RESEARCH ARTICLE

Endovascular Therapy for Patients With Low NIHSS Scores and Large Vessel Occlusion in the 6- to 24-Hour Window

Analysis of the CLEAR Study

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Abstract

Background and Objectives

There is uncertainty about whether patients with an anterior circulation large vessel occlusion (LVO) and a low NIH Stroke Scale (NIHSS) score (≤5) benefit from endovascular therapy (EVT) in the late time window (6–24 hours). We compared the clinical outcomes of these patients receiving EVT with those receiving medical management (MM).

Methods

The CT for Late Endovascular Reperfusion multinational cohort study was conducted at 66 sites across 10 countries from January 2014 to May 2022. This subanalysis included consecutive patients with late-window stroke due to an anterior circulation LVO, defined as occlusion of the internal carotid artery or proximal middle cerebral artery (M1/M2 segments), and a baseline NIHSS score ≤5 who received EVT or MM alone. The primary end point was a 90-day ordinal shift in the modified Rankin Scale (mRS) score. Secondary outcomes were 90-day excellent outcome (defined as mRS scores 0–1 or return to baseline mRS score in patients with a pre-stroke mRS score >1) and favorable outcome (defined as mRS scores 0–2 or return to baseline mRS score in patients with prestroke mRS score >2). Safety outcomes were symptomatic intracranial hemorrhage and 90-day mortality. We used ordinal and binary logistic regression models to test for outcome differences.

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Glossary

AIS = acute ischemic stroke; **aOR** = adjusted OR; **CLEAR** = CT for Late Endovascular Reperfusion; **EVT** = endovascular therapy; **IPTW** = inverse probability of treatment weighting; **IQR** = interquartile range; **IVT** = isolated intravenous thrombolysis; **LSW** = last seen well; **LVO** = large vessel occlusion; **MM** = medical management; **MOSTE** = Minor Stroke Therapy Evaluation; **mRS** = modified Rankin Scale; **mTICI** = modified thrombolysis in cerebral infarction; **NIHSS** = NIH Stroke Scale; **OR** = odds ratio; **RCT** = randomized controlled trial.

Results

Among 5,098 patients, 318 patients were included (median [interquartile range] age 67 [56–76] years; 149 [46.9%] were female; baseline NIHSS score was 4 [2–5]). A total of 202 patients (63.5%) received EVT and 116 MM (36.5%). There was no difference in favorable 90-day ordinal mRS score shift (adjusted common odds ratio [OR] 0.77, 95% CI 0.45–1.32), excellent outcome (adjusted OR 0.86, 95% CI 0.49–1.50), or favorable outcome (adjusted OR 0.72, 95% CI 0.35–1.50) in the EVT group compared with MM. Symptomatic intracranial hemorrhage risk (adjusted OR 3.40, 95% CI 0.84–13.73) and mortality at 90 days (adjusted OR 2.44, 95% CI 0.60–10.02) were not statistically different between treatment groups.

Discussion

In patients with an anterior LVO and low NIHSS score in the 6–24-hour time window, there was no statistical difference in disability outcomes or intracranial bleeding risk between patients treated with EVT compared with MM. The retrospective and observational design limits our findings. Ongoing randomized controlled trials will provide further insight.

Classification of Evidence

This study provides Class III evidence that in adult patients with anterior circulation LVO and low NIHSS score (≤5) presenting in the late time window (6–24 hours), EVT does not improve clinical outcome vs MM.

Trial Registration

This study was registered at clinicaltrials.gov under NCT04096248.

Introduction

Randomized controlled trials (RCTs) have shown the superiority of endovascular therapy (EVT) over medical management (MM) for treating anterior circulation acute ischemic stroke (AIS) due to large vessel occlusion (LVO) in both early and late time windows.[1-4]

In most of these RCTs, patients with mild clinical stroke severity, defined as a NIH Stroke Scale (NIHSS) score ≤5, were excluded. The exception was the inclusion of a limited number of patients in 3 of 8 RCTs.[4-6] As such, while current international guidelines strongly recommend EVT for AIS patients with LVO and a NIHSS score of ≥6 (Class IA), there are no established recommendations for patients with NIHSS scores 0–5.[7,8] Among the abovementioned 3 RCTs, only 1 included patients with mild clinical stroke severity in the late time window.[4]

Based on data from clinical registries, 4%–12% of patients with a NIHSS score ≤5 have an LVO.[9,10] A significant proportion of these patients may experience neurologic deterioration and have unfavorable outcomes, questioning the potential role of EVT in this setting.[11,12] However, meta-analyses of observational studies assessing the efficacy and safety of EVT in patients with AIS with NIHSS score ≤5 and an LVO did not show a clinical benefit of EVT in comparison with MM while showing a potentially higher risk of intracranial bleeding.[13-15] Most patients included in these studies were treated in the early time window, and studies specifically assessing this question in the late window are lacking. Because patients in the late window are less likely to receive intravenous thrombolysis, the impact of EVT may be greater in this subset of patients.

Our study aimed to assess whether in adult patients with anterior circulation LVO and low NIHSS scores (≤5) presenting in the late time window (6–24 hours), EVT improves clinical outcome in comparison with MM.

Methods

We used data from the CT for Late Endovascular Reperfusion (CLEAR) registry (NCT04096248).[16-20] CLEAR is a multicenter cohort study that compared clinical outcomes in consecutive patients with anterior circulation LVO undergoing EVT 6–24 hours after last seen well (LSW) who were selected by either noncontrast CT vs CT perfusion or magnetic resonance imaging. All patients also received CT angiography or magnetic resonance angiography. Patients were recruited from 15 centers in Europe and North America

between January 2014 and December 2020. Patients were included if the baseline NIHSS score was >5 and occlusion of either the internal carotid artery or proximal middle cerebral artery (M1 or proximal M2 segments) was documented on vascular imaging. After the publication of the CLEAR study in 2021, data collection was expanded to a total of 66 centers across 10 countries in Europe, North America, and Japan. The inclusion criteria were broadened to include patients with any prestroke modified Rankin Scale (mRS) score, stroke severity, and all treatment modalities (isolated intravenous thrombolysis [IVT], bridging IVT [IVT + EVT], EVT-only, or conservative treatment). For interim new sites, data collection was expanded to May 1, 2022.

For this study, we included consecutive patients from the CLEAR registry, from January 2014 to May 2022, meeting the following inclusion criteria: age 18 years and older; anterior circulation LVO, defined as occlusion of the internal carotid artery or proximal middle cerebral artery (M1/M2 segments); prestroke mRS scores of 0–4, LSW to the treatment of 6–24 hours; and NIHSS score ≤5. For inclusion in this study, the NIHSS score immediately before the procedure was considered for patients within the EVT group. In patients included in the MM group, the admission NIHSS score was considered. Patients with NIHSS score ≤5 at admission who received EVT after clinical worsening with preprocedural NIHSS score >5 were not included in this study. The MM group included patients receiving isolated IVT or conservative treatment while the EVT group included patients receiving bridging IVT or EVT only. We excluded patients with incomplete baseline characteristics from the statistical analyses (eFigure 1).

For all patients, decisions regarding EVT and MM were made according to local standards and the treating physician's decision in conjunction with the patient or their family.

Outcome Variables

The primary end point was the 90-day ordinal mRS score shift distribution. The secondary outcomes were 90-day excellent outcome (defined as mRS scores 0–1 or return to baseline mRS score in patients with prestroke mRS score >1) and favorable outcome (defined as mRS scores 0–2 or return to baseline mRS score in patients with prestroke mRS score >2). The safety outcomes were symptomatic intracranial hemorrhage (sICH, defined by the European Cooperative Acute Stroke Study III)[21] and 90-day mortality. The 90-day mRS score was collected in person or by teleconsultation and reported by site investigators. All data were collected retrospectively by local investigators using a uniform spreadsheet. Site investigators performed all imaging and outcome analyses.

Statistical Analysis

We tested the normality of continuous variables using a Shapiro-Wilk test, presenting variables with non-normal distribution as median interquartile range (IQR) and normally distributed variables as mean (SD) values. Differences in continuous variables were assessed using a nonparametric Wilcoxon-Mann-Whitney test, and categorical variables were analyzed using a χ^2 test or Fisher exact test when appropriate.

For the primary outcome ordinal mRS score shift, an ordinal logistic regression model was used to predict a 1-point shift toward the lower ordered value with the cumulative logit link function and ordinal distribution. The assumption of proportionality was tested using the score test and graphical methods. Common odds ratios (ORs) with 95% CIs were calculated for unadjusted and adjusted models. In addition, logistic regression models with a logit link function and binomial distribution specifications were used for binary outcomes, and unadjusted and adjusted ORs with a 95% CI were also computed. The following covariates were included a priori in the multivariable (core) model: age, sex, baseline NIHSS score, prestroke mRS score, hypertension, diabetes, atrial fibrillation, intravenous thrombolysis, occlusion site, and time LSW before treatment.

In all analyses, clustering by sites was accounted for using a generalized estimating equation approach. We assumed an independent correlation structure with the smallest quasi-likelihood independence criterion value for the within-site clustering of patients.

Sensitivity Analyses

In the first sensitivity analysis, we used the propensity score–based inverse probability of treatment weighting (IPTW) method to estimate the odds of primary and secondary clinical end points by treatment modality. The IPTW method estimates the average treatment effect (the effect of EVT had the entire population received EVT vs had the entire population received direct MM). The same set of variables used in the core multivariable model was used to generate IPTW estimates.

A second sensitivity analysis was conducted to test the heterogeneity of the effect of treatment on the primary end point ordinal mRS score shift using a multiplicative interaction term in the core multivariable model for the site of arterial occlusion (internal carotid artery/middle cerebral artery segment M1 vs middle cerebral artery segment M2) and stroke onset (witnessed vs unwitnessed). Finally, an analysis was performed, adding the following additional variables to the core multivariable model (all covariates model): witnessed stroke, transfer status, ASPECTS, and imaging modality.

Missing Data Analysis

In addition to performing analysis on patients with all available data (complete case analysis), we repeated the analysis after imputing data values for the missing covariates witness, transfer status, ASPECTS, and imaging modality. The missing data correlated with several covariates (data not presented in tables), so a missing-at-random mechanism was assumed. Multiple imputations were performed in SAS 9.4 using PROC MI, and 10 imputed data sets were generated. A fully conditional specification method was applied. PROC MIANALYZE was used to combine results from logistic regression analysis on

the 10 imputed data sets and produce pooled ORs alongside their 95% CIs.

All statistical calculations were performed on Statistical Analysis System (SAS) version 9.4 (SAS Institute, Cary, NC). All tests were 2-sided, and a p value less than 0.05 was considered to be statistically significant. A correction for multiple testing was not applied because this was a nonconfirmatory study.

Standard Protocol Approvals, Registrations, and Patient Consents

Approval from the local institutional review board or ethics committee was obtained from all participating centers. All data were anonymized and deidentified. Given the retrospective nature of the study, written informed consent was waived. This study was conducted according to the Declaration of Helsinki and reported according to the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.[22]

Data Availability

The senior author (T.N.N.) and lead statistician (M.M.Q.) had access to all data. Anonymized data are available on reasonable request to the corresponding author.

Results

There were 5,098 patients in the CLEAR study, of whom 4,776 were removed because of not meeting study eligibility criteria (e.g., 4,219 were excluded because of NIHSS score ≥ 6), leading to 322 patients. Additional 4 patients were removed because of missing covariate data, leaving 318 patients in this analysis, of whom 202 (63.5%) received EVT (represented by 22 centers) and 116 (36.5%) were medically managed (represented by 27 centers) (eFigure 1). Compared with patients who were medically managed, patients treated with EVT were younger (median [IQR] 66 [54–76] vs 68.5 [60–77]) and had higher baseline NIHSS scores (median [IQR] 4 [2–5] vs 3 [2–4]). There was a higher rate of transfers and IVT treatment in patients receiving EVT than MM (Table 1). The site of occlusion was more proximal in those treated with EVT vs MM (ICA + M1: 68.8% vs 51.7%; M2: 31.2% vs 48.3%). The time LSW to imaging was shorter in those treated with EVT vs MM (9.5 hours vs 12.5 hours). Of patients treated with EVT, general anesthesia was used in 14.6%, and modified thrombolysis in cerebral infarction (mTICI) ≥2b reperfusion was achieved in 81.5% of patients while mTICI ≥2c in 56.0% (Table 1).

The median discharge NIHSS score was 2 (IQR 1–4). In comparison with patients who were medically managed, patients treated with EVT had a higher discharge NIHSS score (median [IQR] 2 [1–5] vs 1 [0–3]; p value = 0.04).

Primary and Secondary End Points

The distribution of clinical outcomes by treatment modality is presented in Table 2. For the primary end point 90-day ordinal mRS score shift, the score test resulted in a χ^2 p value of 0.74, indicating that odds were proportional for the 2 treatment modalities. The plots representing these results are not shown for briefness. On multivariable analysis, there was no difference in the 90-day ordinal mRS score shift between EVT and MM (adjusted common OR 0.77, 95% CI 0.45–1.32; p value = 0.35; Table 3 and Figure). A similar result was observed in the IPTW analysis (common OR 0.78, 95% CI 0.47–1.31; p value = 0.35).

There was no statistically significant difference between treatment groups in excellent outcome (adjusted OR [aOR] 0.86, 95% CI 0.49–1.50; p value = 0.59) or favorable outcome (aOR 0.72, 95% CI 0.35–1.50; p value = 0.39) (Table 3). The results from IPTW analysis corroborated with the multivariable model [excellent outcome (OR 0.90, 95% CI 0.49–1.68; p value = 0.75) or favorable outcome (OR 0.70, 95% CI 0.39–1.26; p value = 0.24)].

Safety Outcomes

Symptomatic intracranial hemorrhage was numerically higher in the EVT group compared with the MM group (6.0% vs 1.7%, aOR 3.40, 95% CI 0.84–13.73; p value = 0.09). Mortality at 90 days was numerically higher in the EVT group compared with the MM group (10.8% vs 4.6%, aOR 2.44, 95% CI 0.60–10.02; p value = 0.22) (Table 3).

Sensitivity Analysis

In multivariable analysis, looking at the interaction of treatment modality and occlusion site on the primary outcome, in patients with occlusion of the middle cerebral artery M2 segment, EVT showed nonsignificant lower odds of a favorable outcome (adjusted common OR 0.51; 95% CI 0.24–1.07) compared with patients with occlusion of the internal carotid artery/middle cerebral artery M1 segment (adjusted common OR 1.06; 95% CI 0.58–1.96; p value for interaction = 0.09).

In the analysis of the interaction of treatment modality and type of stroke onset (witnessed vs unwitnessed) on the primary outcome, no interaction was observed (p value for interaction = 0.33). The adjusted common ORs were 0.73 (95% CI 0.41–1.29) and 0.97 (95% CI 0.55–1.69) in witnessed and unwitnessed stroke, respectively.

The results from sensitivity analysis of adding covariates witnessed stroke onset, transfer status, ASPECTS, and imaging modality to the core multivariable model (all covariates model) are presented in eTable 1. A slightly stronger but statistically nonsignificant effect was observed in the OR estimate for the primary end point of ordinal mRS score shift (adjusted common OR 0.61, 95% CI 0.34–1.10; p value = 0.10). A similar pattern was noted for secondary end points.

Missing Data Analysis

With imputation of missing data, the estimates from all covariates model remained nonsignificant for the primary end point of ordinal mRS score shift (aOR 0.68, 95% CI

Table 1 Baseline Characteristics and Metrics of CLEAR Patients With Low NIHSS Scores in the 6–24-Hour Window

		Treatment		
	Overall (N = 318)	MM (N = 116)	EVT (N = 202)	*p* Value
Age, y	67 (56–76)	68.5 (60–77)	66 (54–76)	0.078
Baseline NIHSS score	4 (2–5)	3 (2–4)	4 (2–5)	0.004
Female	149 (46.9)	57 (49.1)	92 (45.5)	0.537
Prestroke mRS score				0.386
0	223 (70.1)	87 (75.0)	136 (67.3)	
1	45 (14.2)	11 (9.5)	34 (16.8)	
2	20 (6.3)	6 (5.2)	14 (6.9)	
3	26 (8.2)	10 (8.6)	16 (7.9)	
4	4 (1.3)	2 (1.7)	2 (1.0)	
Witnessed stroke onset (n = 294)	77 (26.2)	20 (19.2)	57 (30.0)	0.045
Medical history				
Hypertension	199 (62.6)	64 (55.2)	135 (66.8)	0.039
Diabetes	72 (22.6)	25 (21.6)	47 (23.3)	0.725
Atrial fibrillation	68 (21.4)	16 (13.8)	52 (25.7)	0.012
Transfer patients (n = 266)	132 (49.6)	22 (29.3)	110 (57.6)	<0.0001
Intravenous thrombolysis	51 (16.0)	8 (6.9)	43 (21.3)	0.001
Imaging ASPECTS and modality of selection				
ASPECTS, median (IQR) (n = 299)	9 (8–10)	9 (8–10)	9 (8–10)	0.20
ASPECTS, mean (SD) (n = 299)	8.8 (1.3)	8.7 (1.4)	8.9 (1.3)	
Imaging modality (n = 317)				<0.0001
Unenhanced head CT	121 (38.2)	55 (47.8)	66 (32.7)	
CT with perfusion	101 (31.9)	16 (13.9)	85 (42.1)	
MRI	95 (30.0)	44 (38.3)	51 (25.3)	
Site of arterial occlusion				0.001
Internal carotid artery	61 (19.2)	26 (22.4)	35 (17.3)	
MCA-M1 segment	138 (43.4)	34 (29.3)	104 (51.5)	
MCA-M2 segment	119 (37.4)	56 (48.3)	63 (31.2)	
Time metrics				
LSW to treatment, hours	11.8 (8.4–16.2)	12 (8.5–16.9)	11.7 (8.3–15.9)	0.348
LSW to imaging, hours (n = 236)	10.6 (7.6–15.3)	12.5 (9.1–17.5)	9.5 (6.9–14.4)	<0.0001
Procedural factors				
General anesthesia (n = 164)	—	—	24 (14.6)	—
Balloon guide catheter (n = 159)	—	—	79 (49.7)	—
Reperfusion mTICI ≥2b (n = 200)	—	—	163 (81.5)	—
Reperfusion mTICI ≥2c (n = 200)	—	—	112 (56.0)	—

Abbreviations: ASPECTS = Alberta Stroke Program Early CT score; CLEAR = CT for Late Endovascular Reperfusion; EVT = endovascular treatment; LSW = last seen well; MCA = middle cerebral artery; MM = medical management; MRI = magnetic resonance imaging; mRS = Modified Rankin Scale; mTICI = modified treatment in cerebral ischemia; NIHSS = NIH Stroke Scale.
Values are presented as median (interquartile range) or as numbers (proportions).

Table 2 Clinical Outcomes According to Treatment in Patients With Low NIHSS Scores

	Overall (n = 318)	Treatment		p Value
		MM (n = 116)	EVT (n = 202)	
90-d mRS score	2 (1–3)	1 (0.5–3)	2 (1–3)	0.206
Excellent outcome at 90 d	162 (55.1)	62 (57.4)	100 (53.8)	0.545
Favorable outcome at 90 d	216 (73.5)	84 (77.8)	132 (71.0)	0.202
sICH	14 (4.4)	2 (1.7)	12 (6.0)	0.077
Mortality at 90 d	25 (8.5)	5 (4.6)	20 (10.8)	0.067

Abbreviations: EVT = endovascular treatment; MM = medical management; mRS = modified Rankin Scale; NIHSS = NIH Stroke Scale; sICH = symptomatic intracranial hemorrhage.
Note: 90-d mRS score, discharge NIHSS score, excellent outcome, favorable outcome, sICH, and mortality at 90 d are missing for 24, 51, 24, 24, 3, and 23 patients.
Values are presented as median (interquartile range) or as numbers (proportions).

0.39–1.16; *p* value = 0.16). Complete results from the analysis of imputed data are presented in eTable 1.

This study provides Class III evidence that in adult patients with anterior circulation LVO and a low NIHSS score (≤5) presenting in the late time window (6–24 hours), EVT does not improve clinical outcome vs MM.

Discussion

In patients with anterior circulation LVO and mild stroke severity presenting in the late time window, EVT was not associated with better 90-day functional outcomes, nor was it associated with higher rates of symptomatic intracranial hemorrhage and 90-day mortality. This post hoc analysis of the CLEAR study represents a comprehensive comparison between EVT and MM alone in patients with anterior circulation LVO and low NIHSS scores within the 6–24-hour window.

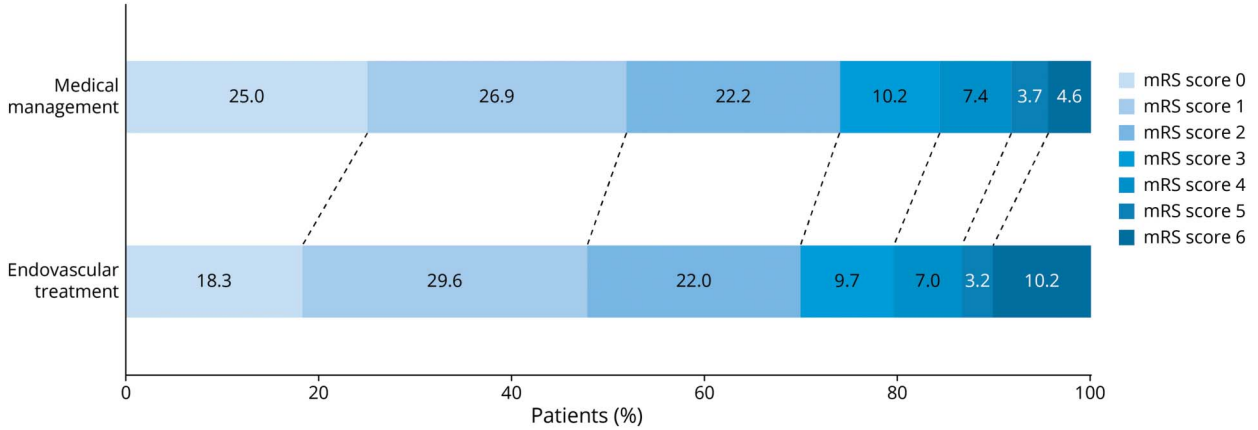
In the endovascular treatment vs no endovascular treatment after 6–24 h in patients with ischaemic stroke and collateral flow on CT angiography (MR CLEAN-LATE) trial, a study that randomized patients with an anterior circulation LVO in the late window and with a NIHSS score ≥ 2, there was no interaction between the baseline NIHSS score and treatment effect.[4] In the intention-to-treat analysis, 142 patients (29%) had a NIHSS score between 1 and 6, with a trend favoring EVT in this subgroup (aOR 1.79, 95% CI 0.95–3.37). Although these results suggested a potential benefit of EVT in mild clinical severity stroke, the use of different baseline

Table 3 Univariable and Multivariable Logistic Regression Analyses of Outcomes by Treatment

	N	Event (%)	Univariable model		Multivariable model	
			OR (95% CI), *p* Value			
Ordinal mRS score shift (n = 294)						
MM	108	—	Reference			
EVT	186	—	0.76 (0.45–1.28)	0.307	0.77 (0.45–1.32)	0.345
Excellent outcome (n = 294)						
MM	108	62 (57.4)	Reference			
EVT	186	100 (53.8)	0.86 (0.53–1.41)	0.550	0.86 (0.49–1.50)	0.588
Favorable outcome (n = 294)						
MM	108	84 (77.8)	Reference			
EVT	186	132 (71.0)	0.67 (0.34–1.33)	0.254	0.72 (0.35–1.50)	0.385
sICH (n = 315)						
MM	115	2 (1.7)	Reference			
EVT	200	12 (6.0)	4.04 (1.0–16.24)	0.049	3.40 (0.84–13.73)	0.086
Mortality at 90 d (n = 295)						
MM	109	5 (4.6)	Reference			
EVT	186	20 (10.8)	2.91 (0.84–0.09)	0.092	2.44 (0.60–10.02)	0.215

Abbreviations: EVT = endovascular treatment; MM = medical management; mRS = modified Rankin Scale; NIHSS = NIH Stroke Scale; OR = odds ratio; sICH = symptomatic intracranial hemorrhage.
Models adjusted for the following variables: age, sex, baseline NIHSS score, prestroke mRS score, hypertension, diabetes, atrial fibrillation, intravenous thrombolysis, occlusion site, and last seen well before treatment.

Figure Modified Rankin Scale Score at 3 Months According to Treatment Groups



NIHSS score ranges (1–6 vs 0–5) and lack of information on the NIHSS before EVT limit its interpretation.

Most patients included in observational studies assessing the outcomes of EVT in patients with low NIHSS scores were treated in the early time window without significant clinical benefit over MM alone.[13-15] Compared with these previous meta-analyses, in our study, patients receiving EVT had numerically lower rates of excellent outcome (53.8% vs 63%–74%) and favorable outcome (71% vs 77%–83%) and a higher mortality rate (10.8% vs 5.3%–9.7%), but similar rates of sICH (6.0% vs 4.4%–6.6%).[13-15] Those receiving MM alone had lower rates of excellent outcome (57.4% vs 60%–70%) while rates of favorable outcome (77.8% vs 74%–85%), mortality (4.6% vs 4.4%–5.7%), and sICH (1.7% vs 0.9%–1.8%) were similar.[13-15] Only 1 meta-analysis reported the estimated proportion of patients achieving successful recanalization after EVT, which was comparable with our study (81% vs 85%).[13] The absence of detailed patient characteristics in these meta-analyses limits the interpretation of these differences. Nevertheless, 2 potential factors could explain the worse outcomes found in our study: the inclusion of a relatively high proportion of patients with a pre-stroke mRS score ≥2 and the low rate of IVT in our study, which would be expected with a later time window of inclusion.

In the late time window, patients with LVO and low NIHSS scores are expected to have high ASPECTS and good collaterals, similar to those in the early time window. Therefore, longer time to treatment likely does not significantly influence the effectiveness of EVT. However, several factors could either increase or decrease the treatment effect size of EVT in the late time window compared with the early time window. Patients presenting later (>6 hours) are less likely to experience early neurologic deterioration because up to 60% of patients with LVO and low NIHSS scores who do experience deterioration do so within the first 6 hours.[11] Therefore, the impact of EVT in preventing early neurologic deterioration in the late time window is expected to be lower, reducing its overall clinical impact. On the contrary, in the late time window, the likelihood of receiving IVT is lower, making patients managed with MM alone less likely to achieve recanalization without EVT compared with those in the early time window. Even so, the TEMPO-2 randomized trial of patients with an arterial occlusion and NIHSS score ≤5 showed no benefit of intravenous tenecteplase compared with standard MM within the 12-hour window, yet higher rates of sICH and mortality with intravenous tenecteplase.[23]

The absence of a benefit from EVT in patients with low NIHSS scores presenting in the late time window may result from the fact that there is a high probability of good outcomes even without EVT.[24] Therefore, in many patients, achieving reperfusion with EVT may not significantly improve functional outcomes. In addition, in cases of milder clinical stroke syndromes, the clinical impact of procedural complications is likely higher.

Because patients with low NIHSS scores and more proximal LVO (internal carotid artery and middle cerebral artery M1 segment) are more likely to experience neurologic deterioration than those with more distal LVO (middle cerebral artery M2 segment),[23] the potential beneficial impact of EVT may also depend on the occlusion site of these patients.[25] In our sensitivity analysis, EVT showed lower odds of a favorable shift in the mRS score at 90 days, in comparison with MM, in patients with middle cerebral artery M2 segment occlusions.

Currently, RCTs are underway to explore the benefits of EVT in patients with low NIHSS scores. The "Endovascular Therapy for Low NIHSS Ischemic Strokes" (ENDOLOW, NCT04167527), "Minor Stroke Therapy Evaluation" (MOSTE, NCT03796468), and "Endovascular Therapy Versus Best Medical Treatment for Acute Large Vessel Occlusion Stroke With Low NIHSS" (NCT06143488) are recruiting patients. ENDOLOW, a North American–based trial, has more restricted inclusion criteria, only randomizing patients up to 8 hours since LSW, and has specific occlusion patterns for patients with M2 occlusion. MOSTE,

a European-based trial, aims at including a large sample of patients (824 vs 200 in ENDOLOW), including patients presenting within 24 hours of symptom onset. The latter RCT (NCT06143488), a Chinese-based trial, aims to include 264 patients, up to 24 hours since LSW, but only considers patients with NIHSS scores 2–5. Results from these studies and potentially future analyses combining their data will help establish the best treatment option for patients with anterior circulation LVO and low NIHSS scores.

Despite the strengths of our study, including the adjustment for potential confounders through multivariable analyses, further limitations must be acknowledged. First, the exclusion of patients experiencing neurologic deterioration after admission and before EVT limits the interpretation of our findings. Nevertheless, by restricting our inclusion criteria to patients with NIHSS score ≤5 before EVT, we can avoid the bias of including patients with higher NIHSS scores, in which EVT was not initially proposed. Second, the nonrandomized nature of our data and selection bias, evident by the higher stroke severity and lower proportion of patients with M2 occlusions in the EVT group, limit the interpretation of our findings. Third, because patients' outcomes were assessed locally by unblinded adjudicators, misclassification bias cannot be excluded. Fourth, the specific devices and reperfusion approaches used during EVT were probably heterogeneous and were selected according to the treating physicians' preference. Fifth, NIHSS score, as a marker of baseline stroke severity, and mRS score, as an outcome measure of functional outcomes, may not be adequate to assess patients with mild clinical stroke severity. Patients with the same low NIHSS score may have disabling or nondisabling deficits, which can influence their outcomes. The low sensitivity of the mRS to detect milder functional impairment may make it challenging to identify differences in functional outcomes between groups. Finally, our sample size may have limited our ability to assess an interaction between treatment modality and occlusion site.

In patients with anterior circulation LVO and low NIHSS scores in the late time window, EVT was associated with similar odds of disability and there were no statistical differences regarding the risk of intracranial bleeding and mortality. While our study contributes insight into EVT in this setting, further research, particularly from ongoing RCTs, is warranted to refine patient selection criteria and determine the optimal treatment approach for these patients.

Author Contributions

J.P. Marto: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data. M. Qureshi: study concept or design; analysis or interpretation of data. S. Nagel: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design. R.G. Nogueira: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. H. Henon: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. L. Tomppo: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. P.A. Ringleb: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. D.C. Haussen: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. M. Abdalkader: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. V. Puetz: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. O.O. Zaidat: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. J. Demeestere: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. J.N. Ramos: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. M. Ribo: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. M. Olive-Gadea: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. M.H. Mohammaden: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. S. Ortega-Gutierrez: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. S. Sheth: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. H. Yamagami: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. A. Dusart: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. J. Raymond: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. F. Caparros: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. D. Kaiser: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. K. Tanaka: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. P. Virtanen: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. A.S. Puri: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. J.E. Siegler: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. S.F. Zaidi: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. M. Aghiad Jumaa: drafting/revision of the

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