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Adrien Marchal, Martin Bretzner, Barbara Casolla, Maéva Kyheng, Julien Labreuche, et al.. Endovascular Thrombectomy for Distal Medium Vessel Occlusions of the Middle Cerebral Artery: a Safe and Effective Procedure.. World Neurosurgery, 2022, World Neurosurgery, 10.1016/j.wneu.2021.12.113 . hal-04391154

HAL Id: hal-04391154

<https://hal.univ-lille.fr/hal-04391154v1>

Submitted on 22 Jul 2024

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Endovascular Thrombectomy for Distal Medium Vessel Occlusions of the Middle Cerebral Artery: a Safe and Effective Procedure

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Running title: Thrombectomy for distal medium vessel occlusions of the middle cerebral artery

Word count : 2798

Tables: 3 ; **Figures:** 3

Abstract

Background Distal, Medium Vessel Occlusions (DMVO) are increasingly recognized as a next target for endovascular thrombectomy (EVT).

Objective To investigate safety and clinical outcomes of EVT for DMVO of the middle cerebral artery (MCA).

Methods We analyzed data of the Lille Reperfusion Registry from January 2017 to September 2020. Patients with a primary or secondary DMVO of the MCA evidenced on pre-treatment angiogram were included. Only patients with a eTICI score 2b50 - 2b67 on initial angiogram were considered. Baseline characteristics, angiographic clinical, and safety outcomes were compared between patients treated with EVT or standard medical treatment (no-EVT).

Results Of the 171 patients included, 96 received EVT (46.9% male, 68.7±15.8 years) and 75 received standard medical treatment (44% male, 73.9±13.1 years). EVT patients had a better improvement of the NIHSS score at discharge (adjusted mean difference 3.71; 95%CI, 1.18 to 6.24). In the distal M2 occlusions subgroup, EVT was significantly associated with a higher rate of early neurological improvement (aOR 3.62 95%CI, 1.31 to 10.03), NIHSS improvement at discharge (adjusted mean difference, 5.23; 95%CI, 2.18 to 8.29), and improved mRS at 3 months (adjusted cOR for 1 point improvement, 3.06; 95%CI 1.30 to 7.23). Symptomatic intracranial hemorrhage occurred in 3.1% in the EVT group and in 9.5% in the no-EVT group.

Conclusion EVT for DMVO of the MCA appears to be safe and may lead to improved clinical outcomes. This effect was especially pronounced in patients with distal M2 occlusions, warranting randomized trials to validate this result.

Key Words: Distal occlusions, acute ischemic stroke, endovascular thrombectomy, reperfusion

Non-standard Abbreviations and Acronyms

ASD : absolute standardized differences

DMVO : Distal, Medium Vessel Occlusion

ENT : Emboli in a new territory

EVT : endovascular thrombectomy

eTICI : expanded Thrombolysis In Cerebral Infarction

INT : Infarcts in a new territory

Introduction

Six years after the publication of pivotal endovascular thrombectomy (EVT) trials, distal medium vessel occlusions (DMVOs) are increasingly considered as a potential new target for EVT [1]. This enthusiasm for DMVOs may be explained by the recent advances in thrombectomy device technology combined with increased expertise of neurointerventionalists in stroke treatment [2]. DMVOs may be seen in 3 different situations: (1) primary DMVO, (2) secondary DMVO due to clot migration between imaging and initial angiogram either spontaneously or after IV thrombolysis, and (3) secondary DMVO due to per-procedural embolization. Intravenous (IV) thrombolysis remains the first-line treatment for eligible patients with primary DMVOs but fails to achieve recanalization in more than 50% [3]. Moreover, secondary DMVOs after IV thrombolysis for proximal large vessel occlusion (PLVO) are frequently observed on the initial angiogram [4]. The RCTs angiographic endpoint of reference is a mTICI score 2b-3, however, its definition still represents only a 50% reperfusion of the MCA territory and some evidence suggest that near complete- or complete reperfusion may lead to better outcomes [5].

Results from randomized trials support the potential benefit from EVT for patients with proximal, large M2 occlusion [6], but EVT for patients with distal M2 or M3-MCA occlusion – which correspond to DMVO of the MCA – is still a matter of debate. Only a few retrospective studies included both anterior and posterior circulation stroke patients with DMVO and showed promising results of distal occlusion thrombectomy [7,8]. However, in the absence of evidence-based guidelines, an international consensus statement recently highlighted the need for data on EVT for DMVOs [2]. Therefore, efforts to provide additional data on the relevance of EVT for DMVOs are warranted to improve stroke care.

This study aimed to evaluate safety and clinical outcomes after EVT for DMVOs of the MCA. We hypothesized that EVT would improve functional outcomes in comparison with medical treatment and would not increase complications.

Methods

The registry was conducted according to French regulations and was approved by the local ethical committee (registration number 10.677). Patients or their legal guardians gave informed consent to participate.

Study Design

We performed a retrospective analysis of prospectively collected data in the *Lille Reperfusion Registry*, which is an institutional approved, ongoing observational registry at Lille University Hospital (Lille, France). This registry was designed to collect a standardized dataset of all consecutive patients with acute ischemic stroke treated by EVT in the Haut-de-France region.

Study population

We included all stroke patients with a primary or secondary DMVO of the MCA on initial cerebral angiogram who received EVT or not between January 2017 and September 2020. We considered patients with an occlusion of distal M2 or M3 segment of the MCA and an expanded Thrombolysis In Cerebral Infarction (eTICI) score of 2b50-2b67 on the pre-treatment cerebral angiogram [5]. Distal M2 occlusion was defined as an occlusion of the dominant M2 branch above the mid-height of the insula or a non-dominant M2 branch beyond the main bifurcation.

Clinical data

We prospectively collected demographic characteristics and vascular risk factors. National Institutes of Health Stroke Scale (NIHSS) scores were evaluated by stroke neurologists prior to groin puncture, at day-1, and at discharge. We recorded times of symptom onset (or time from last known well for patients with wake-up strokes), pre-treatment cerebral imaging, groin puncture, and recanalization as assessed with the eTICI score. Symptomatic intracerebral hemorrhage (sICH) was defined

according to ECASS-3 criteria [9]. Scores on the mRS were assessed at 3-months by a stroke neurologist through formal, structured in-person interviews.

Imaging data

All images (pre-treatment MRI, day-1 follow-up MRI, and angiogram) were reviewed by 2 senior interventional neuroradiologists blinded to clinical data. Infarct volumes were calculated on pre-treatment Diffusion MRI with RAPID AI software. The occlusion site was assessed on the initial angiogram. Scores on the eTICI scale were assessed on initial and final angiogram. Emboli in a new territory (ENT) affecting fields not previously compromised by ischemia were assessed on a control angiogram. Infarcts in a new territory (INT) were assessed on day-1 Diffusion MRI according to Goyal's classification [10].

Thrombectomy Procedures

EVT were performed under conscious sedation by a transfemoral approach using modern revascularization devices (standard or low profile stent-retrievers and aspiration catheters). After initial cerebral angiogram confirming a DMVO of the MCA, the decision to perform EVT was based on clinical severity, eloquence of the occluded artery, operator experience, and potential technical difficulties (access, vascular tortuosity, and patient agitation). First line technique was left at the discretion of the treating physician. Most commonly, we used a 9-F balloon guide catheter and stent-retriever as first line technique. The choice of stent-retriever (standard vs low profile) was based on intracranial tortuosity and vessel size on angiogram. Patients were not treated by intra-arterial thrombolysis. Endovascular reperfusion was based on the eTICI scale. As all patients had a eTICI score ≥ 2 , successful recanalization was defined as an improvement of the eTICI score on final angiogram (Figure 2). Procedural characteristics and procedure related complications (including intracranial perforation and ENT) were collected.

Outcomes

The primary outcome was the rate of favorable outcome, defined as a mRS score 0-2 at 3 months or similar to prestroke mRS score. Excellent outcome was defined as a mRS score 0-1 at 3 months or similar to prestroke mRS.

Early clinical benefit was evaluated by the mean change in NIHSS scores from baseline to day-1, and from baseline to discharge. Early neurological improvement (ENI) was specified as an improvement in NIHSS score at day-1 of at least 4 points or reaching 0 point [11].

Safety outcomes were INT, parenchymal hematoma or subarachnoid hemorrhage on day-1 imaging, sICH, and mortality.

Statistical analysis

Quantitative variables are expressed as means (standard deviation, SD) in the case of normal distribution, or medians (interquartile range, IQR). Categorical variables are expressed as numbers (percentage). Normality of distributions was assessed using histograms and Shapiro Wilk test. Patients were divided in two groups whether endovascular thrombectomy was performed. Between-group imbalances in baseline characteristics were assessed by calculating absolute standardized differences (ASD); an ASD >20% was interpreted as a meaningful difference [12]. Comparisons in outcomes between the two groups were performed before and after adjustment on pre-specified factors (age, NIHSS score at baseline, IVT use, eTICI score on baseline angiogram, and occlusion site distal M2 vs M3). Comparisons in binary outcomes (favorable outcome, excellent outcome, ENI at 24 hours) were performed using logistic regression models; odds ratios (ORs) were calculated as effect size using patients without EVT as reference. Comparison in the overall distribution of mRS was performed using an ordinal logistic regression model (shift analysis with mRS 5 and 6 pooled together); common odds ratio (cOR) for 1 point improvement in mRS were derived from this model as effects size. Comparison in discharge NIHSS was performed using analysis of variance (ANOVA) in unadjusted model and an analysis of covariance (ANCOVA) in adjusted model. Mean difference (EVT

vs. no-EVT) was derived from this model as effect size. The normality of model residuals was checked graphically and by using the Shapiro-Wilk test.

First analyses covered the overall study population; comparisons in main clinical outcomes between the treatment groups were further performed in the subgroup of patients with distal M2 occlusions as sensitivity analyses. Statistical testing was done at the two-tailed α level of 0.05. Data were analyzed using the SAS software package, release 9.4 (SAS Institute, Cary, NC).

Results

Baseline characteristics

A total of 171 consecutive patients were included from January 2017 to September 2020 (Flowchart presented in **online supplemental Figure 1**); 96 received EVT (47% male, 68.7±15.8 years) and 75 received medical treatment (44% male, 73.9±13.1 years).

As shown in **Table 1**, patients treated by EVT had similar baseline characteristics and medical history than patients who did not received EVT, except for age (68.7±15.8 years vs 73.9±13.1 years, ASD=0.36), and diabetes mellitus (23/96 (24.0%) vs 11/75 (14.7%), ASD=0.24). In comparison to the EVT group, patients in the no-EVT group received more frequently IVT (85.3% vs 51.0%, ASD=0.79), and had more frequently a secondary DMVO (77.3% vs 45.8%, ASD= 0.68).

On initial cerebral angiogram, patients treated by EVT had a more proximal occlusion (86.5% distal M2 occlusion and 13.5% M3 occlusion vs 37.3% distal M2 occlusion and 62.7% M3 occlusion ASD=1.17), and had a better eTICI score (70.8% eTICI2b50 and 29.2% eTICI2b67 vs 37.3% eTICI2b50 and 62.7% eTICI2b67, ASD=2.17).

Endovascular outcome and complication

The median time to treat (from first angiogram to final control angiogram) was 24 (17 to 36) min. The first-line revascularization technique was stent-retriever in 66.7%, contact aspiration in 9.3%, and combined in 24% (**online supplemental Figure 2**). Balloon guide catheters were used in 54%. A single

pass of revascularization device was performed in 66.7%, 2 passes in 19.8%, and 3 or more in 13.5%. Successful recanalization was achieved in 79 (82.3%) patients and complete recanalization in 37 (38.5%) patients. First pass successful recanalization was achieved in 55 (57.3%) patients. No patient had a eTICI score 0-2a on final angiogram. Four patients had a procedure-related complication (4 ENT, no intracranial vessel perforation).

Clinical outcomes

Study outcomes are presented in **Table2** and **Table3**. mRS scores at 3 months were available for all patients. Rates of favorable and excellent outcome did not differ significantly between patients with and without EVT (55.2% vs 60.0% and 37.5% vs 44.0% respectively), the adjusted OR for EVT use was 1.09 (95%CI, 0.43 to 2.79) for favorable outcome and 0.97 (95%CI 0.42 to 2.24) for excellent outcome. Similarly, there was no difference in overall mRS distributions (**figure 1**, adjusted cOR, 1.46; 95%CI 0.72 to 2.94) or ENI (OR=1.91, 95%CI 0.83 to 4.43). However, the improvement of the NIHSS score at discharge was significantly higher in the EVT group with an adjusted mean difference of 3.71 points (95%CI, 1.18 to 6.24).

In sensitivity analyses focusing on patients with distal M2 occlusions, patients treated with EVT had better functional outcomes when the overall mRS distribution was analyzed (adjusted cOR 3.06, 95%CI 1.30 to 7.23), a higher rate of ENI (57.8% vs 35.7%) with an aOR of 3.62 (95%CI 1.31 to 10.03), and a better NIHSS score at discharge (ASD in NIHSS scores of 5.23, 95%CI 2.18 to 8.29). However, EVT was not associated with better dichotomized favorable outcomes (adjusted OR, 2.34, 95%CI 0.78 to 6.99) nor dichotomized excellent outcomes (adjusted OR 2.07, 95%CI 0.73 to 5.88).

Safety outcomes

On day-1 MRI, parenchymal hematoma were observed in 2 (2.1%) patients treated with EVT and in 4 (5.4%) no-EVT patients; subarachnoid hemorrhage was observed in 10 (10.4%) patients treated with EVT vs 3 (4.0%) no-EVT patients. Three (3.1%) patients treated with EVT had an INT: 1 type I, 1 type II, and 1 type III INT according to Goyal's classification [10]. sICH was reported in 3 (3.1%) patients

treated with EVT and 7 (9.5%) no-EVT patients. At 3 months, 17 (17.7%) patients treated with EVT had died, vs 14 (18.7%) no-EVT patients.

Discussion

We performed a retrospective observational study investigating the safety and clinical outcomes of endovascular thrombectomy for DMVOs of the middle cerebral artery. We report several findings of clinical relevance: (1) EVT had high rates of successful recanalization; (2) EVT for DMVO of the MCA was safe under conscious sedation; (3) EVT for DMVO might be associated with better clinical outcomes in patients with distal M2 occlusions; (4) The eTICI scale is relevant to identify DMVO and grade post-procedural recanalization. These findings provide additional preliminary evidence that could underpin future clinical trials.

In our study, 3-months good functional outcome was achieved in 55.2%, consistent with the 57.1% reported in the HERMES meta-analysis on patients with M2 segment occlusions [6]. These findings showed that DMVO of the MCA may lead to significant disabilities, stressing the importance of near-complete and complete recanalization. In the analysis of the overall study population, clinical outcomes were not significantly different between groups. However, the NIHSS score at discharge was improved in patients treated by EVT (aOR 1.18 to 6.24). This can be explained by the very coarse granularity of the mRS score, which might fail to capture the effect of reperfusion in patients with DMVO. Indeed, the NIHSS scale may be more sensitive to subtle clinical deficits. This result advocates for the usage of more fine-grained scales in future clinical trials of DMVO of MCA, such as the Fugl-Meyer score, or language and cognitive evaluations.

We observed major differences between treatment groups regarding relevant prognostic factors: patients in the no-EVT group received more frequently IVT (85% vs 51%), had a more distal occlusion (63% M3 occlusion vs 14% M3 occlusion in EVT group), and had a better initial eTICI score (63% eTICI2b67 vs 29% eTICI2b67 in EVT group). Despite rigorous adjustments, such differences between groups probably induced confounding biases, justifying the sensitivity analysis we

performed on the distal M2 occlusion subgroup. This sensitivity analysis suggested a potential clinical benefit of EVT, with a higher rate of ENI at day-1 (aOR 1.31 to 10.03), and an improvement of the overall distribution of mRS scores at 3 months (adjusted cOR 1.30 to 7.23). This last finding is especially relevant for stroke care due to the high prevalence of distal M2 occlusion in DMVO of MCA, warranting further validation on prospective data.

Definitions of distal occlusions in previously published literature remain scarce and heterogeneous. Indeed, few studies included patients with proximal or distal M2 occlusion [8,13,14], and fewer included patients with M2 to M4-MCA, PCA, and ACA occlusions [7,15]. Only a single multicenter case-control study specifically evaluated EVT for DMVOs of the posterior circulation [11]. In the absence of standardization, identifying DMVO of the MCA in the published literature is challenging [2] and our results advocate for a precise definition of DMVO. These occlusions are responsible for limited perfusion defects on initial cerebral angiogram highlighting the need for appropriate tools. The eTICI is a 7-points grading scale recently developed by HERMES Collaborators to refine the reperfusion grading of the MCA distal territory [5]. In our analysis, we identified a eTICI score ranging from 2b50 to 2b67 as a relevant threshold to accurately define DMVO of the MCA, suggesting a robust and reproducible standard for further studies.

A strength of this work was that EVT patients were all treated since 2017 with state-of-the-art thrombectomy devices. Moreover, successful recanalization was achieved in 82.3%, which was similar to Grossberg et al., reporting 83% TICI 2b-3 [7]. Besides the potential beneficial clinical impact of the endovascular recanalization of DMVO, transitioning to clinical practice has been careful because of the potential complications of such a delicate procedure. Indeed, distal vessels tortuosity with a thinner arterial wall may increase the risk of iatrogenic perforation [1]. Therefore, the safety profile of this procedure is of major interest for the development of dedicated RCT and medical devices. In a recent multicenter case-control study evaluating EVT for DMVOs of the posterior circulation [11], Meyer et al. reported 2 cases (1.4%) of iatrogenic perforation and 5 (3.5%) ENT,

which is consistent with our results (0% perforation and 4.2% ENT). Of the 4 ENT we reported, only 3 were associated with an INT on day-1 control MRI: 1 type I, 1 type II, and 1 type III INT according to Goyal's classification [10]. We also showed a 10.4% rate of subarachnoid hemorrhage on day-1, which is similar to a recent publication on M2 thrombectomy reporting a higher rate of subarachnoid hemorrhage compared to M1 thrombectomy (24.7% vs 12.3%) [8]. Except for 3 patients with type-2 parenchymal hematoma combined with subarachnoid hemorrhage, this hemorrhagic complication remained asymptomatic in our cohort. However, in a recent pooled analysis of 10,126 stroke patients treated by EVT published by Lee and al., the authors found an association between poorer outcomes and SAH in both proximal and distal occlusions.[16] The clinical significance of SAH in distal occlusion remains therefore unknown. Overall, it seems that our results add to a growing body of evidence in favor of a relative safety of the EVT of DMVO and highlight the need for prospective data on the clinical benefit of DMVO thrombectomy.

Among 1479 patients treated by EVT from 2017 to September 2020 in our center, only 96 patients with DMVO of the MCA were identified in our single-center registry. Almost half of the patients included in our analyses presented a secondary DMVO providing essential data for patients treated with bridging recanalization therapies. Even if DMVOs of the MCA were rarely treated endovascularly in clinical routine, the present study is to our knowledge the largest series in published literature.

The study has several limitations associated with its retrospective and observational design. Mainly, it suffered from the differences in clinical characteristics between groups, which could be accounted for in a future prospective trial. Secondly, we included both primary and secondary DMVOs who received cerebral angiogram on a case-by-case basis, leading to potential selection bias, especially regarding clinical outcomes. Patients with secondary DMVO due to per-procedural embolization were not included in our study for 2 reasons: First, we considered that these patients might be at higher risk of procedure-related complications because of previous attempts of

thrombectomy and a longer time of procedure. Second, we wanted to evaluate a homogenous population of DMVO of the MCA to limit potential bias. Finally, eTICI grades were scored internally without independent core lab adjudication.

Conclusions

Endovascular thrombectomy for DMVOs of the MCA may be a reasonable option, leading to high rates of successful recanalization without major safety concern. The clinical benefit of thrombectomy in this population remains yet to be determined in clinical trials.

Contributors: study design: AM, NB, TP, HH, MK, JL; study oversight: AM; Data collection: AM, MB, TP, BC, HH, CC, NB; statistical analysis: JL, MK; Manuscript preparation: NB, AM, MB; critical review of the manuscript: all coauthors

Data sharing statement: Data is available for review upon reasonable request, to be addressed to the corresponding author.

Funding: The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interest statement: NB reports conflict of interest (unrelated) with Cerenovus (payment for reading). The other authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper. The manuscript is not supported by industry.

Patient consent for publication: Not required

Acknowledgements: none

Source of funding: none

References

Figure legends

Figure 1. Distribution of the modified Rankin Scale (mRS) scores at 90 days according to use of endovascular treatment in overall (A) and in population with distal M2 occlusion (B)

Common odds ratio (cOR) for 1 point improvement in mRS at 3 months (combined 5 and 6 together) associated with EVT were estimated using an ordinal logistic regression model adjusted on pre-specified factors (age, NIHSS score at baseline, IVT and mTICI score at baseline).

Table 1. Baseline characteristics of DMVO patients according to treatment group

Characteristics	EVT (n=96)	no-EVT (n=75)	ASD
Age, years, mean (SD)	68.7 (15.8)	73.9 (13.1)	0.36
Male	45 (46.9)	33 (44.0)	0.06
Medical History			
Hypertension	66 (68.8)	53 (70.7)	0.04
Diabetes mellitus	23 (24.0)	11 (14.7)	0.24
Hypercholesterolemia	44 (45.8)	32 (42.7)	0.06
Past or active smoking	32 (33.3)	27 (36.0)	0.06
Previous or current AF	45 (46.9)	38 (50.7)	0.08
Pre-stroke mRS 0-1	67 (68.9)	53 (70.7)	0.02
Current stroke event			
Wake up stroke or unknown time of onset	25 (26.0)	22 (29.3)	0.07
Pre-treatment NIHSS score, mean (SD)	12.9 (7.2)	12.5 (6.3)	0.00
IV Thrombolysis	49 (51.0)	64 (85.3)	0.79
Time from last know well to first angiogram, min, median (IQR)	284 (228 to 383)	297 (224 to 490)	0.03
Infarct volume on baseline Diffusion MRI, mL, median (IQR)	8.0 (0 to 28.0)	12.5 (0 to 25.0)	0.12
Secondary DMVO	44 (45.8)	58 (77.3)	0.68
Occlusion site on initial angiogram			1.17
Distal M2-MCA	83 (86.5)	28 (37.3)	
M3-MCA	13 (13.5)	47 (62.7)	
eTICI score on initial angiogram			2.17

eTICI 2b50	68 (70.8)	28 (37.3)
eTICI 2b67	28 (29.2)	47 (62.7)

Abbreviations: AF Atrial Fibrillation, ASD Absolute Standardized Difference, DMVO Distal Medium Vessel Occlusion, eTICI expanded Thrombolysis In Cerebral Infarction, IQR Interquartile range, MCA Middle Cerebral Artery, mRS modified Rankin Scale, NIHSS=National Institutes of Health Stroke Scale, SD Standard deviation.

Table 2. Comparisons in outcomes according to use of endovascular treatment in overall study sample

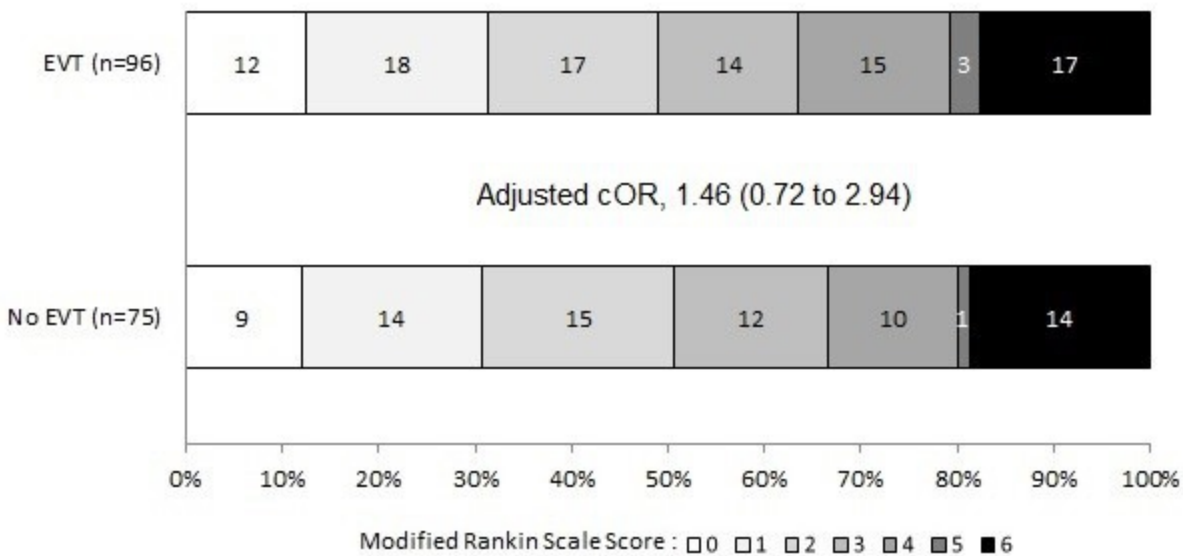
Outcomes	No-EVT (n=75)	EVT (n=96)	Unadjusted ^a		Adjusted ^b	
			OR (95%CI)	p	aOR (95%CI)	p
Favorable outcome^c	45 (60.0)	53 (55.2)	0.82 (0.44 to 1.52)	0.53	1.09 (0.43 to 2.73)	0.86
Excellent outcome^d	33 (44.0)	36 (37.5)	0.76 (0.41 to 1.41)	0.39	0.97 (0.42 to 2.24)	0.94
ENI at 24 hours^e	41 (54.7)	53 (55.2)	1.02 (0.56 to 1.88)	0.94	1.91 (0.83 to 4.43)	0.13
Change in NIHSS at discharge, mean (95%CI)	4.6 (2.9 to 6.3)	6.0 (4.5 to 7.5)	1.40 (-0.85 to 3.65) ^f	0.22	3.71 (1.18 to 6.24) ^f	0.004

^acalculated using no-EVT group as reference, ^bcalculated using no-EVT group as reference after adjustment for age, NIHSS score at baseline, IVT, mTICI score at baseline and site of occlusion distal M2 vs M3), ^cfavorable outcome is defined as an mRS score of 0–2 or equal to pre-stroke mRS, ^dExcellent outcome is defined as an mRS score of 0–1 or equal to pre-stroke mRS, ^e ENI defined as improvement of at least 4 points at day-1, or NIHSS 0-1, ^f Mean difference (95%CI). Abbreviations: CI=confidence interval; ENI= early neurological improvement, NIHSS=National Institutes of Health Stroke Scale; OR=odds ratio

Table 3. Comparisons in outcomes according to use of endovascular treatment in distal M2 occlusion patients.

Outcomes	No-EVT (n=28)	EVT (n=83)	Unadjusted ^a		Adjusted ^b	
			OR (95%CI)	p	OR (95%CI)	p
Favorable outcome^c	13 (46.4)	46 (55.4)	1.44 (0.61 to 3.39)	0.41	2.34 (0.78 to 6.99)	0.13
Excellent outcome^d	9 (32.1)	33 (39.8)	1.39 (0.56 to 3.45)	0.47	2.07 (0.73 to 5.88)	0.17
ENI at 24hours^e	10 (35.7)	48 (57.8)	2.7 (1.02 to 6.00)	0.046	3.62 (1.31 to 10.03)	0.013
Change in NIHSS at discharge, mean (95%CI)	1.1 (-1.5 to 3.7)	5.9 (4.4 to 7.5)	4.84 (1.79 to 7.90) ^f	0.002	5.23 (2.18 to 8.29) ^f	0.001

^acalculated using no-EVT group as reference, ^b calculated using no-EVT group as reference after adjustment for age, NIHSS score at baseline, IVT and mTICI score at baseline, ^c favorable outcome is defined as an mRS score of 0–2 or equal to pre-stroke mRS, ^d Excellent outcome is defined as an mRS score of 0–1 or equal to pre-stroke mRS, ^e ENI defined as improvement of at least 4 points at day-1, or NIHSS 0-1, ^f Mean change (95%CI), Abbreviations: CI=confidence interval; ENI= early neurological improvement, NIHSS=National Institutes of Health Stroke Scale; OR=odds ratio

(A)**(B)**