH risk associated with acute antiplatelet administration was low (4.3%), concerns remain about this detrimental side effect. These concerns are also present with regard to the use of heparin in ischemic stroke. This may be due to the results of the International Stroke Trial, in which 19,435 patients were randomized to receive antiplatelet agents, heparin, both or neither within 48 h after symptom onset[16]. In this study, the beneficial results (i.e., reduced risk of recurrent stroke and improved functional outcome) were offset by a higher sICH risk. Again, the absolute sICH risk was low in this trial, even in the high-dose group receiving 12,500 IU twice daily (2.0%). Yet, the balance between risk and

benefit of these antithrombotic drugs for patients with ischemic stroke is uncertain in the setting of acute MT. Therefore, the aim of this review was to assess the potential safety and functional outcome of periprocedural antiplatelet or heparin use during acute MT for ischemic stroke.

Methods

Search strategy
A search strategy was developed in collaboration with a biomedical information specialist to systematically search *PubMed, Embase, Medline, Web of Science,* and *Cochrane*. The search was conducted in November 2017 and updated in March 2018. Two independent reviewers (RG and VC) screened all identified articles on titles and abstracts for eligibility. Articles identified as potentially eligible underwent a full text review. Disagreements between reviewers were resolved by a consensus meeting with a third reviewer (BR). The complete search strategy is listed as supplemental material.

Inclusion and exclusion criteria
Studies were eligible for inclusion when:
- Periprocedural [consisting of prior, *acute* (<6 hours) or *early* (6-24 hour)], oral or parenteral, anti-platelet agents or heparin were used in patients who underwent MT for ischemic stroke.
- Post-treatment sICH was reported.
- English abstract was available.
- Patients were 18 years or older.

Studies were excluded when:
- Antithrombotic agents other than antiplatelet agents and heparin were used.
- The specific number of patients with prior antiplatelet agents could not be extracted, and differentiation between outcomes of patients with and without prior antiplatelet use was not possible.
- Less than 50% of the endovascular treated patients were treated with MT.
- Less than 20 patients underwent MT.

In addition, studies reporting on patients with "tandem lesions" (i.e., an intracranial large vessel occlusion with simultaneous ipsilateral extracranial carotid occlusion) treated with intracranial MT with or without emergency carotid artery stenting were included through bibliographic review of the included studies. In these studies, antithrombotics were used as a part of protocol-based care to prevent stent occlusion. Finally, large randomized controlled trials (RCTs) investigating the effectiveness of MT, and in which periprocedural antithrombotics were used, were included through bibliographic reviewing.

Data extraction and synthesis

We developed a data extraction form based on elements of the Cochrane Consumers and Communication Review Group's data extraction template[17]. Two reviewers extracted the data independently: one reviewer extracted all the data (RG) and the other reviewer extracted 25% of the data (VC). Extracted data were checked during consensus meetings with three reviewers (RG, VC, and BR). For each included study, we aimed to specifically extract the available data for the patients treated with MT or the most representative group. The following information was extracted: study design, study population characteristics [sample size, age, National Institutes of Health Stroke Scale (NIHSS) at baseline, and occlusion location], recanalization therapy [administration of IV plasminogen activators, administration of intraarterial (IA) plasminogen activators, treatment with MT, and time from symptom onset to recanalization therapy]; study treatment and contrast [type of antithrombotic treatment, indication for antithrombotic administration, time from symptom onset to antithrombotic treatment, number of patients treated with antithrombotic treatment, and information about the control group (when available)]; safety (sICH and all-cause mortality within 6 months); and functional outcome (functional independence after 3–6 months, expressed as a mRS score of 0–2)[18,19]. Special note was made of the definition of sICH in each study.

When available, study characteristics were reported by mean (SDs) or median (interquartile ranges). Outcomes were reported as numbers of cases and percentages. When a comparison was performed or a contingency table could be prepared, odds ratios for both safety (sICH and all-cause mortality) and functional (mRS 0–2) outcomes were reported, with 95% confidence intervals (CIs). If present, adjusted odds ratios (aORs) were also reported. When data were unclear or missing, we extracted data from the related original study (when available) or approached the corresponding author for clarification. Data were reported according to the Preferred Reporting Items for Systematic reviews and Meta-analyses (PRISMA) Statement[20]. The checklist can be found in the supplementary material (Data Sheet S2 in Supplementary Material).

Results

Study selection

The systematic literature search yielded a total of 1,270 studies (Figure 3.1). After removing duplicates, 837 articles remained, of which all titles and abstracts were screened. Full text of 17 articles was retrieved and assessed for eligibility. In addition, eight eligible studies were identified through bibliographic review of the included studies. Seven studies were identified in which tandem lesions were investigated, and one RCT investigating the effectiveness of MT was identified, in which periprocedural antithrombotics were used. A total of 19 articles met the selection criteria and were included in the review[21-39].

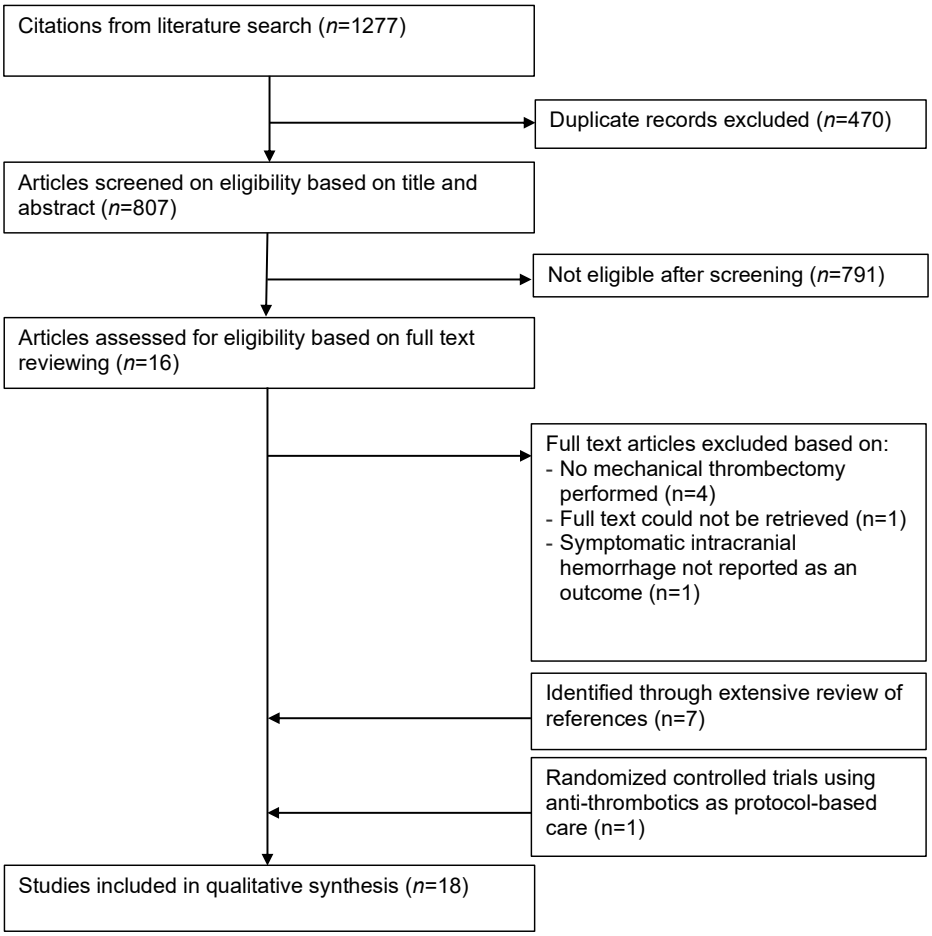

Figure 3.1. Flowchart of the systematic literature search.

Thrombectomy and antiplatelet use

We identified six studies investigating the periprocedural use of antiplatelet agents [22,24,31,32,36,39]. These studies include five cohort studies with sample sizes between 35 and 231 patients [22,24,31,36,39], and one *post hoc* analysis on a phase III RCT of 233 patients (Table 3.1)[32]. The occlusion location varied between anterior circulation only (one study)[32], posterior circulation only (one study)[24], and both anterior and posterior circulation (three studies)[22,36,39]. The occlusion location could not be retrieved in one study[31]. In the cohort studies, 57-100% of the study population underwent MT, and in the *post hoc* analysis on phase III RCT data, all patients (in whom the effect of antiplatelet agents was investigated) underwent MT. The indication for antiplatelet use was mainly based on comorbidity (prior use) and prevention of re-occlusion of the vessel after

recanalization. The sICH risk for periprocedural antiplatelet use ranged from 6 to 17%. Among the patients using antiplatelet agents, mortality varied from 18 to 33%, and functional independence from 23% to 60% (Table 3.2)

Four studies reported unadjusted relative effects of anti-platelet agents on the risk of sICH [22,32,36,39]. Antiplatelet use was associated with a higher relative effect on sICH in two studies in which patients were on prior antiplatelet treatment (OR, 4.80; 95% CI, 1.77–13.02, and OR, 5.43; 95% CI, 1.46–20.13)[32,36], and a neutral effect in the other studies in which patients received acute antiplatelet treatment in one and were on prior antiplatelet treatment in the other (OR, 0.92; 95% CI, 0.24–3.46, and OR, 0.81; 95% CI, 0.25–2.68)[22,39]. Only one study adjusted the estimate of the relative sICH risk, attributable to antiplatelet use, for prognostic factors (glucose level and baseline NIHSS), but not for prior comorbidity or reperfusion[36]. The population of this study was heterogeneous, concerning patients who received IA plasminogen activator and/or MT. The absolute sICH risk was 13% among patients receiving prior antiplatelet treatment and 3% among patients who did not. Prior use of an antiplatelet agent was an independent risk factor for sICH (aOR, 8.03; 95% CI, 1.83–41.70).

Three studies reported unadjusted effect estimates of antiplatelet use on mortality and functional independence[22,32,39]. The relative effect on mortality was neutral in two studies (OR, 0.75; 95% CI, 0.34–1.67, and OR, 0.97; 95% CI, 0.50–1.85)[22,39] and higher in the other (OR, 2.46; 95% CI, 1.27–4.76)[32], when antiplatelet agents were used. In all studies, the effect on functional independency was neutral (OR, 0.61; 95% CI, 0.32–1.17, and OR, 0.54; 95% CI, 0.28–1.05, and OR, 1.11; 95% CI, 0.63–1.97).

The *post hoc* analysis of the Multicenter Randomized CLinical trial of Endovascular treatment for Acute ischemic stroke in the Netherlands (MR CLEAN) was the only study in which prior antiplatelet use was directly compared to no prior antiplatelet use in patients who underwent acute MT[32]. Prior antiplatelet use was associated with a higher risk of sICH (OR, 4.80; 95% CI, 1.77–13.02) and mortality (OR, 2.46; 95% CI, 1.27–4.76). However, prior antiplatelet use did not interact with MT treatment effect and safety parameters like sICH. Moreover, among patients with successful recanalization, patients on prior antiplatelet use were twice as likely to have a favorable functional outcome (39 vs. 18%, $P_{interaction} = 0.025$). One other study that investigated the recanalization rate found that patients on prior antiplatelet treatment have higher odds for successful recanalization[39].

Table 3.1. Characteristics of included studies investigating periprocedural antiplatelet use in patients with ischemic stroke who underwent acute mechanical thrombectomy.

Study Characteristics		Population characteristics				Recanalization therapy				Study treatment and contrast					
Author, year	**Study design**	**N.**	**Age**	**NIHSS score at baseline**	**Occlusion location**	**IV tPA, n/N. (%)**	**IA tPA, n/N. (%)**	**MT, n/N.(%)**	**Time from symptom onset to recanalization therapy, minutes**	**Anti-thrombotic treatment**	**Indication for anti-thrombotic treatment**	**Time from symptom onset to anti-thrombotic treatment***	**Treatment, n/N. (%)**	**Control**	**Control, n/N. (%)**
Broeg-Morvay, 2017	Prospective cohort	231**	Mean*** 69 (±14)	Median*** 15 (2-37)	Anterior + posterior circulation	231/231 (100%)	69/231 (30%)	212/231 (92%)	Mean*** 270 (±83)	ASA loading dose (median 300mg)	-Prevention of reocclusion -Stenting	Acute	50/231 (22%)	No ASA	181/231 (78%)
Ernst, 2014	Retrospective cohort	54**	Mean 65	Median 32	Posterior circulation	0/54 (0%)	54/54 (100%)	31/54 (57%)	Median 198	IV abciximab bolus (0.25 mg/kg) followed by continuous infusion, or, tirofiban bolus (10 mcg/kg) followed by continuous infusion	Protocol-based care	Acute	54/54 (100%)	NR	NR
Memon, 2011	Prospective cohort	35**	Mean 62	Median 13 (5-22)	NR	2/35 (6%)	12/35 (34%)	≥20/35 (≥57%)	Median 230	IA eptifibatide bolus (180mcg/kg)	-Presence of distal emboli -Inaccessible location by MT -Prevention of reocclusion	Acute	35/35 (100%)	NR	NR

Table 3.1. Continued.

Study Characteristics		Population characteristics				Recanalization therapy				Study treatment and contrast					
Author, year	**Study design**	**N.**	**Age**	**NIHSS score at baseline**	**Occlusion location**	**IV tPA, n/N. (%)**	**IA tPA, n/N. (%)**	**MT, n/N.(%)**	**Time from symptom onset to recanalization therapy, minutes**	**Anti-thrombotic treatment**	**Indication for anti-thrombotic treatment**	**Time from symptom onset to anti-thrombotic treatment***	**Treatment, n/N. (%)**	**Control**	**Control, n/N. (%)**
Mulder, 2015	Post hoc analysis on phase III RCT	233	Median 66 (55-76)	Median 17 (14-21)	Anterior circulation	203/233 (87%)	24/233 (10%)	233/233 (100%)	Median 260 (210-313)	Any anti-platelet use (single and dual)	Comorbidity	Prior use	64/233 (27%)	No anti-platelet use	169/233 (73%)
Pandhi, 2017	Retrospective cohort	217	Mean*** 60 (±14)	Median*** 16 (12-21)	Anterior + posterior circulation	141/217 (65%)	0/217 (0%)	217/217 (100%)	Mean 361	Any anti-platelet use (single and dual)	Comorbidity	Prior use	71/217	No anti-platelet use	146/217 (67%)
Sugiura, 2016	Prospective cohort	204**	Mean 71 (±13)	Median 18 (13-22)	Anterior + posterior circulation	80/204 (39%)	42/204 (21%)	170/204 (83%)	Mean 188 (±101)	Any anti-platelet use (single and dual)	Comorbidity	Prior use	48/204 (24%)	No anti-platelet use	156/204 (76%)

Summary: Characteristics of the included studies are presented by sample size (percentage), means (standard deviations), medians (interquartile ranges) or by remarks.

Abbreviations: ASA = acetylsalicylic acid; IA = intra-arterial; IV = intravenous; MT = mechanical thrombectomy (by means of stent retriever or aspiration); NR = not reported; PA = tissue plasminogen activator

Captions: *Time from symptom onset to anti-thrombotic treatment was divided in acute treatment administration [<6 hours] and early administration [6- 24 hours]; **Not solely MT; ***Extracted data from the subgroup that received anti-platelet agents;

Table 3.2. Outcomes of included studies investigating periprocedural antiplatelet use in patients with ischemic stroke who underwent acute mechanical thrombectomy.

Author, year	sICH, n/N. (%)	Mortality, n/N. (%)	mRS (0-2), n/N. (%)	sICH, OR (95%CI)	Mortality, OR (95%CI)	mRS (0-2), OR (95%CI)	sICH, aOR (95%CI)	Mortality, aOR (95%CI)	mRS (0-2), aOR (95%CI)
Broeg-Morvay, 2017	T=3/50 (6%) C=10/181 (6%); [1]	T=9/50 (18%) C=41/181 (23%)	T=17/50 (34%) C=83/181 (46%)	0.92 (0.24 - 3.46)	0.75 (0.34 - 1.67)	0.61 (0.32 - 1.17)	NR	NR	NR
Ernst, 2014	T=7/54 (13%); [2]	T=18/54 (33%)	T=15/54 (28%)	NR	NR	NR	NR	NR	NR
Memon, 2011	T=5/35 (14%); [3]	T=8/35 (23%)	T=21/35 (60%)	NR	NR	NR	NR	NR	NR
Mulder, 2015	T=11/64 (17%) C=7/169 (4%); [3]	T=21/64 (33%) C=28/169 (17%)	T=15/64 (23%) C=61/169 (36%)	4.80 (1.77 - 13.02)	2.46 (1.27 - 4.76)	0.54 (0.28 - 1.05)	NR	NR	NR
Pandhi, 2017	T=4/71 (6%) C=10/146 (7%)[4]	T=18/71 (25%) C=38/146 (26%)	T=33/71 (50%) C=64/146 (48%)	0.81 (0.25 - 2.68)	0.97 (0.50 - 1.85)	1.11 (0.63 - 1.97)	NR	NR	NR
Sugiura, 2016	T=6/48 (13%) C=4/156 (3%); [5]	NR	NR	5.43 (1.46 - 20.13)	NR	NR	8.03 (1.83 - 41.70)*	NR	NR

Abbreviations: C = control; CI = confidence interval; (a)OR = (adjusted) odds ratio; mRS = modified Rankin Scale; sICH = symptomatic intracranial hemorrhage; T = treated with anti-platelet agent

Captions: * Adjusted for: glucose level and NIHSS at baseline

[1] PROACT-II definition [7]

[2] Intracranial hemorrhage resulting in NIHSS increase of > 4 or non-definable neurologic status with PH and severe mass effect or subarachnoid hemorrhage with hydrocephalus

[3] Intracranial hemorrhage resulting in NIHSS increase of ≥ 4

[4] SITS-MOST definition [8]

[5] ECASS-II definition [9]

Antiplatelet use in patients with tandem lesions

We identified eight cohort studies in which patients with tandem lesions—that required intracranial MT with or without combined emergency carotid artery stenting—received antiplatelet agents as mandatory protocol-based care to prevent stent occlusion (Table 3.3)[21,23,25,28-30,34,35]. Antithrombotic agents in these studies included eptifibatide, tirofiban, abciximab, acetylsalicylic acid, clopidogrel, and heparin, alone or in combination. The observed sICH risk in the included studies ranged from 0 to 17% (Table 3.4). Mortality ranged from 0 to 39% and functional independence from 29 to 70%. No relative effects on sICH, mortality, or functional independence were reported.

Thrombectomy and heparin use

Four studies investigated the periprocedural use of heparin (Table 3.5)[27,33,37,38]. Two studies were *post hoc* analyses of RCT data[33,37], one was a cohort study[38], and one an RCT investigating the efficacy of acute endovascular treatment, which could include periprocedural heparin use[27]. All studies investigated the use of unfractionated heparin (UFH). Both anterior and posterior circulation occlusions were included in all studies. The administered heparin dose was reported in all studies and varied between 2,000 and 5,000 IU. Heparin administration was a part of standard care in one study[38], and left to the discretion of the interventionalist in three studies[27,33,37]. The observed risk of sICH varied between 5 and 12%, mortality between 19 and 33%, and functional independence between 19% and 54% (Table 3.6).

Two studies reported an unadjusted effect estimate of heparin on the risk of sICH[33,37]. Both studies suggest that the effect of heparin use on sICH was neutral (8 vs. 11%; OR, 0.73; 95% CI, 0.11–4.77, and 12 vs. 4%; OR, 3.02; 95% CI, 0.91–9.97)[33,37]. Both studies also reported unadjusted effect estimates for mortality and functional independence. For the latter, also adjusted effects were provided. Both studies suggested that the effect on mortality is neutral (OR, 0.73; 95% CI, 0.23–2.28, and OR, 1.08; 95% CI, 0.54–2.16). After adjustment for prognostic factors [age and final revascularization success in one study[33], and intubation during procedure, post-device TICI 2b-3, diabetes mellitus, baseline NIHSS score, study device (Trevo vs. Merci), time from symptom onset to arterial puncture (hours) and congestive heart failure in the other [37]], periprocedural heparin use was positively associated with functional independence in both studies (aOR, 5.89; 95% CI, 1.34–25.92, and aOR, 5.30; 95% CI, 1.70–16.48).

One study—which identified predictors for sICH—used a periprocedural loading dose of 3,000 to 5,000 IU UFH, followed by a continuous infusion of 1,000 IU per hour according to standard care (referred to as systemic heparinization)[38]. The absolute risk of sICH was 5% in patients who underwent MT and received systemic heparinization. No relative effect of heparin on sICH was reported in this study, neither were mortality nor functional independence.

Table 3.3. Characteristics of included studies investigating patients with ischemic stroke caused by a "tandem lesions" who underwent acute mechanical thrombectomy with or without emergency extracranial carotid stenting, who received periprocedural anti-thrombotic drugs as protocol-based care.

Study Characteristics		Population characteristics				Treatment characteristics					Study treatment	
Author, year	**Study design**	**N.**	**Age**	**NIHSS at baseline**	**Occlusion location**	**IV tPA, n/N. (%)**	**IA tPA, n/N. (%)**	**MT, n/N. (%)**	**Stenting, n/N. (%)**	**Time from symptom onset to recanalization therapy, minutes**	**Anti-thrombotic treatment when stent deployment was performed**	**Time from symptom onset to anti-thrombotic treatment***
Behme, 2015	Retro-spective cohort	170	Median 64	Median 15	Anterior circulation	122/170 (72%)	0/170 (0%)	170/170 (100%)	170/170 (100%)	Median 98	**Per procedural:** Center A, loading dose of eptifibatide 180 mcg/kg; Center B, loading dose of ASA 500 mg and clopidogrel 375 mg; Center C, loading dose of tirofiban (weight-adapted); Center D, loading dose of ASA 500 mg IV, plus 5000 IU UFH or tirofiban. **Postprocedural:** Center A, continuous infusion eptifibatide for the first 24 h, hereafter dual anti-platelet treatment (loading clopidogrel 300 mg and ASA 500 mg); Center B, continuation clopidogrel 75 mg/d and ASA 100mg/d for 3 months; Center C, continuous infusion of tirofiban for the first 24 h, hereafter loading 500mg ASA and 300 mg clopidogrel, continuation with 75 mg/d clopidogrel and 100 m/d for 3 months; Center D, loading dose of clopidogrel 500 mg, hereafter ASA 100 mg/d and clopidogrel 75 mg/d for 3 months.	Acute

Table 3.3. Continued.

Study Characteristics		Population characteristics				Treatment characteristics					Study treatment	
Author, year	**Study design**	**N.**	**Age**	**NIHSS at baseline**	**Occlusion location**	**IV tPA, n/N. (%)**	**IA tPA, n/N. (%)**	**MT, n/N. (%)**	**Stenting, n/N. (%)**	**Time from symptom onset to recanalization therapy, minutes**	**Anti-thrombotic treatment when stent deployment was performed**	**Time from symptom onset to anti-thrombotic treatment***
Cohen, 2015	Retrospective cohort	24	Mean 66	Median 18 (14-28)	Anterior circulation	10/24 (42%)	0/24 (0%)	24/24 (100%)	24/24 (100%)	Mean 198	**Per procedural**: Loading dose of 2500 IU UFH (after femoral access, and confirmation for the need of stent implantation), patients not on anti-platelet therapy received a loading dose of 300 mg ASA. **Postprocedural**: Loading dose of clopidogrel 300 mg added to ASA use. Two months dual therapy (clopidogrel 75 mg/d plus ASA 100 mg/d).	Acute
Heck, 2015	Retrospective cohort	23	Mean 70	Median 17 (9-25)	Anterior circulation	7/23 (30%)	0/23 (0%)	23/23 (100%)	23/23 (100%)	NR	**Per procedural:** Loading dose of ASA 300 mg in all patients, 12 pt. loading dose of abciximab 0.25 mg/kg. **Postprocedural**: Loading dose of clopidogrel 600 mg if no abciximab was administered.	NR

Table 3.3. Continued.

Study Characteristics		Population characteristics				Treatment characteristics					Study treatment	
Author, year	**Study design**	**N.**	**Age**	**NIHSS at baseline**	**Occlusion location**	**IV tPA, n/N. (%)**	**IA tPA, n/N. (%)**	**MT, n/N. (%)**	**Stenting, n/N. (%)**	**Time from symptom onset to recanalization therapy, minutes**	**Anti-thrombotic treatment when stent deployment was performed**	**Time from symptom onset to anti-thrombotic treatment***
Lockau, 2015	Retrospective cohort	37	Mean 63	Median 17 (3-30)	Anterior circulation	20/37 (54%)	0/37 (0%)	37/37 (100%)	37/37 (100%)	NR	**Per procedural:** Loading dose of tirofiban (weight-adapted). **Postprocedural:** Continuous infusion of tirofiban for the first 24 h, after exclusion of hemorrhage loading dose of ASA 500 mg and clopidogrel 300 mg. Hereafter, ASA 100 mg/d and clopidogrel 75 mg/d for 3 months.	Acute
Maurer, 2014	Retrospective cohort	43**	Mean 68 (±13)	Mean 13 (±5)	Anterior circulation	33/43 (77%)	20/43 (47%)	27/43 (63%)	39/43 (91%)	NR	**Per procedural:** Loading dose of ASA (500 mg) and IV UFH bolus (5000 IU) before stent placement. **Postprocedural:** Loading dose of clopidogrel 600 mg or ticagrelor 180 mg.	NR
Marnat, 2015	Retrospective cohort	20	Mean 53	Mean 18	Anterior circulation	15/20 (75%)	0/20 (0%)	20/20 (100%)	5/20 (25%)	Mean 263	**Per procedural:** Loading dose of ASA 500 mg. **Postprocedural:** Local protocol.	Acute + Early

Table 3.3. Continued.

Study Characteristics		Population characteristics				Treatment characteristics					Study treatment	
Author, year	**Study design**	**N.**	**Age**	**NIHSS at baseline**	**Occlusion location**	**IV tPA, n/N. (%)**	**IA tPA, n/N. (%)**	**MT, n/N. (%)**	**Stenting, n/N. (%)**	**Time from symptom onset to recanalization therapy, minutes**	**Anti-thrombotic treatment when stent deployment was performed**	**Time from symptom onset to anti-thrombotic treatment***
Rangel-Castilla, 2017	Retrospective cohort	45	Mean 64	Mean 14	Anterior circulation	15/45 (33%)	0/45 (0%)	45/45 (100%)	45/45 (100%)	Mean 139	**Per procedural:** Loading dose of ASA 650 mg and clopidogrel 600 mg or ticagrelor 180 mg. After confirmation of cervical occlusion heparinization at an activated coagulation time of ≥ 250 sec. **Postprocedural:** Local protocol at 24 hours.	Acute
Stampfl, 2014	Retrospective cohort	24	Mean 67 (±10)	Median 18 (15-22)	Anterior circulation	22/24 (92%)	0/24 (0%)	24/24 (100%)	24/24 (100%)	Mean 230 (±131)	**Per procedural:** 17 Pt. continuous infusion of tirofiban; 5 pt. loading dose of ASA and clopidogrel and UFH; 2 pt. (on prior anti-platelet) loading dose of UFH. **Postprocedural**: Patients on tirofiban continuation for the first 24-48 h; all patients 100 mg/d ASA and clopidogrel 75 mg/d.	Acute + Early

Summary: Characteristics of the included studies are presented by sample size (percentage), means (standard deviations), medians (interquartile ranges) or by remarks.
Abbreviations: ASA = acetylsalicylic acid; IA = intra-arterial; IV = intravenous; MT = mechanical thrombectomy (by means of stent retriever or aspiration); NR = not reported; UFH = unfractionated heparin; tPA = tissue plasminogen activator
Captions: *Time from symptom onset to anti-thrombotic treatment was divided in *acute* administration [<6 hours] and *early* administration [6- 24 hours]; **Not solely MT

Table 3.4. Outcomes of included studies investigating patients with ischemic stroke caused by a "tandem lesions" who underwent acute mechanical thrombectomy with or without emergency extracranial carotid stenting, who received periprocedural anti-thrombotic drugs as protocol-based care.

Author, year	sICH, n/N. (%)	Mortality, n/N. (%)	mRS (0-2), n/N. (%)
Behme, 2015	15/170 (9%); [1]	32/170 (19%)	62/170 (36%)
Cohen, 2015	0/24 (0%); [2]	2/24 (8%)	13/24 (54%)
Heck, 2015	5/23 (2%); [3]	9/23 (39%)	12/23 (52%)
Lockau, 2015	4/37 (11%); [4]	7/37 (19%)	17/37 (46%)
Marnat, 2016	1/20 (5%); [1]	0/20 (0%)	14/20 (70%)
Maurer, 2014	5/43 (12%); [5]	9/43 (21%)	14/43 (33%)
Rangel-Castilla, 2017	2/45 (4%); [6]	5/45 (11%)	22/45 (49%)
Stampfl, 2014	4/24 (17%); [1]	4/24 (17%)	7/24 (29%)

Abbreviations: sICH, symptomatic intracranial hemorrhage; mRS, modified Rankin Scale
Captions: [1] ECASS-II definition [9]
[2] Intracranial hemorrhage resulting in NIHSS increase of ≥ 4 within 36 hours
[3] SITS-MOST definition [8]
[4] Intracranial hemorrhage resulting in NIHSS increase of > 4
[5] No specific definition of sICH given
[6] Intracranial hemorrhage resulting in NIHSS increase of ≥ 4 or death

In the one RCT investigating the effectiveness of MT, periprocedural heparin use was left to the discretion of the treating interventionalist[27]. When used, an IV dose of 2,000 IU UFH followed by a subsequent continuous infusion of 500 IU per hour until the end of the procedure was recommended for patients undergoing MT. The risk of sICH in the MT group was 5%. No relative effect on sICH was reported. Both mortality and functional independence occurred in 19% of the patients in this study, but relative effects were not provided.

Thrombectomy and antithrombotic combination use
One study investigated different antithrombotic combination treatments in the early phase (<24 hours) after ischemic stroke[26]. Patients had relatively mild anterior or posterior circulation occlusions with a median baseline NIHSS of 11. The early antithrombotic treatment consisted of antiplatelet, anticoagulant, and combined antiplatelet with anticoagulant treatments (Table 3.7). The sICH rate in this study was 3%, mortality 8%, and functional independence 56% (Table 3.8). In this heterogeneous treatment group, in which patients received IV plasminogen activator, IA plasminogen activator, and/or MT, early antithrombotic treatment was not associated with sICH compared to standard antithrombotic treatment after multivariable adjustment (OR 0.56, 95% CI: 0.35 to 2.10)[26]. However, both the small group that actually received the combination therapy and the lack of subanalyses limit the ability to draw conclusions on combination antithrombotic treatments used during MT. This study is mentioned separately, because it did not report outcomes by separate antithombotic regimens.

Table 3.5. Characteristics of included studies investigating periprocedural heparin use in patients with ischemic stroke who underwent acute mechanical thrombectomy.

Study Characteristics		Population characteristics			Recanalization therapy				Study treatment and contrast					
Author, year	**Study design**	**N.**	**Age**	**NIHSS score at baseline**	**Occlusion location**	**IV tPA, n/N. (%)**	**IA tPA, n/N. (%)**	**MT, n/N. (%)**	**Time from symptom onset to recanalization therapy, minutes**	**Anti-thrombotic treatment**	**Indication for anti-thrombotic treatment**	**Time from symptom onset to anti-thrombotic treatment***	**Treatment, n/N. (%)**	**Control**	**Control, n/N. (%)**
Cohort studies and post hoc analyses															
Enomoto, 2016	Pro-spective cohort	704**	NR	NR	Anterior + posterior circulation	440/704 (63%)	123/704 (17%)	409/704 (58%)	NR	Standard UFH bolus of 3000 - 5000 IU, followed by 1000 IU/h to maintain ACT (250-350 sec.)	Standard care	Acute + Early	409/704*** (58%)	NR	NR
Nahab, 2012	Post hoc analysis on phase IIB RCT	51	Mean**** 75 (±10)	Mean**** 21 (±9)	Anterior + posterior circulation	18/51 (35%)	13/51 (25%)	51/51 (100%)	Mean**** 269 (±86)	UFH (median 3000 IU)	Discretion interventionalist	Acute + Early	24/51 (41%)	No heparin	27/51 (53%)
Winningham, 2017	Post hoc analysis on phase III RCT	173	Mean 68 (±14)	Median 19 (15-21)	Anterior + posterior circulation	NR	96/173 (55%)	173/173 (100%)	<480	UFH (mean 4016 IU)	Discretion interventionalist	Acute + Early	58/173 (34%)	No heparin	115/173 (66%)

Table 3.5. Continued.

Study Characteristics		Population characteristics			Recanalization therapy				Study treatment and contrast					
Author, year	**Study design**	**N.**	**Age**	**NIHSS score at baseline**	**Occlusion location**	**IV tPA, n/N. (%)**	**IA tPA, n/N. (%)**	**MT, n/N. (%)**	**Time from symptom onset to recanalization therapy, minutes**	**Anti-thrombotic treatment**	**Indication for anti-thrombotic treatment**	**Time from symptom onset to anti-thrombotic treatment***	**Treatment, n/N. (%)**	**Control n/N. (%)**
Randomized controlled trials investigating effectiveness of endovascular strategies														
Kidwell, 2013	Phase IIB RCT	64	Mean***** 66 (±13)	Median***** 16 (12-18)	Anterior circulation	44/64 (44%)	NR	64/64 (100%)	Mean***** 318 (±96)	Recommended UFH bolus of 2000 IU, followed by 500 IU/h until end of procedure	Discretion interventionalist	Acute + Early	NR	NR

Summary: Characteristics of the included studies are presented by sample size (percentage), means (standard deviations), medians (interquartile ranges) or by remarks.

Abbreviations: ASA = acetylsalicylic acid; BL = Baseline; IA = intra-arterial; IU = international unit; IV = intravenous; MT = mechanical thrombectomy (by means of stent retrievers or aspiration); NR = not reported; UFH = unfractionated heparin; tPA = tissue plasminogen activator

Captions: *Time from symptom onset to anti-thrombotic treatment was divided in *acute* administration [<6 hours] and *early* administration [6- 24 hours], **Not solely MT; ***Anti-thrombotic treatment was used in all patients in the MT group; ****Extracted data from the subgroup that received heparin; *****Extracted data from the population that received penumbral embolectomy

Table 3.6. Outcomes of included studies investigating periprocedural heparin use in patients with ischemic stroke who underwent acute mechanical thrombectomy.

Author, year	sICH, n/N. (%)	Mortality, n/N. (%)	mRS (0-2), n/N. (%)	sICH, OR (95%CI)	Mortality, OR (95%CI)	mRS (0-2), OR (95%CI)	sICH, aOR (95%CI)	Mortality, aOR (95%CI)	mRS (0-2), aOR (95%CI)
Cohort studies and post hoc analyses									
Enomoto, 2016	T=20/409 (5%); [1]	NR	NR	NR	NR	NR	NR	NR	NR
Nahab, 2012	T=2/24 (8%) C=3/27 (11%); [2]	T=8/24 (33%) C=11/27 (41%)	T=13/24 (54%) C=8/27 (30%)	0.73 (0.11 - 4.77)	0.73 (0.23 - 2.28)	2.81 (0.89 - 8.88)	NR	NR	5.89 (1.34 - 25.92)*
Winningham, 2017	T=7/58 (12%) C=5/115 (4%); [2]	T=17/58 (29%) C=32/115 (28%)	T=23/58 (40%) C=30/115 (26%)	3.02 (0.91 - 9.97)	1.08 (0.54 - 2.16)	1.86 (0.95 - 3.64)	NR	NR	5.30 (1.70 - 16.48)**
Randomized controlled trials investigating effectiveness of endovascular strategies									
Kidwell, 2013	T=3/64 (5%); [4]	T=12/64 (19%)	T=12/64 (19%)	NR	NR	NR	NR	NR	NR

Abbreviations: C = control; CI = confidence interval; (a)OR = (adjusted) odds ratio; mRS = modified Rankin Scale; sICH = symptomatic intracranial hemorrhage; T = treated with heparin.
Captions: * Adjusted for: age and final revascularization success in one study; ** Adjusted for: intubation during procedure, post-device TICI 2b-3, diabetes mellitus, baseline NIHSS score, study device (Trevo vs Merci), time from symptom onset to arterial puncture (hours) and congestive heart failure in the other;
[1] SITS-MOST definition [8];
[2] ECASS-II definition [9];
[3] No specific definition of sICH given

Table 3.7. Characteristics of included studies investigating combined anti-thrombotic treatments use in patients with ischemic stroke who underwent acute mechanical thrombectomy.

Study Characteristics		Population characteristics				Recanalization therapy				Study treatment and contrast					
Author, year	**Study design**	**N.**	**Age**	**NIHSS score at baseline**	**Occlusion location**	**IV PA, n/N. (%)**	**IA PA, n/N. (%)**	**MT, n/N. (%)**	**Time from symptom onset to treatment, hours**	**Anti-thrombotic treatment**	**Indication for anti-thrombotic treatment**	**Time from symptom onset to anti-thrombotic treatment***	**n/N. (%)**	**Control**	**n/N. (%)**
Jeong, 2016	Pro-spective cohort	456**	Mean 68 (±13)	Median 11 (6-18)	NR	285/456 (63%)	NR	297/456 (65%)	Median 174 (102-468)	- Anti-platelet monotherapy (ASA or clopidogrel) - Anti-platelet dual therapy (ASA + clopidogrel or cilostazol) - Anticoagulant (LMWH, UFH, dabigatran, rivaroxaban, warfarine) - Anti-platelet with anticoagulant (LMWH, UFH, dabigatran)	Timing was based on individual physicians choice	Acute + Early	456/456 (100%)	NR	NR

Summary: Characteristics of the included studies are presented by sample size (percentage), means (standard deviations), medians (interquartile ranges) or by remarks.
Abbreviations: ASA = acetylsalicylic acid; BL = Baseline; IA = intra-arterial; IV = intravenous; LMWH = low molecular weight heparin; MT = mechanical thrombectomy (by means of stent retriever or aspiration); NR = not reported; UFH = unfractionated heparin; tPA = tissue plasminogen activator
Captions: *Time from symptom onset to anti-thrombotic treatment was divided in *acute* administration [<6 hours] and *early* administration [6- 24 hours]; **Not solely MT

Table 3.8. Outcomes of included studies investigating combined anti-thrombotic treatments use in patients with ischemic stroke who underwent acute mechanical thrombectomy.

Author, year	sICH, n/N. (%)	Mortality, n/N. (%)	mRS (0-2), n/N. (%)
Jeong, 2016	T=15/456 (3%); [1]	T=36/456 (8%)	T=256/456 (56%)

Abbreviations: sICH = symptomatic intracranial hemorrhage; T = treated with anti-thrombotics; mRS = modified Rankin Scale
Captions: [1] Intracranial hemorrhage resulting in NIHSS increase of ≥ 4

Discussion

Based on the available literature, an increased sICH risk for both periprocedural administration of antiplatelet agents and heparin may be expected. Notwithstanding this higher risk of sICH, we found promising results of early antithrombotics regarding functional outcome in ischemic stroke patients undergoing MT. Future studies, especially RCTs, need to determine if the potentially higher sICH risk can be outweighed by improved functional outcome.

Antiplatelet agents
Most studies reported a small but noteworthy higher risk of sICH. Only one study performed multivariable adjustment, in which an aOR of 8.03 was found[36]. However, the CI was wide (95% CI, 1.83–41.70), and there may have been residual confounding. Promising results on functional outcome were seen when patients were on prior antiplatelet treatment and a complete recanalization was established, as patients were twice as likely to have a favorable functional outcome[32]. This analysis has not been done by the other included studies. Furthermore, the effect of adding antiplatelet agents may have a different result in patients who were treated with IV rtPA[15]. However, none of the included studies performed this additional analysis. No further inference was possible.

Previous large randomized trials have investigated the isolated use of antiplatelet agents in general populations of patients with ischemic stroke (i.e., no endovascular treatment)[16,40]. In these studies, the absolute sICH risk associated with antiplatelet administration was approximately 1% when the treatment was initiated within 48 hours from symptom onset. MT with or without prior IV tPA bears a sICH risk of 4.4%, ranging from 0 to 7.7% in the large trials[1]. The MR CLEAN *post hoc* analysis had not found an interaction between antiplatelet agents and the effect of MT on functional outcome. Taken together, the risk of sICH in patients who undergo MT for ischemic stroke within 6 hours and the risk of sICH contributable to antiplatelet agents, this expected risk of sICH is in line with the range from 6 to 17% presented in our review[1,16].

On the whole, periprocedural use of anti-platelet agents may be a useful adjunct, albeit with a higher sICH risk.

Heparin

Although at least one of the reported studies suggested that periprocedural heparin increased the risk of sICH[37], both studies that reported a relative effect of heparin on functional independence showed favorable results[33,37]. However, the true impact of adjunct heparin use remains difficult to determine in these observational studies. Substantial between-center variability in the use of periprocedural heparin exists. Indications varied from no heparin use, to use at the discretion of the interventionalist, and to standard care.

A large RCT has previously investigated the isolated effect of heparin treatment within 48 h in a general population of patients with ischemic stroke (i.e., no endovascular treatment), which resulted in an absolute sICH risk of 1.2%[16]. Taken together with the sICH risk of MT, this is in line with the sICH range of 5-12% presented in our review[1,16]. This frequency of sICH is also comparable to the sICH risk in patients treated with acute systemic recombinant tPA in the NINDS and ECASS-III trials [41,42]. In the PROlyse (recombinant pro-urokinase) in Acute Cerebral Thromboembolism (PROACT) trial – the only randomized double-blind placebo-controlled trial of IA treatment – the use of heparin, at the outset (acute phase) of IA delivery of placebo or recombinant pro-urokinase (pro-UK), was a significant predictor of both recanalization efficacy and sICH frequency [43]. That study set the heparin protocol for the PROACT-II study, in which heparin was administered in combination with recombinant pro-UK. In PROACT-II both patients in the IA treatment arm and the control arm received heparin; 4,000 IU in total. A non-significant increase of 8% in sICH risk in the endovascular treatment arm compared to the control arm of the study was observed in the univariable analysis, but also an improvement in functional outcome just significant after stratification for stroke severity [44]. Based on the available literature, the overall higher risk of sICH may be offset by the improved odds for a functional independence when heparin is used periprocedurally.

Strengths and limitations

In light of two other reviews describing periprocedural antithrombotic use in ischemic stroke management, the strength of this study is the specific focus on MT, the emphasis on safety, the performance of a thorough systematic literature search and the identification of studies not included in both other reviews[45,46]. Another strength is the structured reporting of data according to the PRISMA-Statement.

A limitation of this study is that some studies investigating periprocedural antithrombotic use in patients with tandem lesions were not identified by the initial search. This was because these studies did not provide keywords related to antithrombotic treatment use. When we became aware of this finding, we managed this problem through an extensive bibliographic review of the included studies related to this topic. We discussed this issue with our biomedical information specialist, and due to heterogeneity among keywords used in these studies, an additional search was not feasible. It is possible that selection bias has occurred regarding this distinct

pathology. On the whole, the risk of sICH seems acceptable in patients with tandem lesions, but the results of this subpopulation should be interpreted with caution, as the causal effects of previous ischemia, misery perfusion, and sudden reperfusion alongside that of antiplatelet treatment cannot be untwined. Because patients with tandem lesions constitute a distinct subpopulation with ischemic stroke, results may also be less generalizable to results in patients with intracranial occlusions only, despite a similar treatment effect of acute MT in these patients[21]. However, since limited evidence is available on the safety of periprocedural antiplatelet use in ischemic stroke patients undergoing acute MT, these studies provide valuable information and could therefore not be omitted.

Other limitations were the wide heterogeneity of inclusion criteria, treatment characteristics, and outcome definitions among studies. We found that some studies included patients with posterior circulation occlusion. These patients have a very poor prognosis with high mortality rates[47]. Inclusion of these patients could have interfered with the reported outcomes. Furthermore, recanalization therapy varied among included studies from solely MT to more heterogeneous groups that received IV plasminogen activators, IA plasminogen activators, and/or MT. As no distinction was made in some studies, data specifically concerning patients who underwent MT could not always be extracted. This could have blurred the actual effect of periprocedural antithrombotic use in MT. Also, the use of IV plasminogen activator and IA plasminogen activator could have masked the actual sICH risk attributable to the antithrombotics. We also observed that the indication for antithrombotic administration depended on standard care, the discretion of the interventionist, and comorbidities, which dictated prior use. Patients with prior antiplatelet and heparin use were *a priori* more likely to have higher odds for worse outcome than the control group (due to comorbidity or occurrence of re-occlusion)—implying confounding by indication—which may hamper the interpretation of the outcomes and effect estimates. Even though few studies performed a multivariable analysis to adjust for confounding factors, this does not exclude the possibility that residual confounding has influenced our findings. Interpretation of the results of our review has been hampered by missing data in most studies regarding example collateral status, infarct size, and underlying medical conditions for which antithrombotics were administered. Besides, we cannot rule out the possibility of publication bias. Moreover, we could not take dosing into account because of the limited number of studies reporting this. As we focused on periprocedural antiplatelet and heparin use, the effect of other antithrombotic drugs such as direct oral anticoagulants (DOACs) and coumarin derivatives remains unanswered. We chose not to include DOACs and coumarin derivatives as these drugs are not readily available to be administered in the acute phase. Besides, there is no evidence that DOACs and coumarin derivatives can restore microvascular obstruction. Furthermore, the time interval between symptom onset and start of antithrombotic treatment ranged from naught (prior use), through 0–6 h (studies administering the antithrombotic drugs in the *acute* phase

during MT), to 6–24 h (studies postponing the antithrombotic treatment to the *early* postprocedural phase). Based on the experimental work, it seems likely that the acute use of specific antithrombotic agents could (I) decrease the incidence of sICH by avoiding the later stages of injury evolution and (II) potentially add to improvement of outcomes by preventing or limiting microvascular occlusion within the regions of ischemic injury[6,7,9]. As the exact underlying pathway by which antithrombotics act—direct link between IMR and antithrombotics—was not in the scope of this review, this should be explored in future research. An example supporting the statement that especially the *acute* phase is of clinical relevance is the use of IV plasminogen activator in current practice. IV plasminogen activator seems safe when used within 4.5 h after stroke onset and improves functional outcome. However, extending this time window increases the risk of sICH significantly offsetting the beneficial effect[48]. Possibly, as no clear distinction in time windows (i.e., *acute* or *early*) for antithrombotic treatment was made in most studies, the antithrombotic treatment effect may have been underestimated. Finally, sICH was defined according to various classifications, which makes it difficult to compare sICH risk among studies. Most studies elaborated on the exact sICH definition used[21-23,25,26,28,29,31,32,34,35,38,39,49]. Most commonly, sICH was defined as neurologic deterioration with a 4 or more point increase in NIHSS score in combination with intracranial hemorrhage on imaging. Not all studies elaborated on the exact definition used. Therefore, heterogeneity among studies could have led to overestimation or underestimation of the actual risk. Due to the large variety in sample sizes and the heterogeneity between studies, a more in-depth exploration will not be helpful.

Conclusions and future directions

Current evidence on periprocedural antiplatelet and heparin use in ischemic stroke patients undergoing acute MT relies on a limited number of post hoc analyses and cohort studies. Methodological limitations of these studies warrant cautious interpretation of the results. RCTs investigating the effect of periprocedural antithrombotic treatment in MT are lacking. Some observational studies report a slight increase in sICH risk, which may be acceptable because they also suggest a beneficial effect on functional outcome. Well-conducted phase III RCTs focusing on the acute use of antithrombotic agents alone and in combinations during MT are therefore required. MR CLEAN-MED ("Multicenter Randomized CLinical trial of Endovascular treatment for Acute ischemic stroke in the Netherlands; the effect of periprocedural MEDication: heparin, antiplatelet agents, both or neither") is an ongoing phase III trial that investigates the effect of periprocedural intravenous use of aspirin and/or UFH on functional outcome of ischemic stroke patients undergoing MT (ISRCTN 76741621). We expect that this trial will provide better insights in the balance between potential risks and benefits of the use of these periprocedural antithrombotics for these patients.

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Supplemental material

Search strategy performed in March 2018

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('brain infarction'/de OR 'brain ischemia'/de OR 'brain stem infarction'/de OR 'cerebellum infarction'/de OR 'cerebrovascular accident'/exp OR 'brain embolism'/exp OR 'occlusive cerebrovascular disease'/exp OR 'anterior circulation stroke'/de OR (((brain* OR cerebr* OR cerebell* OR lacunar* OR intracran* OR vertebrobasil* OR hemispher* OR intracran* OR intracerebral OR infratentorial OR supratentorial OR vertebr* OR 'anterior-circulation') NEAR/3 (infarct* OR ischemi* OR ischaemi* OR embol* OR thromb* OR occlus* OR hypoxi* OR accident OR attack OR stroke*)) OR ((cerebrovascular* OR cva OR cvas OR stroke*) NEAR/3 (ischem* OR ischaem* OR thromb* OR embol*))):ab,ti) AND ('thrombectomy'/exp OR 'embolectomy'/de OR 'endovascular surgery'/de OR (thrombectom* OR embolectom* OR ((endovascular* OR 'intra-arterial' OR intraarterial) NEAR/3 (surger* OR treatment* OR procedur* OR therap*))):ab,ti) AND ('pretreatment'/de OR (early OR (within NEXT/2 hour*) OR pretreatment* OR periprocedur* OR preprocedur* OR perioperative* OR preoperative* OR antecedent* OR ((pre OR before OR prior OR acute OR peri OR pre OR during OR before) NEAR/3 (treatment* OR procedur* OR therap*)) OR prestroke OR 'pre-stroke' OR adjunctive):ab,ti) AND ('anticoagulant agent'/de/mj OR 'anticoagulant therapy'/de OR 'heparin derivative'/exp/mj OR 'antithrombocytic agent'/exp/mj OR (anticoagulant* OR antithrombocyt* OR antithrombotic* OR antiplatelet* OR ((anti) NEXT/1 (thrombotic* OR thrombocytic* OR coagulant*)) OR 'acetylsalicylic-acid' OR clopidogrel OR heparin* OR warfarin* OR ticlopidine OR (fibrinogen* NEAR/3 antagonis*) OR prasugrel* OR abciximab* OR enoxaparin* OR dipyridamole* OR ticagrelor* OR eptifibatide* OR ((platelet* OR 'Factor-Xa' OR 'Factor-X' OR thrombin*) NEAR/3 (inhibitor* OR antagonist* OR anti OR antiaggregat*)) OR antithrombin* OR (GP NEAR/3 (IIb OR IIIa) NEAR/3 inhibitor*)):ab,ti) NOT ([animals]/lim NOT [humans]/lim) NOT ('Conference Abstract' OR Letter OR Note OR Editorial)/it AND english:la

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(exp "Brain Infarction"/ OR "Brain Ischemia"/ OR "Stroke"/ OR exp "Intracranial Embolism and Thrombosis"/ OR (((brain* OR cerebr* OR cerebell* OR lacunar* OR intracran* OR vertebrobasil* OR hemispher* OR intracran* OR intracerebral OR infratentorial OR supratentorial OR vertebr* OR anterior-circulat*) ADJ3 (infarct* OR ischemi* OR ischaemi* OR embol* OR thromb* OR occlus* OR hypoxi* OR accident OR attack OR stroke*)) OR ((cerebrovascular* OR cerebr*-vascul* OR cva OR cvas OR stroke*) ADJ3 (ischem* OR ischaem* OR thromb* OR embol*))).ab,ti,kf.) AND ("Thrombectomy"/ OR exp "Embolectomy"/ OR exp "Endovascular Procedures"/ OR (thrombectom* OR embolectom* OR ((endovascular* OR "intra-arterial" OR intraarterial) ADJ3 (surger* OR treatment* OR procedur* OR therap*))).

ab,ti.) AND ((early OR (within ADJ2 hour*) OR pretreatment* OR periprocedur* OR preprocedur* OR perioperative* OR preoperative* OR antecedent* OR ((pre OR before OR prior OR acute OR peri OR pre OR during OR before) ADJ3 (treatment* OR procedur* OR therap*)) OR prestroke OR "pre-stroke" OR adjunctive).ab,ti,kf.) AND (exp "Anticoagulants"/ OR exp "Heparin"/ OR exp "Platelet Aggregation Inhibitors"/ OR "Ticagrelor".nm. OR (anticoagulant* OR antithrombocyt* OR antithrombotic* OR antiplatelet* OR ((anti) ADJ1 (thrombotic* OR thrombocytic* OR coagulant*)) OR "acetylsalicylic-acid" OR Aspirin* OR clopidogrel OR heparin* OR warfarin* OR ticlopidin* OR (fibrinogen* ADJ3 antagonis*) OR prasugrel* OR abciximab* OR enoxaparin* OR dipyridamole* OR ticagrelor* OR eptifibatide* OR ((platelet* OR "Factor-Xa" OR "Factor-X" OR thrombin*) ADJ3 (inhibitor* OR antagonist* OR anti OR antiaggregat*)) OR antithrombin* OR (GP ADJ3 (IIb OR IIIa) ADJ3 inhibitor*)). ab,ti,kf.) NOT (exp animals/ NOT humans/) NOT ((congresses OR letter OR editorial). pt.) AND english.lg.

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((((brain* OR cerebr* OR cerebell* OR lacunar* OR intracran* OR vertebrobasil* OR hemispher* OR intracran* OR intracerebral OR infratentorial OR supratentorial OR vertebr* OR 'anterior-circulation') NEAR/3 (infarct* OR ischemi* OR ischaemi* OR embol* OR thromb* OR occlus* OR hypoxi* OR accident OR attack OR stroke*)) OR ((cerebrovascular* OR cva OR cvas OR stroke*) NEAR/3 (ischem* OR ischaem* OR thromb* OR embol*))):ab,ti) AND ((thrombectom* OR embolectom* OR ((endovascular* OR 'intra-arterial' OR intraarterial) NEAR/3 (surger* OR treatment* OR procedur* OR therap*))):ab,ti) AND ((early OR (within NEXT/2 hour*) OR pretreatment* OR periprocedur* OR preprocedur* OR perioperative* OR preoperative* OR antecedent* OR ((pre OR before OR prior OR acute OR peri OR pre OR during OR before) NEAR/3 (treatment* OR procedur* OR therap*)) OR prestroke OR 'pre-stroke' OR adjunctive):ab,ti) AND ((anticoagulant* OR antithrombocyt* OR antithrombotic* OR antiplatelet* OR ((anti) NEXT/1 (thrombotic* OR thrombocytic* OR coagulant*)) OR 'acetylsalicylic-acid' OR clopidogrel OR heparin* OR warfarin* OR ticlopidine OR (fibrinogen* NEAR/3 antagonis*) OR prasugrel* OR abciximab* OR enoxaparin* OR dipyridamole* OR ticagrelor* OR eptifibatide* OR ((platelet* OR 'Factor-Xa' OR 'Factor-X' OR thrombin*) NEAR/3 (inhibitor* OR antagonist* OR anti OR antiaggregat*)) OR antithrombin*):ab,ti)

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TS=(((((brain* OR cerebr* OR cerebell* OR lacunar* OR intracran* OR vertebrobasil* OR hemispher* OR intracran* OR intracerebral OR infratentorial OR supratentorial OR vertebr* OR "anterior-circulation") NEAR/2 (infarct* OR ischemi* OR ischaemi* OR embol* OR thromb* OR occlus* OR hypoxi* OR accident OR attack OR stroke*)) OR ((cerebrovascular* OR cva OR cvas OR stroke*) NEAR/2 (ischem* OR ischaem* OR thromb* OR embol*)))) AND ((thrombectom* OR embolectom* OR ((endovascular*

OR “intra-arterial” OR intraarterial) NEAR/2 (surger* OR treatment* OR procedur* OR therap*)))) AND ((early OR (within NEAR/2 hour*) OR pretreatment* OR periprocedur* OR preprocedur* OR perioperative* OR preoperative* OR antecedent* OR ((pre OR before OR prior OR acute OR peri OR pre OR during OR before) NEAR/2 (treatment* OR procedur* OR therap*)) OR prestroke OR “pre-stroke” OR adjunctive)) AND ((anticoagulant* OR antithrombocyt* OR antithrombotic* OR antiplatelet* OR ((anti) NEAR/1 (thrombotic* OR thrombocytic* OR coagulant*)) OR “acetylsalicylic-acid” OR clopidogrel OR heparin* OR warfarin* OR ticlopidine OR (fibrinogen* NEAR/2 antagonis*) OR prasugrel* OR abciximab* OR enoxaparin* OR dipyridamole* OR ticagrelor* OR eptifibatide* OR ((platelet* OR “Factor-Xa” OR “Factor-X” OR thrombin*) NEAR/2 (inhibitor* OR antagonist* OR anti OR antiaggregat*)) OR antithrombin*)) NOT ((animal* OR rat OR rats) NOT (human* OR patient*))) AND DT=Article AND LA=English

CHAPTER IV

Prior antiplatelet therapy in patients undergoing endovascular treatment for acute ischemic stroke: results from the MR CLEAN Registry

International Journal of Stroke, 2020

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Abstract

Background: Antiplatelet therapy may increase the risk of symptomatic intracranial hemorrhage after endovascular treatment for ischemic stroke but may also have a beneficial effect on functional outcome. The aim of this study is to compare safety and efficacy outcomes after endovascular treatment in patients with and without prior antiplatelet therapy.

Methods: We analyzed patients registered in the MR CLEAN Registry between March 2014 and November 2017, for whom data on antiplatelet therapy were available. We used propensity score nearest-neighbor matching with replacement to balance the probability of receiving prior antiplatelet therapy between the prior antiplatelet therapy and no prior antiplatelet therapy group and adjusted for baseline prognostic factors to compare these groups. Primary outcome was symptomatic intracranial hemorrhage. Secondary outcomes were 90-day functional outcome (modified Rankin Scale), successful reperfusion (extended thrombolysis in cerebral infarction score ≥2B) and 90-day mortality.

Results: Thirty percent (n = 937) of the 3154 patients were on prior antiplatelet therapy, who were matched to 477 patients not on prior antiplatelet therapy. Symptomatic intracranial hemorrhage occurred in 74/937 (7.9%) patients on prior antiplatelet therapy and in 27/477 (5.6%) patients without prior antiplatelet therapy adjusted odds ratio 1.47, 95% confidence interval 0.86–2.49. No associations were found between prior antiplatelet therapy and functional outcome (adjusted common odds ratio 0.87, 95% confidence interval 0.65–1.16), successful reperfusion (adjusted odds ratio 1.23, 95% confidence interval 0.77–1.97), or 90-day mortality (adjusted odds ratio 1.15, 95% confidence interval 0.86–1.54).

Conclusion: We found no evidence of an association of prior antiplatelet therapy with the risk of symptomatic intracranial hemorrhage after endovascular treatment, nor on functional outcome, reperfusion, or mortality. A substantial beneficial or detrimental effect of antiplatelet therapy on clinical outcome cannot be excluded. A randomized clinical trial comparing antiplatelet therapy versus no antiplatelet therapy is needed.

Introduction

Approximately 50% of patients with ischemic stroke do not recover to functional independence after endovascular treatment (EVT).[1] Although pre-stroke disability and large baseline infarct core are known causes of these poor outcomes, incomplete microvascular reperfusion – a potentially reversible process – might contribute to these poor outcomes as well. One of the causes of incomplete microvascular reperfusion is the formation of microthrombi occluding the distal capillary bed. These microthrombi are abundantly present after focal cerebral ischemia in the distal vascular territory. The formation of microthrombi might be promoted by vessel wall damage caused by EVT.[2,3] Use of antiplatelet drugs could potentially reduce periprocedural formation of microthrombi by inhibiting platelet aggregation and inflammation of the vessel wall, which could ultimately improve microvascular reperfusion.[2] On the other hand, one randomized trial showed that antiplatelet therapy increases the risk of symptomatic intracranial hemorrhage (sICH) when administered early – within 90 minutes – after intravenous treatment with alteplase.[4] However, this trial did not focus on the subpopulation of patients with ischemic stroke caused by a large vessel occlusion undergoing EVT. In these patients the beneficial effect of platelet inhibition could counterbalance the detrimental effects of increase risk of sICH. As interventionist are familiar with periprocedural use of antiplatelet agents during non-stroke neurovascular procedures (i.e. stenting) this treatment might be an easy applicable therapy of adjunctive value in EVT for stroke. However, as antiplatelet agents are not administered systematically during EVT for acute ischemic stroke current evidence is limited to small observational studies investigating the association of prior antiplatelet therapy with sICH risk and functional outcomes, showing conflicting results.[5] The evaluation of risks and benefits of prior antiplatelet therapy in a large cohort of patients treated with EVT could provide useful information for clinical practice. The aim of this study is to compare safety and efficacy outcomes after EVT of patients with and without prior antiplatelet therapy.

Methods

Study design

We used data from the MR CLEAN Registry, which is a nationwide, multicenter, prospective, observational study including all consecutive patients treated with EVT for ischemic stroke in the Netherlands. The complete methods and definition 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; treatment in a center that participated in the MR CLEAN trial; presence of a proximal intracranial occlusion in the anterior circulation confirmed on computed tomography angiography (intracranial carotid artery [ICA], intracranial carotid artery terminus [ICA-T], middle

cerebral artery [M1/M2], or anterior cerebral artery [A1/A2]); groin puncture within 6.5 hours after symptom onset and known data on prior antiplatelet therapy. The current observational study was guided by the STROBE statement.[7]

Ethical considerations and data availability

The central medical ethics committee of the Erasmus MC, University Medical Center Rotterdam, the Netherlands, evaluated the study protocol and granted permission to carry out the study as a registry (MEC-2014-235). This approval extends to all participating centers in the Netherlands. 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 http://www.mrclean-trial.org/docs/latestprotocol.pdf. Data cannot be made available, as no patient approval has been obtained for sharing coded data. However, syntax files and output of statistical analyses (R 3.5.0) will be made available upon request.

Prior antiplatelet therapy

Prior antiplatelet therapy was defined as the use of any antiplatelet agent at baseline, reported by the local investigators. We compared outcomes of patients that were on antiplatelet therapy prior to the EVT procedure to patients not on antiplatelet therapy. Data on which specific antiplatelet agent was used before EVT were not prospectively collected in the MR CLEAN Registry. For insight into dual antiplatelet usage, we retrospectively evaluated all available patient discharge letters on this specific issue. Acute administration of any antiplatelet agents during EVT is not part of common practice in the Netherlands. At the discretion of the treating physician, acute administration of antiplatelets was possible in those patients requiring immediate carotid artery stenting; this concerns only a few patients and was not recorded in this registry. Patients with non-cardioembolic ischemic stroke received antithrombotic medication according to local guidelines (either clopidogrel or acetylsalicylic acid, with appropriate loading dose). In patients who also received intravenous thrombolytics, antiplatelet therapy was delayed until >24h after stroke thrombolysis.

Outcome measures

The primary outcome was the occurrence of sICH, before final follow-up assessment at 90 days, defined as neurological deterioration (increase of 4 points or more on the National Institutes of Health Stroke Scale [NIHSS]) and a compatible cerebral hemorrhage seen on imaging assessed by an independent imaging core laboratory. Secondary outcomes were functional outcome at 90 days (range ±14 days) on the modified Rankin Scale (mRS), which is a 7-point ordinal scale ranging from 0 'no symptoms' to 6 'dead' (both ordinal and dichotomized for functional independence (0-2 vs. 3-6)[8], successful reperfusion of the distal macrovascular territory (extended Thrombolysis In Cerebral Infarction grade ≥ 2B) at the end of the EVT assessed by an independent imaging core laboratory, NIHSS score 24-48 hours after intervention, and

within 90 days occurrence of mortality, progression of ischemic stroke, new ischemic stroke, extracranial hemorrhage, and cardiac ischemia.

Statistical methods

Differences in baseline characteristics were assessed for both categorical and dichotomous variables using χ^2 test for categorical variables, independent samples t-test for normally distributed continuous variables, and Kruskal-Wallis for non-parametric testing. Any mRS score (except for occurrence of death) assessed within 30 days of symptom onset was considered invalid and treated as missing. We assume "missing" in any (both safety and efficacy) outcome assessment to be distributed at random. For the purpose of unbiased estimation of associations of outcome with baseline characteristics, we used multiple imputation by chained equations and pooled data over five imputed datasets.[9,10] All baseline data and outcomes that are reported are crude and not imputed. A description of the exact imputation settings used is provided in supplemental table 4.1. To reduce possible confounding by indication we performed propensity score matching using a within approach, performing propensity score matching within each imputed dataset averaging the effect estimates.[11] The propensity score for each individual was defined as the probability of being on the treatment (prior antiplatelet therapy) given the patient's baseline characteristics and comorbidities. Variables used to retrieve the propensity score were required to be factors potentially related to the choice of treatment assignment remaining inclusive. In case of uncertainty whether a variable was related to treatment assignment advantage was given to this variable. Subsequently we performed nearest-neighbor matching on the derived propensity score with replacement setting a caliper of 0.25 SD of the logit for propensity score.[12,13] To assess whether the propensity-sore model has been adequately specified we evaluated baseline characteristics distributions before and after matching and evaluated propensity score densities graphically.[14] Within the propensity-score matched cohort, we performed binary and ordinal logistic and linear regression analyses as appropriate and additionally adjusted for important prognostic covariates to optimally reduce residual imbalances in observed covariates between patients with and without prior antiplatelet therapy.[15,16] The selection of covariates was based on prior knowledge and included NIHSS at admission, treatment with intravenous alteplase, location of the intracranial occlusion, Alberta Stroke Program Early Computed Tomography Score (ASPECTS) at baseline, CTA collateral grade at baseline, and time from onset to reperfusion. Sensitivity analyses using binary and ordinal and linear logistic regression for the full cohort (without propensity-score matching) were performed. Additional subgroup analyses on associations of antiplatelet therapy were performed for history of myocardial infarction, history of prior stroke, treatment with both intravenous alteplase and EVT, treatment with EVT only, successful reperfusion, and for prior oral anticoagulant use. Associations are presented as (adjusted common) odds ratio (a(c)OR) with 95% confidence interval (CI). Because there is consensus on the ordering of the outcome scale in this case (each

score on the mRS is more favorable than a one point lower score), the common OR can be presented and interpreted as a summary estimate of the treatment effect, even if the underlying proportional odds assumption would be violated.[17] Therefore, we decided not to formally test this assumption. All statistical analyses were performed with R version 3.5.0 (R foundation for Statistical Computing, Vienna, Austria).

Results

Study population

A total of 3154 patients were analyzed, of which 937 patients (30%) were on prior antiplatelet therapy (Figure 4.1). Based on the retrospective discharge letter evaluation, data on the specific antiplatelet agent used were missing in 360 of the 937 patients. Among patients with available data, 83% (480/577) were on a single antiplatelet therapy and 17% on dual antiplatelet therapy (97/577). Patients on dual antiplatelets used a combination of acetylsalicylic acid and dipyridamole in 51% of the cases (50/97) and a combination of acetylsalicylic acid and clopidogrel in 41% of the cases (40/97). Patients on prior antiplatelet therapy were older, were more often male, had lower international normalized ratios, had more comorbidities (i.e. history of ischemic stroke, atrial fibrillation, hypertension, diabetes, and myocardial infarction), and had higher pre-stroke mRS scores (Table 4.1). Also, these patients were more often using other types of medication, were more often eligible for intravenous alteplase, and differed from patients not on prior antiplatelet therapy in baseline imaging characteristics (i.e. occlusion location, ASPECTS, and collateral filling).

Propensity score matching

On average, 477 patients (number of matches over five imputations ranged between 474 and 478) not on prior antiplatelets were matched to 937 patients who were on prior antiplatelet therapy. In the propensity-score-matched cohort, baseline characteristics were more similar between groups compared to the full cohort suggesting that reasonable balance was obtained (Table 4.1). Also, visual balance check of the propensity score was reasonably improved when comparing the distributions before matching (full cohort) to those after matching (propensity-score-matched cohort; supplemental figure 4.1).

Outcomes

In the propensity-score-matched cohort, no significant difference in sICH risk was observed between patients who were on prior antiplatelet therapy and those not on prior antiplatelet therapy (74/937 [7.9%] vs. 27/477 [5.6%]; aOR 1.47, 95% CI 0.86–2.49; Table 4.2). Also, no associations were found between prior antiplatelet therapy and functional outcome (median mRS 4 [IQR: 2–6] vs. 4 [2–6]; acOR 0.87, 95% CI 0.65–1.16; Figure 4.2), successful reperfusion (aOR 1.23, 95% CI 0.77–1.97), mortality (aOR 1.15, 95% CI 0.86–1.54), or the other secondary outcomes. In the sensitivity analysis, in the

full cohort (without propensity-score matching), we found neither a difference in sICH risk (aOR 1.48, 95% CI 0.99–2.20) nor a difference in functional outcome (acOR 0.92, 95% CI 0.76–1.10; Figure 4.2) between groups. Only in the subgroup of patients with a prior stroke, we found that risk of sICH was increased for patients on prior antiplatelet therapy compared to those not on antiplatelet therapy (aOR 11.08, 95% CI 2.04–60.31). We did not detect a beneficial association on functional outcome of prior antiplatelet therapy in the subgroup analysis of patients with successful reperfusion (eTICI≥2B). Results of the sensitivity analysis are presented together with additional subgroup analyses in the supplemental table 4.2 and supplemental figure 4.2.

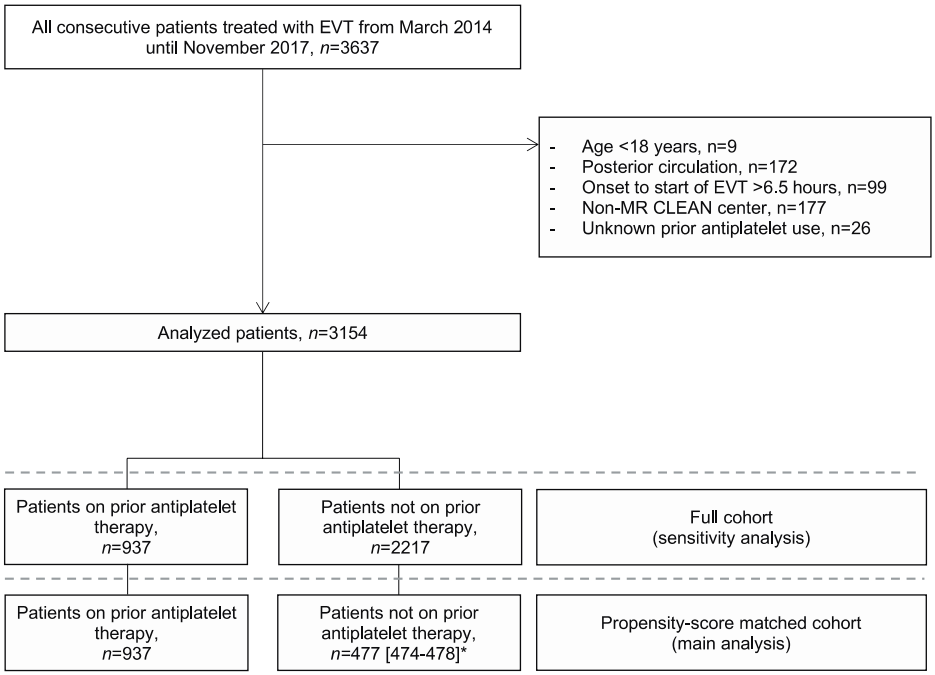

Figure 4.1. Flowchart.
Abbreviations: EVT, endovascular treatment; MR CLEAN, Multicenter randomized clinical trial of endovascular treatment of acute ischemic Stroke.
Captions: * Calculated after handling missing data using multiple imutation procedures and performing propensity score matching within the derived 5 imputation sets. On average 477 patients (number of matches over 5 imputations ranged between 474 and 478) not on prior antiplatelets were matched to 937 patients who were on prior antiplatelet therapy (replacement was possible).

Table 4.1. Baseline demographics before propensity score matching [full cohort] and after matching [propensity-score matched cohort]

	Propensity-score matched cohort		Full cohort		
	Prior APT (n=937)*	No prior APT (n=477)*	Prior APT (n=937)	No prior APT (n=2217)	Missing
Common patient characteristics					
Age	74 (12)	73 (13)	74 (12)	69 (15)	0
Male sex	521 (56)	259 (54)	521 (56)	1121 (51)	0
NIHSS at baseline	16 [11, 20]	16 [12, 20]	16 [11, 20]	16 [11, 19]	14/32
Ischemia in left hemisphere	506 (54)	246 (52)	501 (54)	1169 (53)	8/10
Systolic blood pressure	149 (25)	153 (24)	149 (25)	150 (25)	27/57
Diastolic blood pressure	80 (15)	83 (16)	80 (15)	83 (16)	27/65
INR	1.1 (0.3)	1.2 (0.4)	1.1 (0.3)	1.2 (0.4)	189/398
Glucose level (mmol/L)	7.5 (2.5)	7.6 (2.5)	7.6 (2.5)	7.3 (2.5)	118/239
Trombocyte count (10^9/L)	250 (97)	249 (84)	250 (99)	249 (82)	121/308
Medical history					
Previous stroke	325 (35)	103 (22)	322 (35)	204 (9.2)	9/11
Atrial fibrillation	180 (19)	125 (26)	177 (19)	575 (26)	17/17
Hypertension	632 (68)	301 (63)	615 (68)	1005 (46)	26/31
Diabetes mellitus	210 (23)	93 (20)	210 (23)	291 (13)	3/14
Myocardial infarction	305 (33)	88 (18)	296 (33)	144 (6.6)	26/31
Peripheral arterial disease	171 (18)	66 (14)	166 (18)	124 (5.7)	25/31
Pre-stroke mRS >2	149 (16)	67 (14)	139 (15)	221 (10)	37/32
Medication use					
DOAC	10 (1.1)	11 (2.3)	10 (1.1)	94 (4.3)	10/13
Coumarin	41 (4.4)	53 (11)	41 (4.4)	366 (16.6)	2/8
Blood pressure lowering medication	677 (72)	286 (60)	666 (72)	1018 (46.5)	14/27
Statin	598 (64)	158 (33)	583 (64)	515 (23.6)	19/32
Imaging					
Occluded segment					44/89
Intracranial ICA	38 (4.1)	25 (5.3)	36 (4.0)	119 (5.6)	
ICA-T	170 (18)	101 (21)	161 (18)	468 (22)	
M1	560 (60)	272 (57)	535 (60)	1218 (57)	
M2	157 (17)	75 (16)	151 (17)	310 (15)	
Other (e.g., M3, ACA)	11 (1.2)	3 (0.6)	10 (1.1)	13 (0.6)	
Reperfusion grade before intervention (eTICI)					48/119
0	753 (80)	377 (79)	717 (81)	1667 (80)	
1	47 (5.0)	30 (6.3)	44 (4.9)	141 (6.7)	
2A	46 (4.9)	24 (5.0)	43 (4.8)	101 (4.8)	
2B	65 (7.0)	32 (6.7)	63 (7.1)	136 (6.5)	
2C	15 (1.4)	4 (0.8)	11 (1.2)	16 (0.8)	
3	11 (1.2)	10 (2.1)	11 (1.2)	37 (1.8)	

Table 4.1. Continued.

	Propensity-score matched cohort		Full cohort		
	Prior APT (n=937)*	**No prior APT (n=477)***	**Prior APT (n=937)**	**No prior APT (n=2217)**	**Missing**
ASPECTS	9 [8, 10]	9 [7, 10]	9 [8, 10]	9 [7, 10]	33/70
ASPECTS ≤ 7	226 (24)	123 (26)	216 (24)	549 (26)	33/70
CTA collateral grade					60/141
Grade 0 - Absent collaterals	50 (5.3)	32 (6.6)	48 (5.5)	136 (6.6)	
Grade 1 - Occluded area filling <50%	377 (40)	166 (35)	354 (40)	708 (34)	
Grade 2 - Occluded area filling >50% but <100%	335 (36)	190 (40)	312 (36)	832 (40)	
Grade 3 - Occluded area filling 100%	175 (19)	88 (19)	163 (19)	400 (19)	
Workflow (in minutes)					
Time from symptom onset to admission ER (intervention center)	135 [60, 186]	131 [65, 185]	136 [60, 187]	131 [63, 187]	56/100
Time from admission ER to groin puncture	61 [35, 92]	62 [38, 93]	59 [35, 89]	60.0 [35, 90]	107/180
Duration procedure	58 [39, 85]	59 [38, 85]	58 [39, 84]	59 [38, 83]	88/194
Time from symptom onset to recanalization	250 [201, 307]	250 [198, 314]	251 [202, 305]	250 [198, 312]	69/130
Treatment					
Treatment with intravenous alteplase	744 (79)	355 (75)	741 (79)	1668 (75)	3/5
General anesthetic management	218 (23)	115 (24)	204 (23)	549 (26)	59/134
Administration of intra-arterial thrombolytic	22 (2.3)	11 (2.3)	22 (2.3)	57 (2.6)	0
Periprocedural heparin administration	259 (28)	128 (27)	259 (28)	582 (26)	0

Summary: Baseline variables of patients on prior antiplatelet therapy vs. no prior antiplatelet therapy. Continuous and ordinal 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 CT score; DOAC, direct oral anticoagulant; ER, emergency room; eTICI, extended thrombolysis in cerebral infarction; ICA (T), internal carotid artery (terminus); M(*segment*), middle cerebral artery; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale
Captions: *Calculated after handling missing data using multiple imputation procedures and performing propensity score matching within the derived 5 imputation sets. Variables were averaged over 5 imputation sets. On average 477 patients (number of matches over 5 imputations ranged between 474 and 478) not on prior antiplatelets were matched to 937 patients who were on prior antiplatelet therapy (allowing replacement).

Table 4.2. Primary and secondary outcomes in patients on prior antiplatelet therapy vs. no prior antiplatelet therapy in the propensity-score matched cohort

	Prior APT (n=937)*	**No prior APT (n=477)***	**a(c)OR, (95%CI)†**
Primary outcome			
Symptomatic intracranial hemorrhage	74 (7.9)	27 (5.6)	1.47 (0.86-2.49)
Secondary outcomes			
mRS at 90 days	4 [2, 6]	4 [2, 6]	0.87 (0.65-1.16)
mRS ≤ 2 at 90 days	334 (36)	180 (38)	0.88 (0.64-1.19)
NIHSS at 24-48 hours	11 [4, 18]	11 [4,18]	0.14 (-0.72 to 1.01)‡
Reperfusion grade after intervention (eTICI ≥ 2B)	587 (63)	273 (57)	1.23 (0.77-1.97)
Mortality within 90 days	329 (35)	157 (33)	1.15 (0.86-1.54)
Progression of stroke	71 (7.6)	49 (10)	0.70 (0.41-1.20)
New ischemic stroke	14 (1.5)	9 (2.0)	0.74 (0.28-1.93)
Extracranial hemorrhage	22 (2.3)	13 (2.8)	0.81 (0.37-1.82)
Cardiac ischemia	7 (0.7)	4 (0.8)	1.02 (0.19-5.43)

Summary: Primary and secondary outcomes of patients on prior antiplatelet therapy vs. no prior antiplatelet therapy. Skewed continuous and ordinal data are presented as median [IQR]. Binary data are presented as numbers (%).
Abbreviations: a(c)OR, adjusted (common) odds ratio; APT, antiplatelet therapy; CI, confidence interval; eTICI, extended thrombolysis in cerebral infarction; mRS, modified Rankin Scale
Captions: * Calculated after handling missing data using multiple imputation procedures and performing propensity score matching within the derived 5 imputation sets. Variables were averaged over 5 imputation sets. On average 477 patients (number of matches over 5 imputations ranged between 474 and 478) not on prior antiplatelets were matched to 937 patients who were on prior antiplatelet therapy (allowing replacement). † *Variables used for retrieving propensity-score and matching:* sex, age, pre-stroke disability (mRS), direct oral anticoagulant therapy, vitamin K antagonist therapy, previous stroke, myocardial infarction, peripheral artery disease, diabetes mellitus, hypertension, atrial fibrillation; *Variables in the additional adjustment model:* NIHSS at admission, intravenous alteplase, occlusion segment, ASPECTS at baseline, onset to reperfusion, CTA collateral grade. ‡ Beta (95%CI)

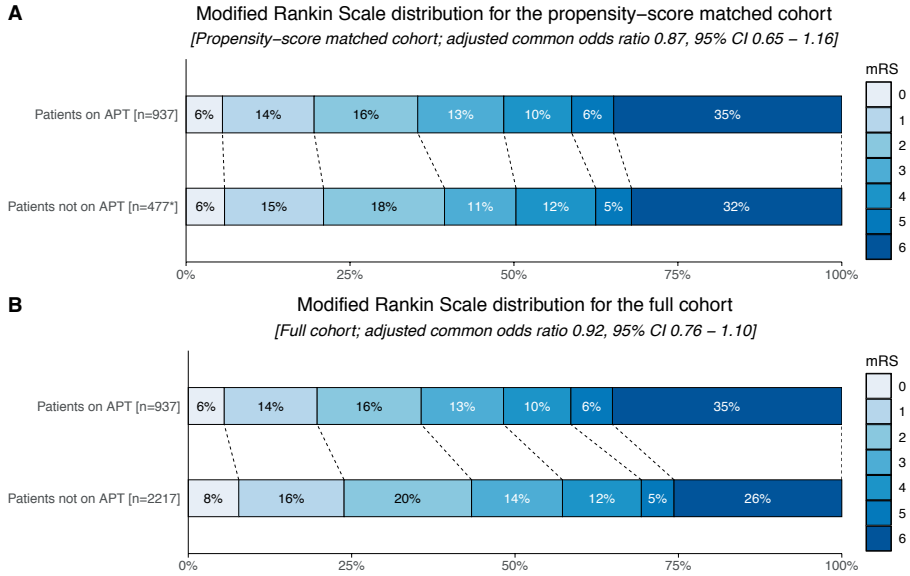

Figure 4.2. Modified Rankin Scale distribution for the propensity-score matched cohort (A) and full cohort (B) for patients on prior antiplatelet therapy and not on prior antiplatelet therapy. Missing values on modified Rankin Scale were handled by multiple imputation in 6.7% of patients.

Abbreviations: APT, antiplatelet therapy; CI, confidence interval; EVT, endovascular treatment; MR CLEAN, Multicenter randomized clinical trial of endovascular treatment of acute ischemic Stroke; mRS, modified Rankin Scale

Captions: * On average 477 patients (number of matches over 5 imputations ranged between 474 and 478) not on prior antiplatelets were matched to 937 patients who were on prior antiplatelet therapy (replacement was possible)

Discussion

Antiplatelet agents may be a promising adjunctive therapy during EVT for stroke. However, as antiplatelet agents are not administered systematically during EVT procedures, we evaluated safety and efficacy of prior antiplatelet therapy in a large observational study of patients treated with EVT for ischemic stroke in the Netherlands. In this study, we did not find an association between prior antiplatelet therapy and any of the safety outcomes. Particularly, the risk of sICH, nor the risk of death within 90 days was increased in patients on prior antiplatelet therapy. The associations with the secondary outcomes for efficacy were not significant. This concerned functional outcome at 90 days, stroke severity at 24h assessed with the NIHSS, and post-EVT reperfusion grade (eTICI).

Our findings are consistent with the results of two smaller observational studies evaluating prior antiplatelet therapy in EVT treated patients, both reporting no significant associations on risk of sICH and functional outcome.[18,19] Our study negates the observation in the MR CLEAN trial of a substantially increased risk of symptomatic intracranial hemorrhage in patients on prior antiplatelet therapy.[20]

The safety of antiplatelet agents in patients treated with intravenous alteplase has been investigated in several studies. In the National Institute of Neurological Disorders and Stroke (NINDS) trial on the effect of intravenous alteplase, clinical deterioration was less common in patients who were on prior antiplatelet therapy.[21] The authors suggested an association with early re-occlusion prevention. These findings formed the rationale for a trial of acetylsalicylic acid directly after intravenous alteplase treatment. This trial was halted prematurely because of futility and increased sICH risk.[4] These results are not generalizable to patients undergoing EVT, because these patients will be more susceptible to re-occlusion and induction of microthrombi by vessel wall damage, and are therefore at higher risk of ischemic complications.

Given the liberal inclusion criteria of this registry and the broad area of common support in propensity scores after matching, we consider the results of this study are generalizable to the larger EVT-eligible population of ischemic stroke patients with an intracranial occlusion of the anterior circulation who are treated within 6.5 h from symptom onset.

Our study has some limitations. First, despite (I) propensity-score matching to obtain properly matched groups of patients with and without prior antiplatelet therapy and (II) additional covariate adjustment to increase robustness of the outcomes, it is still possible that our results are hampered by confounding indications. Factors relating to the patients vascular may not be captured completely in the model. Additionally, occurrence of sICH is impacted by several other factors such as the post (peri)procedural blood pressure management or follow-up infarct volume. These unmeasured characteristics may confound differences between patients with and without prior antiplatelet therapy. Second, re-occlusions were not scored systematically on follow-up imaging in this registry after EVT. Instead, we reported

occurrence of stroke progression and new ischemic stroke, which showed a non-significant trend toward lower occurrence in patients who were on prior antiplatelet therapy. Third, in this study, we were not able to address the question whether dual antiplatelet therapy is associated with different safety and efficacy results as compared to single antiplatelet therapy due to low numbers, which warrants further study. Finally, the compliance with prior antiplatelet therapy in our cohort is unknown. If the compliance was poor, which is conceivable as antiplatelet therapy is paradoxically used in the prevention of stroke, this may have influenced our results.

The results of our observational study do not exclude the possibility of a sizeable beneficial effect of antiplatelet therapy in ischemic stroke patients undergoing EVT. In the ongoing MR CLEAN-MED trial (*Multicenter randomized clinical trial of endovascular treatment for acute ischemic stroke; the effect of periprocedural medication: acetylsalicylic acid, unfractionated heparin, both or neither;* ISRCTN76741621), patients are being randomized to intravenous acetylsalicylic acid and/or unfractionated heparin to investigate whether this will improve functional outcome after EVT. In this trial, intravenous acetylsalicylic acid is administered during EVT, overcoming the issue of non-compliance. This trial will provide new randomized data to answer the question whether platelet inhibition is safe and beneficial for this group of severely affected ischemic stroke patients.

Conclusion

In this observational study, we did not find evidence that prior antiplatelet therapy is associated with sICH, functional outcome, reperfusion, or mortality after EVT for ischemic stroke. Our results do not exclude a beneficial or detrimental effect of antiplatelet therapy on outcome after EVT for ischemic stroke. A randomized trial is therefore justified to evaluate the safety and efficacy of antiplatelet agents administered during EVT.

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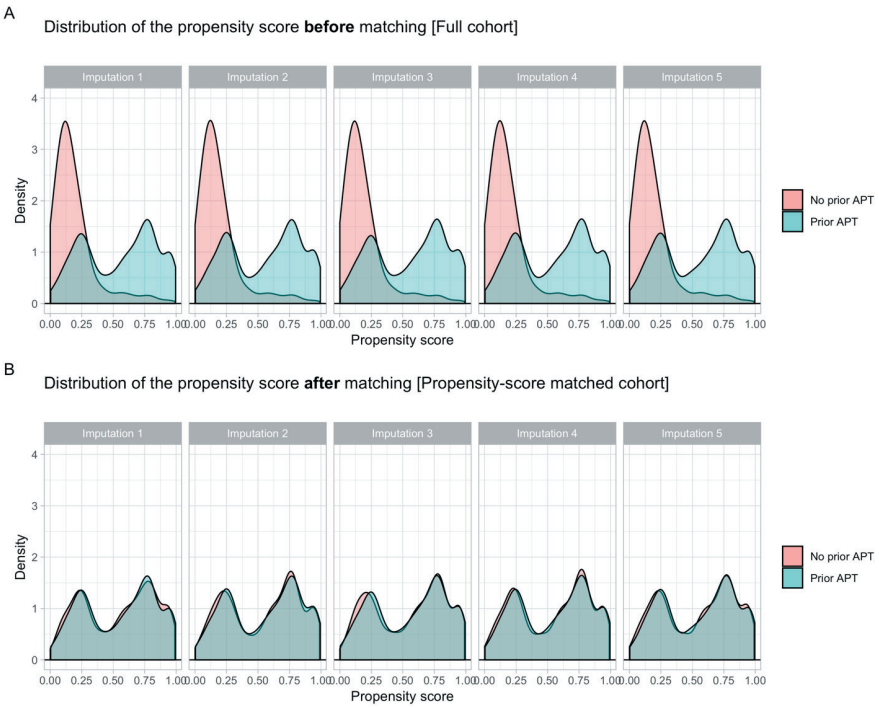
Supplemental material

Supplemental table 4.1. Multiple imputation method

Software	R 3.5.0, and the 'mice' package.
Imputed variables	age, sex, baseline NIHSS score, glucose level, diabetes, thrombocyte count, previous myocardial infarction, previous stroke, hypercholesterolemia, hypertension, peripheral artery disease, atrial fibrillation, drug use (antiplatelet, coumarine, novel oral anticoagulant, statin and antihypertensive), prestroke mRS score, international normalized ratio, blood pressure, baseline ASPECTS, occlusion segment, affected hemisphere, collateral status, time from symptom onset to start of endovascular treatment, time from symptom onset to successful reperfusion or last contrast bolus, procedure duration, center, intravenous alteplase administration, iv heparin use, intra-arterial thrombolysis, general anesthesia performed, extended thrombolysis in cerebral infarction score at the beginning and end of the intervention, NIHSS score after 24-48 hours, new ischemic stroke, progression of stroke, extracranial hemorrhage, cardiac ischemia, sICH, functional outcome expressed on the modified Rankin Scale
Number of imputed datasets	*5*
Seed	*41*



Supplemental figure 4.1. Distribution of propensity scores before and after matching

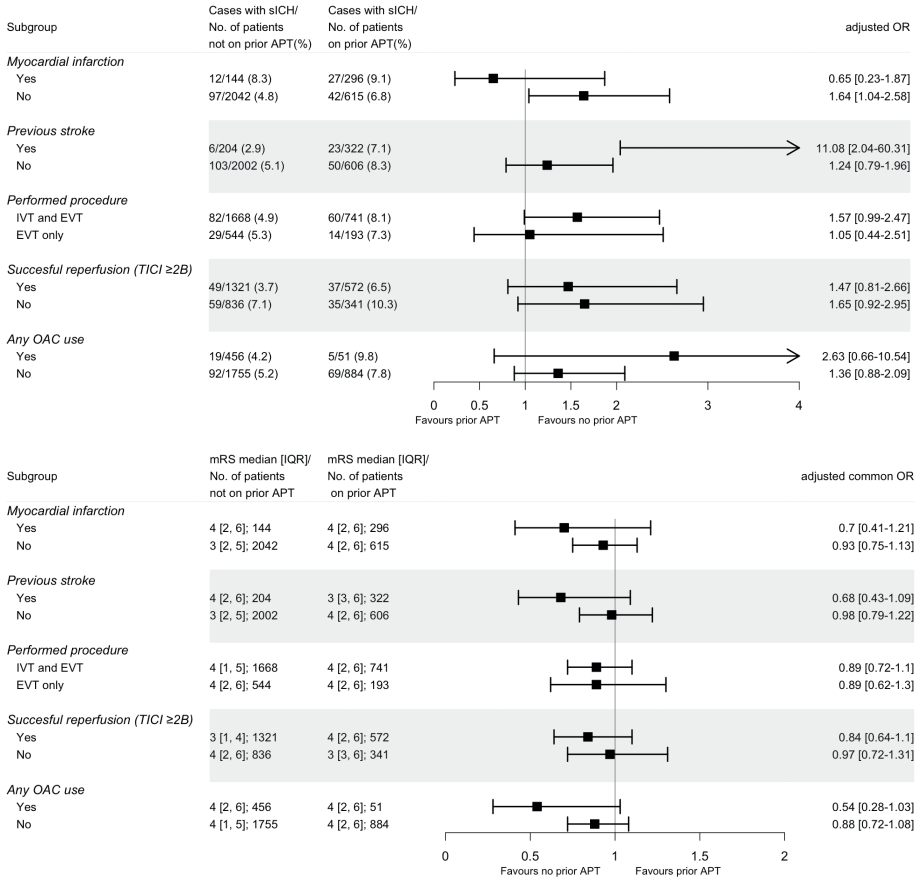
Supplemental table 4.2. Primary and secondary outcomes in patients on prior antiplatelet therapy vs. no prior antiplatelet therapy in the full cohort using logistic and linear regression.

	Prior APT (n=937)	**No prior APT (n=2217)**	**(c)OR, (95%CI)**	**a(c)OR, (95%CI)†**
Primary outcome				
Symptomatic intracranial hemorrhage	74 (7.9)	111 (5.0)	1.63 (1.20-2.21)	1.48 (0.99-2.20)
Secondary outcomes				
mRS at 90 days	4 [2, 6]	3 [2, 6]	0.70 (0.61-0.81)	0.92 (0.76-1.10)
mRS ≤ 2 at 90 days	312 (36)	882 (43)	0.74 (0.63-0.87)	1.00 (0.78-1.28)
NIHSS at 24-48 hours	10 [4, 17]	10 [4,17]	0.70 (0.01-1.39)[2]	-0.05 (-0.79 to 0.70)‡
Recanalization after intervention (eTICI ≥ 2B)	572 (63)	1321 (61)	1.06 (0.90-1.25)	1.07 (0.87-1.31)
Mortality at 90 days	309 (35)	540 (26)	1.53 (1.29-1.81)	1.27 (1.00-1.61)
Progression of stroke	71 (7.6)	211 (9.5)	0.78 (0.59-1.03)	0.81 (0.57-1.16)
New ischemic stroke	14 (1.5)	35 (1.6)	0.95 (0.51-1.77)	0.56 (0.24-1.29)
Extracranial hemorrhage	22 (2.3)	48 (2.2)	1.09 (0.65-1.81)	0.93 (0.49-1.73)
Cardiac ischemia	7 (0.7)	15 (0.7)	1.10 (0.45-2.72)	1.00 (0.33-3.07)

Summary: Primary and secondary outcomes of patients on prior antiplatelet therapy vs. no prior antiplatelet therapy. Skewed continuous and ordinal data are presented as median [IQR]. Binary data are presented as numbers (%).

Abbreviations: a(c)OR, adjusted (common) odds ratio; APT, antiplatelet therapy; CI, confidence interval; eTICI, extended thrombolysis in cerebral infarction; mRS, modified Rankin Scale

Captions: † *Variables in the multivariable logistic regression model:* age, sex, NIHSS at admission, pre-stroke mRS, intravenous alteplase, pre-interventional eTICI score, direct oral anticoagulant therapy, vitamin K antagonist therapy, previous stroke, myocardial infarction, peripheral artery disease, hypertension, atrial fibrillation, diabetes mellitus, intra-arterial thrombolysis, glucose at baseline, systolic blood pressure, anesthesia type (GA vs NGA), occlusion segment, ASPECTS at baseline, international normalized ratio, onset to recanalization, CTA collateral grade, heparin therapy. ‡ Beta (95%CI)



Supplementary figure 4.2. Subgroup analyses for patients on prior antiplatelet versus those patients not on prior antiplatelet therapy for the outcomes sICH and mRS.

CHAPTER V

Endovascular treatment for acute ischemic stroke in patients on oral anticoagulants: results from the MR CLEAN Registry

Stroke, 2020

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Abstract

Background and Purpose: The use of oral anticoagulants (OAC) is considered a contra-indication for intravenous thrombolytics as acute treatment of ischemic stroke. However, little is known about the risks and benefits of endovascular treatment in patients on prior OAC. We aim to compare outcomes after endovascular treatment between patients with and without prior use of OAC.

Methods: Data of patients with acute ischemic stroke caused by an intracranial anterior circulation occlusion, included in the nationwide, prospective, MR CLEAN Registry between March 2014 and November 2017, were analyzed. Outcomes of interest included symptomatic intracranial hemorrhage and functional outcome at 90 days (modified Rankin Scale score). Outcomes between groups were compared with (ordinal) logistic regression analyses, adjusted for prognostic factors.

Results: 3162 patients were included in this study, of whom 502 (16%) used OAC. There was no significant difference in the occurrence of symptomatic intracranial hemorrhage between patients with and without prior OACs (5% versus 6%; adjusted odds ratio, 0.63 [95% CI, 0.38–1.06]). Patients on OACs had worse functional outcomes than patients without OACs (common odds ratio, 0.57 [95% CI, 0.47–0.66]). However, this observed difference in functional outcome disappeared after adjustment for prognostic factors (adjusted common odds ratio, 0.91 [95% CI, 0.74–1.13]).

Conclusions: Prior OAC use in patients treated with endovascular treatment for ischemic stroke is not associated with an increased risk of symptomatic intracranial hemorrhage or worse functional outcome compared with no prior OAC use. Therefore, prior OAC use should not be a contra-indication for endovascular treatment.

Introduction

Oral anticoagulant agents (OAC) are used to reduce the risk of embolic complications. Paradoxically, whenever an embolic complication as ischemic stroke occurs, the perceived risk of hemorrhagic complications limits the options for acute reperfusion therapy. As such, intravenous thrombolytics (IVT) for acute ischemic stroke are contra-indicated for patients taking direct anticoagulants (DOACs) and vitamin K antagonists (VKAs) with international normalized ratio (INR) above 1.7.[1] For patients with ischemic stroke caused by an intracranial large vessel occlusion in the anterior circulation, endovascular treatment (EVT) is the only effective alternative.[2-5] However, it is not known whether prior use of OAC affects outcomes after EVT. In a single-center retrospective study, hemorrhage rates after EVT in patients ineligible for intravenous thrombolysis were similar for patients who were anticoagulated and patients not on anticoagulant therapy.[6]

The aim of the present study was to compare outcomes after EVT between patients with and without prior use of OACs in a large cohort representative of Dutch clinical practice.

Methods

Data availability statement

Source data will not be made available because of legislative issues on patient privacy. However, detailed analytic methods and study materials, including log files of statistical analyses, will be made available to other researchers on reasonable request to the corresponding author.

Study design and patient population

Patients enrolled in the MR CLEAN Registry (Multicenter Randomized Clinical Trial of Endovascular Treatment of Acute Ischemic Stroke in the Netherlands) from March 2014 until November 2017 were included in this study. The MR CLEAN Registry is a multicenter, prospective, observational cohort with EVT treated patients in the Netherlands.[5] All patients undergoing an EVT procedure (defined as 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. EVT consisted of arterial catheterization with a microcatheter to the level of the occlusion, followed by mechanical thrombectomy with or without delivery of a thrombolytic agent. For the present study, we used the following inclusion criteria: arterial puncture within 6.5 hours after symptom onset; age ≥18; occlusion of intracranial carotid (ICA, ICA-T), middle (M1/M2) or anterior (A1/A2) cerebral artery, demonstrated by baseline CT angiography, treatment in a MR CLEAN trial center, and available data on prior OAC use. ASPECT score on baseline noncontrast CT and collateral status on CT angiography were scored using definitions described previously.[7,8] A central medical

ethics committee evaluated the study protocol of the MR CLEAN Registry and granted permission to perform the study as a registry.

Prior oral anticoagulant use

Anticoagulant use before EVT was defined as any VKA or DOAC use before the EVT as reported on the case report form of the MR CLEAN Registry (www.mrclean-trial.org). INR was reported by local investigators, which was taken from blood samples at baseline before administration of IVT (if indicated). Anti-Xa activity, diluted thrombin time, and activated partial thromboplastin time were not measured routinely.

Outcome measures

Outcomes of interest were reperfusion grade according to postintervention digital subtraction angiography, postintervention neurological deficit, occurrence of symptomatic intracranial hemorrhage (sICH), ischemic stroke progression, functional outcome, and mortality at 90 days. Reperfusion was scored by the extended Thrombolysis in Cerebral Ischemia (eTICI) score,[9] which ranges from grade 0 no reperfusion to grade 3 complete reperfusion. An independent core lab, blinded for clinical outcome, assessed all imaging.

Postintervention neurological deficit was measured with the National Institutes of Health Stroke Scale (NIHSS) score, with higher scores indicating greater deficit.[10]

An intracranial hemorrhage was considered symptomatic if the patient had died or had deteriorated neurologically (a decline of at least 4 points on the NIHSS), and the hemorrhage was related to the clinical deterioration (according to Heidelberg criteria[11]). Ischemic stroke progression was defined as neurological deterioration of at least 4 points on the NIHSS, in which an intracranial hemorrhage was excluded with CT as the cause of the deterioration. Functional outcome was measured with the modified Rankin Scale (mRS) score at 90 days, ranging from 0 no symptoms to 6 death.[12]

Missing data

Missing NIHSS scores were retrospectively scored with a standardized score chart based on information from the reported neurological examination. If successful reperfusion was not achieved during EVT, the time of last contrast bolus injection was used as a proxy for time of reperfusion. Any mRS score of 0 to 5 assessed within 30 days was considered missing. These values were, therefore, replaced by mRS scores derived from multiple imputation for the (multivariable) regression analysis.[13] All descriptive analyses include patients with complete data, while all regression models include all patients with imputed data.

Statistical analysis

Baseline characteristics were analyzed using standard statistics. We used ordinal logistic regression models to determine the association between OAC use and post-

EVT reperfusion grade (eTICI) and functional outcome (mRS) at 90 days, and binary logistic regression models for the associations with sICH, ischemic stroke progression, and 90-day mortality. To estimate the association of OAC use with the NIHSS score 24 to 48 hours postintervention, we used linear regression models. Analyses were adjusted for important prognostic factors: age, baseline NIHSS score, prestroke mRS score, time from onset to start of EVT, intravenous thrombolysis, history of hypertension, diabetes mellitus, hypercholesterolemia, ischemic stroke, and prior use of antiplatelet agents. In the case of clinical outcomes (ie, NIHSS score, functional outcome, sICH, stroke progression, and mortality), we additionally adjusted for systolic blood pressure, baseline collateral status, and ASPECT score. To compare functional outcome between patients with or without prior OAC use, we analyzed the shift on the mRS with ordinal logistic regression analysis.

Additionally, we performed subgroup analyses to evaluate the effect of the specific OAC types (ie, VKAs and DOACs) on the outcomes. Besides, we compared outcomes in patients with prior VKA use according to INR subgroups (INR ≤1.7; 1.7–3.0; >3.0). Statistical analyses were performed with Stata/SE 14.1 (StataCorp, TX).

Results

Patient characteristics

Between March 2014 and November 2017, 3637 patients were enrolled in MR CLEAN Registry. After exclusion of patients with age <18 (n=9), treatment in a non-MR CLEAN trial center (n=177), posterior circulation occlusion (n=172), onset to start of EVT >390 minutes (n=99), and missing information on OAC use (n=18), we included 3162 patients for the current study (Figure 5.1). Before EVT, OACs were used in 502 patients (16%), of whom 404 patients were on VKAs and 98 on DOACs. Median INR among VKA users was 1.8 (interquartile range, 1.4–2.3). Patients on OACs were older (median age 78 versus 71, P<0.01), had more severe neurological deficits at baseline (median NIHSS 17 versus 16, P<0.01), more comorbidities (ie, atrial fibrillation (78% versus 13%, P<0.01), diabetes mellitus (20% versus 15%, P=0.02), hypertension (64% versus 49%, P<0.01), hypercholesterolemia (34% versus 29%, P<0.01)), and were less often treated with antiplatelet agents before current stroke (11% versus 35%, P<0.01; Table 5.1). Patients on OACs more often had suffered from stroke in their medical history (28% versus 15%, P<0.01), and prestroke functional status was worse compared with patients not on OACs (pre-mRS 0 in 49% versus 70%, P<0.01). IVT were less frequently administered in patients on prior OACs (34% versus 84%; P<0.01). ASPECT score was slightly better in patients on OACs, with a score of 8 to 10 in 76% versus 72% in patients not on OACs (P=0.03). Occlusion locations and collateral scores were not statistically different between the groups.

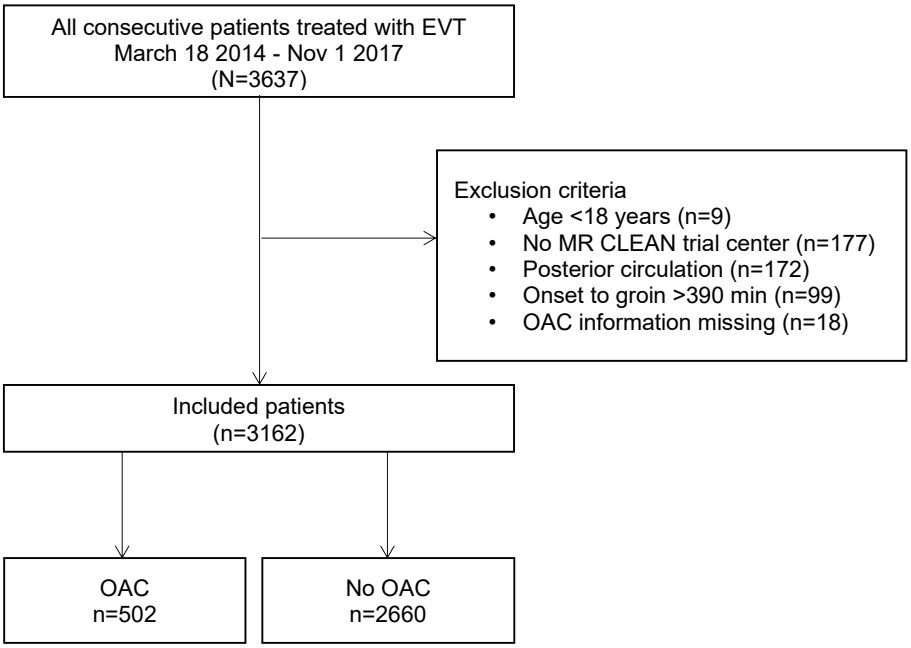

Figure 5.1. Flowchart of patients included in the study.

Table 5.1. Baseline characteristics of 3162 patients who underwent EVT for ischemic stroke, stratified for prior OAC use versus no prior OAC use.

	OAC n = 502	**Non-OAC n = 2660**	**p-value**	**Missing n (%)**
Age - median (IQR)	78 (69-84)	71 (60-80)	<0.01	0 (0)
Male sex – n. (%)	262 (52)	1384 (52)	0.95	0 (0)
NIHSS - median (IQR)	17 (12-20)	16 (11-19)	<0.01	49 (2)
Clinical localization: Left hemisphere – n. (%)	285 (57)	1389 (52)	0.12	2 (0)
Systolic blood pressure - mean mm Hg (SD)	148 (26)	150 (25)	0.12	85 (3)
Intravenous alteplase treatment – n. (%)	173 (34)	2239 (84)	<0.01	10 (0)
Medical history				
Atrial fibrillation – n. (%)	394 (78)	359 (13)	<0.01	36 (1)
Hypertension – n. (%)	322 (64)	1300 (49)	<0.01	60 (2)
Diabetes mellitus – n. (%)	98 (20)	407 (15)	0.02	18 (1)
Hypercholesterolemia – n. (%)	173 (34)	764 (29)	<0.01	131 (4)
Ischemic stroke – n. (%)	143 (28)	387 (15)	<0.01	22 (1)
Prior antiplatelet use – n. (%)	54 (11)	926 (35)	<0.01	27 (1)
Pre-stroke modified Rankin Scale score– n. (%)			<0.01	71 (2)

Table 5.1. Continued.

	OAC n = 502	Non-OAC n = 2660	p-value	Missing n (%)
0	248 (49)	1850 (70)		
1	96 (19)	309 (12)		
2	50 (10)	176 (7)		
>2	98 (20)	264 (10)		
Imaging				
Occlusion location on CTA – n. (%)			0.07	155 (5)
ICA (intracranial)	12 (2)	143 (5)		
ICA-T	109 (22)	525 (20)		
M1	280 (56)	1476 (55)		
M2	72 (14)	366 (14)		
Other: M3 and ACA	3 (1)	21 (1)		
ASPECTS subgroups			0.03	105 (3)
0-4 – n (%)	14 (3)	129 (5)		
5-7 – n (%)	87 (17)	540 (20)		
8-10 – n (%)	381 (76)	1906 (72)		
Collaterals			0.31	202 (6)
Grade 0 – n (%)	37 (7)	147 (6)		
Grade 1 – n (%)	167 (33)	899 (34)		
Grade 2 – n (%)	186 (37)	960 (36)		
Grade 3 – n (%)	81 (16)	483 (18)		
Transfer from primary stroke center – n (%)	269 (54)	1467 (55)	0.51	1 (0)
Onset to arterial puncture (minutes) - median (IQR)	190 (148-250)	195 (150-250)	0.56	14 (0)

Abbreviations: ACA, anterior cerebral artery; ASPECTS, Alberta stroke program early CT score; ICA (T), internal carotid artery (terminus); M(*segment*), middle cerebral artery; EVT, endovascular treatment; IQR, interquartile range; NIHSS, National Institutes of Health Stroke Scale; OAC, oral anticoagulant use; SD, standard deviation.
Captions: *(Common) odds ratios, unless otherwise indicated. Analyses were adjusted for age, baseline NIHSS score, prestroke mRS score, time from onset to start of EVT, intravenous thrombolysis, history of hypertension, diabetes mellitus, hypercholesterolemia, ischemic stroke, and prior antiplatelet use. In the case of clinical outcomes, we additionally adjusted for systolic blood pressure, baseline collateral status and ASPECTS.
†n=2953 (mRS score at 90 d was missing for 209 patients).
‡n=2841 (postintervention NIHSS score was missing for 321 patients).
§n=2685 (patients who underwent an attempt for thrombectomy).

Outcomes

The proportion of patients with successful reperfusion (eTICI 2B or higher) was similar in both groups (61% for patients on OAC versus 64% in patients not on OAC; adjusted odds ratio, 0.91 [95% CI, 0.70–1.18]), as well as the proportion of excellent (eTICI 2C or higher) and complete (eTICI 3) reperfusion (Table 5.2). Intervention characteristics are shown in supplemental table 5.1. NIHSS score at 24 to 48 hours postintervention was higher in patients on OAC compared with patients not on OAC (median 12 versus 10; β, 0.91 [95% CI, 0.02–1.80]). This difference was not statistically significant after adjustment for prognostic factors (adjusted β, −0.46 [95% CI, −1.38 to 0.47]). The proportion of patients with improvement of 4 or more points on the NIHSS was not different between groups (45% versus 49%; adjusted odds ratio, 1.01 [95% CI, 0.78–1.31]). There was no statistically significant difference in the occurrence of sICH between patients with and without prior OACs (5% versus 6%; adjusted odds ratio, 0.79 [95% CI, 0.46–1.35]). Death within 90 days occurred more often in patients on OAC (38% versus 25%; OR, 1.82 [95% CI, 1.49–2.23]) in the univariable analysis. However, after adjustment for prognostic factors, prior OAC use was not associated with an increased mortality at 90 days (adjusted odds ratio, 1.20 [95% CI, 0.91–1.60; Table 5.2). The mRS scores at 90 days were available in 2953/3162 patients (93%). Functional independence (mRS score 0–2) was reached less often by patients using OAC (29% versus 43%; OR, 0.54 [95% CI, 0.43–0.67]; Table 5.2). Use of OACs was associated with a shift towards worse outcomes on the mRS in the unadjusted analysis (cOR, 0.57 [95% CI, 0.47–0.66]; mRS distribution is shown in Figure 5.2). However, there was no statistically significant difference after adjustment for baseline prognostic factors (acOR, 0.88 [95% CI, 0.71–1.10]; Table 5.2).

Table 5.2. Outcomes of 3162 patients who underwent EVT for ischemic stroke, stratified for prior OAC use versus no prior OAC use.

	OAC	**Non OAC**	**Effect estimates (95% CI)***	
	(n=502)	**(n=2660)**	**Unadjusted**	**Adjusted**
sICH – n. (%)	24 (5)	162 (6)	0.77 (0.50-1.20)	0.79 (0.46-1.35)
Hemorrhage type – n. (%)				
PH2	5 (21)	94 (58)		
PH1	10 (42)	33 (20)		
rPH	1 (4)	22 (14)		
SAH	17 (71)	80 (49)		
IVH	5 (21)	74 (46)		
Ischemic stroke progression – n. (%)	37 (7)	244 (9)	0.79 (0.55-1.13)	0.74 (0.48-1.15)
Mortality at 90 days – n. (%)	190 (38)	662 (25)	1.82 (1.49-2.23)	1.20 (0.91-1.60)
mRS at 90 days – median (IQR)[a]	4 (2-6)	3 (2-6)	0.57 (0.47-0.66)	0.88 (0.71-1.10)

Table 5.2. Continued.

	OAC (n=502)	Non OAC (n=2660)	Effect estimates (95% CI)* Unadjusted	Adjusted
mRS 0-1 at 90 days – n. (%)[a]	73 (15)	589 (24)	0.56 (0.43-0.73)	0.85 (0.60-1.19)
mRS 0-2 at 90 days – n. (%)[a]	140 (29)	1058 (43)	0.54 (0.43-0.67)	0.86 (0.63-1.17)
mRS 0-3 at 90 days – n. (%)[a]	206 (43)	1386 (56)	0.58 (0.47-0.70)	0.93 (0.70-1.23)
NIHSS post intervention (24h) - median (IQR)[b]	12 (5-18)	10 (4-17)	ß 0.91 (0.02-1.80)	ß -0.46 (-1.38-0.47)
Improvement on the NIHSS of ≥ 4 points – n. (%)	224 (45)	1297 (49)	0.85 (0.69-1.04)	1.01 (0.78-1.31)
Successful reperfusion (eTICI 2B or higher)[c] – n. (%)	263 (61)	1440 (64)	0.86 (0.70-1.07)	0.91 (0.70-1.18)
Excellent reperfusion (eTICI 2C or higher)[c] – n. (%)	187 (43)	979 (43)	0.99 (0.80-1.21)	1.07 (0.84-1.36)
Complete reperfusion (eTICI 3)[c] – n. (%)	134 (31)	709 (31)	0.97 (0.78-1.22)	1.08 (0.83-1.40)

Abbreviations: ASPECTS, Alberta Stroke Program Early CT Score; EVT, endovascular treatment; eTICI, extended Thrombolysis in Cerebral Ischemia; IQR, interquartile range; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; OAC, oral anticoagulant; and sICH, symptomatic intracranial hemorrhage.
Captions: *(Common) odds ratios, unless otherwise indicated. Analyses were adjusted for age, baseline NIHSS score, prestroke mRS score, time from onset to start of EVT, intravenous thrombolysis, history of hypertension, diabetes mellitus, hypercholesterolemia, ischemic stroke, and prior antiplatelet use. In the case of clinical outcomes, we additionally adjusted for systolic blood pressure, baseline collateral status and ASPECTS.
†n=2953 (mRS score at 90 d was missing for 209 patients).
‡n=2841 (postintervention NIHSS score was missing for 321 patients).
§n=2685 (patients who underwent an attempt for thrombectomy).

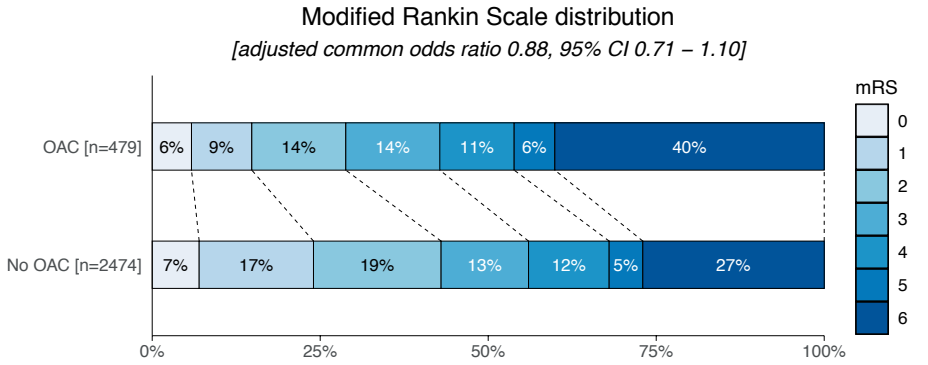

Figure 5.2. Functional outcome on the modified Rankin Scale (mRS); n = 2953 (mRS score at 90 days was missing for 209 patients).

Subgroup and sensitivity analyses

The incidence of sICH was lower in patients on DOACs when compared with patients on VKAs (1/98, 1% versus 23/404, 6%). However, functional outcome did not differ between patients on DOACs and VKAs (supplemental table 5.2). In patients with prior VKA use, complication risk and functional outcome was similar for INR subgroups ≤1.7 and 1.7 to 3.0 (supplemental table 5.3). Only 8 patients presented with a baseline INR >3.0, of whom one patient reached functional independence. Five of these 8 patients died within 90 days, of whom one from sICH.

Discussion

In this observational study representative of Dutch clinical practice, one out of 6 patients who underwent EVT for ischemic stroke was on prior OACs. Although the postprocedural reperfusion status and risk of sICH were similar between patients on prior OAC use compared with patients without prior OAC use, outcomes were worse for OAC users with regard to neurological recovery and functional outcome at follow-up. However, these observed differences disappeared after adjustments for imbalances in baseline prognostic factors. Therefore, EVT should not be withheld in prior OAC users.

Several observational studies reported on the prevalence of OAC use in patients eligible for mechanical thrombectomy, which ranged from 3% to 23%.[14-24] The lowest prevalence was observed in studies which included patients from a very early period, from 1992 to 2002, respectively.[15,17] Back then, EVT was new, which might have led to cautious attitude towards this treatment, resulting in exclusion of patients on OACs. Prevalence in our study was in the upper range, with 16% of EVT eligible patients on OACs, and consistent with current practice described in most recently reported studies.[21,23]

In theory, prior OAC use may facilitate successful reperfusion, as the pharmacological mechanism is to reduce fibrin formation and, therefore, might reduce thrombus formation. On the contrary, achievement of successful reperfusion might be impaired by composition of the thrombus in cardio-embolic stroke (more prevalent in patients on OAC), which may be more difficult to retrieve.[25] Nevertheless, successful reperfusion was not significantly different between the groups in our study, consistent with previous studies.[15,16,19-22,25]

As in the majority of previous studies evaluating prior OAC use in EVT treated patients, risk of sICH was not increased, and even lower for patients on OACs in our study.[14-17,19-22] This finding could partly be due to the fact that IVT was withheld more often in patients who were on prior OACs (34% versus 84% in no OAC users), which may have resulted in a lower bleeding risk in this group. Nevertheless, after adjustment for IVT in regression analyses, the association with lower risk of sICH for patients on OAC persisted.

A previous meta-analysis showed that patients on OACs reached functional independence less often compared with nonusers.[26] In line with our study, this difference could not be explained by differences in recanalization or occurrence of sICH, but by older age and more cardiac co-morbidity. Three observational studies, thereafter, reported similar findings to our study with respect to functional outcome.[6,22-24] One multicenter study from the Madrid Stroke Network, however, reported similar functional outcome.[21] In this study, DOAC use was suggested to have a positive influence compared with the most frequently reported use of VKAs. However, only 8% of OAC users were on DOACs, compared with 20% in our study. Other explanations could have been baseline imbalances concerning right hemispheric and vertebrobasilar stroke, and lower NIHSS score in patients on OACs in that study.

Only few small observational studies investigated the relation between INR and risk of sICH after EVT. Increasing INR did not result in higher risk of ICH according to a small observational study.[20] Three small observational studies included 18, 21, and 10 patients who underwent EVT with INR>1.7.[17,27,28] In these studies, the risk of sICH or poor functional outcome were not increased for patients with INR >1.7. Only in one other small 2-center study with 21 patients, occurrence of sICH was increased (18% versus 7%) in patients with INR >1.7, but the difference was not significant. In our study, we found similar sICH rate and functional outcome compared with patients on VKAs with INR ≤1.7. Of note, only 8 patients with INR >3 were included in the study. Even though 5 of these patients died, only one died from sICH, which suggests hemorrhagic diathesis was not the primary cause of death. Nevertheless, strong conclusions about the safety of EVT in patients with INR >3 should not be drawn from this small sample size.

This study has some limitations. First, we reported observational, nonrandomized data. This might have resulted in confounding by indication, because patients on OACs were mainly patients with risk of cardio-embolic stroke and had cardiac co-morbidity with potential influence on outcomes. We adjusted for these prognostic factors in the

regression analyses. However, this confounding may not be eliminated completely. Second, we were unable to report the time elapsed between administration of OACs and puncture for EVT. This may have had influence on hemorrhagic diathesis during and after the interventional procedure. Third, patients who were excluded from receiving EVT because of OAC use were not registered. However, we expect this number to be limited because in Dutch practice the standard is to treat patients with thrombectomy regardless of OAC use and an INR up to 3, or in some centers without INR limit.

Conclusions

Prior OAC use is not associated with an increased risk of sICH or worse functional outcome in patients treated with EVT for acute ischemic stroke compared with no prior OAC use. Therefore, prior OAC use should not be a contra-indication for EVT.

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Supplemental Material

Supplemental table 5.1. Intervention characteristics of 3162 patients who underwent EVT for ischemic stroke, stratified for prior OAC use versus no prior OAC use.

	OAC n = 502	**Non-OAC n = 2660**	**p-value**
Duration between arterial puncture and reperfusion (minutes) – median (IQR)	49 (30-75)	50 (30-75)	0.78
Total thrombectomy attempts[a] – median (IQR)	2 (1-3)	2 (1-3)	0.43
Thrombectomy modality[ab]			0.19
Stent retriever – n (%)	298 (72)	1474 (69)	
Direct aspiration – n (%)	98 (24)	574 (27)	
Intra-arterial thrombolysis – n (%)	5 (1)	17 (1)	
Other – n (%)	13 (3)	69 (3)	
Heparin used during intervention – n (%)	120 (24)	721 (27)	0.14
Heparin dose (IU)– median (IQR; range)	5000 (5000-5000; 1000-10000)	5000 (5000-5000; 1250-10000)	0.58
Anesthetic management			0.76
Local anesthesia – n. (%)	301 (60)	1536 (58)	
Conscious sedation – n. (%)	57 (11)	304 (11)	
General anesthesia – n. (%)	115 (23)	642 (24)	
Unknown – n. (%)	29 (6)	178 (7)	

Abbreviations: IQR, interquartile range; OAC, oral anticoagulant treatment;
Captions: [a] In patients who underwent an attempt for thrombectomy, n =2685; [b] In 137 patients information about thrombectomy modality was missing, n = 2548

Supplemental table 5.2. Outcomes for 3162 patients who underwent EVT for ischemic stroke, stratified for prior use of VKA or DOAC versus no prior use of OAC.

	No OAC (n=2660)	**VKA (n=404)**		**DOAC (n=98)**	
	median (IQR) or n-(%)	**median (IQR) or n-(%)**	**a(c)OR (95% CI)** [d]	**median (IQR) or n-(%)**	**a(c)OR (95% CI)** [d]
sICH	162 (6)	23 (6)	0.74 (0.44-1.26)	1 (1)	0.16 (0.02-1.16)
Mortality at 90 days	662 (25)	157 (39)	1.08 (0.81-1.44)	33 (34)	0.99 (0.58-1.68)
mRS at 90 days[a]	3 (2-6)	4 (2-6)	0.93 (0.74-1.17)	4 (2-6)	0.84 (0.56-1.26)
mRS 0-1 at 90 days[a]	589 (24)	58 (15)	0.87 (0.60-1.24)	15 (15)	0.79 (0.41-1.50)
mRS 0-2 at 90 days[a]	1058 (43)	109 (29)	0.87 (0.63-1.21)	31 (32)	0.81 (0.47-1.37)
mRS 0-3 at 90 days[a]	1386 (56)	165 (43)	1.02 (0.76-1.38)	41 (42)	0.72 (0.43-1.20)
NIHSS post intervention (24h)[b]	10 (4-17)	12 (5-18)	-0.66 (-1.62-0.29)	12 (7-18)	0.35 (-1.32-2.02)
Successful Reperfusion (eTICI 2B or higher)[c]	1440 (64)	207 (60)	0.84 (0.65-1.10)	56 (65)	1.07 (0.65-1.75)

Abbreviations: a(c)OR, adjusted (common) odds ratio; CI, confidence interval; DOAC, direct oral anticoagulant use; eTICI, extended thrombolysis in cerebral infarction; IQR, interquartile range; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; OAC, oral anticoagulant treatment; sICH, symptomatic intracranial hemorrhage; VKA, vitamin K antagonist use.

Captions: [a] n = 2953 (mRS score at 90 days was missing for 209 patients); [b] n = 2841 (post-intervention NIHSS score was missing for 321 patients); [c] n = 2685 (patients who underwent an attempt for thrombectomy); [d](common) odds ratios, unless otherwise indicated. Analyses were adjusted for age, baseline NIHSS score, pre-stroke mRS score, time from onset to start of EVT, intravenous thrombolysis, history of hypertension, diabetes mellitus, hypercholesterolemia, or ischemic stroke. In the case of clinical outcomes, we additionally adjusted for systolic blood pressure, baseline collateral status and ASPECT score.

Supplemental table 5.3. Outcomes of patients who underwent EVT for ischemic stroke under prior VKAs, stratified by INR subgroups (n = 398; INR was missing in 6 patients).

	<1.7 n = 187	**1.7-3.0 n = 203**	**≥3.0 n = 8**	**p-value**
sICH – n. (%)	12 (6)	9 (4)	1 (13)	0.47
Mortality at 90 days – n. (%)	79 (42)	72 (35)	5 (63)	0.15
mRS at 90 days - median (IQR)[a]	4 (2-6)	4 (2-6)	6 (4-6)	0.87
mRS 0-1 at 90 days – n. (%)[a]	26 (15)	31 (16)	0 (0)	0.46
mRS 0-2 at 90 days – n. (%)[a]	46 (26)	61 (31)	1 (13)	0.31
mRS 0-3 at 90 days – n. (%)[a]	70 (40)	92 (47)	2 (25)	0.18
NIHSS post intervention (24h) - median (IQR)[b]	12 (5-19)	11 (5-17)	17 (7-20)	0.57

Abbreviations: INR, international normalized ratio; IQR, interquartile range; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; sICH, symptomatic intracranial hemorrhage; VKA, vitamin K antagonist use.
Captions: [a] n = 379, mrs score was missing for 19 patients; [b] n = 358, NIHSS post intervention was missing in 40 patients

CHAPTER VI

Periprocedural intravenous heparin during endovascular treatment for ischemic stroke: results from the MR CLEAN Registry

Stroke, 2019

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Abstract

Background and Purpose: Intravenous (IV) administration of heparin during endovascular treatment (EVT) for ischemic stroke may improve outcomes. However, risks and benefits of this adjunctive therapy remain uncertain. We aimed to evaluate periprocedural IV heparin use in Dutch stroke intervention centers, and to assess its efficacy and safety.

Methods: Patients registered between March 2014 and June 2016 in the MR CLEAN Registry, including all patients treated with EVT in the Netherlands, were analyzed. The primary outcome was functional outcome (modified Rankin Scale) at 90 days. Secondary outcomes were successful recanalization (extended Thrombolysis In Cerebral Infarction ≥ 2B), symptomatic intracranial hemorrhage (sICH) and mortality at 90 days. We used multilevel regression analysis to evaluate the association of periprocedural IV heparin on outcomes, adjusted for center effects and prognostic factors. To account for possible unobserved confounding by indication we analyzed the effect of center preference to administer IV heparin, defined as percentage of patients treated with IV heparin in a center, on functional outcome.

Results: 1488 Patients from 16 centers were analyzed, of whom 398 (27%) received IV heparin (median dose 5000 IU). There was substantial between-center variability in the proportion of patients treated with IV heparin (range: 0%-94%). There was no significant difference in functional outcome between patients treated with IV heparin and those without (adjusted common odds ratio (acOR) 1.17, 95% confidence interval (CI) 0.87-1.56), successful recanalization (aOR 1.24, 95% CI 0.89-1.71), sICH (aOR 1.13, 95% CI 0.65-1.99) or mortality (aOR 0.95, 95% CI 0.66-1.38). Analysis at center-level showed that functional outcomes were better in centers with higher percentages of heparin administration (acOR 1.07 per 10% more heparin, 95% CI 1.01-1.13).

Conclusions: Substantial between-center variability exists in periprocedural IV heparin use during EVT, but the treatment is safe. Centers using heparin more often had better outcomes. A randomized trial is needed to further study these effects.

Introduction

About one third of the patients with ischemic stroke caused by an intracranial large vessel occlusion do not recover to functional independence, despite early and complete recanalization by endovascular treatment (EVT).[1] Although EVT is successful in re-opening large intracranial arteries, it does not always restore microvascular perfusion. This incomplete microvascular reperfusion, also described as the "no-reflow" phenomenon, has first been reported in animal studies.[2-4] One of the causes of microvascular obstruction is the formation of neutrophil extracellular traps (NETs), which are known to be present in all thrombi of ischemic stroke patients irrespective of stroke etiology[5]. NETs are resistant to recombinant tissue plasminogen activator (r-tPA), but experimental studies show that unfractionated heparin is able to dissolve NETs at the microvascular level.[6-9] The effect of unfractionated heparin on NETs in humans has not been evaluated. In the pre-EVT era no benefit of heparin use on outcome in ischemic stroke patients was seen, with a concomitant 1.2% increase in occurrence of symptomatic intracranial hemorrhage (sICH).[10] However, as the rate of successful recanalization is high in patients treated with EVT, heparin is now more capable of penetrating the downstream microvessels and targeting the "no-reflow" areas. That heparin may contribute to the treatment effect of EVT is not a new concept but originates from cardiology practices: periprocedural heparin has been used since the first percutaneous coronary intervention (PCI) performed in 1977 and is standard practice since then.[11] By contrast, heparin is not the standard anticoagulant in EVT for ischemic stroke, which might be related to the perceived risk of sICH. In a systematic literature review we found that heparin use during EVT indeed seems to be associated with an increased risk of sICH, but this increase appears to be outweighed by a higher overall chance of a good functional outcome.[12] The risk-benefit ratio of periprocedural IV heparin in patients with ischemic stroke undergoing EVT is still unclear. The uncertainty regarding this risk-benefit ratio is also reflected in the wide variation in the use of heparin in randomized trials that investigated the effect of EVT.[13] We aimed to evaluate the use of IV heparin during EVT in Dutch stroke intervention centers, and to assess its efficacy and safety.

Methods

Study design

We used data from the MR CLEAN Registry, which is an ongoing, nationwide, multicenter, prospective, observational study including all consecutive patients treated with EVT for ischemic stroke in the Netherlands. The complete methods and description of variables of the MR CLEAN Registry have been described elsewhere.[14] For the present study, we selected patients who were registered between March 2014 and June 2016 and adhered to the following criteria: age of 18 years or older; treatment in a center that participated in the MR CLEAN trial; presence of a proximal

intracranial occlusion in the anterior circulation confirmed on non-invasive vascular imaging (intracranial carotid artery [ICA/ICA-T], middle cerebral artery [M1/M2], anterior cerebral artery [A1/A2]); and groin puncture within 6.5 hours after symptom onset. The current observational study was guided by the STROBE statement.[15] Data cannot be made available, as no patient approval has been obtained for sharing coded data. However, syntax files and output of statistical analyses in R will be made available upon request.

Unfractionated heparin administration

Heparin administration was defined as any IV dose of unfractionated heparin administered during EVT. We explored the variability in doses of heparin used and percentages of patients treated with heparin within and between centers and over time. When information on heparin administration was missing, we assumed no heparin was administered to the patient. We performed two sensitivity analyses on this matter. First, we compared baseline characteristics of the group of patients who we assumed not to have been treated with heparin to the patients explicitly registered as not treated with heparin. Second, we performed a complete case analysis of the primary and secondary outcomes in patients explicitly registered as treated with heparin vs. no heparin.

Outcome measures

The primary outcome was functional outcome at 90 days (range 14 days either way), assessed with the modified Rankin Scale (mRS), which is a 7-point ordinal scale ranging from 0 'no symptoms' to 6 'dead'[16]. Secondary outcomes were good functional outcome (mRS ≤ 2) at 90 days, successful recanalization rate (extended Thrombolysis In Cerebral Infarction grade ≥ 2B) assessed by an independent imaging core laboratory, occurrence of sICH, defined as patient neurological deterioration (decline of 4 points or more on the NIHSS) and a compatible hemorrhage seen on imaging assessed by an independent imaging core laboratory (according to the Heidelberg criteria), mortality at 90 days, progression of ischemic stroke (resulting in a decline of at least 4 points on the NIHSS), new ischemic stroke (imaging of new brain infarction with corresponding clinical neurologic deficit), extracranial hemorrhage, and cardiac ischemia (myocardial ischemia confirmed by ECG, and release of appropriate biomarkers).

Statistical methods

Differences in baseline characteristics were analyzed for both categorical and dichotomous variables using χ^2 statistics. Continuous data was assessed for normality both visually and by means of Kolmogorov-Smirnov testing. One-way ANOVA was used for parametric and Kruskal-Wallis for non-parametric testing. A p-value of <0.05 was considered significant in all applied tests. All baseline data and outcomes that are reported are crude and not imputed. 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 values when missing in less than 10% of the patients (e.g. mRS) by values derived from multiple imputation.[17] Multiple imputed data were used in the adjusted outcome analyses. We used multilevel logistic and ordinal regression analyses to compare outcomes of patients treated with and without periprocedural IV heparin, with center as random effect and relevant factors as fixed effects (i.e. heparin use, age, sex, NIHSS at admission, pre-stroke mRS, antiplatelet use, direct oral anticoagulant use, coumarin use, previous stroke, diabetes mellitus, glucose level at baseline, International Normalized Ratio (INR), baseline systolic blood pressure, occlusion segment, Alberta Stroke Program Early CT Score (ASPECTS) at baseline, collateral grading, treatment with IV alteplase, anesthesia type, pre-interventional eTICI score, intra-arterial thrombolysis, and onset-to-reperfusion time). Effects are presented as (adjusted common) odds ratios (OR) with 95% confidence intervals (CI). To account for possible confounding by indication we also analyzed the effect of center preference to administer heparin, defined as percentage of patients treated with heparin in a center, on outcome. All statistical analyses were performed with R version 3.5.0 (R foundation for Statistical Computing, Vienna, Austria) with the packages: *tableone*, *mice*, *Hmisc, ggplot* and *ordinal*.

Results

Patient population

From the total cohort of 1627 patients, 1488 patients from 16 centers were included and analyzed, of whom 398 (27%) received IV heparin (Figure 6.1). Among patients who received IV heparin, the median dose was 5000 international units (IU), ranging from 1250 IU to 10000 IU (supplemental figure 6.1). The percentage of patients within a center treated with IV heparin ranged from 0 to 94% (Figure 6.2). Over the investigated time period, both the total proportion of patients receiving heparin and the proportion of patients receiving heparin per center remained stable (supplemental figure 6.2). Patients receiving heparin presented more often with a stroke in the left hemisphere (233/398 [59%] vs. 563/1090 [52%], p=0.03) and used coumarins less often (39/398 [10%] vs. 151/1090 [14%], p=0.04; Table 6.1). Median time from emergency room admission at the intervention center to groin puncture (80 [51, 114] vs. 66 [38, 99] minutes, p<0.01) and time from symptom onset to reperfusion (282 [225, 338] vs. 265 [214, 327] minutes, p=0.01) were both longer in the heparin group. In the heparin group, patients received more often general anesthesia (215/398 [57%] vs. 164/1090 [16%], p<0.01) and intra-arterial thrombolytics (33/398 [8.3%] vs 20/1090 [1.8%], p<0.01) during EVT. The sensitivity analysis showed no substantial baseline differences between patients in whom '*no heparin use*' was explicitly registered and those with missing heparin administration in whom we assumed no heparin was administered (supplemental table 6.1).

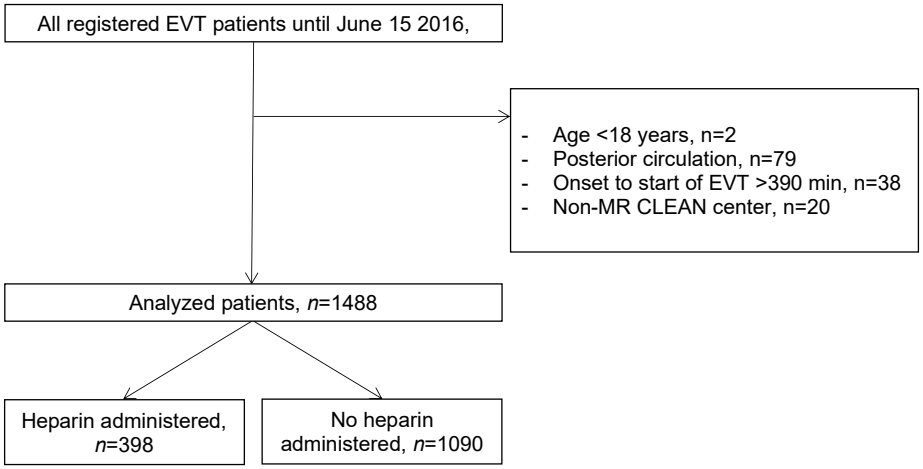

Figure 6.1. Flowchart

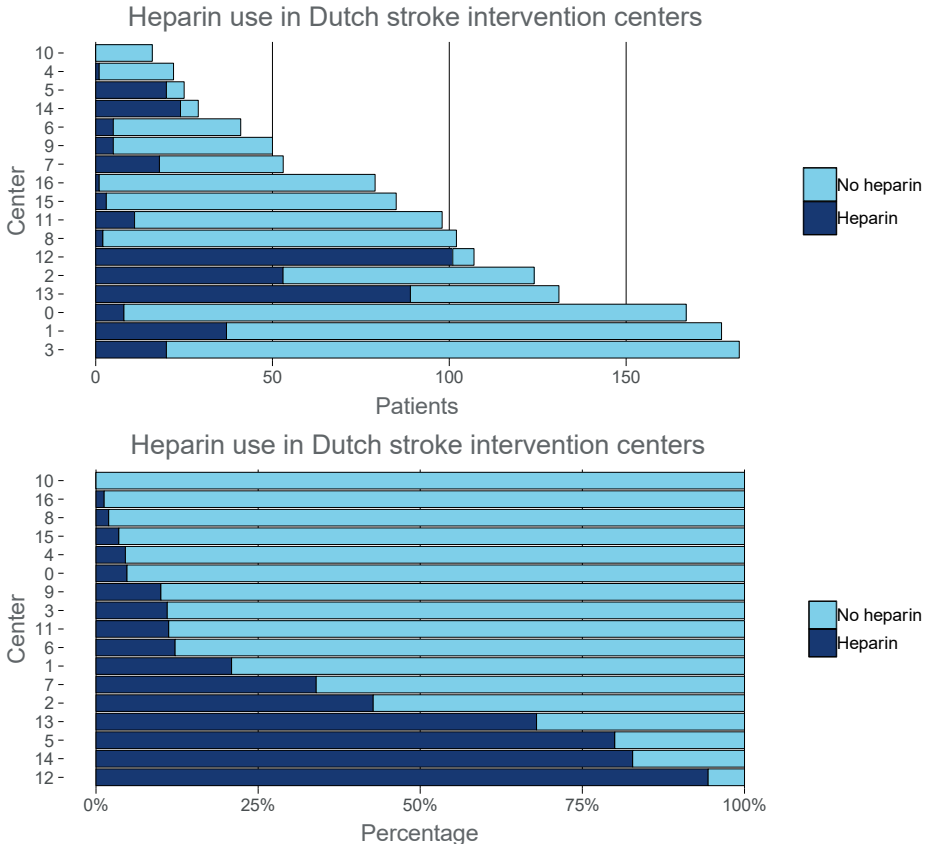

Figure 6.2. Heparin use during the total time period among Dutch stroke intervention centers in frequencies (A), and in percentages (B)

Table 6.1. Baseline demographics

	Heparin (n=398)	No heparin (n=1090)	P-value	Missing
Common patient characteristics				
Age	68 (15)	69 (14)	0.68	0
Male sex	206 (52%)	588 (54%)	0.49	0
NIHSS at baseline	16 [12, 20]	16 [11, 20]	0.77	18/12
Ischemia in left hemisphere	233 (59%)	563 (52%)	0.03	2/10
Systolic blood pressure	149 (25)	150 (24)	0.81	20/22
Diastolic blood pressure	81 (15)	82 (16)	0.56	19/28
Treatment with IV alteplase	300 (76%)	861 (79%)	0.16	1/2
INR	1.1 (0.4)	1.2 (0.4)	0.15	45/229
Glucose level	7.4 (2.3)	7.5 (2.7)	0.52	27/145
Trombocyte count	253 (90)	251 (93)	0.72	31/156
Center volume (patients treated per center per year)	55 [48, 58]	55 [38, 79]	0.08	0
Medical history				
Previous stroke	66 (17%)	183 (17%)	0.98	2/7
Atrial fibrillation	78 (20%)	249 (23%)	0.19	5/17
Hypertension	185 (47%)	560 (52%)	0.10	5/14
Diabetes mellitus	57 (14%)	198 (18%)	0.10	4/5
Myocardial infarction	58 (15%)	169 (16%)	0.74	9/20
Peripheral arterial disease	39 (10%)	96 (9.0%)	0.65	6/22
Pre-stroke mRS >2	57 (15%)	114 (11%)	0.05	8/19
Medication use				
Antiplatelet	140 (35%)	353 (33%)	0.44	1/18
DOAC	5 (1.3%)	32 (3.0%)	0.09	2/24
Coumarin	39 (10%)	151 (14%)	0.04	0/11
Blood pressure lowering medication	193 (49%)	568 (53%)	0.16	4/24
Statin	143 (36%)	379 (36%)	0.90	3/28
Imaging				
Occluded segment			0.11	20/55
Intracranial ICA	28 (7%)	54 (5%)		
ICA-T	68 (18%)	245 (24%)		
M1	226 (60%)	599 (58%)		
M2	52 (14%)	123 (12%)		
Other (e.g., M3, ACA)	4 (1.1%)	14 (1.4%)		

Table 6.1. Continued.

	Heparin (n=398)	No heparin (n=1090)	P-value	Missing
Reperfusion before intervention (eTICI)			0.34	27/111
0	308 (83%)	799 (82%)		
1	29 (7.8%)	56 (5.7%)		
2A	7 (1.9%)	31 (3.2%)		
2B	10 (2.7%)	28 (2.9%)		
2C	3 (0.8%)	16 (1.6%)		
3	14 (3.8%)	49 (5.0%)		
ASPECTS	9 [7, 10]	9 [7, 10]	0.81	14/51
ASPECTS ≤ 7	110 (29%)	324 (31%)	0.39	14/51
Collaterals			0.30	25/82
Grade 0 - Absent collaterals	27 (7.2%)	70 (6.9%)		
Grade 1 - Occluded area filling <50%	122 (33%)	339 (34%)		
Grade 2 - Occluded area filling >50% but <100%	157 (42%)	378 (38%)		
Grade 3 - Occluded area filling 100%	67 (18%)	221 (22%)		
Workflow (in minutes)				
Time from symptom onset to admission ER (intervention center)	133 [68, 190]	135 [59, 189]	0.73	20/53
Time from admission ER to groin puncture	80 [51, 114]	66 [38, 99]	<0.01	42/89
Duration procedure	62 [40, 87]	65 [40, 95]	0.07	34/123
Time from symptom onset to reperfusion	282 [225, 338]	265 [214, 327]	0.01	20/67
Procedural				
General anesthetic management	215 (57%)	164 (16%)	<0.01	18/85
Administration of intra-arterial thrombolytic	33 (8.3%)	20 (1.8%)	<0.01	0

Summary: Baseline variables with heparin vs. no heparin. 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; ASPECTS, Alberta stroke program early CT score; DOAC, direct oral anticoagulant; ER, emergency room; eTICI, extended thrombolysis in cerebral infarction including a 2C grade; ICA (T), internal carotid artery (terminus); IV, intravenous; M(*segment*), middle cerebral artery; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale

Outcome measures

No statistically significant difference in median mRS was observed between patients who received heparin and those who did not (3 [2, 6] vs. 3 [2, 6]; acOR 1.17, 95% CI 0.87-1.56; Figure 6.3). No statistically significant associations were found between heparin use and good functional outcome (aOR 1.29, 95% CI 0.88-1.88; Table 6.2), successful recanalization (aOR 1.24, 95% CI 0.89 -1.79), sICH (aOR 1.13, 95% CI 0.65-1.99) and mortality (aOR 0.95, 95% CI 0.66-1.38). There were also no statistically significant differences between both groups in any of the other secondary outcomes. Multiple imputation was performed for 125/1488 (less than 10%) of the main outcome. The complete case analysis showed similar results (supplemental table 6.2). The analyses of center preference to administer heparin showed that functional outcomes were better in centers with higher percentages of heparin administration (acOR 1.07 per 10% increase in heparin use, 95% CI 1.01-1.13; and for good functional outcome aOR 1.10 per 10% increase in heparin, 95% CI 1.02-1.18; Table 6.3). In the center preference analyses, there was no association between an increase in heparin use and successful recanalization (aOR 1.07, 95% CI 0.96-1.19), sICH (aOR 0.98, 95 % CI 0.88-1.10), mortality (aOR 0.95, 95% CI 0.90-1.01), and other secondary outcomes.

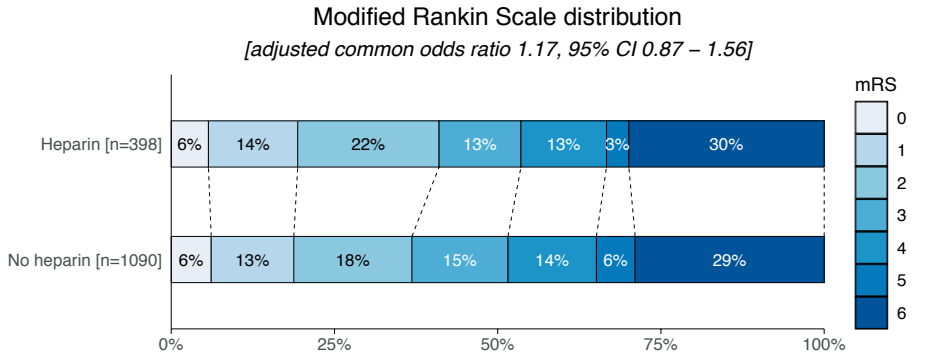

Figure 6.3. Primary outcome on the modified Rankin Scale at patient level

Table 6.2. Secondary outcomes in patients treated with heparin vs. no heparin

	Heparin (n=398)	No heparin (n=1090)	P-value	(c)OR, (95%CI)	a(c)OR, (95%CI)*
mRS ≤ 2 at 90 days	144 (41%)	373 (37%)	0.19	1.19 (0.93-1.53)	1.29 (0.88-1.88)
Reperfusion after intervention (eTICI ≥ 2B)	245 (62%)	604 (56%)	0.05	1.28 (1.01-1.62)	1.24 (0.89-1.71)
Symptomatic intracranial hemorrhage	25 (6.3%)	61 (5.6%)	0.71	1.13 (0.70-1.83)	1.13 (0.65-1.99)
Mortality at 90 days	105 (30%)	293 (29%)	0.78	1.05 (0.80-1.37)	0.95 (0.66-1.38)
Progression of stroke	40 (10%)	100 (9.2%)	0.68	1.11 (0.75-1.63)	0.89 (0.54-1.45)
New ischemic stroke	7 (1.8%)	17 (1.6%)	0.97	1.13 (0.47-2.75)	0.80 (0.26-2.46)†
Extracranial hemorrhage	13 (3.3%)	20 (1.8%)	0.14	1.81 (0.89-3.67)	1.66 (0.68-4.05)
Cardiac ischemia	5 (1.3%)	7 (0.6%)	0.40	1.97 (0.62-6.24)	2.05 (0.49-8.48)‡

Summary: Primary and secondary outcomes in patients treated with heparin vs. no heparin. Categorical data are presented as numbers (%).
Abbreviations: a(c)OR, adjusted (common) odds ratio; CI, confidence interval; eTICI, extended thrombolysis in cerebral infarction including a 2C grade; mRS, modified Rankin Scale
*Captions: * Variables in the model:* (fixed effects) heparin use, age, sex, NIHSS at admission, pre-stroke mRS, intravenous alteplase, pre-interventional eTICI score, antiplatelet use, direct oral anticoagulant use, coumarin use, previous stroke, diabetes mellitus, intra-arterial thrombolysis, glucose at baseline, systolic blood pressure, anesthesia type, occlusion segment, ASPECTS at baseline, INR, onset to reperfusion, collateral grading, time per month || (random effect) center
† Direct oral anticoagulant use not in model due to lack of convergence
‡ Intra-arterial thrombolysis not in model due to lack of convergence

Table 6.3. Primary and secondary outcomes associated with percentage heparin use per center (per 10 percent heparin increase)

	a(c)OR, (95%CI) (per 10 percent heparin increase)*
Primary outcome	
mRS at 90 days	1.07 (1.01-1.13)
Secondary outcomes	
mRS ≤ 2 at 90 days	1.10 (1.02-1.18)
Reperfusion after intervention (eTICI ≥ 2B)	1.07 (0.96-1.19)
Symptomatic intracranial hemorrhage	0.98 (0.88-1.10)
Mortality at 90 days	0.95 (0.90-1.01)†
Progression of stroke	1.00 (0.89-1.13)

Table 6.3. Continued.

	a(c)OR, (95%CI) (per 10 percent heparin increase)*
New ischemic stroke	1.10 (0.84-1.44)‡
Extracranial hemorrhage	1.08 (0.90-1.29)
Cardiac ischemia	1.13 (0.82-1.55)†

Summary: Primary and secondary outcomes associated with 10% increase in percentage of patients treated with heparin at center level.
Abbreviations: a(c)OR, adjusted (common) odds ratio; CI, confidence interval; eTICI, extended thrombolysis in cerebral infarction including a 2C grade; mRS, modified Rankin Scale
*Captions: * Variables in the model:* (fixed effects) percentage heparin use per 10%, age, sex, NIHSS at admission, pre-stroke mRS, intravenous alteplase, pre-interventional eTICI score, antiplatelet use, direct oral anticoagulant use, coumarin use, previous stroke, diabetes mellitus, intra-arterial thrombolysis, glucose at baseline, systolic blood pressure, anesthesia type, occlusion segment, ASPECTS at baseline, INR, onset to reperfusion, collateral grading, time per month || (random effect) center
† Intra-arterial thrombolysis not in model due to lack of convergence
‡ Direct oral anticoagulant use not in model due to lack of convergence

Discussion

In the present observational study, substantial between-center variability was found in the percentage of patients treated with periprocedural IV heparin. We did not find a significant effect of IV heparin use on functional outcome at the level of the individual patient. After mitigating potential unmeasured confounding by indication through an analysis at the center level, we found a modest beneficial effect of heparin on functional outcome. Patients in centers that treat more patients with IV heparin had better functional outcomes, without increased sICH risk.

One of the first studies that introduced periprocedural use of IV heparin during EVT (by means of intra-arterial prourokinase) was the PROACT II trial, in which a non-significant increase in the risk of sICH was observed in the EVT arm compared to the control arm, with an improvement in functional outcome (significant after stratification for stroke severity).[18] Patients in both arms received a total dose of 4000 IU of heparin. Afterwards several EVT trials implemented this as part of their protocol with doses ranging from 2000 IU to 5000 IU, whereas other trials did not.[12,13] The uncertainty regarding the risk-benefit ratio and absence of recommendations in the guidelines explains the variability in periprocedural IV heparin use in Dutch stroke intervention centers.[19] In prior studies on periprocedural heparin use the doses used are comparable to the median dose of 5000 IU of heparin in this study.[13,20-22] Furthermore, we found

that patients receiving heparin were less often on coumarins, which suggests that interventionists are more cautious to administer heparin in anticoagulated patients because of an allegedly higher sICH risk or the indication to administer heparin has already been treated by the coumarin. By contrast, we found that patients who received heparin were more likely to receive intra-arterial thrombolytics, which could probably be related to center policy. This might also be the case for general anesthesia, which was also more often used in the heparin group. The longer emergency room to groin puncture time in the heparin group may be explained by the fact that heparin was less often used in the three largest centers, in which the workflow may be more optimized in comparison to the workflow of the other centers. The median duration of the procedure was, however, comparable between groups.

Two smaller post-hoc analyses of randomized controlled trials (Multi MERCI and TREVO-II) investigating the effects of EVT also addressed the question whether periprocedural heparin is beneficial.[21,22] In both studies periprocedural IV heparin use was associated with higher rates of good functional outcomes. The beneficial effect might be explained by the ability of IV heparin to restore incomplete microvascular reperfusion. The use of periprocedural heparin seems safe. In all our analyses, there was no statistically significant association between heparin use and sICH or mortality. This is also in line with the findings of the two aforementioned post-hoc analyses of trials, which however did not adjust for risk factors for sICH. Finally, it is important to realize that periprocedural use of heparin is not novel in EVT practices as heparin has been used ever since the introduction of PCI in cardiology.[23] The rationale for heparin use during PCI is that the intervention is associated with factors that predispose to thrombosis (e.g. stasis within the coronary artery, stasis within the catheters, and exposure of blood coagulation factors to injured endothelium, catheters and guidewires) and is therefore used as part of protocol care.[11] One reason why neuro-interventionists have not fully adopted heparin use in current practice might be the fear of sICH, which, based on our results, seems to be unjustified.

Given the variability in heparin administration among Dutch stroke intervention centers and the promising results regarding outcome, a randomized controlled trial is warranted to prospectively evaluate adjunctive therapy and assess whether this is beneficial. In the ongoing trial MR CLEAN-MED (*Multicenter Randomized CLinical trial of Endovascular treatment for Acute ischemic stroke in the Netherlands; the effect of periprocedural MEDication: heparin, antiplatelet agents, both or neither*, ISRCTN76741621), patients are randomized to IV heparin and/or acetylsalicylic acid to investigate whether this will affect microvascular reperfusion and improve functional outcome. Our observational study showed a non-significant absolute difference of 4% in good functional outcome (mRS 0-2) in favor of heparin. This supports the sample

size calculation of MR CLEAN-MED, which is powered to detect an absolute difference in good functional outcome of 5%.

Limitations

Because of the observational design of our study, confounding by indication could have influenced the results. For example, patient-related factors that are associated with the outcome could have influenced the treating physician's decision whether or not to administer heparin. For this reason, we adjusted for relevant prognostic factors that were likely to be associated with the administration of heparin. Furthermore, we performed an additional analysis in which we incorporated center preference to administer heparin to reduce the risk of possible unmeasured confounding by indication. In the latter analysis, confounding by indication at the interventionist level diminishes as the analysis at center level is less likely to suffer from this type of confounding (not decision or indication dependent). Also, this analysis takes into account specific center-related factors not included in the model – residual confounding – which could have influenced the physician's choice to administer heparin. However, even in this center preference analysis some residual confounding might be present. Possible examples of residual confounding are that centers using heparin more frequently could have been better equipped, or that interventionists administering heparin have more experience. Unfortunately, we could not adjust for this. Furthermore, as the distribution of heparin use among centers varied widely, we considered it interesting to explore if center preference is actually the preference of the specific center or rather the preference of the specific interventionist within the center. However, since some interventionists work at different sites and as part of an intervention team with changing staff, it was not feasible to perform this more in-depth exploration. Another limitation regarding this study is that activated clotting times were not measured, leaving the question unanswered if activated clotting times were adequately influenced by the treatment.

Conclusion

Substantial between-center variability exists in IV heparin use during EVT procedures in patients with ischemic stroke, but treatment is safe. Patients treated in centers that treat more patients with IV heparin have better functional outcomes. A randomized trial is warranted to further study the effects of this treatment.

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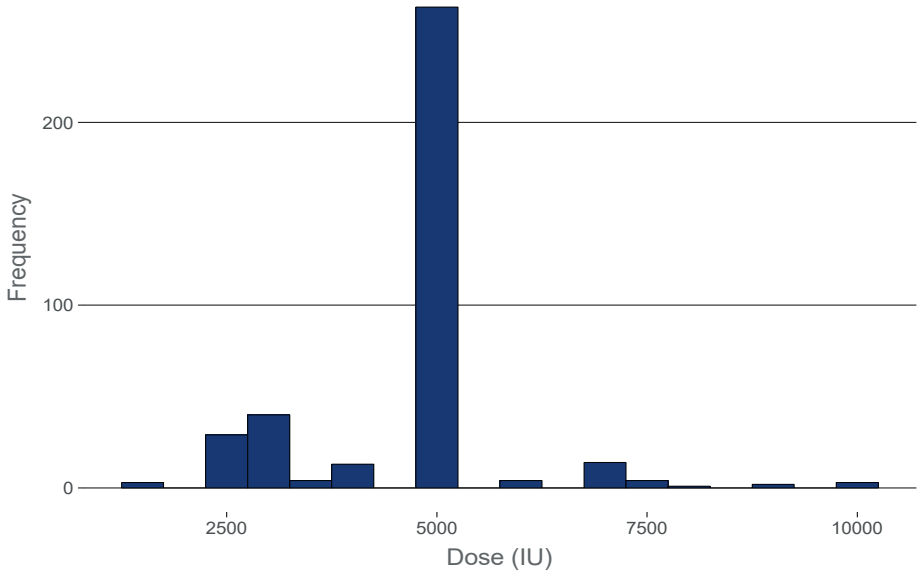
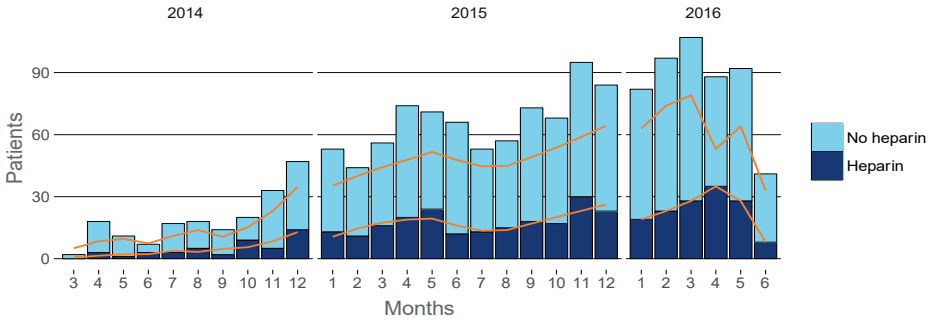
Supplemental material



Supplemental figure 6.1. Distribution of doses (IU) heparin administered



Supplemental figure 6.2. Heparin use over time in Dutch stroke intervention centers (per year and month)

Supplemental table 6.1. Sensitivity analysis of assumed no heparin vs. explicitly registered as no heparin

	Explicitly registered as no heparin (n=98)	**Assumed no heparin (n=992)**	**P-value**
Common patient characteristics			
Age	65 (14)	69 (14)	0.01
Male sex	58 (59%)	530 (53%)	0.32
NIHSS at baseline	15 [11, 18]	16 [11, 20]	0.06
Ischemia in left hemisphere	57 (58%)	506 (52%)	0.25
Systolic blood pressure	152 (26)	149 (24)	0.38
Diastolic blood pressure	83 (19)	82 (16)	0.46
IV alteplase	78 (80%)	783 (79%)	1.00
INR	1.2 (0.4)	1.2 (0.4)	0.53
Trombocyte count	251 (91)	251 (93)	0.95
Medical history			
Previous stroke	15 (15%)	168 (17%)	0.76
Atrial fibrillation	18 (18%)	231 (24%)	0.29
Hypertension	50 (51%)	510 (52%)	0.91
Diabetes mellitus	16 (16%)	182 (18%)	0.70
Myocardial infarction	13 (13%)	156 (16%)	0.60
Peripheral arterial disease	2 (2.1%)	94 (10%)	0.02
Pre-stroke mRS >2	8 (8.2%)	106 (11%)	0.53
Medication use			
Antiplatelet	28 (29%)	325 (33%)	0.44
DOAC	4 (4.1%)	28 (2.9%)	0.73
Coumarin	8 (8.2%)	143 (15%)	0.11
Blood pressure lowering medication	46 (47%)	522 (54%)	0.27
Statin	35 (36%)	344 (36%)	0.96
Imaging			
Occluded segment			0.86
Intracranial ICA	7 (7.4%)	47 (5.0%)	
ICA-T	20 (21%)	225 (24%)	
M1	55 (59%)	544 (58%)	
M2	11 (12%)	112 (12%)	
Other (e.g., M3, ACA)	1 (1.1%)	13 (1.4%)	

Supplemental table 6.1. Continued.

	Explicitly registered as no heparin (n=98)	Assumed no heparin (n=992)	P-value
Reperfusion before intervention (eTICI)			0.15
0	76 (84%)	723 (81%)	
1	8 (8.9%)	48 (5.4%)	
2A	4 (4.4%)	27 (3.0%)	
2B	1 (1.1%)	27 (3.0%)	
2C	0 (0%)	16 (1.8%)	
3	1 (1.1%)	48 (5.4%)	
ASPECTS	8 [7, 10]	9 [7, 10]	0.09
ASPECTS ≤ 7	38 (41%)	286 (30%)	0.05
Collaterals			0.12
Grade 0 - Absent collaterals	4 (4.3%)	66 (7.2%)	
Grade 1 - Occluded area filling <50%	27 (29%)	312 (34%)	
Grade 2 - Occluded area filling >50% but <100%	33 (35%)	345 (38%)	
Grade 3 - Occluded area filling 100%	29 (31%)	192 (21%)	
Workflow (in minutes)			
Time from symptom onset to IV alteplase	26 [21, 30]	24 [18, 31]	0.35
Time from symptom onset to admission ER (intervention center)	144 [67, 185]	134 [58, 189]	0.28
Time from admission ER to groin puncture	62 [40, 94]	66 [38, 100]	0.70
Duration procedure	72 [50, 98]	60 [39, 85]	<0.01
Time from symptom onset to reperfusion	272 [226, 334]	264 [212, 326]	0.25
Procedural			
General anesthetic management	18 (20%)	146 (16%)	0.46
Intra-arterial thrombolysis	5 (5.1%)	15 (1.5%)	0.03

Summary: Baseline demographics with heparin vs. no heparin. 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; ASPECTS, Alberta stroke program early CT score; DOAC, direct oral anticoagulant; ER, emergency room; eTICI, extended thrombolysis in cerebral infarction including a 2C grade; ICA (T), internal carotid artery (terminus); IV, intravenous; M(*segment*), middle cerebral artery; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale

Supplemental table 6.2. Complete case analysis of the primary and secondary outcomes in patients explicitly registered as treated with heparin vs. no heparin.

	Heparin (n=398)	**No heparin (n=98)**	**P-value**	**(c)OR, (95% CI)**	**a(c)OR, (95% CI)***
Primary outcome					
mRS at 90 days	3 [2, 6]	3 [2, 5]	0.77	1.06 (0.71-1.57)	1.51 (0.73-3.11)
Secondary outcomes					
mRS ≤ 2 at 90 days	144 (41%)	30 (33%)	0.10	1.39 (0.85-2.26)	2.21 (0.82-5.97)
Reperfusion after intervention (eTICI ≥ 2B)	245 (62%)	53 (55%)	0.25	1.33 (0.85-2.09)	1.28 (0.52-3.17)
Symptomatic intracranial hemorrhage	25 (6.3%)	1 (1.0%)	0.07	6.50 (0.87-48.58)	1.83 (0.19-17.31)†
Mortality at 90 days	105 (30%)	19 (21%)	0.13	0.70 (0.25-2.02)	0.70 (0.25-2.02)

Summary: Complete case analysis of the primary and secondary outcomes in patients explicitly registered as treated with heparin vs. no heparin. Continuous data are presented as median [IQR] for skewed data. Categorical data are presented as numbers (%).
Abbreviations: a(c)OR, adjusted (common) odds ratio; CI, confidence interval; eTICI, extended thrombolysis in cerebral infarction including a 2C grade; mRS, modified Rankin Scale
*Captions: *Variables in the model:* (fixed effects) percentage heparin use per 10%, age, sex, NIHSS at admission, pre-stroke mRS, intravenous alteplase, pre-interventional eTICI score, antiplatelet use, direct oral anticoagulant use, coumarin use, previous stroke, diabetes mellitus, intra-arterial thrombolysis, glucose at baseline, systolic blood pressure, anesthesia type, occlusion segment, ASPECTS at baseline, INR, onset to reperfusion, collateral grading, time per month || (random effect) center
† Direct oral anticoagulant use and coumarin use not in model due to lack of convergence

CHAPTER VII

Multicenter randomized clinical trial of endovascular treatment for acute ischemic stroke. The effect of periprocedural medication: acetylsalicylic acid, unfractionated heparin, both or neither (MR CLEAN-MED). Rationale and study design

Trials, 2020

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Abstract

Background: Despite evidence of a quite large beneficial effect of endovascular treatment (EVT) for ischemic stroke caused by anterior circulation large vessel occlusion, many patients do not recover even after complete recanalization. To some extent this may be attributable to incomplete microvascular reperfusion, which can possibly be improved by antiplatelet agents and heparin. It is unknown whether periprocedural antithrombotic medication in patients treated with EVT improves functional outcome. The aim of this study is to assess the effect of acetylsalicylic acid (ASA) and unfractionated heparin (UFH), alone, or in combination, given to patients with an ischemic stroke caused by an intracranial large vessel occlusion in the anterior circulation during EVT.

Methods: MR CLEAN-MED is a multicenter phase III trial with a prospective, 2x3 factorial randomized, open label, blinded end-point (PROBE) design, which aims to enroll 1500 patients. The trial is designed to evaluate the effect of intravenous ASA (300 mg), UFH (low or moderate dose), both or neither as adjunctive therapy to EVT. We enroll adult patients with a clinical diagnosis of stroke (NIHSS$\geq^{3}$2) and with a confirmed intracranial large vessel occlusion in the anterior circulation on CTA or MRA, when EVT within 6 hours from symptom onset is indicated and possible. The primary outcome is the score on the modified Rankin Scale (mRS) at 90 days. Treatment effect on the mRS will be estimated with ordinal logistic regression analysis, with adjustment for main prognostic variables. Secondary outcomes include stroke severity measured with the NIHSS at 24 hours and at 5-7 days, follow-up infarct volume, symptomatic intracranial hemorrhage (sICH), and mortality.

Discussion: Clinical equipoise exists whether antithrombotic medication should be administered during EVT for a large vessel occlusion, as ASA and/or UFH may improve functional outcome, but might also lead to an increased risk of sICH. When one or both of the study treatments show the anticipated effect on outcome, we will be able to improve outcome of patients treated with EVT by 5%. This amounts to more than 50 patients annually in the Netherlands, more than 1800 in Europe and more than 1300 in the United States.

Trial registration: ISRCT, ISRCTN76741621. Applied Nov 1, 2017; Assigned Dec 6, 2017. http://www.isrctn.com/ISRCTN76741621

Background

Despite the quite large beneficial effect of endovascular treatment (EVT) on functional outcome after ischemic stroke, about 50% of treated patients die or remain dependent at three months.[1] These unfavorable outcomes may not be attributable to unsuccessful recanalization alone, as approximately one third of patients do not recover even when complete recanalization is reached early after stroke onset.[2] The high risk of a poor outcome after complete recanalization may be partially explained by incomplete microvascular reperfusion (IMR), which is known to negatively affect tissue recovery.[3-6] Two main causes of IMR are (I) the formation of microthrombi embolized from the original proximal thrombus, formed in situ by local platelet activation or induced by the EVT itself through vascular endothelial damage, and (II) the formation of neutrophil extracellular traps (NETs), in which platelets, erythrocytes and other particles conglomerate.[7-10] Microvascular reperfusion might be restored by counteracting these two processes. First, formation of microthrombi could be reduced by the administration of a platelet aggregation inhibitor, such as acetylsalicylic acid (ASA). Second, contrary to tissue plasminogen activators (tPA), unfractionated heparin (UFH) removes histones from the chromatin fibers that form the core of the NETs, making thrombi with a large proportion of NETs more easily dissolvable.[11,12] In addition, the anticoagulant effect of UFH is also based on inactivation of factor IIa (thrombin) and factor Xa, after binding to and activating the enzyme inhibitor antithrombin. By inactivating thrombin, heparin prevents fibrin formation and also inhibits thrombin-induced activation of platelets and of factors V and VIII.[13] It is therefore likely that in patients treated with EVT for an intracranial large vessel occlusion, periprocedural administration of ASA and/or UFH could improve microvascular reperfusion. This potentially leads to improved functional outcome. However, periprocedural use of ASA and/or UFH may also increase the risk of symptomatic intracranial hemorrhage (sICH).

There are no randomized controlled trials (RCTs) on the effects of periprocedural treatment with platelet aggregation inhibitors in ischemic stroke patients treated with EVT.[14] The ARTIS trial focused on the effect of acute ASA administration in alteplase eligible patients (patients eligible for EVT were underrepresented). This trial demonstrated that ASA increased the risk of sICH without affecting functional outcome.[15] However, the absolute risk of hemorrhage in this trial of 4.3% was much lower than the 6-7% in the pivotal NINDS rtPA trial[16] and in the SITS MOST registry[17]. The potential benefits in EVT – reduce vessel wall inflammation and microthrombi formation – are much larger than in the ARTIS trial. A number of observational and post hoc studies have investigated the periprocedural use of platelet aggregation inhibitors; in several of them they were used for indications other than acute treatment itself (e.g. prior use of ASA based on comorbidity).[18-24] The occurrence of sICH in these studies varied between 6% and 17%. ASA use during EVT is not reported in the current stroke management guidelines.[25] Based on the results of the post hoc analysis

of the MR CLEAN trial and results from the large observational MR CLEAN registry, periprocedural use of ASA may be an useful and safe adjunct to EVT.[21,24]

Although RCT data on the effect of periprocedural UFH use in ischemic stroke patients treated with EVT are lacking as well,[14] several studies have investigated the use of intravenous (IV) UFH during EVT.[26-29] The occurrence of sICH in these studies varied between 5% and 12%. However, the risk of sICH appears to be outweighed by a higher overall chance of good functional outcome, suggesting benefit of administering UFH during EVT. Heparin use during EVT is not reported in the current stroke management guidelines.[25] Nevertheless, UFH is actively being used by some neuro-interventionists during EVT, occasionally also as part of standard care. In the Netherlands substantial center variability exists regarding the use of UFH as well.[30] This underlines the equipoise about periprocedural heparin use. Moreover, patients had better functional outcomes when treated in Dutch centers that treat more patients with UFH, without an increased risk of sICH.

Based on the pathophysiology of IMR, the theoretical and reported expected benefits and the reported safety profile of the two antithrombotic drugs to be evaluated, we designed an RCT to evaluate the benefits and risks of ASA and UFH, alone, or in combination, and most importantly, their effect on functional outcome after EVT.[14]

Research question

The primary objective of the multicenter randomized clinical trial of endovascular treatment for acute ischemic stroke – the effect of periprocedural medication (MR CLEAN-MED), is to assess the effect of periprocedural ASA and UFH, alone, or in combination, on functional outcome at 90 days in patients who undergo EVT for acute ischemic stroke caused by a confirmed intracranial large vessel occlusion in the anterior circulation.

Methods

Design

MR CLEAN-MED is a multicenter phase III trial with a prospective, randomized, open label blinded end-point (PROBE) design (Figure 7.1). Patients are randomized to receive either IV ASA (loading dose only) or IV UFH (low dose or moderate dose, both consisting of a loading dose and continuous infusion for 6 hours), both, or neither, as adjunctive treatment to EVT, in a 2x3 factorial design. An overview of the treatment arms and main study procedures is provided in Figure 7.2 and Figure 7.3. Patient inclusion started in January 2018.

MR CLEAN MED

Figure 7.1. Trial logo

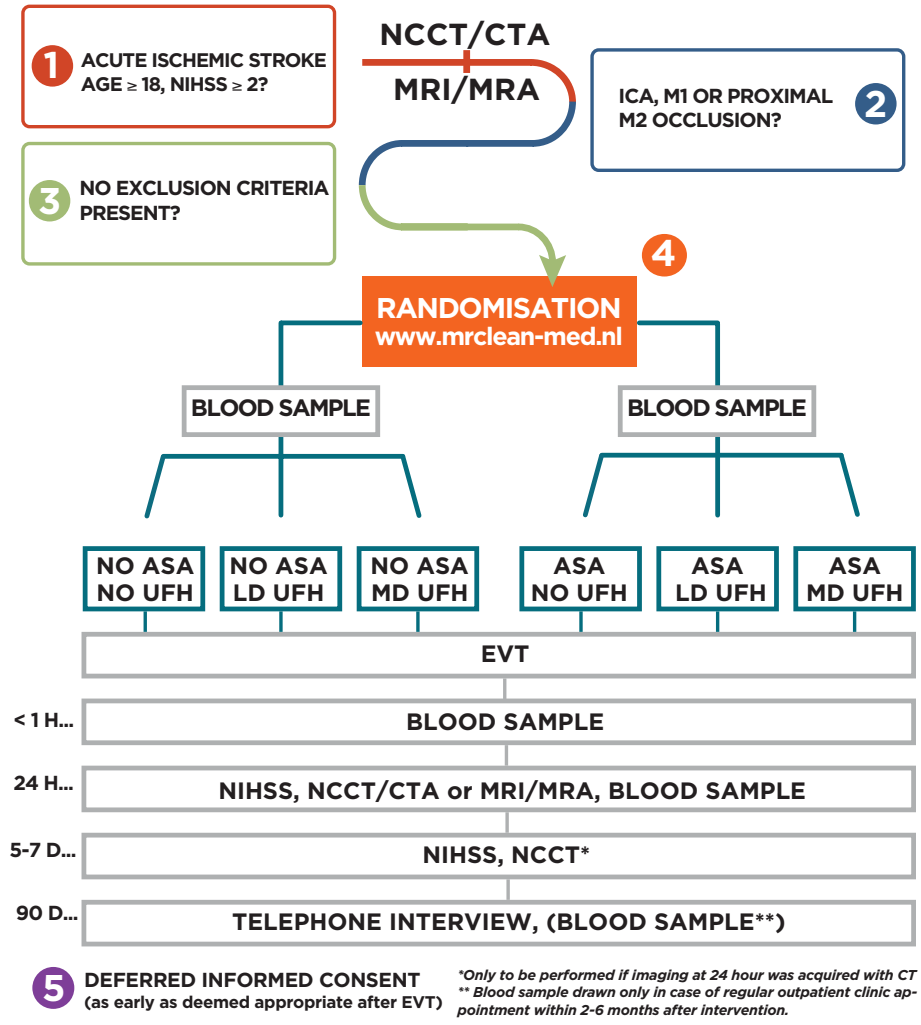

Figure 7.2. Flow of patients in the MR CLEAN-MED – in first approved protocol version. *Abbreviations:* ASA, intravenous acetylsalicylic acid; CTA, Computed tomography angiogram; UFH, intravenous unfractionated heparin; EVT, endovascular treatment; LD, low dose; MD, moderate dose; MRI, Magnetic Resonance Imaging; MRA, Magnetic Resonance Angiography; NCCT, non-contrast computed tomography; NIHSS, National Institutes of Health Stroke Scale

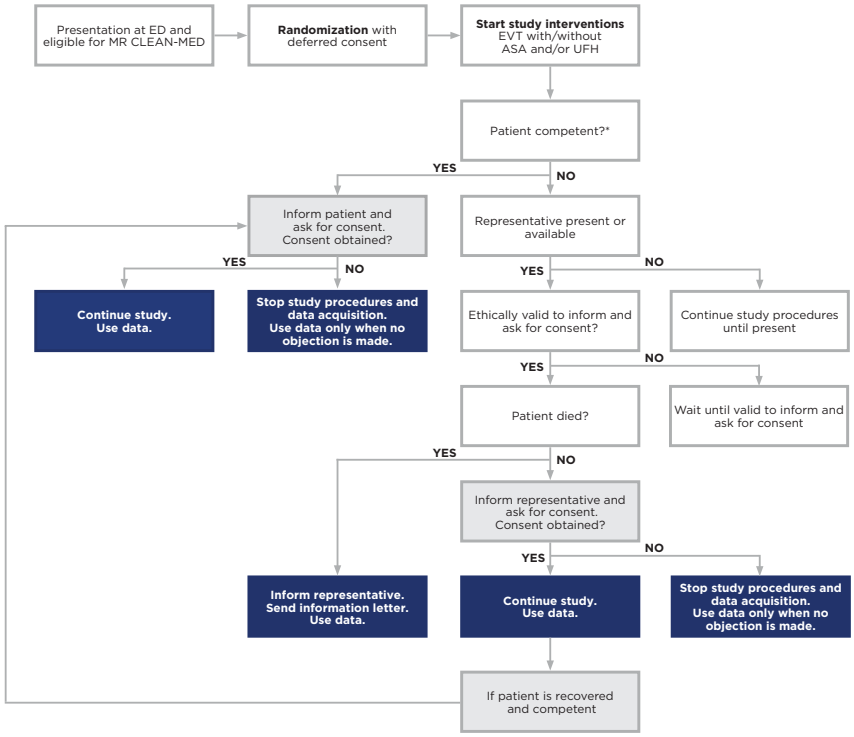

Figure 7.3. Flow of informed consent procedure in the MR CLEAN-MED *
Abbreviations: MR CLEAN-MED: Multicenter randomized clinical trial of endovascular treatment for acute ischemic stroke. The effect of periprocedural medication: acetylsalicylic acid, unfractionated heparin, both or neither; ED, emergency department; EVT, endovascular treatment; ASA, intravenous acetylsalicylic acid; UFH, intravenous unfractionated heparin.
Captions: *The patient or representative will be asked to provide consent as early as deemed appropriate and reasonable after hospital admission, ideally before upcoming study procedures after EVT and ultimately before final outcome assessment.

Patient inclusion and exclusion criteria

The study population will be drawn from patients with ischemic stroke who enter the emergency department of the EVT center. Patients are eligible for inclusion in the MR CLEAN-MED when they are 18 years or older, have a score of at least 2 on the National Institutes of Health Stroke Scale (NIHSS), present with a clinical diagnosis of acute ischemic stroke, have a non-contrast computed tomography (NCCT) or magnetic resonance imaging (MRI) ruling out intracranial hemorrhage, and have a large vessel occlusion in the intracranial anterior circulation (distal intracranial carotid artery or middle [M1/proximal M2] cerebral artery) confirmed by CT angiography (CTA) or magnetic resonance angiography (MRA). Groin puncture should be possible within 6 hours from symptom onset or last seen well. Pretreatment with IV recombinant

tissue plasminogen activator (rtPA) according to national guidelines is allowed. Patients already on antiplatelet agents before the index stroke, are allowed in the trial.

Exclusion criteria for enrollment in the MR CLEAN-MED are:
- Pre-stroke disability, which interferes with the assessment of functional outcome at 90 days (i.e., pre-stroke modified Rankin Scale [mRS] score >2);
- Treatment with rtPA, given despite one or more of the following contra-indications: cerebral infarction in the previous 6 weeks with residual neurological deficit or signs of recent infarction on neuroimaging, previous intracerebral hemorrhage within the previous 3 months, INR > 1.7, use of a direct oral anticoagulant (DOAC), rtPA infusion >4.5 hours after symptom onset;
- Contra-indications for ASA or UFH;
- heparin use in therapeutic dosages that cannot be discontinued;
- INR > 3.0;
- Known hemorrhagic diathesis or known thrombocytopenia (<90*10^9/L);
- Participation in medical or surgical intervention trials other than the current or Multicentre Randomised trial of Acute Stroke treatment in the Ambulance with a nitroglycerin Patch (MR ASAP, ISRCTN99503308)[31] or A reduction in Time with Electronic Monitoring in Stroke (ARTEMIS, NCT02808806).

Eligibility criteria for participating centers
Centers should be certified or meet national quality criteria for EVT to be eligible for participation in the MR CLEAN-MED.[32]

Randomization and blinding
Patients who are eligible for inclusion in the MR CLEAN-MED will be randomized by the treating physician, before endovascular treatment is started. The randomization procedure is computer- and web-based, using permuted blocks. Back-up assistance by telephone is provided. The allocation sequence has been generated by the independent trial statistician. Randomization is stratified for participating center, and in case of participation in MR ASAP for the inclusion in the active treatment arm (nitroglycerine patch group). For each patient that withdraws before the final outcome assessment, an additional patient will be included.

Both patient and treating physician will be aware of the treatment allocation. This open label design was chosen from a safety perspective to avoid potential delay in treatments for serious adverse events (e.g. administer IV protamine sulfate) required for unblinding of the study intervention. Clinical outcomes, such as NIHSS, and serious adverse events are reported by trained research personnel. Trained research personnel unaware of treatment allocation will assess information on outcome at three months using standardized forms and procedures during a telephone interview.[33,34] To guarantee unawareness of the research personnel assessing the outcome at three months, they will have no access to the medical records of the patients, instruct patients

or relatives before starting the interview not to say anything about the performed procedure or the admission in the hospital, and they will enter the outcome data in a database that is kept separated from the main clinical database. Final assessment of the mRS score at 90 days will be performed by the outcome committee, consisting of trained investigators blinded to the treatment allocation, based on the reports of the telephone interview. Neuroimaging on CT, MRI and DSA will be assessed by a core laboratory blinded to study treatment allocation. Information concerning treatment allocation will be kept separate from the 90-day follow-up outcome database. The steering committee will be kept unaware of the results of safety assessments and interim analyses. An independent trial statistician will combine data on treatment allocation with the clinical and outcome data to report summaries of trial progress, regular safety assessments and interim analyses on efficacy and safety to the data safety monitoring board (DSMB).

Study treatments

The study treatments, IV ASA and/or IV UFH, should be started directly after groin puncture, and in case no rtPA has been administered, prior to EVT. If rtPA administration is not finished at the time of groin puncture, the study treatment should be delayed until the moment that the infusion of the full dose of rtPA is completed. The study treatment should however be started before the EVT procedure has been terminated, i.e. before the catheter has been withdrawn and the entry location has been closed. For both study interventions, IV instead of oral administration was chosen to prevent exclusion of patients with dysphagia, and to guarantee fast uptake.

IV ASA will be administered in a single dose of 300 mg. IV UFH will be administered either in a low dose (loading dose of 5000 IU followed by 500 IU/hour x 6 hours) or a moderate dose (loading dose of 5000 IU followed by 1250 IU/hour x 6 hours). Study treatments will be combined to increase efficiency of the trial, under the assumption of independence in mechanisms of action between study treatments, study treatments will be combined. According to the 2x3 factorial design the six possible combinations are (Figure 7.2): (I) No ASA and no UFH; (II) No ASA and low dose UFH; (III) No ASA and moderate dose UFH; (IV) ASA and no UFH; (V) ASA and low dose UFH; (VI) ASA and moderate dose UFH. When the occlusion seen on CTA or MRA is no longer present on first intracranial DSA during EVT before initiation of mechanical treatment (i.e., groin puncture), and the patient has been randomized for UFH, the UFH infusion should be continued for 6 hours. In case an untoward event occurs after randomization (e.g., perforation, neurological deterioration) the decision to withhold ASA and/or UFH is left to the discretion of the treating physician. All patients in the study will start or continue non-trial antithrombotic medication for secondary prevention according to local guidelines, which mostly concerns treatment with antiplatelet agents.

Study procedures

Patients undergo assessment of the NIHSS at baseline, 24 hours, and 5-7 days. Certified assessors will carry out the NIHSS assessment. Patients will undergo NCCT and CTA at baseline, as part of usual care. For baseline imaging, MRI and MRA is also permitted. Follow-up imaging can be performed with either NCCT and CTA at 24 hours (±12 hours) and NCCT at 5-7 days or discharge, or MRI and MRA at 24 hours (±12 hours). If follow-up imaging at 24 hours (±12 hours) is performed with MRI, no additional imaging at 5-7 days or discharge is required. The protocol "MRI follow-up investigations" should consist of at least diffusion weighted imaging (DWI), fluid attenuation inversion recovery (FLAIR), T2 weighted image (T2*w), and intracranial three-dimensional time-of-flight (3D-TOF) MRA sequences.

The choice of post-EVT imaging modality (CT or MRI) is left to the individual participating centers, but the chosen modality should be adhered to during the trial in order to prevent confounding by indication. Only in case of contra-indications for MRI, CT-imaging may be performed instead and vice versa. The condition of the patient should not drive the decision to deviate from the standard imaging protocol. Follow-up imaging is not part of usual care in every hospital.

Blood samples will be taken from patients when logistics at the participating centers allow this. Blood samples will be drawn at the following time points: (1) within 1 hour before groin puncture, (2) within 1 hour after EVT, and (3) at 24 hours after EVT, if possible during routine blood drawings. We will also take a blood sample if the patient has a regular (not-trial-related) outpatient clinic appointment (2-6 months after treatment). One tube EDTA (+/- 5 mL), one tube without anticoagulant (+/- 7 mL) and two tubes citrated blood (2.7 mL) will be drawn every time, which adds up to no more than 20 mL. Substudies may require additional blood tubes, never exceeding 20 mL per drawing. If continuous venous access is available, commonly the case in patients at time point 1, 2 and 3, this will be used. Samples will be stored at minus 80 degrees Celsius for later analysis of procoagulant and genetic factors that may interact with treatment effect. In addition, "waste material" (i.e., retrieved thrombi and blood aspirated during the EVT) will be stored. All biomaterials will be stored for 15 years.

Deferred consent

MR CLEAN-MED will investigate an acute intervention in an emergency situation concerning a life-threatening disorder. For several ethical and legal reasons, the investigators ask all patients or their representative for written consent after the study treatment(s) and EVT have been carried out (i.e., deferred informed consent). The patient or representative will be asked to provide consent as early as deemed appropriate and reasonable after hospital admission, ideally before upcoming study procedures after EVT and ultimately before final outcome assessment. If a patient or his/her representative refuses to provide consent, participation in the trial will be terminated immediately. Participation in MR CLEAN-MED is voluntary, and the patient or representative may – at any given time – withdraw informed consent without

explanation. When consent by proxy has been obtained and the patient recovers, we will again ask for written consent from the patient. If a patient has died before deferred consent was obtained, the representative will be informed about trial participation (Figure 7.3).

Study outcomes
The primary outcome is the score on the modified Rankin Scale at 90 days (± 14 days).[35] The mRS is the preferred disability parameter of clinical trials in stroke.[36] The mRS is an ordinal hierarchical scale that describes the range of disability encountered post stroke and incorporates six categories from 0 (no symptoms) to 5 (severe disability), and a score of 6 has been added to include 'Death'. Assessment of outcome on the mRS will be performed by independent assessors, blinded to the allocated and received study treatment.

Secondary outcomes include:
- Recanalization grade (extended Treatment In Cerebral Ischemia [eTICI] score) on final digital subtraction angiography (DSA) after EVT;[37]
- Recanalization grade at 24 hours (±12 hours), assessed with CTA or TOF-MRA;[38]
- Score on the NIHSS at 24 hours and 5-7 days, or at discharge;[39]
- Follow-up infarct volume, at 5-7 days assessed with NCCT, or at 24 hours (±12 hours), assessed with DWI-MRI. Follow-up infarct volume will be assessed with the use of an automated, validated algorithms;[40]
- All possible dichotomizations of the mRS at 90 days (± 14 days);
- Score on the EQ-5D-5L and Barthel index at 90 days (± 14 days).[41,42]

Safety outcomes include:
- Intracerebral hemorrhage according to the Heidelberg Bleeding Classification[43];
- SICH scored according to the Heidelberg Bleeding Classification (with the addition of sICH that led to death and that was identified as the predominant cause of the neurologic deterioration)[43];
- Extracranial hemorrhage requiring transfusion or resulting in death;
- Embolization in new territory on DSA during EVT;
- Infarction in new territory within 5-7 days assessed with NCCT or 24 hours (±12 hours) assessed with DWI-MRI;
- Death from all causes within 90 days

All imaging-related outcomes on CT, MRI and DSA will be assessed by an independent core laboratory blinded to study treatment allocation. Clinical outcomes such as NIHSS and serious adverse events are reported by trained research personnel.

(Serious) adverse event reporting
Safety is an issue of concern as both ASA and UFH could increase bleeding risk. Adverse events are defined as any undesirable experience occurring to a subject during the study, whether or not it is considered related to the investigational product. All adverse events reported spontaneously by the subject or observed by the investigator or his/her staff will be recorded. A serious adverse event is any untoward medical occurrence or effect that: (I) results in death; (II) is life threatening (at the time of the event); (III) requires hospitalization or prolongation of existing inpatients' hospitalization; or (IV) results in persistent or significant disability or incapacity. The (local) investigator will report the following SAEs occurring in the study period to the sponsor without undue delay of obtaining knowledge of the events: Death from any cause, sICH defined according to the Heidelberg criteria, extracranial hemorrhage, cardiac ischemia, pneumonia, allergic reactions, new ischemic stroke in a different vascular territory. Events that result in any of the outcomes listed, according to appropriate medical judgement, if no medical or surgical intervention would have been carried out, will also be considered a serious adverse event. Serious adverse events that meet the aforementioned criteria will be reported to the sponsor, within 24 hours after coming to notice of the (local) investigator, by making use of the appropriate forms in the eCRF, which will automatically lead to notification of the study coordinator. Elective hospital admission will not be considered a serious adverse event. Technical complications or vascular damage at the target lesion such as perforation or dissection that do not lead to clinically detectable SAEs, and neurological deterioration not caused by intracranial hemorrhage or new ischemic stroke, are considered as consistent with the natural course of the ischemic stroke and should be reported at the patient's 90 days follow-up.

Safety registry
Due to the deferred consent procedure, the study treatment will have been administered to patients prior to obtaining informed consent. The procedure requires that all information on patients who did not provide consent after EVT is discarded and deleted. This may be against the interest of patients who did provide consent, and against the interest of the general public, as patients with sICH and other serious adverse events might be more likely to refuse consent for participation. Not considering these records might very well result in an underestimation of the true safety and validity of the data, and it might lead to undetected safety concerns for all consenting patients in the trial. To overcome this concern, we will register the following variables in a strictly anonymized safety registry for all patients, irrespective of whether a patient has provided written informed consent: patient's study number, study treatment, in-hospital sICH occurrence (*yes/no*), and in-hospital survival status (*yes/no*). All other information will be completely erased from the patient's study record in case no consent is provided. The link to the study database will be erased from the patient's medical record.

Data and Safety Monitoring Board

The independent Data and Safety Monitoring Board (DSMB) consists of a neurologist, a neuro-interventionist, and an independent statistician. The DSMB will meet at least annually or after inclusion of each 300 patients (whichever comes first) to monitor the efficacy and safety of the study treatments. The DSMB will evaluate the occurrence of unwanted effects by study treatments and by center. During the period of patient enrollment, short safety reports are made by the independent statistician of the trial after the occurrence of every 5 sICHs or after the occurrence of every 10 deaths, whichever comes first. Depending on the results of previous analyses, the DSMB may propose to the steering committee to relax the criterion of 5 sICH or 10 deaths. Safety of the study treatments in terms of sICH risk and all-cause mortality will be evaluated based on the safety registry. Also, during the period of patient enrollment interim analyses on major endpoints (including serious adverse events believed to be due to treatment) will be supplied by the independent statistician of the trial (annually or as soon as possible after inclusion of 300 patients, whichever comes first), in strict confidence, to the chairman of the DSMB along with any other analyses that the committee may request. In the light of the safety reports and interim analyses, the DSMB will advise the chairman of the steering committee if, in their view, the randomized comparisons in the trial have provided both (1) "proof beyond reasonable doubt" that for all, or for some specific types of patients, one particular treatment is clearly indicated or clearly contraindicated in terms of a net difference in outcome, and (2) evidence that might reasonably be expected to materially influence patient management. Appropriate criteria of proof beyond reasonable doubt cannot be prespecified precisely, but a difference of at least 3 standard deviations in an interim analysis of a major endpoint may be needed to justify halting or modifying the study prematurely. This criterion has the practical advantage that the number of interim analyses is of little importance. The principal investigators (PIs), study personnel and steering committee will remain blinded to the treatment allocation in the dataset and to the results of the safety assessments and interim analyses.

Sample size

Power was estimated by simulation.[44] For the control arm in the study, the distribution over the 7-point mRS was based on data of the MR CLEAN trial: mRS 0: 3%; mRS 1: 9%; mRS 2: 21%; mRS 3: 18%; mRS 4: 22%; mRS 5: 6%; mRS 6: 21%. For both ASA and UFH, we assume a favorable effect with a common odds ratio of 1.27, which corresponds to an absolute risk difference of having a score on the mRS of 0-2 of approximately 5%. Covariate adjustment will be used, which reduces the required sample size by approximately 25%.[45,46] We aim to include 1500 patients, which will provide 84% power to detect a true difference in outcome between the ASA and the control arm; and 78% power to detect a true difference in outcome between any of the low dose UFH, moderate dose UFH, and control arm (two-sided alpha=0.05). No adjustments for multiple comparisons will be made.

Statistical analyses
The analysis and reporting of the trial will be in accordance with the CONSORT guidelines.[47]

The main treatment contrasts that will be analyzed are:
- ASA vs. no ASA
- Any dose UFH vs. no UFH

In addition, as secondary analysis, we will compare:
- Low dose UFH vs. no UFH
- Moderate dose UFH vs. no UFH
- Low dose UFH vs. moderate dose UFH

All analyses will be performed according to the intention-to-treat principle. Baseline data by treatment allocation will be reported with standard statistical procedures, and missing values for baseline characteristics will be reported. Missing baseline characteristics will be imputed using multiple regression imputation. The primary effect estimate, which is the common odds ratio for a shift on the 7-category mRS at 90 days, will be assessed by means of an ordinal logistic regression analysis. Secondary effect estimates will be assessed by means of linear, logistic, or ordinal logistic regression analyses, as appropriate. Pre-specified adjustments will be made for known prognostic variables including: age, time from onset to door of EVT center, time from door EVT center to groin puncture, baseline NIHSS, pre-stroke mRS, and collateral score. Adjusted and unadjusted estimates will be reported as a beta, odds ratio or common odds ratio with their 95% confidence intervals. We assume the effects of ASA and UFH to be independent, but this assumption will be tested with a test for interaction. Before follow-up of all included patients is completed, a statistical analysis plan will be developed and published that specifies the hypotheses to be tested and the more detailed statistical methods to analyze treatment effects on secondary outcomes, adjustments for covariates and subgroup analyses. We will interpret the common odds ratio as the best estimate of an average treatment effect, and therefore, no formal testing of the proportionality assumption is necessary.

Data management
All MR CLEAN-MED data are entered into a web-based trial management system that allows for edit and audit trails, by trained local research nurses. Case report forms can be found on the website (http://www.mrcleanmed.nl/). Patient records are coded by a unique study number. The local investigators will keep a list showing codes and names. Unique documents with identifying information will be stored separately from the study database in digital files, categorized by study number on a secure drive system, only accessible to the study coordinators. Data will be monitored for completeness, consistency and validity by the study coordinators through automated data checks.

25% of local data are carefully reviewed against source data, based on a pre-assessed risk evaluation and in accordance with Dutch standards, by an independent monitor performing two to three visits per year during the study period (Appendix 2). The database will be closed within one month after the last scheduled follow-up date of the last included patient.

Study organization

MR CLEAN-MED is embedded in the Collaboration for New Treatments of Acute Stroke (CONTRAST) consortium, a nationwide collaboration of clinical and translational scientists. The CONTRAST consortium will perform five large RCTs in stroke patients to test novel treatment strategies, aimed at preservation of ischemic tissue and improving outcome after stroke (Multicentre randomised trial of acute stroke treatment in the ambulance with a nitroglycerin patch [MR ASAP, ISRCTN99503308][31]; Intravenous treatment followed by endovascular treatment versus direct endovascular treatment for acute ischemic stroke caused by a proximal intracranial occlusion [MR CLEAN-NO IV, ISRCTN80619088]; The current study: Multicenter randomized clinical trial of endovascular treatment for acute ischemic stroke. The effect of periprocedural medication: acetylsalicylic acid, unfractionated heparin, both or neither [MR CLEAN-MED, ISRCTN76741621]; Multicenter Randomized Clinical Trial of Endovascular Treatment of Acute Ischemic Stroke in The Netherlands for Late arrivals [MR CLEAN-LATE, ISRCTN19922220]; The Dutch ICH Surgery Trial - pilot study; minimally-invasive endoscopy- guided surgery for spontaneous intracerebral hemorrhage [DIST, NTR7180]. Although, MR CLEAN-NO IV, MR CLEAN-MED and MR CLEAN-LATE, which all aim to improve outcome after EVT by focusing on the optimization of EVT and the expansion of its indication, draw from the same pool of patients with acute ischemic stroke, there is no competition between the three trials (Figure 7.4). All studies are independent clinical trials, but investigators collaborate closely and the trials share the same data structure and format, imaging and clinical assessment procedures, and outcome, imaging and SAE assessment committees. Patients enrolled in MR CLEAN-NO IV, MR CLEAN-MED or MR CLEAN-LATE can also participate in MR ASAP, for which patients will be stratified.

The MR CLEAN-MED is guided by several MR CLEAN-MED-organized and CONTRAST-organized committees:

The steering committee of the trial consists of all local PIs of the participating centers. Each participating center has two local PIs: a vascular neurologist and a neuro-interventionist. The steering committee will meet at least annually. Final decisions concerning protocol changes, publication and reporting will be made by the steering committee. The steering committee is chaired by the central PIs of the trial. Decisions will be made in consensus, but if unavoidable by majority vote. Day to day conduct of the trial will be managed by the trial coordinators, who will be supervised by the central PIs of the trial.

The executive committee of the trial consists of the central PIs of the trial, a representation of local PIs, including the PIs of the two other MR CLEAN II trials, and of the study coordinators. They meet regularly, discuss trial progress and prepare information for the steering committee.

The writing committee consists of the executive committee and local PIs of the five collaborating centers that have contributed the most patients to the trial in the first two years of trial execution. The task of the writing committee is to prepare the main publication which will be drafted by the study coordinators, supervised by the two central PIs. Typically, the main paper will be authored by the study coordinators, the local PIs, the committee members, the central PIs, the coordinators of the two other MR CLEAN trials, and data management group, in name of all MR CLEAN-MED investigators. Authorship has to comply with the criteria of the International Committee of Medical Journal Editors (IMCJE at http://www.icmje.org/).48

The other trial committees are not trial specific and will be formed in collaboration with the four CONTRAST randomized clinical trials on acute stroke: MR ASAP, MR CLEAN-LATE, MR CLEAN-MED and MR CLEAN-NO IV. These are: *the imaging committee, the adverse event committee, and the outcome committee.* The committees will regularly report to the steering committees of the involved trials.

The imaging committee is chaired by the CONTRAST imaging work package leaders (CM and AL) and consists of neuroradiologists from the collaborating centers. Their task is to assess and evaluate masked baseline and follow-up imaging, which is performed per protocol and stored in a central web-based database (XNAT, https://www.xnat.org/). Assessments will be stored in research forms and entered in the clinical database, which will be accessible to investigators after approval by the Steering committee.

The adverse event committee consists of at least 3 members, including a neurologist and a neuroradiologist. Their task is to oversee and review all reported serious adverse events.

The outcome committee consists of at least 3 members, all seasoned neurologists. Their task is to evaluate all coded and masked structured reports of the outcome assessments at 90 days of patients in the trials. This way, we can ensure blind outcome assessment.

The investigators and collaborators of MR CLEAN-MED are listed in Appendix 1. Strategies for improving adherence to the intervention protocol and other study procedures, and for achieving adequate participant enrollment include training sessions at all participating centers, regular newsletters and research meetings with all collaborators, and monthly telephone meetings with the study coordinators and central PIs of the MR ASAP, MR CLEAN-NO IV, MR CLEAN-MED, and MR CLEAN-LATE.

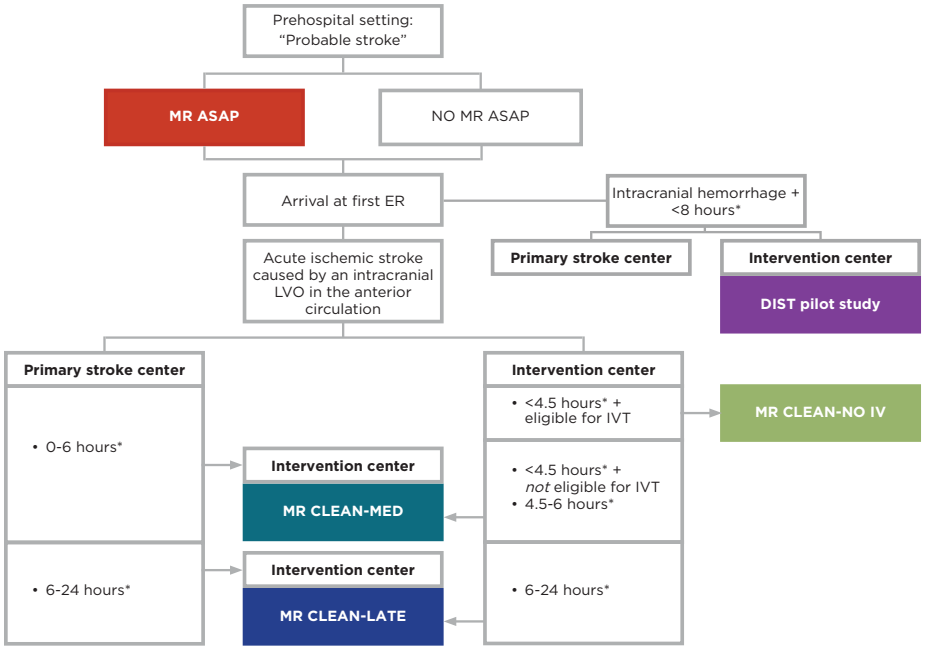

Figure 7.4. Flow of patients in the acute stroke trials of the Collaboration for New Treatments of Acute Stroke (CONTRAST) consortium*

Abbreviations: MR ASAP, Multicentre Randomised trial of Acute Stroke treatment in the Ambulance with a nitroglycerin Patch; ED, Emergency Department; DIST pilot study, Dutch Intracerebral Hemorrhage Surgery Trial - pilot study; minimally-invasive endoscopy-guided surgery for spontaneous intracerebral hemorhage; LVO: large vessel occlusion; IVT: intravenous thrombolysis with alteplase; MR CLEAN-MED: Multicenter randomized clinical trial of endovascular treatment for acute ischemic stroke. The effect of periprocedural medication: acetylsalicylic acid, unfractionated heparin, both or neither; MR CLEAN-NO IV: Intravenous treatment followed by endovascular treatment versus direct endovascular treatment for acute ischemic stroke caused by a proximal intracranial occlusion; MR CLEAN-LATE: Multicenter Randomized Clinical Trial of Endovascular Stroke treatment in The Netherlands for Late arrivals.

Captions: *Considerations: The CONTRAST trials are independent clinical trials. Patients included in MR ASAP may also be included in one of the other trials. We will perform pre-specified subgroup analyses to test for interaction between the different study treatments. At the first ED (i.e., primary stroke center or participating EVT center), all patients with a probable diagnosis of acute stroke will undergo non-invasive imaging to differentiate between cerebral infarction or intracranial hemorrhage, and to assess an intracranial LVO in the anterior circulation. When the first ED is a primary stroke center and the patient could be eligible for DIST pilot study, MR CLEAN-MED or MR CLEAN-LATE, the patient should be transferred to a participating EVT center. Patients arriving at a primary stroke center first, will generally not be eligible for MR CLEAN-NO IV, since IVT cannot be withheld until after patient transfer to the EVT center, unless the perceived contraindications for IVT are not present anymore upon arrival at the EVT center. Then inclusion in MR CLEAN-NO IV will have priority over

Ethical considerations
The MR CLEAN-MED protocol, including the template informed consent forms, which can be found on http://www.mrcleanmed.nl/ has been approved for the Netherlands by the central medical ethics committee and research board of the Erasmus MC University Medical Center, Rotterdam, the Netherlands (MEC-2017-366) before start of the trial. The study will be conducted according to the principles of the Declaration of Helsinki (7th revision, October 2013), ICH-GCP, the Dutch Medical Research Involving Human Subjects Act (WMO) and when it becomes applicable in accordance with regulations of other countries with participating centers. The current manuscript is based on protocol version 1.6 (April 2019). The most up to date approved trial protocol, including protocol version and amendments can be found on the website (http://www.mrcleanmed.nl/).

Trial status

The initial approval of the MR CLEAN-MED trial protocol by the ethical board covered approval of patient enrollment in the four organizing centers of four stroke trials performed by the CONTRAST collaboration. For logistic reasons, approval was given for 16 other centers at a later stage. The first patient was enrolled in the MR CLEAN-MED in January 2018. The DSMB did not report any safety concerns following the first three safety assessments. However, after receipt of the 4th safety report on April 16th 2019, the DSMB recommended unanimously that the steering committee should consider stopping the moderate dose UFH arm of the trial, but should continue the other arms of the trial. The grounds for stopping this specific arm were related to safety rather than efficacy. The steering committee of the trial has acted upon receiving this advice, and directly stopped inclusion in the moderate dose UFH arms of the trial. At the time point of receiving the DSMB's advise 137 patients were enrolled in the trial, of which 46 patients in the moderate dose UFH arm. No patients have been included in the moderate dose UFH arm after receipt of the DSMB recommendation. After consulting the medical ethics committee, the inclusion of patients in the ASA and low dose UFH arms was continued the next day (Figure 7.5). Meanwhile, patients, family and representatives were contacted personally and regulatory bodies were notified. In the 4th safety report the DSMB advised to further evaluate the efficacy and safety of the moderate dose UFH arm, which will be compared to the blinded data of the other arms. Results from this analysis have been reported on scientific meetings and will be submitted for publication.[49,50] On May 31, 2020 a total of 15 Dutch and 5 French sites agreed to participate in MR CLEAN MED, and 441 patients were included in the trial by 13 enrolling centers. Recruitment is expected to be completed by the end of 2021. More information about the MR CLEAN-MED, including progress of the trial and participating centers can be found on the website (http://www.mrcleanmed.nl/).

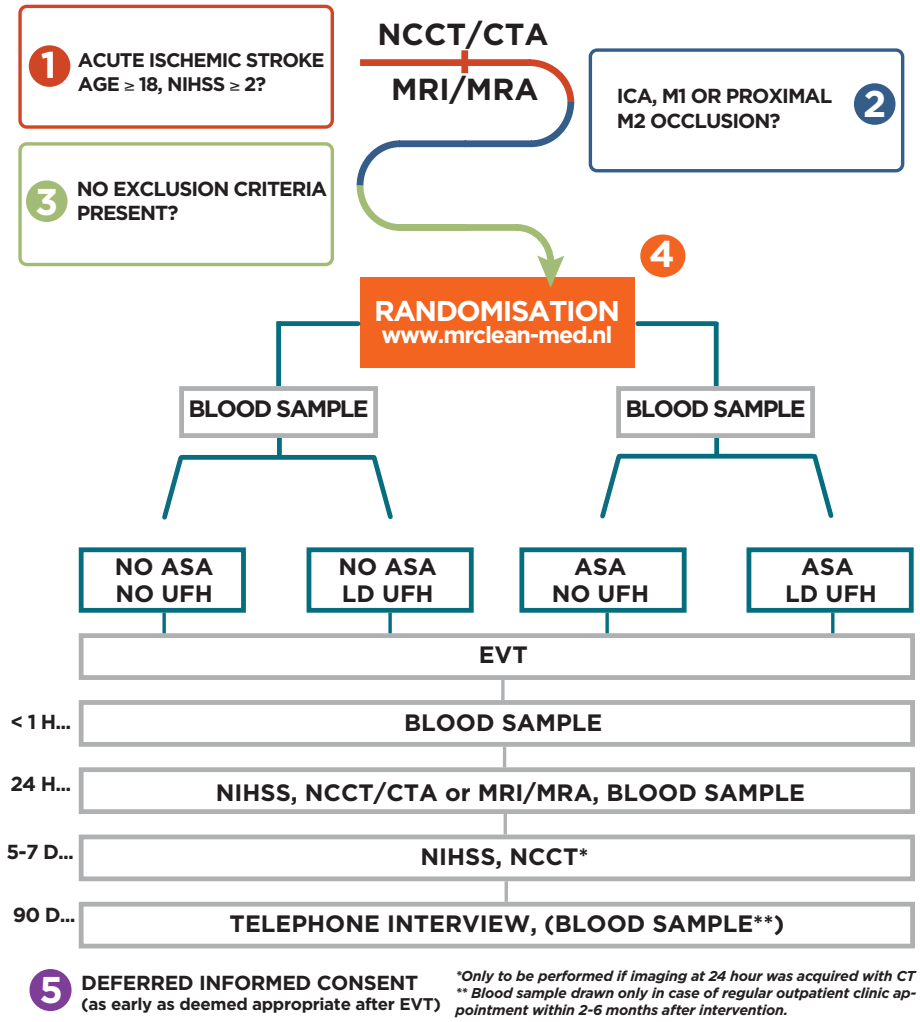

Figure 7.5. Flow of patients in the MR CLEAN-MED – modification after the recommendation of the DSMB to stop recruiting patients for moderate dose unfractionated heparin
Abbreviations: ASA, intravenous acetylsalicylic acid; CTA, Computed tomography angiogram; UFH, intravenous unfractionated heparin; EVT, endovascular treatment; LD, low dose; MD, moderate dose; MRI, Magnetic Resonance Imaging; MRA, Magnetic Resonance Angiography; NCCT, non-contrast computed tomography; NIHSS, National Institutes of Health Stroke Scale

Discussion

MR CLEAN-MED – a multicenter RCT investigating the effect of periprocedural ASA and UFH, alone or in combination, in patients with acute ischemic stroke who undergo

EVT within 6 hours after symptom onset for a confirmed intracranial large vessel occlusion in the anterior circulation – is being conducted in the framework of the CONTRAST consortium (https://www.contrast-consortium.nl/) in continuation of the MR CLEAN trial[51] and the MR CLEAN-Registry[52] to further improve outcomes for patients who undergo EVT. This trial will provide evidence whether adjunctive periprocedural therapy with ASA and/or UFH leads to improved microvascular reperfusion and better outcomes despite a possibly increased risk of sICH in these patients.

Other ongoing trials
Next to the MR CLEAN-MED, there are currently no other ongoing trials investigating the effect of ASA and/or UFH in patients with acute ischemic stroke who will undergo EVT.

Expected benefit
The trial design is pragmatic and the trial results should be generalizable and representative of clinical practice. We chose to include the most unselected patient population – in which EVT was proven effective – in the MR CLEAN-MED, so that the study treatments may be extrapolated to the broadest and most diverse patient group, if proven effective. This implies that both ASA and UFH as an adjunctive treatment to EVT may be given to a broad selection of patients undergoing EVT. We consider both ASA and UFH suitable for evaluation with a phase 3 RCT, as both study treatments are well known and have been used for similar endovascular procedures in the fields of neurology and cardiology for several decades. There is extensive clinical experience with the use of both agents, they are both widely accessible, cheap, easy to administer, and for UFH the activity is easily reversed – also in adjunction to EVT. Therefore, if a significant treatment effect of ASA and/or UFH will be proven in the MR CLEAN-MED, both treatments could also be easily implemented in clinical practice on a large scale. Considering the low costs of this medication, we expect the treatment to be cost-effective as well. Consequently, a substantial number of patients could potentially profit from these treatments.

Limitations and concerns
The underlying assumption of independence of study treatment effect on the primary outcome in a randomized trial with a factorial design is important, because it allows analysis of treatment effects separately for both treatments. We consider the assumption reasonable for the main effects on functional outcome, as the underlying mechanisms differ (inhibition of platelet activation versus interference with coagulation factors thrombin, factor Xa, other proteases through activation of antithrombin and by degrading NETs). However, we will analyze whether the assumption of independence of the effect of aspirin and heparin on the occurrence of sICH is true. If the assumption of independence is violated we will analyze stratified treatment effects.

Inherently to the acute setting of the trial and necessity for deferral of consent bias could have been introduced by selective patient refusal (e.g. in case of a poor clinical condition). The trial will provide generalizable results regarding safety of the study treatments, as all randomized patients will be registered in the safety registry providing information on in-hospital sICH risk and mortality. It is not possible to register mRS scores of randomized patients who refused to provide consent out of respect of each patient's autonomy. Therefore, the estimate of the treatment effect on the primary outcome should be interpreted in the light of the refusal rate. As we expect the refusal rate to be low, we anticipate that the impact on the generalizability of the trial's results will be low.

Based on the available literature, upon start of the trial, we considered the risk of sICH associated with the administration of both UFH doses and/or ASA acceptable in the light of expected improved functional outcomes. This was also reflected by the systematic use of UFH for this indication in a substantial number of centers in the Netherlands, and in other countries.[28-30] Moreover, experimental work showed that the immediate use (<6 hours) of ASA and/or UFH could add to improvement of outcomes by preventing or limiting microvascular occlusion within the regions of ischemic injury.[5,53,54] The risk of sICH risk remains an important concern in the MR CLEAN-MED. We monitor the occurrence of sICH strictly by performing regular safety assessments in consultation with the DSMB. We also evaluate the safety of the study medication in terms of sICH rate and all-cause mortality in the anonymized safety registry, which includes all treated patients.

There is no clear evidence which UFH dose and regimen may be most effective and safe. We had chosen to investigate the efficacy of two different UFH doses to evaluate a possible dose effect. The protocol for the different dosages of UFH are based on findings from the PROACT I and II and IST trials, and on experience in later thrombectomy studies.[28-30,55,56] The PROACT I trial compared intra-arterial recombinant pro-urokinase in combination with IV UFH to IV UFH alone for patients with a visible middle cerebral artery occlusion. The bleeding risk in the UFH alone arm of 7.1% seemed acceptable for both the high dose (100 IU/kg bolus followed by 1000 IU/h continuous infusion for 4 hours) and low dose arms (dose 2000 IU bolus followed by 500 IU/h continuous infusion for 4 hours). In the high-dose UFH group of the International Stroke Trial (IST), in which patients received 12500 IU UFH subcutaneous twice daily up to 14 days, the absolute risk of sICH was low (2.0%).[56] These results suggested that the low and moderate doses of UFH in MR CLEAN-MED would both be associated with acceptable risks. Nevertheless, the DSMB recommended the steering committee to stop enrollment in the moderate dose UFH arm of the trial based on safety concerns. Therefore, this arm has been removed from the trial and safety and outcome results will be reported separately, without compromising the blinding of investigators to results of the other trial arms. As inclusion in the moderate dose UFH arm of the trial has been permanently discontinued, we will now only investigate treatment effects for ASA and for low dose UFH.

The steering committee of the MR CLEAN-MED advised per July 19, 2019 for reasons of homogeneity among centers to limit intra-arterial flushing of the sheath with UFH during EVT up to 2500 IU per liter.

Deferral of consent

In MR CLEAN-MED, we use a deferred consent procedure. The primary reason for this approach is that in ischemic stroke, acute treatments are based on the 'time is brain' principle, in order to reduce loss of brain tissue as time progresses. In patients treated with EVT, each hour delay to reperfusion is associated with an increase in absolute risk of disability of 6-7%.[1] First of all, experience in MR CLEAN indicates that a proper informed consent procedure takes more than one hour, even when a legal representative is involved. This would lead to an unacceptable delay, considering the time-dependent effect of EVT. Second, most patients with acute neurological deficits (such as impaired consciousness or aphasia) are not capable of decision making before enrollment in a trial. In the MR CLEAN Registry, 80% to 96% of the acute ischemic stroke patients eligible for EVT were in retrospect considered to lack decision-making capacity at admission, based on neurological symptoms potentially interfering with their capacity to decide about trial participation.[57] Exclusion of these patients might lead to selection bias and reduced generalizability of the trial results. Lastly, the decision-making capacity for trial participation in an emergency situation is also reduced by stress and by the complexity and volume of the provided information. Thus, the use of the deferred consent procedure is likely to increase patient enrollment and to reduce selection bias. However, if a substantial number of patients or representatives object to enrollment after EVT this could actually contribute to a different kind of selection bias, particularly if this disproportionally concerns patients with adverse events and poor clinical outcome. Postponing consent seems tolerated by patients and their relatives in several clinical studies and trials.[58-65] However, a substudy of the ESCAPE trial (The Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion With Emphasis on Minimizing CT to Recanalization Times), showed that the majority of patients or their representatives disagreed with the use of deferred consent.[66] Yet, none of the patients enrolled with deferred consent in this trial withdrew consent later, and patients agreed with the conditions used to justify deferred consent procedures. A separate substudy within the CONTRAST consortium, in the form of a survey, will be carried out to further elucidate the acceptability of the deferred consent procedure in acute stroke trials.

Conclusion

MR CLEAN-MED is a pragmatic randomized clinical trial with a PROBE design. ASA and UFH are well known and available everywhere. When one or both of the study treatments show the anticipated effect on outcome, we will be able to improve outcome of patients treated with EVT by 5%. This amounts to more than 50 patients

annually in the Netherlands, more than 1800 in Europe and more than 1300 each year in the United States.[67,68]

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CHAPTER VIII

Safety of moderate-dose unfractionated heparin during endovascular treatment for ischemic stroke: interim results of a randomized trial

Submitted

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Abstract

Background: Many patients with ischemic stroke due to large vessel occlusion do not recover after endovascular treatment (EVT). Periprocedural therapy with unfractionated heparin (UFH) might improve clinical outcome, despite an increased risk of symptomatic intracranial hemorrhage (sICH). We evaluated the safety of moderate-dose UFH administration during EVT.

Methods: We report the results of a safety interim analysis of the MR CLEAN-MED trial. This is a multicenter, prospective, randomized, open-label, blinded-endpoint trial with a 2x3 factorial design. We enrolled patients, in fifteen Dutch sites, with a clinical diagnosis of acute ischemic stroke and confirmed intracranial anterior circulation occlusion eligible for EVT within 6 hours after last seen well. Patients were randomized for intravenous treatment with acetylsalicylic acid (ASA, 300 mg bolus) or no ASA, and for UFH in a low-dose (5000 IU bolus, and 500 IU/hour during 6 hours), UFH in a moderate-dose (5000 IU bolus, and 1250 IU/hour during 6 hours) or no UFH. For the present analysis, we compared outcomes of patients allocated to moderate-dose UFH to those of patients not allocated to this study treatment. Outcomes for this interim safety analysis were sICH and death within 90 days.

Results: In April 2019, after enrollment of 132 patients, the results of the 4th pre-planned safety interim analysis, performed by the Data Safety and Monitoring Board (DSMB), revealed an increased risk of sICH (p=0.001) for patients allocated to moderate-dose UFH (11/43, 26%) compared with patients not allocated to this study treatment (5/89, 6%; adjusted odds ratio [aOR] 10.9, 95%CI 2.7 to 44.1). Moderate-dose UFH was also associated with an increased mortality risk (20/43, 47% vs. 20/89, 22%; aOR 5.38 95%CI 2.05 to 13.7).

Conclusion: Periprocedural treatment with moderate-dose UFH is associated with increased sICH and mortality risks and should be avoided.

Trial registration: ISRCTN76741621

Introduction

Endovascular treatment (EVT) of ischemic stroke due to large vessel occlusion is highly effective in improving functional outcome.[1] However, even among patients in whom EVT leads to early and successful reperfusion of the proximal intracranial artery, approximately 30% of patients do not recover to functional independence.[2] This may partly be explained by incomplete microvascular reperfusion.[3] It is likely that periprocedural antithrombotic treatment, such as acetylsalicylic acid [ASA] or unfractionated heparin [UFH], improves microvascular reperfusion.[4,5] Observational studies suggested that periprocedural antithrombotic treatment may have a beneficial effect on functional outcome, but may also increase the risk of symptomatic intracranial hemorrhage (sICH).[6] Whether the benefit outweighs the risk is unknown. In the *Multicenter randomized clinical trial of endovascular treatment for acute ischemic stroke. The effect of periprocedural medication: acetylsalicylic acid, unfractionated heparin, both or neither* (MR CLEAN-MED), we evaluate the safety and efficacy of periprocedural use of ASA and a low or moderate-dose of UFH. On April 16th 2019, the independent Data Safety and Monitoring Board (DSMB) performed the 4th pre-planned safety interim analysis of the trial. Following this analysis, the DSMB advised to stop assigning moderate-dose UFH to new study participants, because of a safety issue. Here, we present the results of this safety interim analysis to evaluate the safety of moderate-dose UFH administration during EVT for ischemic stroke.

Methods

Study Design

MR CLEAN-MED is a multicenter phase III trial with a prospective, randomized, open label blinded end-point (PROBE) design. The detailed trial protocol was published elsewhere.[7] Every participant or their representative was asked for written consent after the study treatment and EVT had been carried out (i.e., deferred informed consent). To overcome the concern of selection bias that may have occurred by refusal to provide consent by patients with a poor outcome, we used a strictly anonymized safety registry for all randomized patients. This safety registry contains data on the study treatment assignment, in-hospital sICH occurrence, and in-hospital survival status. Regular safety assessments were performed after every 5 sICH and/or 10 deaths. The trial protocol was approved by a central medical ethics committee and the research board of each participating center.

Participants

Participants were ≥18 years with ischemic stroke caused by an intracranial arterial occlusion of the anterior circulation eligible for EVT. Initiation of EVT had to be possible within 6 hours after stroke onset.

Study Interventions
This trial had a 2x3 factorial design, providing 6 study arms (supplemental figure 8.1). Patients were randomized to receive IV ASA (300mg bolus), IV UFH (either in a low-dose [5,000IU bolus, followed by 500 IU/hour during 6 hours] or in a moderate-dose [5,000IU bolus, followed by 1,250 IU/hour during 6 hours]), both, or neither. Both IV ASA and IV UFH were started directly after groin puncture. In this report, we compared outcomes of patients randomized to moderate-dose UFH (with or without ASA) to patients not randomized to moderate-dose UFH. The latter group received ASA, low-dose UFH, both or neither. We remained blinded for the allocation and outcomes of ASA and low-dose UFH as the analyses were performed by the independent trial statistician.

Outcomes
The outcomes of the safety interim analysis were any sICH and death within 3 months. SICH was scored according to the Heidelberg Bleeding Classification.[8] Venous blood samples were drawn at 1 hour after EVT to determine activated partial thromboplastin times (APTT) and anti-Xa levels.

Statistical analysis
All analyses were based on the intention-to-treat principle. For the primary analysis, we used data of patients of whom deferred consent was obtained (main cohort). We used binary logistic regression analyses to assess the effect of treatment with moderate-dose UFH on both safety outcomes, adjusted for prespecified prognostic factors: age, pre-stroke mRS, time from onset to door of EVT center, time from door of EVT center to groin puncture, baseline NIHSS, and collateral score. Effects are reported as unadjusted and adjusted odds ratios with 95% confidence intervals. As a sensitivity analysis, we also estimated these effects in the safety registry. All analyses were performed using R version 3.5.2.

Results

Baseline characteristics and study interventions
Between January 22th, 2018, and April 16th, 2019, 137 patients were randomized in 4 centers and were registered in the safety registry (Figure 8.1). Five patients did not provide deferred consent, leaving 132 participants for the main analysis. Forty-three (34%) patients were allocated to moderate-dose UFH and 89 (66%) patients were not allocated to moderate-dose UFH. Patient, clinical and imaging factors at baseline were evenly distributed between groups (Table 8.1).

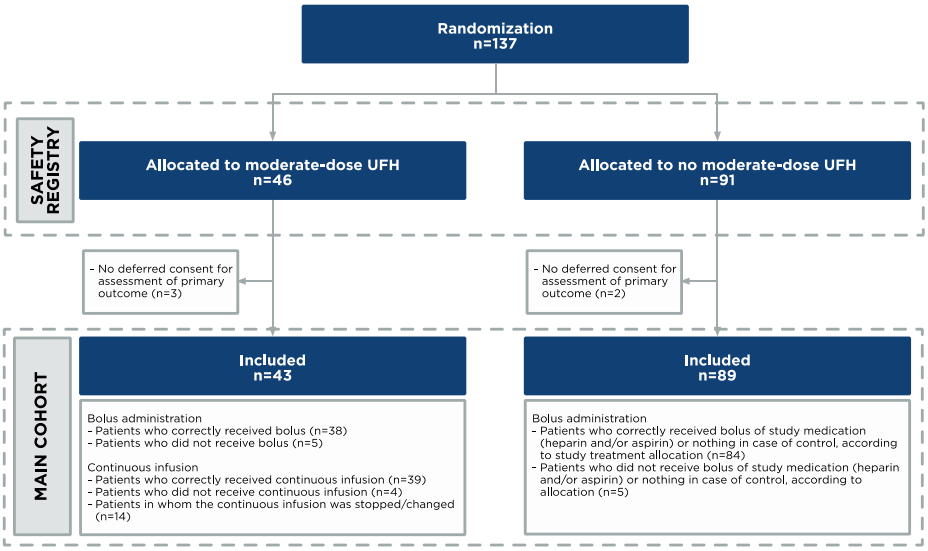

Figure 8.1. Patient flowchart

Table 8.1. Baseline characteristics.

	MD UFH [n=43]	NO MD UFH [n=89]
Patient characteristics		
Age, median (IQR)	77 (69 to 83)	74 (66 to 82)
Male sex, n (%)	19 (44%)	46 (52%)
NIHSS, median (IQR)	15 (10 to 18)	16 (11 to 20)
Occlusion side left hemisphere, n (%)	23 (53%)	34 (38%)
Intravenous thrombolysis, n (%)	34 (79%)	65 (73%)
Medical history		
Atrial fibrillation, n (%)	14 (33%)	28 (31%)
Diabetes mellitus, n (%)	8 (19%)	14 (16%)
Chronic heart failure, n(%)	5 (12%)	14 (16%)
Hypertension, n (%)	23 (53%)	46 (52%)
Hypercholesterolemia, n(%)	10 (23%)	21 (24%)
Intracranial hemorrhage, n(%)	0 (0%)	2 (2%)
Mechanical aorta and/or mitral valve replacement, n(%)	1 (2%)	2 (2%)
Myocardial infarction, n (%)	6 (14%)	13 (15%)
Peripheral arterial disease, n (%)	2 (5%)	5 (6%)
Previous ischemic stroke, n (%)	9 (21%)	17 (19%)

Table 8.1. Continued.

	MD UFH [n=43]	**NO MD UFH [n=89]**
Prior medication use		
Antiplatelet therapy, n (%)	11 (26%)	25 (28%)
Vitamin K antagonist, n (%)	7 (16%)	13 (15%)
Pre-stroke mRS		
0	23 (53%)	51 (58%)
1	11 (26%)	18 (20%)
2	7 (16%)	12 (14%)
>2	2 (5%)	7 (8%)
Imaging		
Occluded segment, n (%)		
Infraclinoid ICA	13 (31%)	18 (21%)
Supraclinoid ICA	4 (9.5%)	8 (9.1%)
M1	15 (36%)	42 (48%)
M2	10 (24%)	20 (23%)
Other (e.g. M3, ACA)	13 (31%)	18 (21%)
ASPECTS, median (IQR)	9 (8, 10)	9 (8, 10)
Collaterals, n (%)		
Score 0 (absent collaterals)	1 (2.4%)	8 (9.4%)
Score 1 (filling ≤50% of occluded area)	18 (43%)	21 (25%)
Score 2 (>50% but less <100%)	16 (38%)	39 (46%)
Score 3 (100% of occluded area)	7 (17%)	17 (20%)
Performed procedure		
Intravenous thrombolysis, n (%)	34 (79%)	65 (73%)
Catheterization only	1 (2%)	1 (1%)
Cerebral DSA only	5 (12%)	7 (8%)
Endovascular treatment	36 (86%)	77 (87%)
Other	0 (0%)	0 (0%)
No procedure performed	0 (0%)	4 (4%)
Workflow		
Transferred from a primary stroke center, n (%)	39 (91%)	79 (89%)
Time from stroke onset to IVT, min, median (IQR)	78 (56 to 90)	65 (50 to 90)
Time from stroke onset to groin puncture, min, median (IQR)	160 (140 to 183)	180 (144 to 218)

Table 8.1. Continued.

	MD UFH [n=43]	**NO MD UFH [n=89]**
Door intervention hospital to groin puncture, min, median (IQR)	35 (25 to 48)	30 (25 to 44)
Duration procedure, min, median (IQR)	60 (37 to 90)	54 (36 to 74)

Abbreviations: ACA, anterior cerebral artery; ER, emergency room; eTICI, modified thrombolysis in cerebral infarction including a 2C grade; GCS, Glasgow Coma Scale; ICA, internal carotid artery; IQR, interquartile range; LA, local anesthesia at the groin puncture site; M(*segment*), middle cerebral artery; MD UFH, moderate-dose unfractionated heparin; NIHSS, National Institutes of Health Stroke Scale; SD, standard deviation.

Of patients allocated to moderate-dose UFH, 38/43 (88%) actually received the bolus and in 39/43 (91%) continuous infusion of heparin was started. In 14/43 (36%) continuous infusion of heparin was changed or stopped prematurely.

Outcomes

We observed an increased risk of sICH in the moderate-dose UFH group (Table 8.2). The increased risk of sICH was accompanied by an increase in mortality. The sensitivity analysis of the safety registry on sICH and mortality provided similar results (supplemental table 8.1).

Of patients allocated to moderate-dose UFH, 19/43 blood samples drawn at 1 hour after EVT were available. Median activated partial thromboplastin time (APTT) among patients who developed sICH was >180 seconds (interquartile range [IQR] 68 to >180) compared to 74 seconds in patients without sICH (IQR 44 to >180; p=0.46). The median anti-Xa level of patients with sICH was 1.2U/ml (IQR 0.6 to 1.3) compared to 0.8U/ml in patients without sICH (IQR 0.6 to 1.2; p=0.59).

Table 8.2. Effects of moderate-dose unfractionated heparin on safety outcomes.

Main cohort	**MD UFH [n=43]**	**NO MD UFH [n=89]**	**Unadjusted OR MD UFH vs. NO MD UFH (95%CI)**	**Adjusted OR MD UFH vs. NO MD UFH (95%CI)***
Safety outcomes				
Symptomatic intracranial hemorrhage	11 (26%)	5 (6%)	5.77 (1.86, 17.9)	10.9 (2.71, 44.1)
Death from any cause	20 (47%)	20 (22%)	3.00 (1.38, 6.54)	5.38 (2.05, 13.7)
Other serious adverse events				
Stroke progression	2 (5%)	10 (11%)	0.39 (0.08, 1.84)	0.43 (0.08, 2.31)
New ischemic stroke	1 (2%)	2 (2%)	1.04 (0.09, 11.8)	0.70 (0.05, 9.71)
Extracranial hemorrhage	1 (2%)	3 (3%)	0.68 (0.07, 6.76)	0.76 (0.04, 14.6)
Cardiac ischemia	1 (2%)	3 (3%)	0.68 (0.07, 6.76)	0.76 (0.04, 14.6)
Allergic reaction	0 (0%)	0 (0%)	-	-
Pneumonia	5 (12%)	13 (15%)	0.77 (0.26, 2.53)	0.65 (0.18, 2.42)
Other infection	6 (14%)	9 (10%)	1.44 (0.48, 4.35)	1.53 (0.42, 5.51)
Other SAE	7 (16%)	11 (12%)	1.38 (0.49, 3.85)	1.38 (0.47, 4.07)
Patients with no SAE reported	15 (35%)	43 (48%)	0.57 (0.27, 1.22)	0.47 (0.20, 1.11)

Abbreviations: MD UFH, moderate-dose unfractionated heparin; OR, odds ratio; SAE, serious adverse event
Captions: *Adjusted for age, pre-stroke mRS, time from onset to door of EVT center, time from door EVT center to groin puncture, baseline NIHSS, and collateral score

Discussion

Periprocedural treatment with moderate-dose UFH in patients with ischemic stroke who undergo EVT was associated with an increased sICH and mortality risk. The increased risk of sICH exceeded the prespecified p=0.001 (3 standard deviations) boundary needed to justify halting or modifying the study prematurely. The sICH risk in patients who were not randomized to moderate-dose UFH (6%) was within the range of the sICH risks found in the EVT trials (0% to 7.7%) and the largest prospective registry (5.8%).[1, 9] Therefore, the Steering Committee followed the advice of the DSMB to stop assigning moderate-dose UFH, but to continue the inclusion of patients in the other study arms, effective April 2019.

Since then, the trial has continued with a 2x2 factorial design, comparing ASA 300 mg, and/or low-dose UFH with neither (supplemental figure 8.2). According to protocol, six safety analyses and one formal interim analysis have followed without concerns. However, after the last interim analysis in January 2021, the Steering Committee has decided to stop inclusion in all arms per advice of the DSMB for

reasons of safety rather than efficacy. We will now finalize follow-up to allow a detailed safety and efficacy analysis.

Prior to the start of the MR CLEAN MED trial there was no clear evidence which UFH dose and regimen would be most effective and safe in patients undergoing EVT. The doses were therefore based on findings from previous studies (i.e. PROACT I and II and IST trials), on experience in later thrombectomy studies, and on the rationale that NETs and microtrombi would not dissolve instantly.[10-15] These results suggested that the low and moderate-doses of UFH in MR CLEAN-MED would both be associated with acceptable risks and the continuous infusion for 6 hours was set, necessary to dissolve NETs and microthrombi over time.

This study has some limitations. The sample size was too small to evaluate a potential interaction between ASA and UFH on the risk of sICH. This also limited in-depth evaluations of the observation that post-EVT APTT values were prolonged and anti-Xa levels were higher in patients with sICH compared to patients without sICH, albeit not significant. Evaluation of interaction between study treatments and of possible associations between the study treatments, coagulation abnormalities and the occurrence of sICH, will be reported after final database closure.

Conclusion

Periprocedural treatment with moderate-dose UFH (5000 IU bolus, followed by 1250 IU/hour during 6 hours) during endovascular treatment for acute ischemic stroke increases the risk of sICH and death and should be avoided.

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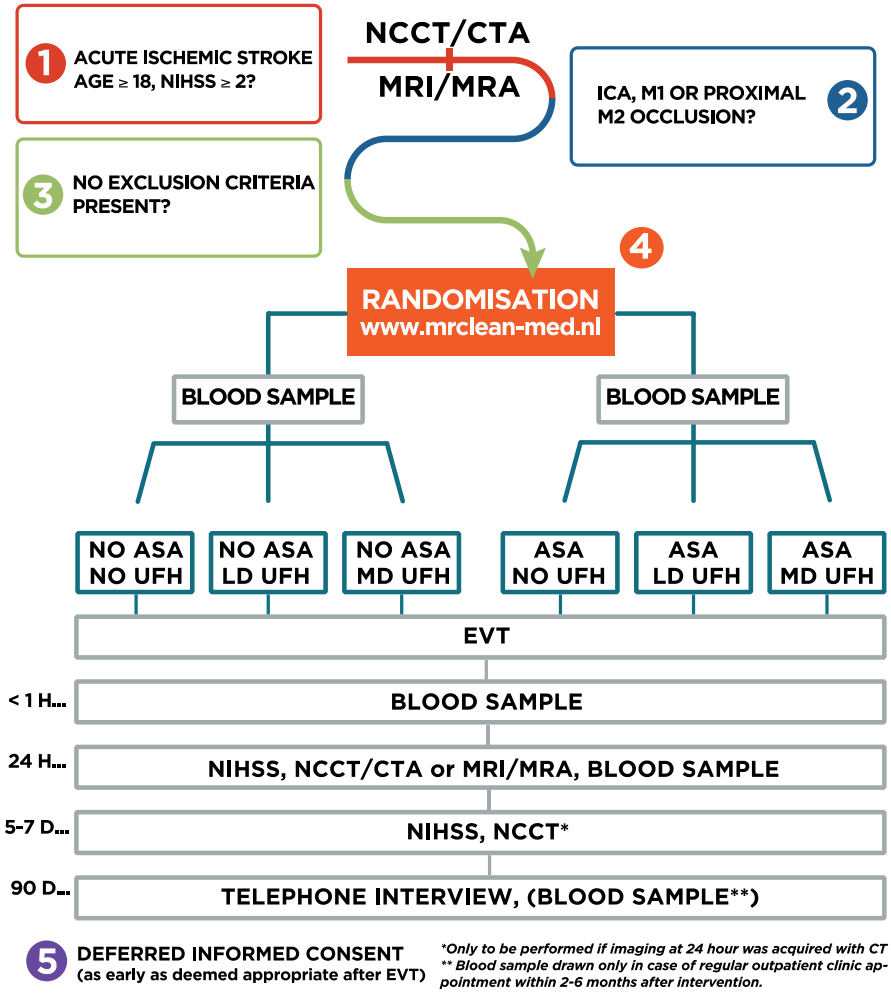
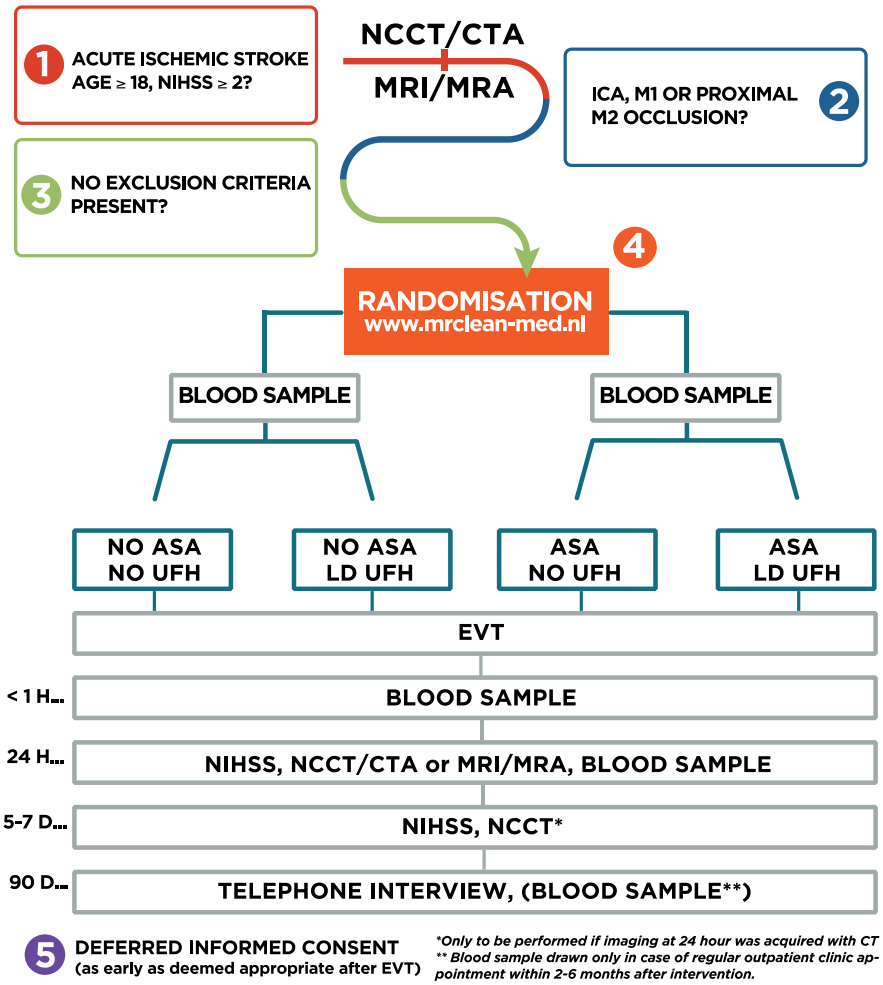
Supplemental material



Supplemental figure 8.1. Flowchart of study procedures



Supplemental figure 8.2. Flowchart of study procedures, after protocol change

Supplemental table 8.1. Sensitivity analysis of effects of moderate-dose unfractionated heparin on safety outcomes in the safety registry.

Safety registry	**MD UFH [n=46]**	**NO MD UFH [n=91]**	**Unadjusted OR MD UFH vs. NO MD UFH (95%CI)**	**Adjusted OR MD UFH vs. NO MD UFH (95%CI)***
Symptomatic intracranial hemorrhage	12 (26%)	5 (5%)	6.07 (1.99, 18.5)	8.61 (2.22, 33.3)
Death from any cause	21 (46%)	21 (23%)	2.80 (1.31, 5.97)	4.96 (1.90, 12.9)

Abbreviations: MD UFH, moderate-dose unfractionated heparin; OR, odds ratio
*Adjusted for age, time from onset to door of EVT center, time from door EVT center to groin puncture, baseline NIHSS, pre-stroke mRS and collateral score

PART II

Optimization of periprocedural anesthetic and hemodynamic management

CHAPTER IX

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

Neurology, 2018

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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 9.1). 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 9.1).

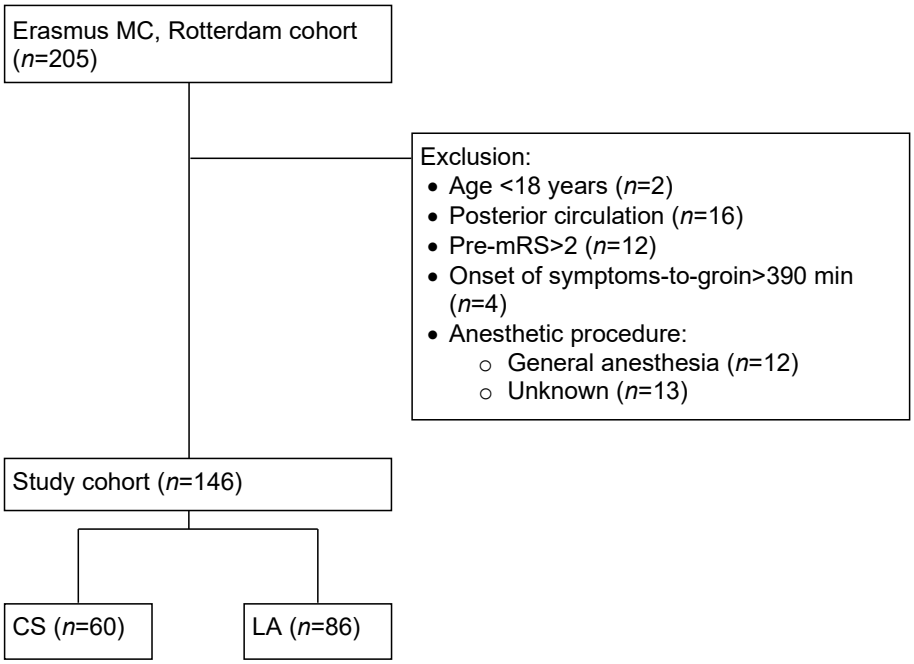

Figure 9.1. Flowchart of patients included from Erasmus MC in MR CLEAN Registry from March 2014 until June 2016

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 9.1. 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 9.1. 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 9.2. 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 9.2. 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 9.2). 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 X

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 10.1).[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]

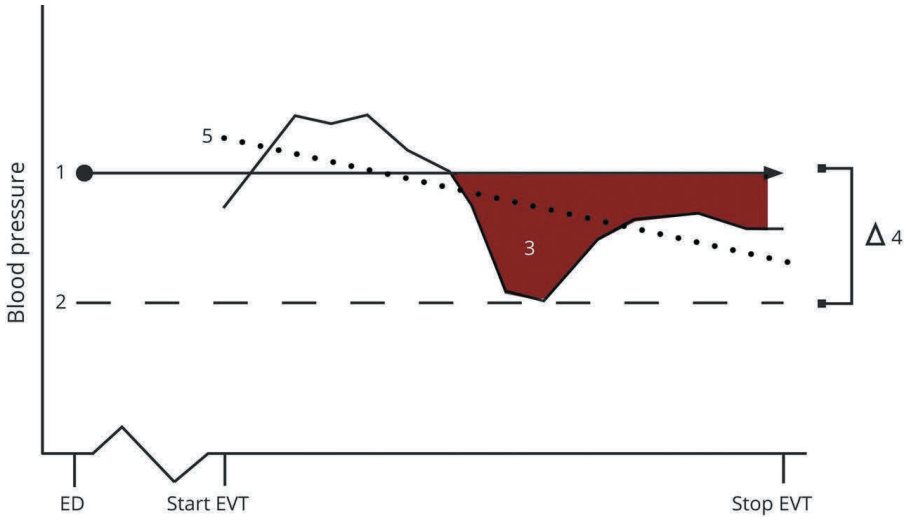

Figure 10.1. Schematic illustration procedural blood pressure parameters.
Summary: 1. mean arterial pressure (MAP) value on admission; 2. Lowest MAP; 3. Area under the threshold (AUT); 4. Relative difference between baseline MAP and lowest MAP (ΔLMAP); 5. Average trend (slope). *Abbreviations*: ED, emergency 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 10.2).

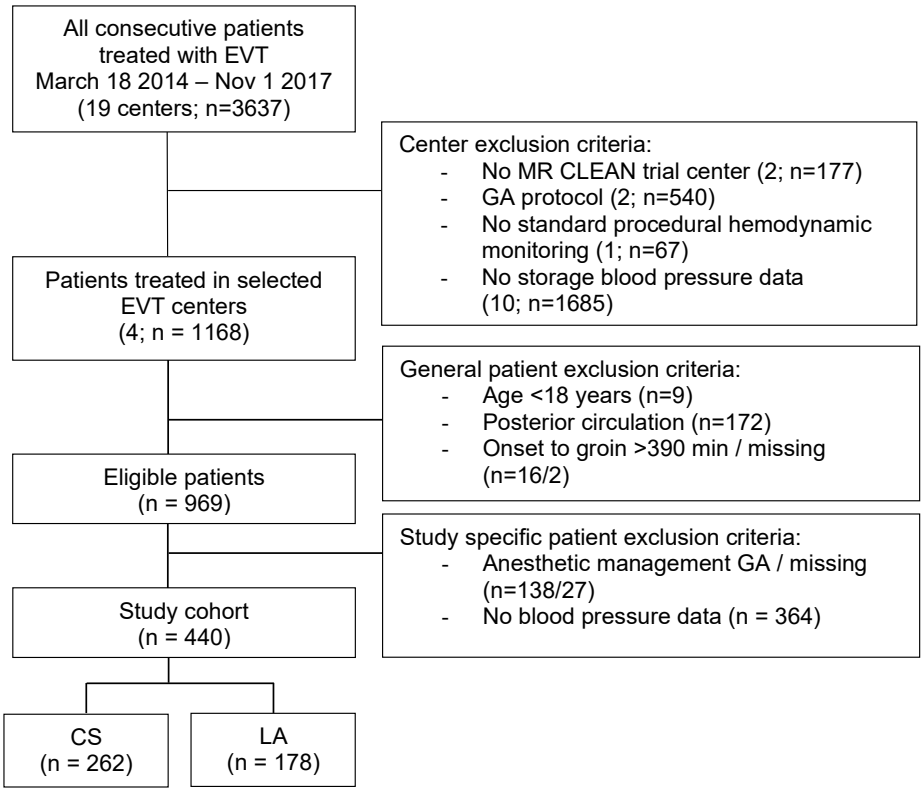

Figure 10.2. Flowchart of patient selection.
Abbreviations: GA, general anesthesia; LA, local anesthesia; min, minutes; CS, conscious sedation.

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 10.1). 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 10.1. 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 10.1. 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 10.3, Table 10.2). 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 10.2). Conversion to GA requiring intubation occurred in 3 patients in the CS group and in 3 patients in the LA group.

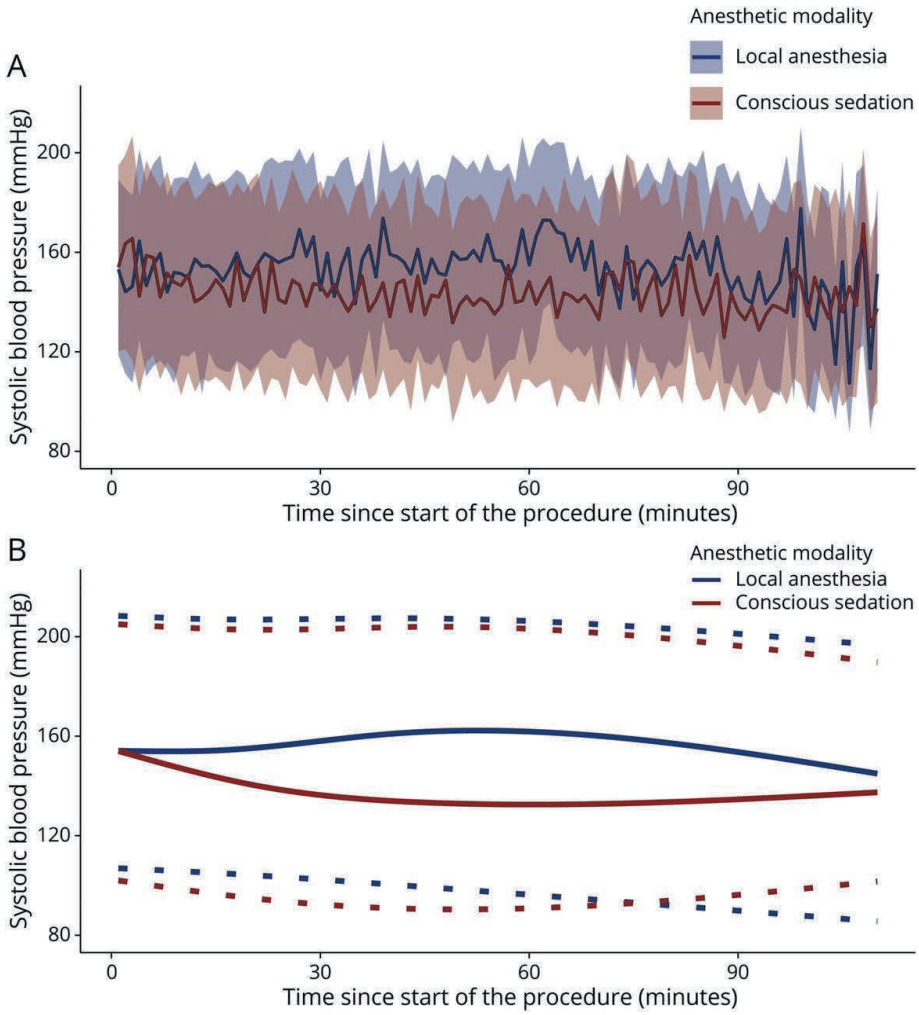

Figure 10.3. Procedural blood pressure for patients treated under conscious sedation or local anesthesia.

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 10.2. 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 10.3, column B, Figure 10.4). 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 10.3, column C). Also, ΔLMAP and AUT did not explain the association between anesthetic modality and any of the secondary outcomes.

Table 10.3. 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)	

Table 10.3. 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)**
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)	
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.

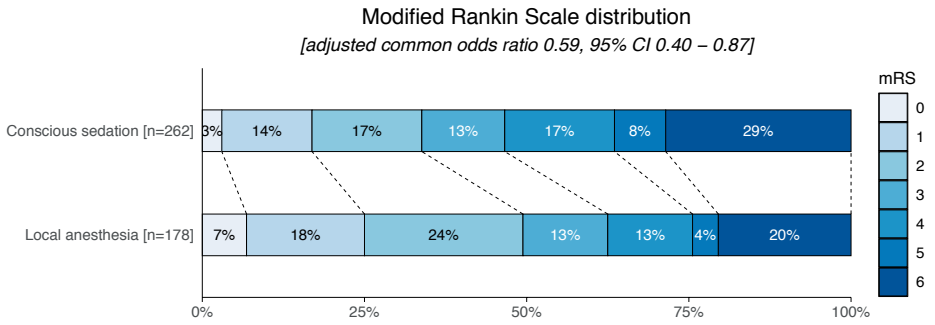

Figure 10.4. Primary outcome on the modified Rankin Scale by preferred anesthetic method. *Abbreviations*: mRS, modified Rankin Scale.

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.

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CHAPTER XI

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

Accepted for publication

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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 11.1.

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 11.1). 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 11.1). 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 11.1. 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 11.1. 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.

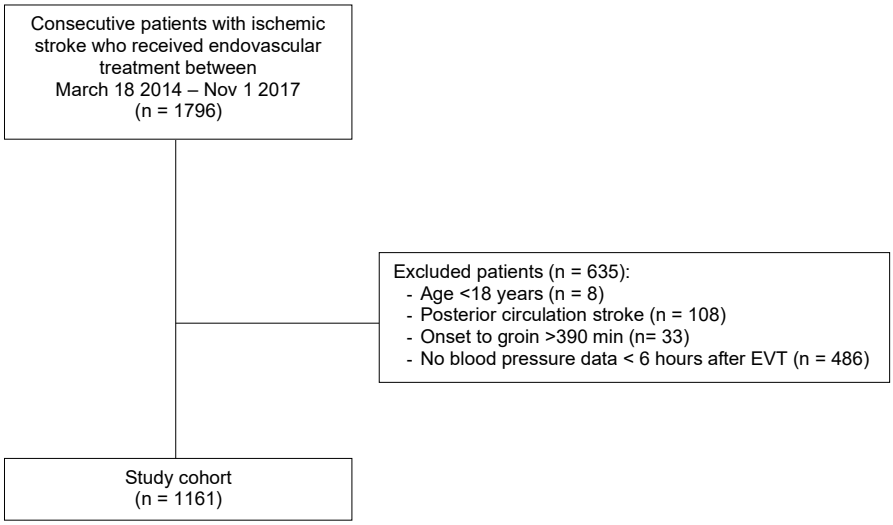

Figure 11.1. Flowchart of patient inclusion.
Abbreviations: EVT; endovascular treatment; min, minutes; n, number

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 11.2A, 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 11.2). 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 11.2). 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 11.2).

Association of minimum systolic blood pressure with outcomes
The association between minimum SBP and functional outcome was non-linear (Figure 11.2B) 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 11.3).

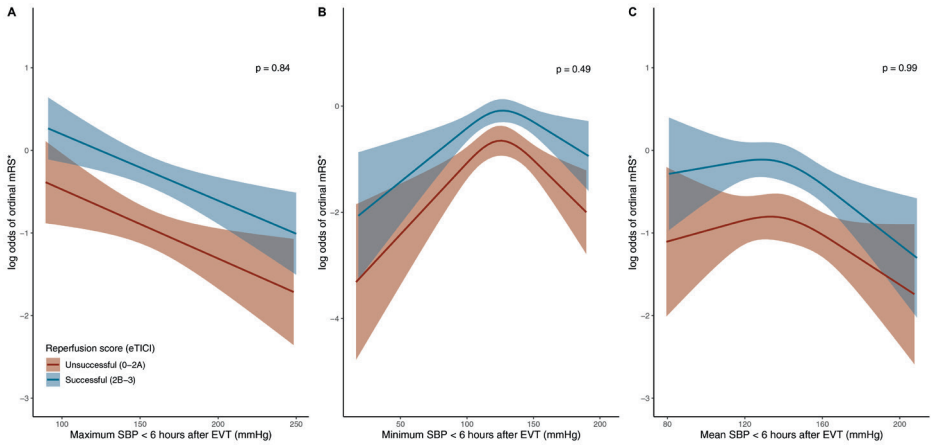

Figure 11.2. Relationship of systolic blood pressure and shift toward better functional outcome.
Summary: The models are fitted with a linear function for maximum SBP and restricted cubic spline function with 3 knots for minimum SBP and mean SBP parameters. All models include the following variables: 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 11.2C) 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 11.4). The distribution of outcomes according to maximum, minimum and mean SBP tertiles is shown in supplemental figure 11.1.

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 11.2) or any of the secondary outcomes (supplemental figure 11.2). 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 11.3).

Table 11.2. 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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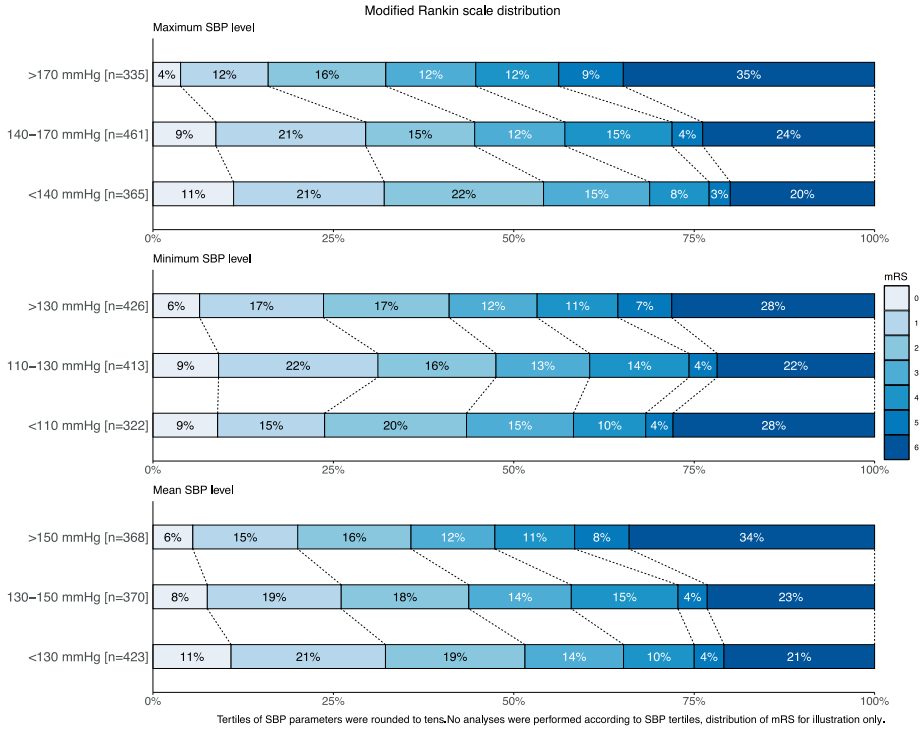
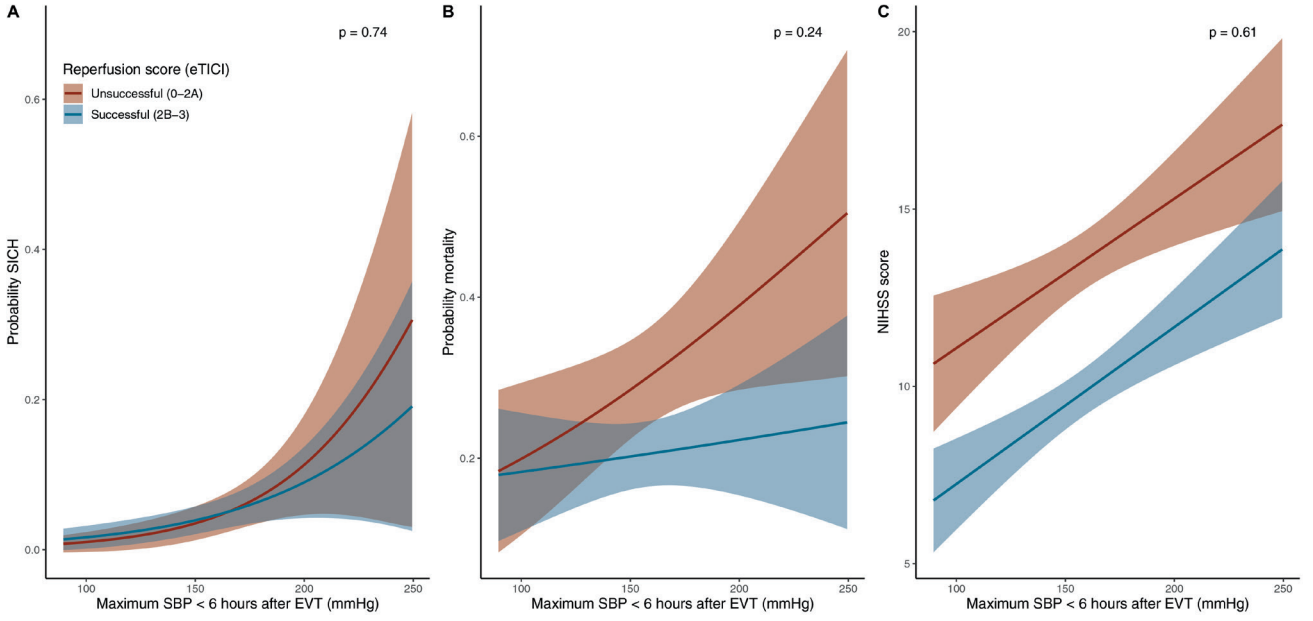
Supplemental material



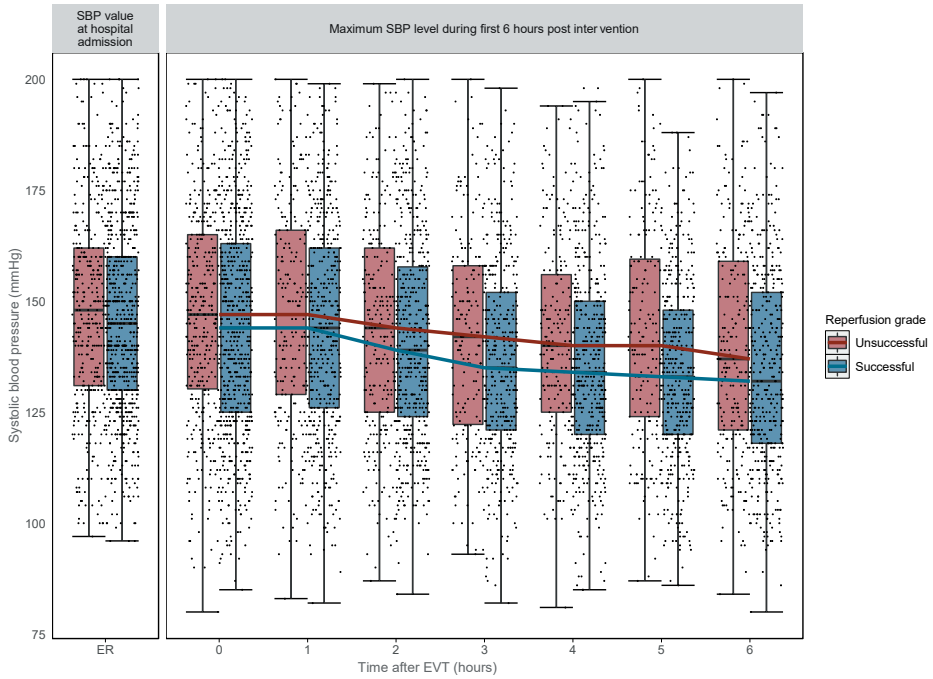
Supplemental figure 11.1. Distribution of modified Rankin scale according to tertiles of maximum, minimum and mean SBP during the first 6 hours following EVT. SBP tertiles are used for data inspection only, analysis is based on the fulle range of SBP measures.
Abbreviations: EVT, endovascular treatment; mRS, modified Rankin Scale; n, number; SBP, systolic blood pressure.



Supplemental figure 11.2. 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 11.3. 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 11.1. 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 11.2. 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 11.3. 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 11.4. 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 11.4. 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				
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).

GENERAL DISCUSSION

The overall aim of this thesis was to assess which factors, aimed at improvement of reperfusion, contribute to better outcomes of patients undergoing EVT for acute ischemic stroke. The specific aims were:

- to identify the most important modifiable and non-modifiable factors associated with poor outcome after EVT despite good macrovascular reperfusion (**Part I**).
- to assess whether adjunctive antithrombotic treatment to EVT is safe and could improve functional outcome (**Part I**).
- to assess the most optimal periprocedural approach regarding anesthetic and hemodynamic management, associated with functional outcome (**Part II).**

The most important modifiable and non-modifiable factors

We found that non-modifiable patient factors such as pre-stroke mRS, age and NIHSS at baseline were the most important factors in the association with 90-day functional outcome **(Chapter 2)**. We additionally found that postprocedural adverse events such as sICH were substantial contributors to poor outcome, which suggests that prevention of these adverse events would be an important next step in the improvement of functional outcome in successfully reperfused patients. Results of this study did not show directly that the modifiable factors anesthesia type, blood pressure, antithrombotic treatment (e.g. antiplatelet agents and periprocedural heparin) provided a large contribution to functional outcome after successful reperfusion. However, based on the observational nature of the dataset it is to be expected that results regarding these specific factors are hampered by confounding by indication as these modifiable factors were not randomly distributed. Moreover, we studied outcome and not treatment effect. Besides, concerning antithrombotic treatment, the role of therapy compliance and therapy resistance are unclear. Further in-depth evaluation of these factors is warranted as these factors could be modified directly.

Several studies have sought to solve the question why some patients with successful reperfusion recover well and others do not.[1-6] In most studies it was observed that the non-modifiable factors NIHSS and age were very important. Also, expert researchers addressed that unfavorable non-modifiable patient factors (reflecting limited "brain reserve") are the most notable factors explaining why patients do not recover despite reperfusion.[7] Remarkably, none of these studies considered postprocedural factors, such as sICH, pneumonia and new ischemic stroke. Potentially, patients could benefit from additional targeted treatment interventions if the causative factors can be modified.

Safety of antithrombotic treatment

First, we systematically reviewed published studies in **Chapter 3.** From 837 studies we included 19 studies for qualitative synthesis. Of these studies, we identified seven studies evaluating the effect of periprocedural antiplatelet therapy and four studies investigating the effect of periprocedural heparin use (a subgroup of 8 studies considered a different underlying pathology, which is tandem lesion occlusion). None

of these studies were randomized controlled trials. The retrieved studies aimed to evaluate the effects of periprocedural use of antithrombotic agents during EVT on the outcome in ischemic stroke. We observed that the indication for antithrombotic administration varied from "standard care", via "at the discretion of the interventionist", to "depending on prior use because of comorbidity". We found that clinical equipoise existed whether antithrombotic medication should be administered during EVT for a large vessel occlusion, as acetylsalicylic acid and/or unfractionated heparin may improve functional outcome, but might also lead to an increased risk of sICH.

The systematic review was based on small observational studies. We therefore performed three additional studies using data from the large observational MR CLEAN Registry, resembling clinical practice. We specifically evaluated the risks and benefits of prior antiplatelet therapy **(Chapter 4)**, prior oral anticoagulant therapy **(Chapter 5)** and periprocedural heparin administration **(Chapter 6)**. In these studies, the absolute risk of sICH was 6.3% for prior antiplatelet therapy, 6% for prior oral anticoagulant therapy and 7.9% for periprocedural unfractionated heparin use (median dose 5000IU). More important, we demonstrated that the risk of sICH was in all three studies not significantly different from the complementary non-exposure group. The sICH risks obtained from these studies seems acceptable in light of the MR CLEAN trial, which showed a sICH risk in the EVT arm of 6.4% and a sICH risk of 7.7% in the non-EVT arm. The results seem also acceptable in light of the MR CLEAN Registry, showing a sICH risk of 5.8%.[8,9] Moreover, for heparin we concluded that centers administering more heparin had better functional outcomes.

Based on the pathophysiology of incomplete microvascular reperfusion, the theoretical and reported expected benefits of acetylsalicylic acid and unfractionated heparin in literature, the reported safety profile from the observational data, the ease in mode of administration and the wide-gained experience with these treatments in the interventional setting, we designed a randomized controlled trial **(Chapter 7).** This randomized trial evaluates the benefits and risks of acetylsalicylic acid and unfractionated heparin, alone, or in combination, and most importantly, their effect on functional outcome after EVT. Patients were randomized to receive either intravenous acetylsalicylic acid (loading dose of 300 mg) or intravenous unfractionated heparin either in a low dose (loading dose of 5000 IU followed by 500 IU/hour x 6 hours) or a moderate dose (loading dose of 5000 IU followed by 1250 IU/hour x 6 hours), both, or neither (2x3 factorial), as adjunctive treatment during EVT. Data from the interim safety analysis of the MR CLEAN-MED showed that, after enrollment of 137 patients, periprocedural treatment with moderate-dose unfractionated heparin (5000 IU bolus, and 1250 IU/hour during 6 hours) was associated with increased sICH and mortality risks and should be avoided **(Chapter 8)**. In this study we found a sICH risk of 6% in the aggregated study arm with patients who were not randomized to moderate-dose UFH (i.e. composite of control, acetylsalicylic acid and low-dose UFH), which was within the range of the sICH risks found in the EVT trials (0% to 7.7%) and the largest prospective registry (5.8%).[9,10] Therefore, the Steering Committee followed the advice of the Data

Safety and Monitoring Board to stop assigning moderate-dose UFH, but to continue the inclusion of patients in the other study arms, effective April 2019. Since then, the trial has continued with a 2x2 factorial design, comparing acetylsalicylic acid 300 mg, and/or low-dose UFH with no treatment. Yet, after the 2nd planned interim analysis and the 11th safety analyses in January 2021, the Steering Committee has decided to stop inclusion in all arms per advice of the DSMB for reasons of safety rather than efficacy. We will now finalize follow-up to allow a detailed safety and efficacy analysis. Results will be reported as soon as possible after database closure.

Translational studies have identified neutrophil extracellular traps (NETs) playing a major role in the formation of stroke thrombi of various origins. Moreover, it has been demonstrated that NETs contribute to microvascular reperfusion resistance.[11] It has been proposed to target these NETs through cleavage of DNA-strengs by administering a pharmacological cocktail that specifically includes DNAse to dissolve NETs.[12] We proposed that readily available candidate drugs with similar potency to dissolve NETs rather than suggesting new techniques might be a more opportune approach to improve microvascular reperfusion and consequently functional outcome. We suggested possible beneficial roles for the candidate drugs unfractionated heparin and acetylsalicylic acid.[13,14] Moreover, vessel wall inflammation and microthrombi formation induced during EVT might be reduced using antithrombotic medications.[15] Given the presented results, we did not find such a beneficial effect. Further, in-depth evaluation of trial results is required to evaluate whether specific subgroups benefit from additional antithrombotic treatment. Moreover, we suggest that new techniques (e.g. DNAse 1 but also ADAMTS 13), aimed at improvement of reperfusion, deserve further exploration.

The most optimal periprocedural anesthetic and hemodynamic strategy

We found that conscious sedation was associated with poor functional outcome **(Chapter 9)** and confirmed that local anesthesia is the best first line approach**.** As we expected the difference in outcome potentially to be confounded by blood pressure course during the procedure, we explored this relation (**Chapter 10)**. We found that patients treated under conscious sedation had lower average procedural blood pressure and more blood pressure drops compared to patients treated under local anesthesia. Consequently, more hemodynamic interventions were required to increase blood pressure in patients treated under conscious sedation. Although we did not find that procedural blood pressure trend modified the effect of anesthesia type, we do suggest to maintain a strict blood pressure regimen during the procedure, mainly focusing on prevention of hypotensive episodes with baseline blood pressure as the reference, as this is independently associated with poor functional outcome.

Furthermore, we found **(chapter 11)** that blood pressure control should not be restricted to the EVT procedure alone but its effects also extend to the first hours following EVT. Once more, this underlines the importance of patient monitoring and support in the subacute phase following EVT. Based on my findings, we advocate

that ideally, systolic blood pressure (SBP) levels in the 6 hours following EVT should be maintained as stable as possible around 120-125 mmHg.

Due to the lack of evidence regarding optimal blood pressure management in patients treated with EVT, the variation in hemodynamic management among EVT centers and the possibility of a modifiable effect on functional outcome within 90 days associated with optimal SBP control a clinical trial seems justified. Ideally, such a trial should evaluate multiple blood pressure regimens either in the procedural and in postprocedural period. At least including an intensive treatment arm avoiding any hypotensive episodes during the procedure and avoiding both episodes of very high and low blood pressure in the first hours following EVT, which could improve outcomes further. The BP TARGET Trial was the first randomized controlled trial, designed to compare the effect of two SBP target strategies, after EVT reperfusion, on any ICH. In this trial patients were randomly assigned to either an intensive systolic blood pressure target group (100-129 mmHg) or a standard care systolic blood pressure target group (130-185 mmHg). Yet, despite the associations found between postprocedural blood pressure and outcomes in observational studies this trial did not demonstrate such an effect for the outcome sICH.[16,17]

Little attention has been paid to perform EVT under local anesthesia at the groin puncture site, as many considered conscious sedation or general anesthesia to be the optimal approach. The lack of interest in local anesthesia during EVT was reflected by an opinion review, from esteemed researchers in the field of stroke, evaluating poor outcomes despite successful reperfusion, again leaving local anesthesia outside their scope.[7] In our exchange with the authors we raised the issue that local anesthesia might solve the puzzle regarding the varying results obtained from trials comparing conscious sedation with general anesthesia.[18-20] In this debate it was recognized by the authors that in the search for the most optimal anesthetic strategy during EVT the current focus on conscious sedation versus general anesthesia did not do justice to a potentially safer strategy of using local anesthesia at the groin puncture site only.[18] Parallel to this topic it has been demonstrated that periprocedural blood pressure course is associated with functional outcome after EVT.[21-23] Since blood pressure is an important factor affecting cerebral perfusion, it is likely that blood pressure plays an important role in recovery. Justifying local anesthesia as a potential safer and more hemodynamically stable strategy besides conscious sedation and general anesthesia could optimize perfusion prerequisites and thus outcomes.

Strengths and limitations

One of the limitations of the research described in Part I is that we were restricted to the evaluation of available factors which could have introduced unobserved confounding. Factors such as baseline CT perfusion imaging or MR imaging at baseline as well as, follow-up infarct volume at a later stage were not available and thus could not be evaluated. The role of additional predictors not included in the model, such as

follow-up infarct volume (as this was not available in the observational setting), needs to be assessed in future studies.

A second question that could arise from Part I is whether the contribution of incomplete microvascular reperfusion to poor functional outcome is well-estimated and whether the estimated reversibility was accurate. In particular when evaluating the expected benefits in the MR CLEAN-MED trial, in which a 5% absolute effect for both acetylsalicylic acid and unfractionated heparin on the ordinal mRS scale was anticipated. Some concerns that might arise are: I) how much does incomplete microvascular reperfusion add to the likelihood of poor outcome, II) is incomplete microvascular reperfusion present in all patients, III) what is the potency of acetylsalicylic acid and unfractionated heparin in restoring incomplete microvascular reperfusion. We can eliminate most but not all concerns. First, results of the MR CLEAN Registry substudy on periprocedural heparin administration, in which a median dose of 5000 units was administered in about 400 patients, showed an absolute (albeit not significant) benefit on functional independence of 4%[24]. With the anticipated ±700 patients receiving heparin in MR CLEAN MED this would provide, based on observational data, definite confidence showing if present an assumed effect of 5%. Whether the estimated effect also accounted for the acetylsalicylic acid arm in the trial, remained difficult to predict based on the available observational data. For this treatment, confounding by indication plays a more prominent role in observational studies, as it concerned only patients who were using acetylsalicylic acid because of a comorbid condition that occurred before the index event. Ultimately, we expected that the effects of acetylsalicylic acid and unfractionated heparin will not solely be restricted to incomplete microvascular reperfusion dissolvement, but also e.g. to prevention of on-catheter thrombosis. In interventional cardiology, this was the reason for implementing these medications since the first coronary interventions.[25]

Finally, when reflecting on the results presented in Part II it remains difficult in the observational setting to assess which factor, i.e. anesthesia type or blood pressure course during the EVT is the key driver behind the outcomes.[20] Although we did not find that blood pressure course during EVT did mediate the effect of anesthesia type on outcome this should receive special attention. To overcome this problem, we suggest that any future trial implementing a local anesthesia arm besides conscious sedation and general anesthesia, should commit to strict monitoring of blood pressure and hemodynamic interventions, because it remains conceivable that the association between anesthetic management and functional outcome could partially be explained by intraprocedural hypotension and vice versa. Another concern in blood pressure evaluation is to assess whether the associations found are causal. Although we paid special attention to timing of sICH (exclusion of sICH that occurred early) to reduce the possibility of reverse causality determination of exact onset of sICH remains difficult.

Recommendations
As the most extensive model evaluating poor outcomes despite reperfusion explained only 47% of the variation in outcome, improvement is still possible. This mainly suggests that new predictors are to be determined or more accurate assessment of current predictors is required to ultimately understand poor clinical outcome despite good reperfusion. In this search, potentially modifiable factors deserve special attention.

Periprocedural use of moderate dose unfractionated heparin during endovascular treatment for acute ischemic stroke is associated with an excessive risk of symptomatic intracranial hemorrhage and should be avoided. The additive value of acetylsalicylic acid and low dose unfractionated heparin during EVT will be further evaluated in the MR CLEAN MED trial.

Furthermore, local anesthesia must be considered the most optimal first line approach during EVT in absence of a randomized trial. Yet, a randomized trial, probably on center level, remains necessary to evaluate whether these results were not confounded. Moreover, I do advocate a strict blood pressure regimen, mainly focusing on prevention of hypotensive episodes with baseline blood pressure as the reference, as this was still independently associated with worse functional outcome. Systematic hemodynamic monitoring must be improved to evaluate further whether the determined associations can be reproduced.

Future perspectives

Understanding the concept of the microcirculation
In my opinion it is relevant to first better understand the principle of poor outcomes despite macrovascular reperfusion. Special attention must be paid to quality of reperfusion, ideally at a stage that an intervention is still possible. As incomplete microvascular reperfusion is a multifactorial process and the microcirculation is complex, understanding the driving forces behind this phenomenon, could lead to more targeted approaches with regard to treatment. Besides some factors contributing to incomplete microvascular reperfusion studied in this thesis (i.e. microthrombi and NET's), other factors deserve further exploration as well. Some examples of factors that could contribute to incomplete microvascular reperfusion are hemodynamic factors (e.g. flow, microvessel diameter, red cell flux), but also other biological factors (e.g. endothelial swelling, astrocyte swelling, pericyte contraction), should be studied in future studies. Early evaluation with MRI could potentially add to the knowledge on restoration of reperfusion and infarct evolution. This evaluation is especially important in the acute phase directly after reperfusion, as the tissue at risk – due to incomplete microvascular reperfusion – is still salvageable and treatment is still possible. Another promising technique to improve reperfusion evaluation is the intra-arterial evaluation of the affected territory. Learning from the field of interventional cardiology in which intra-arterial measurements are commonly performed to guide treatment decisions (e.g. for example in stenting), this could be a useful tool applicable

in the neuro-interventional setting too. To substantiate this hypothesis, it has recently been demonstrated that intra-arterial absolute flow measurements are both accurate (operator independent) and easy to obtain, and could be of value in disease evaluation aiming at the microcirculation in cardiology.[26] Such measurements have the potency to be used to guide treatment decisions directly in the interventional setting but also provide answers on gaps in knowledge in research.

Adjunctive treatment strategies

Ideally, MR CLEAN-MED would have demonstrated an additive value of antithrombotic agents during EVT improving outcomes. However, irrespective of its in-depth results, adjunctive treatments besides EVT will remain one of the cornerstones in the common aim to improve functional outcome after stroke. Possibly, combinations of treatments are required as it is possible that one additional drug in adjunction to EVT may not be sufficient to improve outcomes in the overall stroke patient population. Combining various pharmacological agents capable of enhancing thrombolysis at the level of both the macro and microcirculation, without increasing the risk of hemorrhagic transformation, could be more promising. In the more experimental setting it is worth noting that possible benefits could be expected from targeting von Willebrand factor with ADAMTS 13 (a disintegrin and metalloprotease with thrombospondin type I repeats-13) or from DNAse 1 by targeting NETs directly.[27] Another interesting treatment, learned from interventional cardiology, would be Cangrelor as an alternative to acetylsalicylic acid. Cangrelor, which is administered intravenously and has a rapid onset and offset, does not require transformation to active metabolites and is given as a bolus plus an infusion, providing immediate and consistent platelet inhibition.[28,29] Cangrelor is deactivated rapidly, restoring platelet function within 1 hour after discontinuation, but possibly also with less therapeutic resistance. Previous studies have shown the benefit of cangrelor over clopidogrel with fewer thromboembolic complications in patients undergoing PCI.[30-33]

Furthermore, I expect that future studies will provide more evidence on the effectiveness of neuroprotective agents in the early phase following ischemic stroke treated with EVT.[34] Although some neuroprotective agents have been investigated in the past without large successes this field is back to square in this new era with higher reperfusion rates.

Improving periprocedural management

Next, randomized trials investigating the causal relation of anesthesia type on functional outcome are warranted. It has been emphasized after the publication of our study that inclusion of a local anesthesia arm in future randomized clinical trials on evaluation of anesthesia strategy in stroke is recommended.[35] Currently, no trial has been registered evaluating GA versus CS versus LA. In such an evaluation special attention should be paid to consistent treatment of blood pressure which could negate the effect.

Closing message

Modification of periprocedural management of EVT for acute ischemic stroke has the potential to improve outcomes further. A medical intervention in addition to EVT is an inevitable next step.

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APPENDICES

Summary

Despite the large success of endovascular treatment for patients who present with a stroke caused by a proximal occlusion in the anterior circulation still a large proportion of patients do not recover to functional independence. Possibly outcomes could be improved further if adjunctive treatments are administered, for example antithrombotics. Moreover, it might be possible that optimization of periprocedural anesthetic and/or hemodynamic management could also improve outcomes.

The overall aim of this thesis was to assess which factors, aimed at improvement of reperfusion, contribute to better outcomes of patients undergoing EVT for acute ischemic stroke. The specific aims were:

- to identify the most important modifiable and non-modifiable factors associated with poor outcome after EVT despite good macrovascular reperfusion (**Part I**).
- to assess whether adjunctive antithrombotic treatment to EVT is safe and could improve functional outcome (**Part I**).
- to assess the most optimal periprocedural approach regarding anesthetic and hemodynamic management, associated with functional outcome (**Part II).**

Part I Microvascular reperfusion and antithrombotic treatment

In the first part of this thesis, we evaluated the relative importance of currently known modifiable and non-modifiable factors associated with poor outcome despite visual macrovascular reperfusion achieved by EVT. Also in this part we aimed to assess whether adjunctive antithrombotic treatment to endovascular treatment is safe and could improve functional outcome.

In **Chapter 2,** we demonstrated that baseline patient factors and postprocedural adverse events are the most important predictors of poor functional outcome in successfully reperfused patients. This implies that prevention of postprocedural adverse events has the greatest potential to further improve outcomes. Moreover, identification of additional factors contributing to poor outcomes in succesfully reperfused patients is warranted to better understand the mechanisms behind poor outcomes despite good reperfusion.

In the systematic review presented in **Chapter 3,** we showed that randomized controlled trials investigating the effect of periprocedural antithrombotic treatment in EVT are lacking. Some observational studies report a slight increase in sICH risk, which may be acceptable since these studies also suggest a beneficial effect on functional outcome. Therefore, randomized controlled trials are warranted to address the question whether the potentially higher risk of sICH could be outweighed by improved functional outcome.

Based on data from the large observational MR CLEAN Registry we performed three studies evaluating antithrombotic and anticoagulant treatment in current clinical practice. In **Chapter 4** we found no evidence of an association of prior antiplatelet

therapy with the risk of sICH after EVT, nor on functional outcome, reperfusion or mortality when compared to no prior antiplatelet therapy. However, as therapy resistance and compliance were not assessed a substantial beneficial or detrimental effect of antiplatelet agents on functional outcome could not be excluded. In **Chapter 5** we explored the influence of prior OAC use (i.e. use of direct anticoagulants (DOACs) or vitamin K antagonists) in patients treated with EVT for ischemic stroke and demonstrated that this was not associated with an increased risk of sICH or worse functional outcome compared to no prior OAC use. Therefore, in contrary to intravenous rtPA patients on prior OAC use should not routinely be excluded from EVT. In **Chapter 6,** we showed that there is a substantial between-center variability in periprocedural intravenous heparin use during EVT in the Netherlands, ranging from centers administering heparin in 0% of patients to centers administering heparin in 94% of patients. Periprocedural use of heparin was not associated with an increase in sICH. Centers using heparin more often had better outcomes. We designed a randomized controlled in **Chapter 7** to evaluate the safety and efficacy of acetylsalicylic acid and unfractionated heparin. This decision was based on: I) the pathophysiology of incomplete microvascular reperfusion, II) the theoretical and reported expected benefits of acetylsalicylic acid and unfractionated heparin, III) the reported safety profile from the observational data, IV) the ease in mode of administration and V) the wide-gained experience with these treatments in the interventional setting. Based on the results of an interim safety analysis of the randomized MR CLEAN-MED trial as presented in **Chapter 8** periprocedural use of moderate dose unfractionated heparin during endovascular treatment for acute ischemic stroke is associated with an excessive risk of symptomatic intracranial hemorrhage and should be avoided.

Part II

Optimization of periprocedural anesthetic and hemodynamic management

In the second part of this thesis we aimed to determine the most optimal strategy with regard to the perfusion facilitators anesthetic type and blood pressure. In **Chapter 9,** we described our finding that conscious sedation was associated with poor functional outcome and increased mortality rates in comparison to local anesthesia. Furthermore, conscious sedation did not reduce duration of intervention or interventional complications. we advocate that local anesthesia should be performed instead of conscious sedation during EVT for ischemic stroke if this is considered safe. In **Chapter 10,** we elaborated further on these findings and evaluated whether outcomes differences between conscious sedation and local anesthesia could be explained by periprocedural blood pressure course. We found that blood pressure drops and procedural blood pressure trend did not explain the worse outcomes in the conscious sedation group. Still, we consider that large drops in blood pressure should be avoided as these were independently associated with worse functional outcomes. As it is conceivable that optimization of perfusion through blood pressure course is

not restricted to the endovascular procedure alone we evaluated the association of blood pressure in the 6 hours following EVT on functional outcome in **Chapter 11.** I found that higher maximum SBP levels in the first 6 hours following EVT are associated with worse functional outcome and increased risk of sICH. Both higher and lower SBP than 120-125 mmHg minimum SBP level are associated with worse outcomes. A randomized trial seems justified to evaluate whether modifying blood pressure result in better outcomes.

Samenvatting

Ondanks het grote succes van de endovasculaire trombectomie (EVT) voor patiënten met een beroerte, veroorzaakt door een proximale occlusie in de anterieure circulatie, herstelt een groot deel van de patiënten nog steeds niet en blijft afhankelijk van zorg in het dagelijkse leven. Uitkomsten in deze patiënten zouden verder verbeterd kunnen worden middels additionele behandelingen tijdens de EVT, bijvoorbeeld middels de toediening van antitrombotica. Bovendien is het denkbaar dat optimalisatie van periprocedurele anesthesie en / of hemodynamische behandeling ook de resultaten ten gunste kunnen beïnvloeden.

Het algemene doel van dit proefschrift was om te beoordelen welke factoren, gericht op verbetering van reperfusie, bijdragen aan betere resultaten van patiënten die EVT ondergaan voor een acute ischemische beroerte. De specifieke doelstellingen waren:

- Identificeren van de belangrijkste modificeerbare en niet-modificeerbare factoren die geassocieerd zijn met een slechte uitkomst na EVT ondanks goede macrovasculaire reperfusie (Deel I).
- Evalueren of aanvullende antitrombotische behandeling bij EVT veilig is en de functionele uitkomst verder kunnen verbeteren (Deel I).
- Evalueren wat de meest optimale periprocedurele strategie is om uitkomsten te verbeteren met betrekking tot anesthesie en hemodynamiek (Deel II).

Deel I Microvasculaire reperfusie en antitrombotische behandeling

In het eerste deel van dit proefschrift hebben we het relatieve belang geëvalueerd van bekende modificeerbare en niet-modificeerbare factoren geassocieerd met een slechte uitkomst ondanks visuele macrovasculaire reperfusie bereikt door EVT. Daarnaast hebben we in dit deel geëvalueerd of aanvullende antitrombotische behandeling naast de bestaande EVT van het herseninfarct veilig is en de functionele uitkomst verder zou kunnen verbeteren.

In **Hoofdstuk 2** hebben we aangetoond dat patiëntfactoren bepaald bij binnenkomst op de spoedeisende hulp en post procedurele complicaties de belangrijkste voorspellers zijn van een slechte functionele uitkomst na 90 dagen bij patiënten met succesvolle reperfusie. Dit impliceert dat de preventie van post procedurele complicaties het grootste potentieel heeft om de resultaten verder te verbeteren. Bovendien is het noodzakelijk om het principe te begrijpen waarom sommige patiënten alsnog slechte uitkomsten hebben ondanks succesvolle reperfusie en het belang van identificatie van nieuwe factoren speelt hierin een belangrijke rol.

In het literatuuroverzicht gepresenteerd in **Hoofdstuk 3**, hebben we laten zien dat gerandomiseerde studies naar het effect van periprocedurele antitrombotische behandeling bij EVT in patiënten met een herseninfarct op dit moment ontbreken. Sommige van de beschikbare observationele onderzoeken melden een lichte toename

van het symptomatische intracraniële bloedingsrisico (sICH), wat aanvaardbaar lijkt omdat deze onderzoeken ook een gunstig effect op de functionele uitkomst suggereren. Gebaseerd op deze resultaten lijkt een gerandomiseerde studie gerechtvaardigd om de vraag te evalueren of een potentieel hoger risico op sICH kan worden gecompenseerd door een grotere verbetering op functionele uitkomst.

Op basis van gegevens van de grote observationele MR CLEAN-Registry hebben we drie onderzoeken uitgevoerd waarin we het effect van antitrombotica en anticoagulantia in de huidige klinische praktijk hebben geëvalueerd. In **Hoofdstuk 4** vonden we geen bewijs van een associatie tussen het gebruik van plaatjesaggregatieremmers en het risico op sICH na EVT. Ook vonden wij geen associatie tussen de plaatjesaggregatieremmer en functionele uitkomst, reperfusie of mortaliteit in vergelijking met patiënten die geen plaatjesaggregatieremmers gebruikten. Aangezien therapieresistentie en therapietrouw niet kon worden geëvalueerd in deze studie kon een substantieel gunstig of schadelijk effect van plaatjesaggregatieremmers op de functionele uitkomst niet worden uitgesloten. In **Hoofdstuk 5** onderzochten we de invloed van eerder anticoagulantia-gebruik (dat wil zeggen het gebruik van directe anticoagulantia (DOAC's) of vitamine K-antagonisten) bij patiënten die werden behandeld met EVT voor een ischemische beroerte en toonden we aan dat dit niet geassocieerd was met een verhoogd risico op sICH of een slechtere functionele uitkomst in vergelijking met patiënten die niet reeds een OAC gebruikte. Gebaseerd op deze resultaten mogen, in tegenstelling tot bij de intraveneuze rtPA, patiënten die reeds een OAC gebruiken niet routinematig worden uitgesloten voor EVT. In **Hoofdstuk 6** hebben we laten zien dat er een substantiële variabiliteit is in Nederland tussen centra in het periprocedureel intraveneus heparine gebruik tijdens EVT. We vonden dat dit varieerde van centra die heparine toedienen bij 0% van de patiënten tot centra die heparine toedienen bij 94% van de patiënten. Periprocedureel gebruik van heparine ging niet gepaard met een toename van sICH. Centra die vaker heparine gebruikten, hadden betere uitkomsten. Vervolgens hebben we in **Hoofdstuk 7** een gerandomiseerde studie ontworpen om de veiligheid en werkzaamheid van acetylsalicylzuur en ongefractioneerde heparine te evalueren. We hebben specifiek voor deze antitrombotica gekozen vanwege: I) de onderliggende pathofysiologie van incomplete microvasculaire reperfusie, II) de theoretische en gerapporteerde verwachte voordelen van acetylsalicylzuur en ongefractioneerde heparine, III) het gerapporteerde veiligheidsprofiel van beide medicamenten in de bestaande literatuur, IV) het gemak van toediening en V) de ruime ervaring met deze medicamenten in de interventionele setting. Desalniettemin bleek op basis van de resultaten van een tussentijdse veiligheidsanalyse van de gerandomiseerde MR CLEAN-MED studie welke ik presenteerde in **Hoofdstuk 8** dat periprocedureel gebruik van middelhoge dosis ongefractioneerde heparine tijdens EVT voor acute ischemische beroerte geassocieerd is met een overmatig risico op sICH en met overlijden en dus vermeden dient te worden.

Deel II Optimalisatie van periprocedurale anesthesie en hemodynamiek

In het tweede deel van dit proefschrift hebben wij ons gericht op het bepalen van de meest optimale strategie met betrekking tot het anesthesietype en de bloeddruk. In **Hoofdstuk 9** beschreven we dat sedatie geassocieerd was met een slechte functionele uitkomst en een verhoogde sterfte in vergelijking met lokale anesthesie tijdens EVT. Bovendien was sedatie niet geassocieerd met een kortere duur van de interventie of reduceerde dit de interventie gerelateerde complicaties niet. We adviseerden daarom dat lokale anesthesie moet worden uitgevoerd in plaats van sedatie tijdens EVT voor ischemische beroerte, indien dit veilig mogelijk is. In **Hoofdstuk 10** heb ik deze bevindingen verder uitgewerkt en geëvalueerd of verschillen in uitkomst tussen sedatie en lokale anesthesie verklaard kunnen worden door het periprocedurele bloeddrukverloop. We ontdekten dat bloeddrukdalingen en procedurele bloeddruktrend de slechtere resultaten in de sedatie groep niet verklaarden. Toch zijn we van mening dat grote bloeddrukdalingen moeten worden vermeden, omdat deze onafhankelijk geassocieerd waren met slechtere functionele uitkomsten. Aangezien het denkbaar is dat optimalisatie van de perfusie door het bloeddrukverloop niet beperkt is tot de EVT alleen, evalueerden wij de associatie van bloeddruk in de 6 uur na EVT met functionele uitkomst in **Hoofdstuk 11**. We ontdekten dat hogere maximale systolische bloeddruk (SBP) waarden in de eerste 6 uur na EVT zijn geassocieerd met een slechtere functionele uitkomst en een verhoogd risico op sICH. Zowel een hogere als ook een lagere SBP dan 120-125mmHg minimum SBP-niveau waren geassocieerd met slechtere resultaten. Een gerandomiseerde studie lijkt gerechtvaardigd om te evalueren of het intensiveren van het bloeddruk beleid tot betere resultaten leidt.

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List of publications

1. Chalos V, **van de Graaf RA**, Roozenbeek B, A CGMvE, H MdH, Staals J, van Dijk L, S FMJ, R JvO, W HvZ, Y BWEMR, C BLMM, H FL, van der Lugt A, D WJD and investigators MC-M. Multicenter randomized clinical trial of endovascular treatment for acute ischemic stroke. The effect of periprocedural medication: acetylsalicylic acid, unfractionated heparin, both, or neither (MR CLEAN-MED). Rationale and study design. *Trials*. 2020;21:644.
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Name PhD candidate:	PhD period: sep 2017- dec 2020
- Rob van de Graaf	Promotor(s):
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Erasmus MC Departments:	- Prof. dr. D.W.J. Dippel
- Radiology & Nuclear Medicine	Co promotor(s):
- Neurology	- B. Roozenbeek

1. PhD training

	Year	Workload (Hours/ECTS)
General research skills		
NIHES		
- Advanced Clinical Trials	2017- 2020	1.9
- Cardiovascular epidemiology		0.9
- Logistic regression		1.4
- Repeated measurements		1.7
- Missing values		1.7
- Cohort studies		0.7
- Study design		4.3
COEUR		
- Vascular clinical epidemiology	2018	0.5
- Imaging for Ischemic Heart and Brain Disease	2018	0.5
- Large animal stroke models: rationale, techniques and practical experience	2018	0.5
	2018	0.5
- Sex and Gender in Cardiovascular Research	2018	0.5
- Aneurysmal disease	2018	0.5
Imaging		
- MRI course GE Healthcare	2017	1
- CTA stroke cursus Erasmus MC	2018	0.3
- MRI Basic Course on Applied MR Techniques [ESMRMB]	2019	0.3
- MRI Advanced Course on Applied MR Techniques [ESMRMB]	2019	0.3
- ESOR Neuroradiology	2019	0.3
Other		
- BROK	2017	1.5
- NIHSS training	2017	0.2
- CPO course	2018	0.3
- Wetenschappelijke integriteit	2018	0.2
- Peer reviewer International Scientific Journals	2017-2020	1.5
- Clinical Development (Futurelab)	2020	1.5

Symposia			
-	Young at heart symposium, Utrecht	2018	0.3
-	IAT symposium, Erasmus MC, Rotterdam	2018	0.3
-	Presentation 'Heparin substudy' MR CLEAN-Registry Workshop	2018	0.3
-	NNW Vergadering; 2x Oral presentation 'MR CLEAN MED protocol'	2018	1.2
-	NVN-Wetenschapsdagen, Nunspeet;1x Oral presentation 'Periprocedural heparin use'	2018	0.6
-	NVvR-Radiologendagen; Oral presentation 'Periprocedural heparin use'	2019	0.3
-	NVN-Wetenschapsdagen, Nunspeet; Oral presentation 'Periprocedural heparin use'	2019	0.3
-	Neurointervention, MUMC+, Maastricht	2020	0.3
International conferences			
-	European Stroke Organisation Congress, Gothenburg; 3x Poster presentation	2018	3.1
-	ESMINT, Nice	2018	1.0
-	ESNR Annual meeting; 1x Oral presentation 'Periprocedural heparin use in IAT'	2018	1.6
-	European Stroke Organisation Congress, Milan, Italy; 1x Poster presentation and 1x E-poster discussion	2019	2.2
-	International Stroke Conference, Honolulu; 1x Poster presentation	2019	1.0
-	WFITN, Naples; 1x Oral presentation 'Prior APT use in IAT'	2019	1.6
-	European Stroke Organisation Congress, Vienna, Austria; 1x Plenary oral presentation 'Moderate-dose heparin MR CLEAN MED'	2020	1.6
-	European Society of Radiology, Vienna, Austria; 1x Clinical Trials in Radiology session 'Moderate-dose heparin MR CLEAN MED'	2020	1.6
-	ESNR Annual meeting online	2020	1.0

2. Teaching activities		
	Year	Workload (Hours/ECTS)
Supervising Bachelor/Master theses		
- Co-supervising with dr. T. van Walsum of 4 Bachelor students from the TU Delft/EMC (Bachelor Thesis, Technical Medicine). Topic: Quantification of bloodflow on DSA.	2019	2.0
- Co-supervising Jan van Rees (Master student). Topic: DOAC and VKA safety in IAT	2018	2.0
- Co-supervising Carlijn van den Berg (Master thesis, Medicine). Topic: Hemodynamics during EVT in patients receiving CS or LA.	2018	2.0
- Co-supervising with dr. T. van Walsum of 4 Bachelor students from the TU Delft/EMC (Bachelor Thesis, Technical Medicine). Topic: Quantification of bloodflow on DSA.	2019	2.0

About the author

Rob A. van de Graaf was born in 1991 in Zwijndrecht. Having a passion for mathematics and biology, he was selected during the last two years of secondary school to participate in Junior Med School at the Erasmus MC University Medical Center in Rotterdam. Through successful completion of Junior Med School, Rob was granted access to the Bachelor of Medicine at the Erasmus MC, which he started in 2010. From mid 2011 to 2015, he worked as part of a student team at the department of Anesthesiology, where he assisted in general nursing tasks. Being passionate about wind, the beach and kitesurfing, Rob was also involved during this same period (2011 to 2015) as a coast-guard at Hoek van Holland and kitesurfing instructor at the Brouwersdam. Despite, spending numerous hours of kitesurfing on the water, he felt obtaining a doctorate was necessary, perhaps to surf more. After finishing his Master of Medicine in 2017, he got the opportunity to start as a PhD-candidate at the departments of Radiology & Nuclear Medicine and Neurology of the Erasmus MC, University Medical Center. He wrote his thesis under the supervision of prof. dr. Aad van der Lugt (Department of Radiology & Nuclear Medicine), prof. dr. Diederik Dippel and dr. Bob Roozenbeek (Department of Neurology). His main project considered the coordination of the MR CLEAN-MED trial. Part of the trial results are presented in this thesis. He presented his work at numerous (inter)national conferences. Rob aspires a career as a Radiologist and will start his residency in Radiology in October 2021.