RESEARCH ARTICLE

Endovascular vs Medical Management for Late Anterior Large Vessel Occlusion With Prestroke Disability

Analysis of CLEAR and RESCUE-Japan

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Abstract

Background and Objectives

Current guidelines do not address recommendations for mechanical thrombectomy (MT) in the extended time window (>6 hours after time last seen well [TLSW]) for large vessel occlusion (LVO) patients with preexisting modified Rankin Scale (mRS) > 1. In this study, we evaluated the outcomes of MT vs medical management in patients with prestroke disability presenting in the 6- to 24-hour time window with acute LVO.

Methods

We analyzed a multinational cohort (61 sites, 6 countries from 2014 to 2020) of patients with prestroke (or baseline) mRS 2 to 4 and anterior circulation LVO treated 6–24 hours from TLSW. Patients treated in the extended time window with MT vs medical management were compared using multivariable logistic regression and inverse probability of treatment weighting (IPTW). The primary outcome was the return of Rankin (ROR, return to prestroke mRS by 90 days).

Results

Of 554 included patients (448 who underwent MT), the median age was 82 years (interquartile range [IQR] 72–87) and the National Institutes of Health Stroke Scale (NIHSS) was 18 (IQR 13–22). In both MV logistic regression and IPTW analysis, MT was associated with higher odds of ROR (adjusted OR [aOR] 3.96, 95% CI 1.78–8.79 and OR 3.10, 95% CI 1.20–7.98,

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Glossary

ASPECTS = Alberta Stroke Program Early Computed Tomography Scale; **CLEAR** = CT for Late Endovascular Reperfusion; **IPTW** = inverse probability of treatment weighting; **IQR** = interquartile range; **IVT** = intravenous thrombolysis; **LVO** = large vessel occlusion; **MCA** = middle cerebral artery; **mRS** = modified Rankin Scale; **MT** = mechanical thrombectomy; **MV** = multivariable; **NIHSS** = National Institutes of Health Stroke Scale; **PS** = propensity score; **RESCUE-Japan Registry 2** = Recovery by Endovascular Salvage for Cerebral Ultra-Acute Embolism Japan Registry 2; **ROR** = return of Rankin; **SMR** = standardized mortality ratio; **TLSW** = time last seen well; **UW** = utility weighted.

respectively). Among other factors, premorbid mRS 4 was associated with higher odds of ROR (aOR, 3.68, 95% CI 1.97–6.87), while increasing NIHSS (aOR 0.90, 95% CI 0.86–0.94) and decreasing Alberta Stroke Program Early Computed Tomography Scale score (aOR per point 0.86, 95% CI 0.75–0.99) were associated with lower odds of ROR. Age, intravenous thrombolysis, and occlusion location were not associated with ROR.

Discussion

In patients with preexisting disability presenting in the 6- to 24-hour time window, MT is associated with a higher probability of returning to baseline function compared with medical management.

Classification of Evidence

This investigation's results provide Class III evidence that in patients with preexisting disability presenting 6–24 hours from the TLSW and acute anterior LVO stroke, there may be a benefit of MT over medical management in returning to baseline function.

Of the nearly one million strokes that occur in the United States each year, 1 in 5 occurs in patients with a prior stroke and 20%–30% in patients with preexisting disability.[1,2] However, such patients are frequently excluded from interventional trials, which often select patients with no or minimal premorbid disability.[3-5] Based on published trial results that have established the efficacy of mechanical thrombectomy (MT) in acute large vessel occlusion (LVO), the American Heart Association and Japan Stroke Society recommend endovascular thrombectomy for proximal intracranial occlusions in patients who meet strict imaging and clinical criteria, including no prestroke disability as defined by a modified Rankin Scale (mRS) score of 0 or 1.[6-8] The absence of high-quality trial data and/or absence of guideline recommendations for this patient population may discourage clinicians from pursuing interventions with limited trial evidence but may be potentially efficacious in acute stroke.

Previous studies of patients with stroke presenting mainly in the early time window (0–6 hours) have found that the use of MT in patients with moderate premorbid disability achieves similar rates of return to prestroke disability levels as it does in patients with no-to-mild premorbid disability, while increased baseline disability increases mortality risk.[1,3,9-11] Recent work has shown that MT may be more effective than medical management in some patients with moderate premorbid disability who present with stroke in the early time window.[12] However, there is a paucity of data regarding outcomes of patients with preexisting disabilities, with LVO presenting in the extended time window (6–24 hours).

In this prespecified analysis of the CT for Late Endovascular Reperfusion (CLEAR) study,[13,14] in collaboration with the Recovery by Endovascular Salvage for Cerebral Ultra-Acute Embolism Japan Registry 2 (RESCUE-Japan Registry 2) investigators,[15] we sought to determine whether a preexisting disability was associated with differential efficacy of MT in acute LVO.

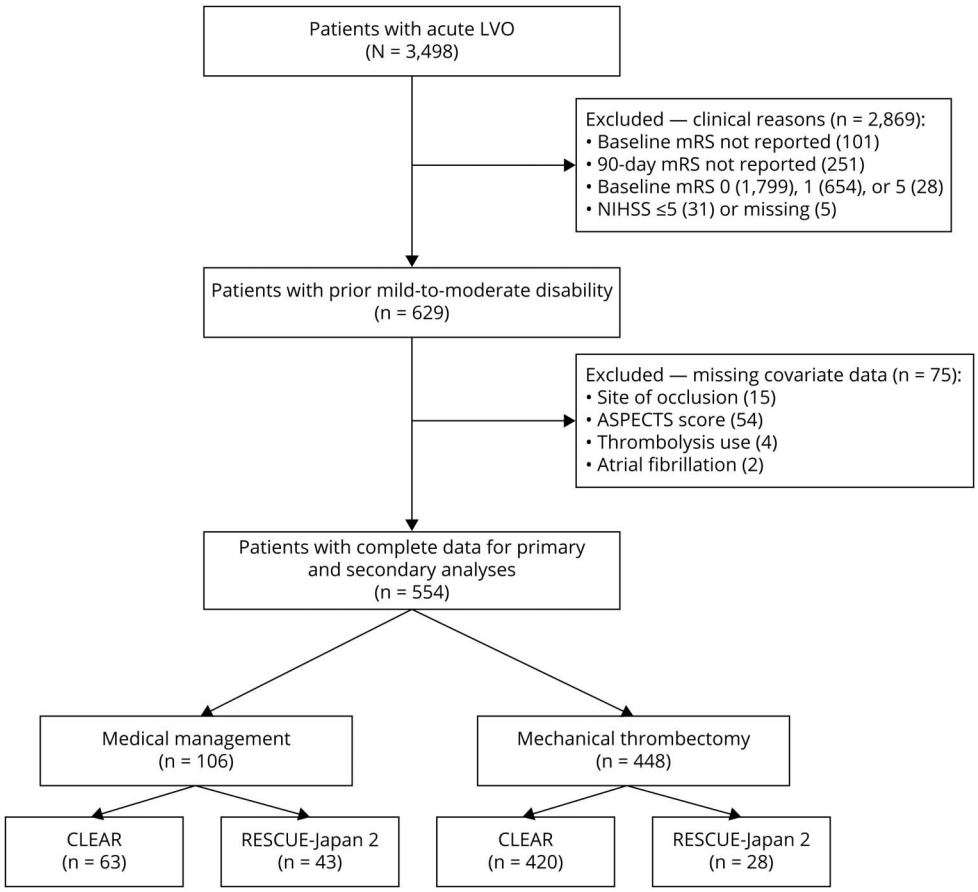
Methods

Data included in the CLEAR and RESCUE-Japan 2 studies will be made available on reasonable request of the investigators.

Patients

Consecutive adult patients (≥18 years) from the CLEAR (15 sites, 5 countries, 2014–2020) and RESCUE-Japan Registry 2 (46 sites in Japan, 2014–2016) studies were eligible for inclusion in this prespecified analysis of CLEAR if their prestroke mRS was reported by site investigators as 2 to 4 (mild-to-moderate disability without complete dependence on others). Although this analysis was prespecified by the CLEAR investigators (NCT04096248), CLEAR patient-level data were consolidated with RESCUE-Japan because of the underrepresentation of medically managed patients from CLEAR. During the data collection phase of CLEAR, all sites were required to report consecutively managed LVO patients treated with MT. Although sites were encouraged to report patient-level data regarding individuals with LVO managed medically, this was not required. Patients with a baseline National Institutes of Health Stroke Scale (NIHSS) score of

Figure Flow Diagram of Patient Selection



<6 and those who underwent MT within 6 hours of time last seen well (TLSW) were excluded to permit transportability of CLEAR results to those of the late time window thrombectomy trials.[16,17] Patients with anterior circulation occlusion of the internal carotid, proximal middle cerebral (MCA-M1), or branch (MCA-M2) arteries were included. Patients were excluded from this analysis if baseline or 90-day mRS were unavailable or if there were missing covariate data for multivariable analysis (Figure).

Statistical Analyses

Descriptive statistics were calculated for baseline demographic data (age, sex, and medical history), imaging findings, treatment times, complications, and outcome measures. For comparison between the patient groups stratified by prestroke mRS, Kruskal-Wallis and chi-square tests were used for continuous and categorical variables, respectively.

The primary outcome was the return of the mRS (ROR) to prestroke baseline, which we defined as no worsening in the mRS at 90 days, as previously reported.[18] Secondary outcomes included the difference in mean utility weighted (UW)-mRS at 90 days as compared with the prestroke UW-mRS between groups, symptomatic intracranial hemorrhage (defined as a 4-point worsening in the NIHSS attributed to an intracranial hemorrhage), and severe disability or death (mRS 5–6) by 90 days. UW-mRS scores were derived from the DAWN trial, with scores of 10.0, 9.1, 7.6, 6.5, 3.3, 0, and 0 assigned to mRS scores of 0, 1, 2, 3, 4, 5, and 6, respectively.[17] The UW-mRS was included among the secondary outcomes given the (generally) minimal difference in disability between scores of 0, 1, and 2 as compared with the substantive disability in patients with scores >2, with expected ceiling effects observed among patients with very low prestroke mRS scores (e.g., patients with a prestroke mRS of 0 or 1 are likely to do well with thrombectomy but are unlikely to return to a 0 or 1 at 90 days).

For the primary analysis, we compared patients who underwent MT with a prestroke mRS of 2, 3, or 4 with patients treated with medical management. In this analysis, a mixed-effects logistic regression model accounting for clustering by sites was used to estimate the odds of ROR. The following covariates were included a priori in the multivariable model: age, sex, NIHSS, prestroke mRS (ordered variable), hypertension, diabetes, atrial fibrillation, treatment with intravenous thrombolysis (IVT), Alberta Stroke Program Early Computed Tomography Scale (ASPECTS) score, and occlusion location (internal carotid vs MCA-M1 vs MCA-M2) in the model. This analysis was

repeated with the use of a multiplicative interaction term to further evaluate the association between endovascular treatment and each independent variable on the outcome, ROR. The model was fitted using PROC GENMOD in SAS 9.4 (SAS Institute, Cary, NC), with logit link function and binomial distribution specifications.

Furthermore, to account for selection bias, we used 2 propensity score (PS)-based methods: the inverse probability of treatment weighting (IPTW) with weights and standardized mortality ratio (SMR). Using a multivariable logistic regression model, we first estimated the probability of MT assignment (PS) conditional on the above covariates. For IPTW, the MT group received weights of [1/PS] and medical management received weights of (1/[1 − PS]). The weights for MT and medical management groups were stabilized by replacing the numerator "1" with the proportion of patients receiving MT and medical management, respectively. For SMR, MT groups received weights of 1 and medical management received weights of (PS/[1 − PS]). The adequacy of model specification for the IPTW method was assessed using standardized mean differences. With IPTW, we estimate the average treatment effect (the effect of MT had the entire population received MT vs had the entire population received medical management).[19] The SMR weighting estimates the treatment effect in the treated patients (the effect of MT had the MT group received MT vs had the MT group received medical management). In both analyses, the primary outcome of ROR was evaluated using unadjusted, mixed-effects logistic regression, using the above approach.

Missing Data Analysis

In addition to performing a complete case analysis, we conducted a sensitivity analysis after imputing data values for missing covariates atrial fibrillation, IVT, ASPECTS, and location of the occlusion. As the missing data correlated with several covariates (eTable 1, links.lww.com/WNL/C469), a missing at random mechanism was assumed. Multiple imputations were then performed in SAS 9.4 using PROC MI, and 5 imputed data sets were generated. A fully conditional specification method was applied. The imputation model included age, baseline NIHSS, sex, baseline mRS, medical history of hypertension, diabetes, atrial fibrillation, IVT, ASPECTS score, location of the occlusion, management group, and the dependent variables. PROC MIANALYZE was used to pool results from logistic regression analysis performed on the 5 imputed data sets and generate pooled ORs along with 95% CI.

All statistical computations were performed on the SAS 9.4 system. All tests were two-sided, and a p-value of <0.05 was considered statistically significant. No adjustments were made for multiple comparisons.

Ethics

This was an investigator-initiated study. The study funder had no role in the study design, analysis, management, or writing of this report. The corresponding author (T.N.N.) and lead statistician (M.M.Q.) had access to all data in the study. Local institutional review board or ethics committee approval was obtained from all sites. Written informed consent was waived because of the retrospective nature of this study and because the research was considered no more than minimal risk.

Results

Patient Characteristics

Of the 3,498 patients consolidated from the CLEAR and RESCUE-Japan registries, there were 629 patients with prior mild-to-moderate disability (mRS 2–4) before the index stroke, of whom 554 had complete covariate data for analysis (eTable 1, links.lww.com/WNL/C469), including 448 (80.9%) who were treated with MT (Figure). There was a disproportionately higher volume of medically managed patients from the RESCUE-Japan registry (compared with CLEAR), with 6 of the 15 sites in CLEAR reporting patient-level data for medically managed individuals. The median age of the cohort was 82 years (IQR 72–87), with a median NIHSS of 18 (IQR 13–22) and most of the occlusions occurring in the MCA-M1 segment of the middle cerebral artery (54.7%; Table 1).

Across the spectrum of prestroke mRS scores, there was a gradient of numerically fewer patients having a more severe prestroke disability (73 with mRS 4, 205 with mRS 3, and 276 with mRS 2), with patients having greater prestroke disability being less likely to undergo MT ($p = 0.02$). When compared across prestroke mRS categories, patients with more severe prestroke disability were older ($p < 0.01$) and had nonsignificantly more frequent atrial fibrillation ($p = 0.10$) when compared with patients with less severe prestroke disability (Table 1). There was no significant difference in ASPECTS score, thrombolytic use, general anesthesia use, a balloon-guided catheter, or successful reperfusion (treatment in cerebral infarction 2b-3) across the mRS strata. Compared with those treated without MT, patients who underwent thrombectomy had a lower prestroke mRS, were younger, had more frequent diagnoses of hypertension, and had more favorable ASPECTS scores with more proximal occlusions of the ICA or MCA-M1 vs MCA-M2 segments (Table 2 for complete results).

Primary Outcome

With IPTW, MT and medically managed patients were well-matched, without significant differences in medical history, thrombolysis, ASPECTS, or occlusion location (Table 2). In the multivariable logistic regression model, after adjusting for age, premorbid mRS, baseline NIHSS, sex, medical history, IVT, ASPECTS score, and location of the occlusion, MT was associated with higher adjusted odds of ROR (adjusted OR, aOR 3.96, 95% CI 1.78–8.79; Table 3). The SMR and IPTW analyses also reported higher odds of ROR after weighing the abovementioned factors (SMR: OR 3.0, 95% CI 1.10–8.15, IPTW: OR 3.10, 95% CI 1.20–7.98). The results from weighted analyses were attenuated compared with the multiple logistic regression model.

Table 1 Baseline Characteristics According to Prestroke Disability

		Prestroke mRS			
	Overall (N = 554)	2 (N = 276)	3 (N = 205)	4 (N = 73)	*p* Value
Age, median y (IQR)	82 (72–87)	79.8 (70–86)	83 (77–88)	84 (75–88.8)	0.0003
Baseline NIHSS, median (IQR)	18 (13–22)	17.5 (13–22)	18 (13–23)	20 (15–23)	0.136
Female, no. (%)	367 (66.3)	173 (62.7)	144 (70.2)	50 (68.5)	0.202
Medical history, no. (%)					
Hypertension	429 (77.4)	220 (79.7)	151 (73.7)	58 (79.5)	0.264
Diabetes	169 (30.5)	86 (31.2)	59 (28.8)	24 (32.9)	0.765
Atrial fibrillation	276 (49.8)	125 (45.3)	110 (53.7)	41 (56.2)	0.098
Transfer, no. (%)[a]	260 (53.9)	130 (53.3)	108 (58.4)	22 (41.5)	0.090
Intravenous thrombolysis, no. (%)	75 (13.5)	37 (13.4)	31 (15.1)	7 (9.6)	0.493
Imaging and clot location					
Imaging modality, no. (%)[a]					0.0002
Unenhanced head CT	167 (32.7)	84 (32.6)	51 (27.4)	32 (47.8)	
CT with perfusion	173 (33.9)	102 (39.5)	62 (33.3)	9 (13.4)	
MRI	171 (33.5)	72 (27.9)	73 (39.3)	26 (38.8)	
ASPECTS, median (IQR)	8 (7–9)	8 (7–9)	8 (7–9)	8 (7–9)	0.393
Location of occlusion, no. (%)					0.375
Internal carotid artery	146 (26.4)	81 (29.4)	44 (21.5)	21 (28.8)	
MCA-M1 segment	303 (54.7)	144 (52.2)	119 (58.1)	40 (54.8)	
MCA-M2 segment	105 (19.0)	81 (29.4)	44 (21.5)	21 (28.8)	
Mechanical thrombectomy, no. (%)	448 (80.9)	233 (84.4)	164 (80.0)	51 (69.9)	0.018
Clinical outcomes					
Return of Rankin,[a] no. (%)	126 (22.7)	56 (20.3)	44 (21.5)	26 (35.6)	0.018
UW-mRS 90 d, mean (SD)	2.6 (3.2)	3.4 (3.5)	2.1 (2.8)	1.4 (2.0)	<0.0001
Mean change in UW-mRS at 90 d (SD)	−4.0 (3.2)	−4.2 (3.5)	−4.4 (2.8)	−1.9 (2.0)	<0.0001
sICH, no. (%)[b]	31 (5.8)	15 (5.6)	10 (5.1)	6 (8.7)	0.526
Mortality 90 d, no. (%)[b]	218 (39.4)	96 (34.8)	90 (43.9)	32 (44.4)	0.083
Procedural factors for the MT group (N = 448)					
TLSW to groin puncture, median h[b]	11.1 (7.8–14.3)	10.8 (7.5–13.8)	11.2 (8–14.8)	11.7 (8.3–14)	0.276
General anesthesia, no. (%)[b]	88 (21.4)	43 (20.2)	39 (24.8)	6 (14.3)	0.278
Balloon guide catheter, no. (%)[b]	193 (51.5)	104 (56.5)	70 (46.7)	19 (47.5)	0.172
Reperfusion mTICI ≥2b, no. (%)[b]	370 (83.2)	196 (84.9)	131 (79.9)	43 (86.0)	0.365

Abbreviations: ASPECTS = Alberta Stroke Program Early CT Score; h = hours; IQR = interquartile range; MCA = middle cerebral artery; mRS = modified Rankin Scale; MT = mechanical thrombectomy; mTICI = modified treatment in cerebral infarction; N = total number of patients; NIHSS = National Institutes of Health Stroke Scale; sICH = symptomatic intracranial hemorrhage; TLSW = time last seen well; UW = utility weighted; y = years.
[a] The outcome, return of Rankin, indicates a recovery to the prestroke modified Rankin Scale score by 90 days after stroke.
[b] Transfer, imaging modality, TLSW to groin puncture, sICH, mortality at 90 d, general anesthesia, balloon guide catheter, and reperfusion TICI are missing for 72, 43, 43, 19, 1, 36, 74, and 3 patients, respectively.

In multivariable regression, the association between thrombectomy and ROR persisted and remained statistically significant, with the exception of patients with a prestroke mRS of 4 (OR 4.00, 95% CI 0.76–21.01, $p = 0.10$; Table 3). The higher odds of ROR for MT also persisted in the IPTW and SMR models across individual mRS subgroups, with the odds

Table 2 Baseline Characteristics Before and After the Inverse Probability of Treatment Weighting

	Unweighted				IPTW-adjusted cohort			
	Medical management (N = 106)	Mechanical thrombectomy (N = 448)	*p* Value	SMD	Medical management	Mechanical thrombectomy	*p* Value	SMD
Age, median y (IQR)	83.4 (77–88)	81.6 (72–87)	0.015	−0.28	82.9 (70–86)	82 (72–87)	NA	0.04
Baseline NIHSS, median (IQR)	19 (14–24)	18 (13–22)	0.013	−0.32	16 (13–21)	18 (13–22)	NA	0.08
Female, no. (%)	73 (68.9)	294 (65.6)	0.526	−0.07	68.0%	65.7%	0.641	−0.05
Premorbid mRS, no. (%)			0.018	0.29			0.291	0.16
2	43 (40.6)	233 (52.0)			42.5%	50.2%		
3	41 (38.7)	164 (36.6)			43.7%	36.8%		
4	22 (20.8)	51 (11.4)			13.8%	13.1%		
Medical history, no. (%)								
Hypertension	70 (66.0)	359 (80.1)	0.002	0.32	79.4%	78.3%	0.793	−0.03
Diabetes	25 (23.6)	144 (32.1)	0.085	0.19	23.5%	31.0%	0.104	0.17
Atrial fibrillation	48 (45.3)	228 (50.9)	0.299	0.11	51.4%	50.2%	0.805	−0.02
Intravenous thrombolysis, no. (%)	7 (6.6)	68 (15.2)	0.020	0.28	15.5%	14.1%	0.691	−0.04
ASPECTS, median (IQR)	6 (4–9)	8 (7–9)	<0.001	0.89	9 (7–10)	8 (7–9)	NA	−0.19
Location of occlusion, no. (%)			0.012	0.31			0.996	0.01
Internal carotid artery	50 (47.2)	253 (56.5)			55.7%	55.3%		
MCA-M1 segment	16 (15.1)	89 (19.9)			19.3%	19.6%		
MCA-M2 segment	40 (37.7)	106 (23.7)			25.0%	25.2%		

Abbreviations: ASPECTS = Alberta Stroke Program Early CT Score; IPTW = inverse probability of treatment weighting; IQR = interquartile range; mRS = modified Rankin Scale; MCA = middle cerebral artery; N = the total number of patients; NIHSS = National Institutes of Health Stroke Scale; SMD = standardized mean difference; y = years.

of achieving ROR ranging from 2-4-fold higher among MT-treated patients; however, the effect estimate failed to achieve statistical significance for these comparisons.

Covariates and ROR

We tested interaction effects between treatment and covariates on Rankin (ROR, return to prestroke mRS by 90 days). No significant interactions were found (data not shown in tables). Among all patients irrespective of thrombectomy, the ROR was observed with greater frequency among patients with higher prestroke mRS compared with lower prestroke mRS (35.6% vs 21.5% vs 20.3% for mRS 4, 3, and 2, respectively; $p = 0.02$; Table 1). Patients with a prestroke mRS of 4 were more likely to achieve ROR when compared with patients with a prestroke mRS of 2 (unadjusted OR 2.17, 95% CI 1.24–3.81; adjusted OR 3.68, 95% CI 1.97–6.87; eTable 2, links.lww.com/WNL/C469). In the fully adjusted multivariable model, increasing NIHSS (aOR 0.90, 95% CI 0.86–0.94) and decreasing ASPECTS (aOR per point 0.86, 95% CI 0.75–0.99) were associated with lower odds of ROR. Age, pretreatment with thrombolysis, and location of intracranial occlusion were not independently associated with achieving ROR, eTable 2.

Missing Data Analysis

With imputation of missing data, the odds of ROR with thrombectomy persisted in the multivariable model (aOR 2.85, 95% CI 1.52–5.33), SMR model (OR 3.35, 95% CI 1.42–7.91), and IPTW model (OR 3.19, 95% CI 1.48–6.86).

Secondary Outcome Assessment

Among the secondary outcomes, compared with patients with a lower prestroke mRS, patients with a higher prestroke mRS score had an expectedly lower 90-day UW-mRS ($p < 0.01$) but also less of a change in the UW-mRS at 90 days when compared with prestroke mRS ($p < 0.01$; Table 1). Mortality was non-significantly more common among patients with a higher prestroke mRS 44.4% vs 43.9% vs 34.8% for mRS of 4, 3, and 2, respectively; $p = 0.08$). Compared to patients treated with medical management, those treated with MT had a better 90-day UW-mRS (mean 3.0 [±2.5] vs 1.3 [±2.2], $p < 0.01$) with a less significant worsening of the UW-mRS by 90 days compared to their baseline UW-mRS (mean difference −3.7 [±3.3] vs −5.0 [±2.5], $p < 0.01$), but a higher risk of sICH (7% vs 0%, $p < 0.01$) in unadjusted comparisons (eTable 3, links.lww.com/WNL/C469). Although 90-day mortality of the entire cohort was high,

Table 3 Multivariable Logistic Regression, SMR, and IPTW Evaluation of Thrombectomy for Return of Rankin[a]

	Multivariable model		SMR model OR (95% CI), *p*		IPTW model	
			Overall mRS 2–4 (n = 554)			
Medical management	Referent					
Mechanical thrombectomy	3.96 (1.78–8.79)	0.001	3.00 (1.10–8.15)	0.032	3.10 (1.20–7.98)	0.020
			Premorbid mRS 2 (n = 276)			
Medical management	Referent					
Mechanical thrombectomy	4.36 (1.01–18.79)	0.048	2.99 (0.47–19.07)	0.247	3.18 (0.53–19.05)	0.206
			Premorbid mRS 3 (n = 205)			
Medical management	Referent					
Mechanical thrombectomy	3.80 (1.01–14.24)	0.048	4.40 (0.86–22.50)	0.075	4.22 (0.91–19.54)	0.066
			Premorbid mRS 4 (n = 73)			
Medical management	Referent					
Mechanical thrombectomy	4.00 (0.76–21.06)	0.102	2.03 (0.38–10.93)	0.410	2.21 (0.45–10.79)	0.325

Abbreviations: IPTW = inverse probability of treatment weighting; mRS = modified Rankin Scale; SMR = standardized mortality/morbidity ratio.
[a] The outcome, return of Rankin, indicates a recovery to the prestroke modified Rankin Scale score by 90 d after stroke.

there was a nonsignificant 7.3% absolute risk reduction in mortality at 90 days with MT vs medical management (38.0% vs 45.3%, $p = 0.17$).

Classification of Evidence

This investigation's results provide Class III evidence that in patients with preexisting disability presenting 6–24 hours from the TLSW and acute anterior large vessel occlusion stroke, there may be a benefit of MT over medical management in returning to baseline function.

Discussion

In this multinational observational cohort of stroke patients with acute LVO and preexisting mild-to-moderate disability

Table 4 Summary of Previous Studies Investigating Outcomes After Mechanical Thrombectomy in Patients With Prestroke Disability

	Study	Methodology	Cohort size	Primary outcome	Findings	Limitations
1	Tanaka et al. 2021[10]	Retrospective multicenter cohort of patients with prestroke mRS 2–4, MT vs medical management	339	No worsening of mRS at 90-day poststroke	Odds of achieving favorable outcome were greater in patients with MT vs medical management	Nonrandomized, mRS evaluators not blinded to patients' clinical history
2	Larsson et al. 2020[9]	Retrospective cohort: patients who underwent MT, prestroke mRS 0–2 vs ≥3	566	No worsening of mRS at 90-day poststroke	Proportion of patients with favorable outcome did not significantly differ between groups	Nonrandomized, cannot identity patients with transient prestroke disability
3	Salwi et al. 2020[3]	Retrospective multicenter cohort, patients who underwent MT, prestroke mRS 0–1 vs 2-3	761	mRS of 0–1 or no worsening of mRS at 90-day poststroke	Odds of achieving favorable outcome did not significantly differ between groups	Nonrandomized, cannot identity patients with transient prestroke disability
4	Seker et al. 2019[7]	Retrospective cohort, patients who underwent MT, prestroke mRS 3-4	136	No worsening of mRS at 90-day poststroke	21% achieved a favorable outcome	Nonrandomized, no comparison with patients with prestroke mRS 0-2
5	Slawski et al. 2018[8]	Retrospective cohort, patients ≥80 yrs who underwent MT, prestroke mRS 0–1 vs 2-4	96	mRS of 0–2 or no worsening of mRS at 90-day poststroke	Proportion of patients with favorable outcome did not significantly differ between groups	Nonrandomized, only included patients ≥80 yrs, cannot identify patients with transient prestroke disability

Abbreviations: mRS = modified Rankin Scale, MT = mechanical thrombectomy.

presenting in the extended 6- to 24-hour time window, treatment with MT was associated with a greater probability of return to baseline function than medical management. Furthermore, the probability of returning to baseline function was greatest among those with greater prestroke disability in multivariable modeling. The exclusion of patients with preexisting disabilities from clinical trials evaluating MT was to establish efficacy with MT in the early and extended time windows. However, increasing data supports the benefit of aggressive treatment even with a mild-to-moderate preexisting disability. Whether these patients may experience significant recovery, and return to a prior level of function, has not been previously explored in a large, diverse cohort that reflects the treatment and outcomes across multiple centers and countries.

Establishing long-term functional independence (mRS 0–2) as a historically desired, dichotomized outcome among patients with acute LVO has influenced stroke trialists in their methodology. Although functional independence is only achieved in 10%–15% of patients with anterior circulation LVO treated with medical management in the extended time window,[16,17] it is impractical to expect this favorable outcome in patients with preexisting disability. Instead, it is more reasonable to aim for recovery to baseline disability among patients believed to have a reasonable quality of life despite preexisting functional impairment. For this reason, we believe the outcome of ROR is an acceptable indicator of treatment effect in a population with a prior disability.

Although the mRS is a less-than-comprehensive assessment of functional impairment when disability is present, it sufficiently distinguishes major categories of independence: independent gait with some dependence on others for daily activities (mRS 3) vs requirement for assistance with gait and daily activities (mRS 4) vs total dependence with the need for constant nursing care (mRS 5). It is important to note that the mRS can be a useful indicator of good outcomes when dichotomized (e.g., 0–2 vs 3–6); however, the lack of proportional differences between 2 and 5 on the mRS can significantly impair ordinal analyses. For this reason, the UW-mRS score,[17,20] which is a linear transformation of the mRS, may be more useful for quantifying functional recovery across a broader range of expected outcomes. Our study captured both dichotomized outcomes with the ordinal mRS and the spectrum of outcomes using the UW-mRS regarding the baseline to estimate the recoverability after MT. That said, both the mRS and the UW-mRS remain limited by the fact that higher mRS scores (other than 6) can indicate a wide range of disabilities and may not discriminate accumulated disability within the mRS strata from which the patient started. A patient with an mRS of 4 may be more likely to worsen after the stroke, but the follow-up mRS remains the same. For example, a patient who can ambulate with spousal assistance but requires help paying bills may qualify as an mRS of 4 before the stroke. After a stroke, they may become wheelchair-bound and require help with toileting and bathing (mRS still a 4), yet this would constitute a significant functional decline from baseline. This variability within higher mRS disability categories may explain why patients with a prestroke mRS of 4 were significantly more likely to remain 4 at 90 days than patients with a prestroke mRS of 2.

Although prestroke disability has been strongly tied to age[21] and both are independent predictors of long-term outcomes after stroke,[22,23] we found age was not an independent modifier of MT in this cohort. Older patients were less likely to undergo MT; however, in multivariable modeling (including adjustment for MT and prestroke mRS), age was not associated with a lower probability of returning to a prior level of function. This may be related to the generally higher age distribution in this population of patients with preexisting disabilities, in which three-quarters of the population was older than 72 years. In addition, the use of thrombolysis before MT was not an independent predictor of ROR. This is supported, in part, by recent randomized clinical trials which have been unable to confirm noninferiority of MT over thrombolysis with MT.[24-28] Unsurprisingly, initial stroke severity remained a strong and independent effect modifier for the outcome of ROR, with each point on the NIHSS being associated with a 10% lower odds of ROR in multivariable regression. This finding is consistent with other studies which associated NIHSS and a more favorable long-term mRS target (e.g., 0–2[22,23,29] or 0–1[30]).

To date, several groups have reported their experience with MT in patients with a premorbid disability that are outside AHA recommendations.[6] A prospective registry at 2 centers reported their observations, including 259 patients with mild-moderate prestroke disability (mRS 2–3).[3] Despite important differences in comorbidities and disease severity, they found that more than 1 in 4 (27%) patients treated with MT returned to their prestroke disability (or were better) by 90 days. Our results are unique from this report in that we report across multiple sites in multiple countries, including patients treated >6 hours from TLSW (75% of patients from the 2-center prospective registry were treated <7 hours) and including patients with moderate prestroke disability (mRS 4). A single center study also reported a similar experience with MT among 49 patients with prestroke disability, indicating no greater risk of accumulated disability after thrombectomy when compared with patients without prestroke disability.[1] However, only 5 of the included patients had a prestroke mRS of 4, and more than 75% of patients were treated <6 hours from TLSW. Others have reported that MT leads to functional recovery (to prestroke baseline) in approximately 20%–35% of patients; however, nearly all reports are limited to patients treated within the early time window (<6 hours from TLSW).[9-11,31,32]

The recently reported results from the prospective RESCUE-Japan Registry 2, including 339 patients with a prestroke mRS of 2–4 and an ICA or MCA-M1 occlusion treated at 46 stroke centers in Japan, are one of the few studies which describe a medically managed control arm.[12] Compared with the 164 patients treated without thrombectomy, the 175 patients treated with MT were nearly 3 times more likely to recover to their baseline disability. It is important that these patients were

treated quickly after TLSW (75% arrived at the hospital within 4.5 hours of TLSW, with 39% receiving concomitant thrombolysis), and 40% had a prestroke mRS of 2. The investigators reported a nearly fourfold higher odds of a return to prestroke baseline with thrombectomy in the adjusted multivariable model based on propensity matching (adjusted OR, 3.90; 95% CI, 1.36–11.22). Patients from the RESCUE-Japan Registry 2 who were treated beyond 6 hours were consolidated with those from the CLEAR study[13] in this investigation to estimate a more robust association of MT vs medical management in patients with LVO and preexisting disability in the late window.

Our study is not without limitation. The nonrandomized nature of the treatment, and underreported cases of medically managed patients with prestroke disability across participating centers, likely contributed to a selection bias favoring more positive outcomes among thrombectomy-treated individuals with a prestroke disability. In the absence of randomization, there is likely residual confounding. For example, without consent and randomization, it is unclear whether some patients treated medically (or their caregivers) would have preferred MT or if those treated with MT might have preferred medical management—or even comfort measures—if they had no desire to return to their prestroke level of disability. Such residual confounding may have affected the positive outcomes seen with MT. The assessment of change in UW-mRS at 90 days vs prestroke baseline is also contingent on retrospective estimation by local investigators. However, in one comparative study, investigators reported moderate interrater agreement with the assignment of prestroke mRS scores.[33] Furthermore, the use of mRS is an oversimplified index of functional status after a stroke. The application of more detailed indices that reflect functional disability would be ideal for estimating differences in outcomes in future prospective studies. We also observed a higher rate of symptomatic intracranial hemorrhage after MT than has been previously reported, and this may reflect the cumulatively greater burden of comorbidity in our cohort (including older age, unreported comorbid conditions associated with aging, and possibly differential use of antithrombotics before stroke) compared with prior trials which excluded patients with prestroke disability. Finally, comparisons were made based on available data from 2 consolidated multicenter cohorts, with one cohort (CLEAR) accounting for proportionally more thrombectomy patients and fewer patients treated with medical management (94% and 59%, respectively). The relatively higher proportion of patients from RESCUE-Japan 2 in the medical management arm might have confounded the association between MT and ROR.

Based on these findings, we believe some patients with mild-to-moderate preexisting disabilities may benefit from MT when an acute LVO is identified.[6] Although these patients (who have a preexisting disability) are unlikely to become free of any disability with MT, their likelihood of returning to a prestroke level of function is not any different. It should be noted that this association was identified using the limited mRS score, with scores of 3 and 4 representing a broader range of disability (and potentially overestimating treatment benefits). A more comprehensive measure of functional recovery would more optimally capture treatment effects in a population with prior disability.

Although randomized trials would provide the highest quality of evidence to support thrombectomy in patients with preexisting disability, there may not be equipoise in randomizing persons to medical management with a prestroke mRS of 2 or 3 with the ongoing expansion of indications for EVT.[34] The ATTENTION trial included patients with prestroke mRS 0 to 2, and preliminary results demonstrated a benefit of thrombectomy over medical management in patients with basilar artery occlusion.[35] Still, there may be equipoise in randomizing patients with more significant disability (mRS of 4) to medical management, and the safety and efficacy of endovascular treatment certainly warrant further exploration in this population using larger observational cohorts or randomized controlled trials.

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Appendix *(continued)*

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Continued

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