

Endovascular treatment: the role of dominant caliber M2 segment occlusion in ischemic stroke

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ABSTRACT

Background and purpose It is unclear whether endovascular treatment (EVT) is beneficial for patients with acute ischemic stroke with occlusion of the M2 segment of the middle cerebral artery. We aimed to compare functional outcomes, technical aspects and complications of EVT between patients with acute ischemic stroke due to an M2 and M1 occlusion in clinical practice. Furthermore, outcome and complications after EVT in dominant- and non-dominant caliber M2 division occlusions were studied.

Methods Data were obtained from the MR CLEAN-Registry which is an ongoing observational study in 16 Dutch centers performing EVT in The Netherlands. Functional outcome was measured with the modified Rankin Scale (mRS) score at 90 days. Neurological recovery (delta-NIHSS), successful reperfusion rates (eTICI \geq 2B) and safety outcomes were also investigated. Associations between occlusion location and outcome were analyzed with ordinal logistic regression models, with adjustment for other prognostic factors.

Results In total, 244 (24%) patients with an M2 and 759 (76%) patients with an M1 occlusion who underwent EVT were analyzed. Functional outcomes were not significantly different between patients with M2 versus M1 occlusions (adjusted common odds ratio (acOR) 1.24; 95%CI 0.87–1.73). Occurrence of sICH was also similar for M2 and M1 occlusions (6.6% versus 5.9%; p 0.84). Further analysis regarding dominance of an M2 branch was performed in 175 (72%) patients. Neurological recovery was comparable (mean delta-NIHSS -2 ± 10 for dominant M2, -5 ± 5 for non-dominant M2 and -4 ± 9 (p 0.24) for M1 occlusions). Furthermore, the effect of reperfusion status on functional outcome was comparable between occlusion divisions (cOR 1.27 (95%CI 1.06-1.53) for dominant M2, 1.32 (95%CI 0.93-1.87) for non-dominant M2 and 1.35 (95%CI 1.24-1.46) for M1 occlusions).

Conclusions Outcomes and complication rates after EVT were similar in patients with M2 and M1 occlusions. Although based on observational data and a limited sample size, a similar association of reperfusion status with functional outcome for all subgroups provides no evidence that patients with either a dominant or non-dominant M2 occlusion should be routinely excluded from EVT.

INTRODUCTION

Acute endovascular treatment (EVT) has become part of the usual care for appropriately selected patients with ischemic stroke caused by an occlusion in the proximal intracranial anterior circulation. However, the role of EVT for patients with more distal occlusions in the second-order branches (M2) of the middle cerebral artery (MCA) is less certain given that this population was underrepresented in randomized controlled trials¹⁻³.

Considering the distal location, smaller diameter and thinner walls of the M2 arterial segment, an M2 occlusion may result in more challenging endovascular procedures and an increased risk of periprocedural complications¹. These drawbacks potentially counterbalance the benefit of reperfusion. Furthermore, IVT alone is more effective for recanalizing M2 occlusions relative to more proximal occlusions and therefore might limit the additional benefit of EVT^{4,5}.

A recent meta-analysis reported that patients with M2 occlusions achieved similar reperfusion and mortality rates as patients with M1 occlusions⁶. Although symptomatic intracerebral hemorrhages (sICH) were observed more frequently with M2 occlusions, rates of functional independence were higher among patients with an M2 occlusion. A lower baseline NIHSS score in M2 occlusion compared to M1 occlusion patients might explain this observation⁶.

The wide anatomical variation regarding the branching pattern of the MCA strongly influences the arterial territory at risk in case of an M2 occlusion. Several MCA branching patterns have been described in the anatomical and neuroradiological literature^{7,8}. The most important variation is in the blood supply to the parietal lobe, which can be fed by the inferior or superior M2 division or both. The M2 division that supplies the majority of the parietal lobe has a larger caliber than the dominant M2 division. In some patients, a dominant M2 division can even approximate the diameter of the M1 segment. Owing to their larger territory at risk, dominant M2 occlusions typically lead to worse clinical outcomes than non-dominant M2 occlusions^{3,8}.

Previous studies of the effect of EVT in patients with ischemic stroke did not distinguish between occlusion of dominant and non-dominant M2 divisions. It is probable that an occlusion of a dominant M2 may yield similar outcomes and treatment benefit as an M1 occlusion, whereas non-dominant M2 branch occlusions may have a better natural history and reduced treatment effect.

Current stroke guidelines concluded that it may be reasonable to treat patients suffering from an M2 occlusion with EVT, but further evidence is warranted⁹. The aim of this study is to investigate three-month functional outcome and the technical and safety aspects of EVT in patients with ischemic stroke due to M2 versus M1 occlusions. Additionally, differences in outcome between dominant and non-dominant M2 division occlusions are studied.

METHODS

Data were obtained from the MR CLEAN Registry, which is an ongoing prospective observational study in all centers performing EVT in The Netherlands. Detailed study design and methods have been described previously¹⁰. The MR CLEAN Registry was approved by the ethics committee of the Erasmus MC, Rotterdam, The Netherlands (MEC-2014-235). With this approval it was approved by the research board of each participating center. At UMC Utrecht, approval to participate in the study has been obtained from their own research board and ethics committee. Source data are not be made available because of legislative issues on patient privacy, but detailed analytic methods and study materials, including log files of statistical analyses, will be made available to other researchers on request (e-mail: mrclean@erasmusmc.nl).

Patients

All patients aged 18 years and older with a clinical diagnosis of acute ischemic stroke due to a proximal arterial occlusion in the anterior circulation demonstrated by computed tomography angiography (CTA) and in whom EVT was initiated (defined as arterial puncture) within 6.5 hours after stroke onset were studied¹⁰. For the present study, only patients with a documented M1 or M2 target occlusion on baseline digital-subtraction angiography (DSA) were included. EVT consisted of mechanical thrombectomy and/or aspiration whether or not combined with arterial delivery of a thrombolytic agent. Method of EVT was left to the discretion of the interventionist. Patients included in this analysis were treated between March 16, 2014 and June 15, 2016.

Image analysis

Non-contrast CT (NCCT), CTA and DSA were scored by a core lab, except for the anatomical classification of the M2 branch which was assessed by one experienced neurointerventionist (AvE). Imaging analyses were performed blinded to clinical characteristics and outcomes. Alberta Stroke Program Early CT Score (ASPECTS) was measured on baseline NCCT, collateral score on baseline CTA and both occlusion segment and extended Thrombolysis In Cerebral Infarction (eTICI) score was measured on DSA¹¹⁻¹³. DSA-only procedures were cases in which the target occlusion resolved or migrated too distally (M3 or M4 branches) due to contrast flushing or manipulation with the catheter, without actual performing of intended endovascular treatment.

In accordance with previously used definitions, the M1 segment and M2 branches were defined as follows on DSA: the M1 (horizontal or sphenoidal) segment extends from the bifurcation of the internal carotid artery (ICA) below the anterior perforated substance to the limen insulae¹. At the limen insulae, the M1 makes a postero-superior turn (genu) into the insula. The anterior temporal artery is identified as the artery that sup-

plies the anterior temporal pole regardless of its size and whether it continues into the Sylvian fissure. All anatomical variations of the anterior temporal branch are considered M1 branches in this study. The M2 branches are considered those branches that are distal to the main bifurcation at the distal end of the horizontal M1 segment. M2 branches extend from the postero-superior turn (genu) of M1 to the circular sulcus of the insula.

For the purpose of this study, caliber dominance was considered present if one M2 branch had a larger diameter than the other on DSA or if the perfusion defect associated with the occluded M2 branch was larger than 50% of MCA territory (Figure 1). Only when the diameters of both the inferior and superior branches were equal and the associated

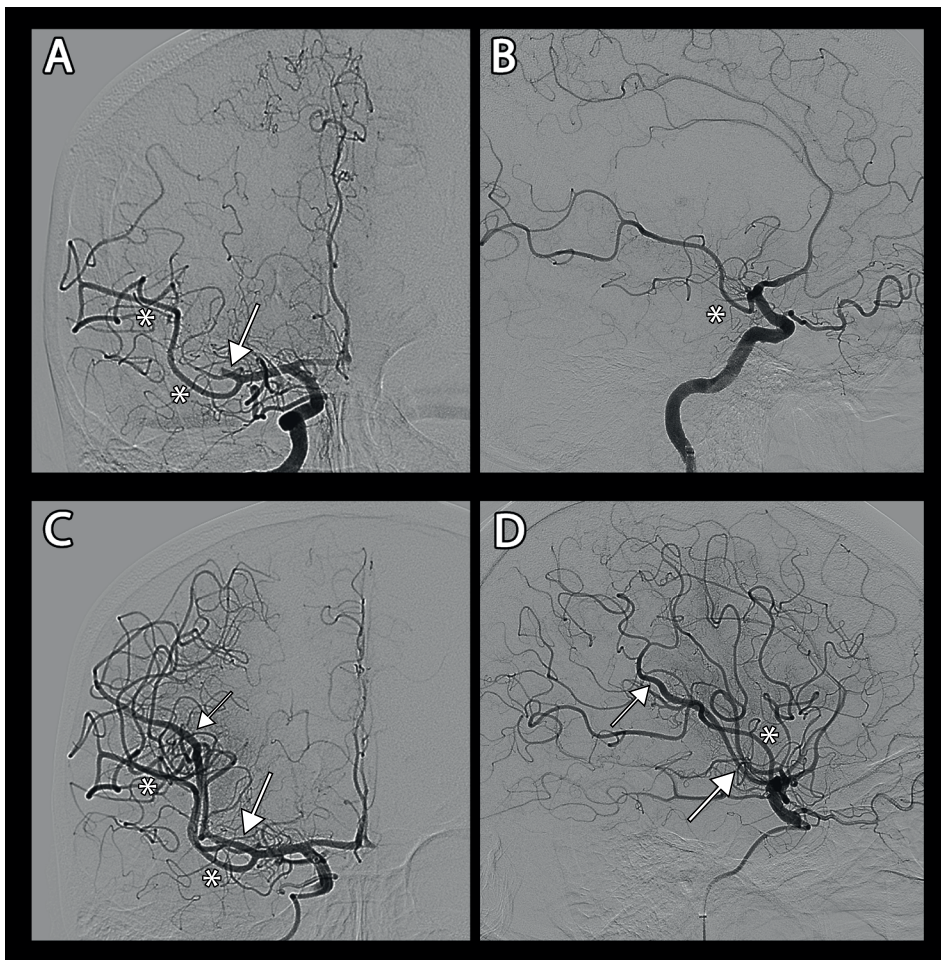


Figure 1. Case example of a dominant M2 superior division on DSA. Arrows indicate the superior M2 division. Asterisks indicate the inferior M2 division. **(A)** AP view on DSA pre-EVT, where a large part of the parietal lobe not perfused. **(B)** Lateral view on DSA pre-EVT. **(C)** AP view on DSA after EVT. The parietal lobe is reperfed. **(D)** Lateral view on DSA after EVT.

perfusion defect was approximately 50% of MCA territory, the branches were considered co-dominant.

Outcomes

Primary outcome was functional outcome assessed with the modified Rankin Scale (mRS) score at 90 days ranging from 0 (no symptoms or disability) to 6 (death)¹⁴. Secondary outcomes were functional independence (mRS 0-2), stroke severity, and change in stroke severity. Stroke severity was measured using the National Institute of Health Stroke Scale (NIHSS) which ranges from 0 to 42 points (higher score indicating a more severe stroke). Follow-up NIHSS was assessed at 24-48 hours after treatment. Missing follow-up NIHSS scores in patients who died within 48 hours were assigned 42 points. Change in stroke severity was assessed with delta-NIHSS which was calculated as the absolute difference between baseline and follow-up NIHSS: a negative value indicates a neurological improvement while a positive value indicates a neurological decline. Evaluation of technical aspects included post EVT reperfusion status (eTICI score), procedural duration, number of stent retriever passes and procedural complications (defined as vasospasm, vessel dissection or perforation, presence of distal thrombi, and new clots in a different vascular territory). Complete DSA runs including anteroposterior and lateral views were required to reach an eTICI score of 2B or higher. A missing lateral view resulted in a maximum possible score of 2A. Successful reperfusion was considered when eTICI 2B or higher was achieved. Safety aspects included symptomatic intracranial hemorrhage¹⁵ and stroke progression (defined as a neurological deterioration by at least 4 points on the NIHSS).

Statistical analyses

Patients who underwent EVT for acute ischemic stroke due to an M2 occlusion were compared to those treated with an M1 occlusion. Baseline characteristics of both patient groups were compared by means of the Wilcoxon rank sum test or student's *t* where appropriate and a χ^2 test for categorical variables.

The difference in functional outcome between M2 and M1 occlusions was expressed as a common odds ratio obtained from multivariable ordinal logistic regression¹⁶. Adjustments were made for age, sex, NIHSS at baseline, time from stroke onset to groin puncture, intravenous thrombolysis (IVT), prestroke mRS and CTA collateral status. For regression analysis, missing values were imputed by multiple imputations¹⁷. To compare the association between functional outcome and reperfusion grade in each subgroup of occluded division, unadjusted ordinal logistic regression was performed. Unadjusted and adjusted common odds ratios (acOR) were reported with 95% confidence interval (95%CI). All analyses were performed with R (version 3.4.2) and packages *rms*, *ggplot2*, *Hmisc*, *readxl*, *tableone* and *haven*. Probability values of <0.05 were considered significant for all tests.

RESULTS

Baseline patient characteristics

Of the 1003 included patients, 244 (24%) patients had an M2 occlusion and 759 (76%) had an M1 occlusion (Suppl. Figure I). No significant differences were observed between patients with an M2- and M1 occlusion regarding age, sex and clinical risk factors for ischemic stroke, collateral grading score and time from stroke onset to groin puncture (Table 1). Compared to patients with M1 occlusions, those with M2 occlusions had significantly lower median NIHSS scores (14 versus 16; $p < 0.001$), higher ASPECT scores

Table 1. Baseline characteristics of analyzed patients.

	M2 occlusion (n=244)	M1 occlusion (n=759)	P-value
Age – (years) median [IQR]	72 [62-79]	70 [60-79]	0.48
Sex (male) (%)	128 (53)	404 (53)	0.89
Smoking (%)	55 (29)	186 (33)	0.39
Diabetes mellitus (%)	39 (16)	138 (18)	0.48
Atrial fibrillation (%)	50 (21)	176 (24)	0.40
Hypertension (%)	128 (53)	386 (52)	0.71
Previous myocardial infarction (%)	41 (17)	122 (17)	0.89
Previous stroke (%)	38 (16)	143 (19)	0.30
Hypercholesterolemia (%)	65 (28)	239 (33)	0.22
Collateral grading score ^a			0.89
0	15 (7)	39 (6)	
1	75 (33)	223 (32)	
2	91 (40)	288 (41)	
3	46 (20)	153 (21.8)	
NIHSS score – median [IQR] ^b	14 [9-18]	16 [12-20]	<0.001
ASPECTS – median [IQR] ^c	9 [8-10]	9 [7-10]	0.01
Prestroke modified Rankin scale 0-2 (%) ^d	221 (88)	657 (88)	>0.999
Treatment with IV thrombolysis (%)	203 (83)	575 (76)	0.03
Time onset to groin (min) –median [IQR]	200 [152-274]	210 [160-260]	0.60
DSA-only (%) ^e	28 (12)	12 (2)	<0.001

^a Assessed at baseline CTA. A score of 0 indicated absent collateral supply to the occluded territory, 1: filling of >0% but ≤50%, 2: filling of >50% but <100%, 3: filling of 100% collateral supply of the occluded territory.

^b National Institute of Health Stroke scale (Scores range from 0 to 42, higher scores indicating severe stroke).

^c Alberta Stroke Program Early Computed tomography Score (Scores range from 0 to 10 lower scores indicating more early ischemic changes on baseline NCCT).

^d Functional disability before stroke onset, score ≤2 indicates functional independence.

^e Digital subtraction angiography without thrombectomy or aspiration, indicating spontaneous reperfusion.

(median 9 IQR [8-10] versus 9 IQR [7-10]; p 0.01) and greater IVT treatment (83% versus 76%; p 0.03). DSA-only procedures due to reperfusion before EVT occurred more often in the M2 occlusion group (12% versus 2%; p<0.001).

In 69 patients (28%) with an M2 occlusion dominance of the M2 branch could not be reliably assessed due to poor quality or insufficient DSA imaging. This left 175 (72%) patients for further analysis. Dominance of either superior or inferior division was observed in 137 (78%) and co-dominance of M2 branches was observed in 38 (22%) patients with M2 occlusion. Dominance of a branch was equally often observed in the superior or inferior division (resp. 49% versus 51%; p>0.99). In patients with a dominant M2 branch, the occlusion was located in the dominant division in 124 of the cases and in 51 of the cases in the non-dominant branch. Baseline NIHSS was lower in patients with a dominant M2 occlusion than in patients with an M1 occlusion (median [IQR] 14 [9-17] versus 16 [12-20]; p<0.001) (Suppl. Table I).

Patients with an occlusion in a co- or non-dominant division had a lower NIHSS at baseline than patients with an M1 occlusion (median [IQR] 14 [9-17] versus 16 [12-20]; p 0.002) and they had more DSA only procedures (25% versus 2%; p<0.001) (Suppl. Table I).

Outcomes

There was no significant difference in functional outcome between patients with an M2 occlusion and patients with an M1 occlusion (acOR 1.24; 95%CI 0.92–1.68) (Figure 2). Likewise, the proportion of patients who achieved functional independence (mRS score 0-2) at follow up did not differ (101 (46%) for M2 occlusions versus 270 (39%); p 0.10). Patients with an M2 occlusion had lower follow up NIHSS scores (median [IQR] 8 [3-16] versus 11 [4-18]; p 0.01). However, the difference in delta-NIHSS between the groups was not statistically significant (mean [IQR] -3 ±9 versus -4 ±9; p 0.49) (Table 2).

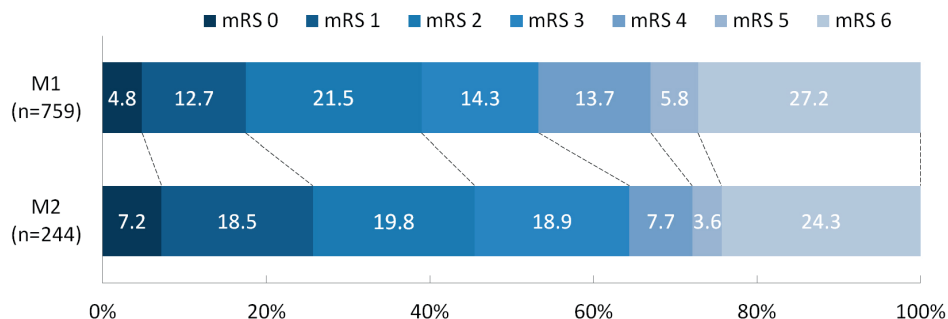


Figure 2. Modified Rankin Scale scores at 90 days: M1 versus M2 occlusion. Functional outcomes were statically significant different between patients with an M2 and M1 occlusion (common odds ratio, 1.40; 95%CI 1.07 - 1.83). However, after adjustment for age, sex, NIHSS baseline, time from stroke onset to groin puncture, intravenous thrombolysis (IVT), prestroke mRS and collateral status, functional outcome was no longer statistically different (adjusted common odds ratio, 1.24; 95%CI 0.92 – 1.68).

Table 2. Clinical, technical and safety outcomes in patients with an M2 occlusion on DSA compared to patients with an M1 occlusion.

	M2 (n=244)	M1 (n=759)	P-value
Clinical			
mRS score at 90 days – median [IQR] ^a	3 [1-5]	3 [2-6]	0.02
mRS score 0-2 at 90 days (%)	101 (46)	270 (39)	0.10
NIHSS follow up (24 – 48 h) – median [IQR]	8 [3-16]	11 [4-18]	0.01
Delta-NIHSS – mean (sd) ^b	-3 (9)	-4 (9)	0.49
Technical			
Successful reperfusion (%) ^c	135 (57)	454 (60)	0.33
Duration procedure – min - median [IQR]	50 [36-83]	65 [41-90]	0.01
Total stent passes – median [IQR]	1 [0-2]	2 [1- 3]	<0.001
Procedural complications on DSA (%)	57 (28)	213 (29.5)	0.64
Vasospasm (%)	13 (6)	56 (8)	0.57
Vessel dissection (%)	1 (1)	21 (3)	0.08
Vessel perforation (%)	5 (2)	9 (1)	0.37
Distal thrombus present (%)	30 (15)	104 (14)	>0.999
New thrombus different vascular territory (%)	10 (5)	35 (5)	>0.999
Safety			
Symptomatic intracranial hemorrhage(%) ^d	16 (7)	45 (6)	0.84
Progression of the stroke (%) ^e	18 (7)	66 (9)	0.61
Mortality at 90 days (%)	54 (22)	188 (25)	0.45

^a Modified Rankin scale score was assessed at 90 days after stroke onset.

^b Absolute difference between baseline NIHSS and follow-up NIHSS.

^c eTICI ≥ 2B, score of 0 indicates no perfusion or anterograde flow beyond occlusion site, 1: penetration of contrast but not perfusion, 2A: some perfusion <50% of vascular territory, 2B: substantial perfusion ≥50%, 2C: almost complete perfusion 90-99%, 3: complete perfusion of vascular territory.

^d Clinical deterioration due to intracranial hemorrhage defined by the Heidelberg bleeding classification.

^e Neurological deterioration by at least 4 points on the NIHSS.

Successful reperfusion was similar in patients with M2 or M1 occlusions (454 (60%) versus 135 (57%); p 0.33) while duration of procedure was shorter in patients with an M2 occlusion (median 50 [IQR] [36-83] versus 65 [41-90] minutes). There were no significant differences regarding procedural complications or symptomatic intracranial hemorrhage in both groups (28% versus 30%; p 0.64).

In patients with dominant M2 occlusions, EVT resulted in a similar functional outcomes compared to M1 occlusions (acOR 1.19; 95%CI 0.79-1.80) and the proportion of patients with functional independence was not significantly different (42 (39%) versus 270 (39%); p >0.99) (Suppl. Figure II). Compared to M1 occlusions, the proportion of functional independence stratified by reperfusion grade were similar to patients with a

dominant M2 branch (Table 3). Additionally, NIHSS at follow up and delta-NIHSS did not differ and technical and safety aspects were either equivalent or favorable in patients with a dominant M2 division occlusion (Table 4).

Table 3. Proportions of functional independence stratified by reperfusion grades *

	M1		Dominant M2		Co- or non-dominant M2	
	(n=759)		(n=124)		(n=51)	
eTICI- score ^a	n (%)	mRS 0-2 (%)	n (%)	mRS 0-2 (%)	n (%)	mRS 0-2 (%)
0-1	117 (16%)	10 (2%)	35 (28%)	8 (7%)	6 (12%)	3 (6%)
2a	182 (24%)	59 (9%)	18 (15%)	6 (6%)	8 (16%)	5 (10%)
2b-3	454 (60%)	199 (29%)	71 (57%)	28 (26%)	35 (71%)	20 (41%)
cOR (95%CI)†	1.35 (1.24-1.46)		1.27 (1.06-1.53)		1.32 (0.93-1.87)	

* eTICI scores were missing for 6 patients with an M1 occlusion on DSA and missing for 2 patients with a co- or non-dominant M2 occlusion on DSA.

^a eTICI score of 0 indicates no perfusion or antegrade flow beyond occlusion site, 1: penetration of contrast but not perfusion, 2A: some perfusion <50% of vascular territory, 2B: substantial perfusion ≥50%, 2C: almost complete perfusion 90-99%, 3: complete perfusion of vascular territory.

† Complete scales of mRS score (dependent variable) and eTICI (independent) were used in the ordinal regression models.

Patients with co- or non-dominant division occlusions of the M2 branch had better functional outcomes than patients with an M1 occlusion (acOR 2.22; 95%CI 1.27-3.87) (Suppl. Figure III). Also, patients with a co- or non-dominant M2 branch occlusion became functionally independent more often than patients with an M1 occlusion (29 (59%) versus 270 (39%); $p < 0.01$). NIHSS at follow up was lower in the co- or non-dominant division occlusions, but delta-NIHSS was equal between both groups. Safety aspects did not differ between both groups (Table 4).

DISCUSSION

In this study, we found that patients with ischemic stroke due to an M2 occlusion had similar functional outcomes compared to stroke patients with an M1 occlusion. Additionally, regarding neurological recovery (delta-NIHSS) no significant differences were observed between both groups. Furthermore, no significant differences in occurrence of sICH or other safety aspects were observed. The majority of the M2 occlusions in our study were occlusions of a caliber dominant M2 branch. These occlusions, and may be are often responsible for perfusion of the main part of the MCA territory¹⁸. This can explain the similarity in clinical outcome between M1 and M2 occlusions. Furthermore, the association of reperfusion with functional outcome was similar between M1 and

Table 4. Clinical, technical and safety outcomes in patients with an M1, or dominant M2 division, or co- or non-dominant M2 division occlusion.

	M1 occlusion (n=759)	Dominant M2 division occlusion (n=124)	Co- or non- dominant M2 division occlusion (n=51)	P-value
Functional				
mRS score at 90 days – median [IQR] ^a	3 [2-6]	3 [2-5]	2 [1-3]	0.01
NIHSS follow up (24 – 48 h) – median [IQR]	11 [4-18]	11 [3-17]	6 [3-13]	0.03
Delta-NIHSS – mean (sd) ^b	-4 (9)	-2 (10)	-5 (5)	0.24
Technical				
Successful reperfusion (%) ^c	454 (60)	71 (57)	35 (71)	0.22
Duration procedure – min - median [IQR]	65 [41-90]	56 [35-85]	52 [34-69]	0.01
Total stent passes – median [IQR]	2 [1- 3]	1 [1-2]	1 [0-2]	<0.001
Procedural complications (%)	213 (30)	29 (26)	11 (28)	0.73
Vasospasm (%)	56 (8)	7 (6)	2 (5)	0.73
Vessel dissection (%)	21 (3)	0	0	0.11
Vessel perforation (%)	9 (1)	4 (4)	0	0.12
Distal thrombus present (%)	104 (14)	14 (13)	6 (15)	0.85
New thrombus different vascular territory – no. (%)	35 (5)	5 (5)	3 (8)	0.71
Safety				
Symptomatic intracranial hemorrhage (%) ^d	45 (6)	9 (7)	1 (2)	0.40
Progression of the stroke (%) ^e	66 (9)	11 (9)	1 (2)	0.24
Mortality at 90 days (%)	188 (25)	27 (22)	7 (14)	0.13

^a Modified Rankin scale score was assessed at 90 days after stroke onset.

^b Absolute difference between baseline NIHSS and follow up NIHSS.

^c eTICI ≥ 2B, score of 0 indicates no perfusion or antegrade flow beyond occlusion site, 1: penetration of contrast but not perfusion, 2A: some perfusion <50% of vascular territory, 2B: substantial perfusion ≥50%, 2C: almost complete perfusion 90-99%, 3: complete perfusion of vascular territory.

^d Clinical deterioration due to intracranial hemorrhage defined by the Heidelberg bleeding classification.

^e Neurological deterioration by at least 4 points on the NIHSS.

caliber dominant M2 occlusions. Compared to these occlusions, patients with occlusions of the non-dominant M2 branch had better functional outcomes, likely owing to the smaller territory at risk and hence better natural history.

In accordance with a recent meta-analysis, we observed similar clinical outcomes in patients with M2 and M1 occlusions⁶. Interestingly, we found lower complication rates which might be explained by advances in endovascular devices and increasing

experience of neurointerventionists. Similar to previous studies, we also found that NIHSS scores at baseline were lower in patients with M2 occlusions than in patients with M1 occlusions, indicating that M2 occlusion strokes are on average less severe^{1,19}. A previous population-based study showed that M2 occlusions were as often located in the superior as in the inferior division²⁰. However, other studies reported no differences in NIHSS scores at baseline which might be explained by differences in M2 segment definition, patient selection, or both³. Furthermore, as in our study, no differences in technical and safety aspects between M2 and M1 occlusion segments were observed in previous studies^{18,21}. Distal occlusions can still cause functional dependence, indicating that reperfusion of small brain regions is important, as they may involve eloquent areas^{22,23}. A recent study of 212 patients compared outcomes after thrombectomy for M1 or M2 occlusions. Dominancy of caliber was not taken into account²⁴. M2 occlusions were more often located in the superior branch. However, occlusion in a specific branch was not a predictor for clinical outcome.

Limitations

This study has several limitations beyond the common limitations of an observational study. First, we used DSA to identify thrombus location, while decision making in clinical practice is based on CTA findings. Therefore, results cannot be directly generalized to clinical decision making in the ER. Our objective was to assess technical and safety aspects of EVT in patients with an M2 occlusion²⁵. Second, ischemic stroke patients with a large vessel occlusion who did not undergo EVT are not registered in the MR CLEAN Registry. Therefore, patients with distal M2 occlusions may have been excluded, which could have resulted in selection bias. Nevertheless, patients with prestroke functional dependence, poor collateral grading scores, and poor vascular status were not excluded from the MR CLEAN Registry, and our results represent current routine practice. Third, anatomical variation of the M2 division branching pattern could not be assessed in all patients due to insufficient imaging of M2 branches in our retrospective analysis. Although we did not use advanced imaging such as perfusion scans to determine dominance, the anatomical distribution of dominant M2 branches as was described in the present study is in line with previously published anatomical studies. Also, our simple definition of dominant division observation during intervention on DSA makes it applicable during interventional procedures. However, adequate imaging of M2 branches is important in these patients from our experience. Fourth, in line with our third limitation, the precision of our estimates is limited, and results must be interpreted with care. Fifth, our study was based on an observational multicenter registry. Although covariable-adjusted regression analyses were performed, there might still be residual confounding in our study. Finally, follow-up imaging was not required in our registry, which precludes the analysis of infarct volume and asymptomatic hemorrhage as a secondary outcome.

In conclusion, outcomes and complication rates after EVT were similar in patients with M2 and M1 occlusions. Although based on observational data and a limited sample size, a similar association of reperfusion status with functional outcome for all subgroups provides no evidence that patients with either a dominant or non-dominant M2 occlusion should be routinely excluded from EVT.

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SUPPLEMENTAL DATA

Suppl. Table I. Baseline characteristics of patients with an M1, or dominant M2 division, or co- or non-dominant M2 division occlusion.

	M1 occlusion (n = 759)	Dominant M2 division occlusion (n = 124)	Co- or non- dominant M2 division occlusion (n = 51)	P-value
Superior dominant division – no. (%)	NA	63 (51)	NA	
Inferior dominant division – no. (%)	NA	61 (49)	NA	
Age (years) – median [IQR]	70 [60-79]	71 [60-77]	72 [62-79]	0.91
Sex (male) – no. (%)	404 (53)	64 (52)	25 (49)	0.81
Smoking – no. (%)	186 (33)	28 (28)	10 (28)	0.54
Diabetes mellitus – no. (%)	138 (18)	21 (17)	9 (18)	0.93
Atrial fibrillation – no. (%)	176 (24)	28 (23)	10 (20)	0.81
Hypertension – no. (%)	386 (52)	72 (59)	24 (48)	0.30
Previous myocardial infarction – no. (%)	122 (17)	16 (13)	10 (20)	0.53
Previous stroke – no. (%)	143 (19)	21 (17)	8 (16)	0.77
Hypercholesterolemia – no. (%)	239 (33)	33 (28)	10 (21)	0.19
Collateral grading score ^a				0.45
0	39 (6)	6 (5)	3 (6)	
1	223 (32)	46 (41)	15 (30)	
2	288 (41)	45 (40)	23 (46)	
3	153 (22)	16 (14)	9 (18)	
NIHSS score – median [IQR] ^b	16 [12-20]	14 [9-17]	14 [9-17]	<0.001
ASPECTS – median [IQR] ^c	9 [7-10]	9 [7-10]	9 [8-10]	0.03
Prestroke modified Rankin scale 0-2 – no. (%) ^d	657 (88)	107 (88)	44 (88)	>0.999
Treatment with IV thrombolysis – no. (%)	575 (76)	97 (78)	45 (88)	0.13
Time onset to groin (min) – median [IQR]	210 [160-260]	208 [152-275]	205 [171-268]	0.99
DSA-only – no. (%) ^e	12 (2)	9 (7)	12 (25)	<0.001

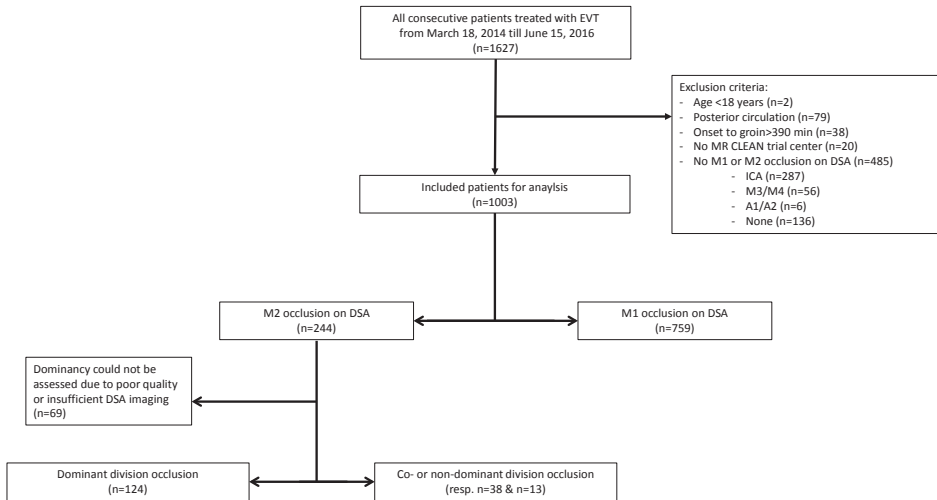
^a Assessed at baseline CTA. A score of 0 indicated absent collateral supply to the occluded territory, 1: filling of >0% but ≤50%, 2: filling of >50% but <100%, 3: filling of 100% collateral supply of the occluded territory.

^b National Institute of Health Stroke scale (Scores range from 0 to 42, higher scores indicating severe stroke).

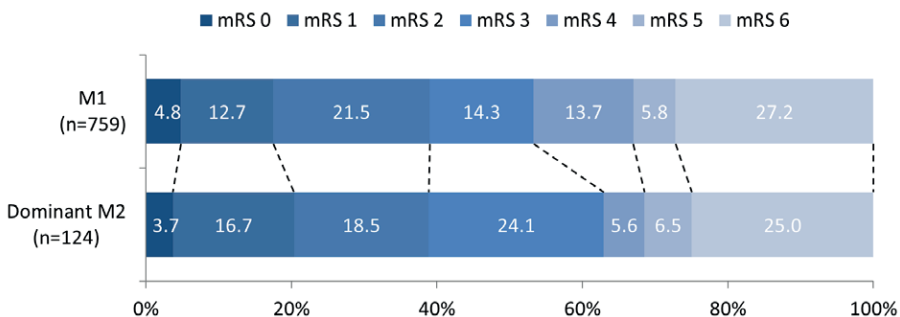
^c Alberta Stroke Program Early Computed tomography Score (Scores range from 0 to 10 lower scores indicating more early ischemic changes on baseline NCCT).

^d Functional disability before stroke onset, score ≤2 indicates functional independence.

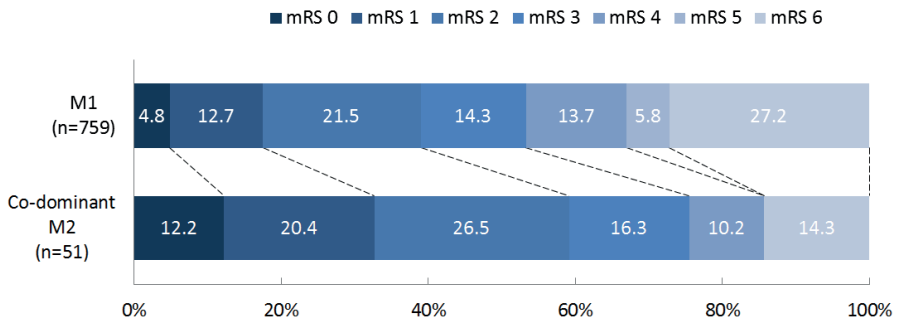
^e Digital subtraction angiography without thrombectomy or aspiration, indicating spontaneous reperfusion.



Suppl. Figure I. Flow diagram of patient selection for analysis. EVT indicates endovascular treatment, DSA, digital subtraction angiography.



Suppl. Figure II. Modified Rankin Scale scores at 90 days: M1 versus dominant M2 division occlusion. Functional outcomes were statically significant different between patients with an M2 and M1 occlusion (common odds ratio, 1.15; 95%CI 0.80 - 1.64). However, after adjustment for age, sex, NIHSS baseline, time from stroke onset to groin puncture, intravenous thrombolysis (IVT), prestroke mRS and collateral status, functional outcome was no longer statistically different (adjusted common odds ratio, 1.19; 95%CI 0.79 - 1.80).



Suppl. Figure III. Modified Rankin Scale Scores at 90 days: M1 versus co- or non-dominant M2 division occlusion. Functional outcomes were statically significant different between patients with an M2 and M1 occlusion (common odds ratio, 2.41; 95%CI 1.44 - 4.03). After adjustment for age, sex, NIHSS baseline, time from stroke onset to groin puncture, intravenous thrombolysis (IVT), prestroke mRS and collateral status, functional outcome was no longer statistically different (adjusted common odds ratio, 2.22; 95%CI 1.27 – 3.87). No patient with a co- or non-dominant M2 division occlusion was observed with a mRS score of 5.