Outcomes and safety of endovascular treatment from 6 to 24 hours in patients with a pre-stroke moderate disability (mRS 3): a multicenter retrospective study

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ABSTRACT

Background Approximately 30% of patients presenting with acute ischemic stroke (AIS) due to large vessel occlusion have pre-stroke modified Rankin Scale (mRS) scores ≥2. We aimed to investigate the safety and outcomes of endovascular treatment (EVT) in patients with AIS with moderate pre-stroke disability (mRS score 3) in an extended time frame (ie, 6–24 hours from the last time known well).

Methods Data were collected from five centers in Europe and the USA from January 2018 to January 2023 and included 180 patients who underwent EVT in an extended time frame. Patients were divided into two groups of 90 each (Group 1: pre-mRS 0–2; Group 2: pre-mRS 3; 71% women, mean age 80.3±11.9 years). Primary outcomes were: (1) 3-month good clinical outcome (Group 1: mRS 0–2, Group 2: mRS 0–3) and ΔmRS; (2) any hemorrhagic transformation (HT); and (3) symptomatic HT. Secondary outcomes were successful and complete recanalization after EVT and 3-month mortality.

Results No between-group differences were found in the 3-month good clinical outcome (26.6% vs 25.5%, P=0.974), any HT (26.6% vs 22%, P=0.733), and symptomatic HT (8.9 vs 4.4%, P=0.232). Unexpectedly, ΔmRS was significantly smaller in Group 2 compared with Group 1 (1.64±1.61 vs 2.97±1.69, P<0.001). No between-group differences were found in secondary outcomes.

Conclusion Patients with pre-stroke mRS 3 are likely to have similar outcomes after EVT in the extended time frame to those with pre-stroke mRS 0–2, with no difference in safety.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ While several observational data are available on outcomes of endovascular treatment in the early time window in patients with acute ischemic stroke presenting with a moderate pre-stroke disability (modified Rankin Scale (mRS) 3), only one study has explored the outcome of endovascular treatment for late anterior large vessel occlusion in patients with pre-morbid disability (mRS 2–4).

WHAT THIS STUDY ADDS

⇒ Patients with acute ischemic stroke with pre-stroke mRS 3 are likely to have similar outcomes after endovascular treatment for anterior large vessel occlusion in the extended time window to patients with pre-stroke mRS 0–2, with no differences in safety.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The results from this multicenter international retrospective cohort study support the use of endovascular treatment in the extended time window in patients with a pre-stroke mRS score of 3.

INTRODUCTION

Endovascular thrombectomy (EVT) is currently the standard of care for selected patients with acute ischemic stroke (AIS) due to emergent large vessel occlusion (LVO) of the anterior circulation. This intervention is recommended either within the initial 6 hours from the onset of symptoms[1 2] or within the extended time frame (ET) of 6–24 hours after the time patients were last known to be well (LKW), based on perfusion mismatch.[3 4] Patients who present with disability in their daily activities, as indicated by a modified Rankin Scale (mRS) score ≥2, have been excluded from most trials on EVT for AIS in the anterior LVO.[5] Thus, although these patients account for approximately 30% of all patients with LVO,[6 7] randomized data on the efficacy and safety of EVT in this group are scant.[8] Although several observational studies have shown a comparable safety and potential effectiveness of EVT,[9–13] definitive evidence is lacking on the efficacy of reperfusion therapies in patients with substantial pre-morbid disability or dementia with respect to those untreated or without pre-stroke

disability.[8] Since many patients with AIS have pre-existing disability, it is important to establish real-world outcomes and safety of EVT in these cases. Patients with AIS and slight pre-morbid disability (mRS 2) are routinely treated by EVT in clinical practice according to data from a few multicenter registries.[14 15] Conversely, the use of EVT in patients with moderate pre-stroke disability (mRS 3) is debatable. This subgroup of patients deserves particular attention among those with full dependence (mRS 3–5), since they preserve the ability to walk without the assistance of another individual, thus maintaining a non-negligible degree of autonomy. While several observational data are available on EVT outcomes in the early time window in these often neglected disabled patients,[9–13 16] only one study has explored the outcome of EVT for late anterior LVO in patients with pre-morbid disability (mRS 2–4).[13] We therefore aimed to investigate the safety and outcomes of EVT in patients with moderate pre-stroke disability (mRS 3) treated in the ET in a multicenter international retrospective cohort study.

METHODS

Data provided in this paper are reported in compliance with the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) statement.

Study population

This is a retrospective, observational, multicenter cohort study including patients with a pre-stroke moderate disability (mRS score 3) who underwent endovascular treatment for AIS in the anterior circulation beyond 6 hours and up to 24 hours from LKW (LKW to groin puncture time) from January 1, 2018 to January 31, 2023. The site of occlusion included the following: isolated middle cerebral artery (MCA)–M1, isolated MCA–M2, isolated anterior cerebral artery, tandem occlusion, terminal internal carotid artery T-type. Where indicated, patients received IV thrombolysis as a bridging therapy before undergoing mechanical thrombectomy.

We collected data from five international centers: (1) Stroke Center and Interventional Neuroradiology Unit, University Hospital of Rome Tor Vergata, Rome, Italy; (2) Diagnostic and Interventional Neuroradiology, Boston Medical Center, Boston, USA; (3) Interventional Neuroradiology, Vall d'Hebron University Hospital, Barcelona, Spain; (4) Department of Neuroradiology, University Hospital of Padova, Padua, Italy; and (5) Interventional Neuroradiology Unit, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy. Data were collected on consecutive patients with pre-stroke functional independence (mRS 0–2, Group 1) and pre-stroke moderate disability (mRS 3, Group 2) treated with EVT in the same center. Information was collected by the study coordinator of each center, who received a dataset to complete and send back to the coordinator center (Rome Tor Vergata). Age (±5 years) and gender matching between the two groups was also performed by the study coordinator who was blinded to patient information except that used for matching. Patients were paired using a custom-made approach in which each patient in Group 2 was paired with the first patient in Group 1 having the same value in the variables of interest (±5 for age and the same for gender). In the second permutation, each patient in Group 2 was paired with the second patient in the patient list of Group 1 having the same characteristics. About five permutations filled all patients in Group 2 and the best one in terms of similar average and SD was chosen. An independent neurologist/interventional radiologist at each center blinded to group allocation accurately collected clinical and neuroradiological data from patients' records that were used to perform group comparison. Only for one center (Padua), the matching was performed with the same procedure by the coordinator center of Rome Tor Vergata with patients treated locally. We collected the following data: (1) demographic characteristics; (2) vascular risk factors; (3) clinical presentation at baseline; (4) neuroradiological features; and (5) treatment characteristics. Pre-stroke functional status was estimated according to the mRS[17] and reported by the local study coordinator based on information provided by patients, their families, or derived from medical records. Reasons for dependence were assessed and categorized, according to Benali and coworkers,[16] as follows: previous stroke, cardiopulmonary disease, cognitive impairment, musculoskeletal disease (including rheumatoid arthritis, osteoarthritis, and amputation), neurological disorders other than stroke and dementia, other disease (malignancy, alcohol/drug abuse, glaucoma or other visual impairments, peripheral artery disease), need for assistance due to unspecified comorbidities, unknown or missing causes.

Outcome measures

The outcome measures detailed below were calculated for each group separately and compared.

Primary outcomes

The primary outcome was a good outcome at 3 months, defined as a corrected mRS score, measured 3 months after stroke, of 0–2 for Group 1 and 0–3 for Group 2. As a co-primary measure for efficacy, we also calculated the change in mRS (ΔmRS), defined as mRS at 3 months minus baseline mRS. The use of this ΔmRS was based on three main reasons: (1) it is strongly associated with worse long-term outcomes and increased healthcare costs in both pre-morbid disabled patients[7] and the general stroke population[18]; (2) its use has been specifically encouraged in trials that enrolled patients both with and without pre-stroke disability[7 8]; and (3) as previously described by Benali and coworkers,[16] in some cases (ie, the reason for disability resolved within the 90-day assessment period or erroneously high measurement of the pre-stroke mRS score) patients could present a functional improvement compared with pre-stroke status.

Our primary safety outcomes were any hemorrhagic transformation (HT), symptomatic or asymptomatic, as classified by the European Cooperative Acute Stroke Study-II (ECASS-II) definition (hemorrhagic infarction (HI) 1 and 2, and parenchymal hematoma (PH) 1 and 2) and symptomatic HT.[19] Symptomatic HT was defined, according to the ECASS-III definition,[19] as an intracranial hemorrhage that is associated with deterioration of ≥4 points in the National Institutes of Health Stroke Scale (NIHSS) score and the main reason for neurological deterioration.[19]

Secondary outcomes

Secondary outcomes were the rate of successful and complete reperfusion, respectively defined as expanded Thrombolysis in Cerebral Ischemia scale (eTICI) 2b–3 and eTICI 2c–3 after EVT, and the mortality rate at 3 months.

Statistical analysis

Statistical analyses were conducted using the Statistical Package for the Social Sciences (SPSS) version 26.0 (IBM Corp, Armonk, USA). For categorical variables, between-group comparisons were performed with the χ^2 test with Yates' correction or Fisher exact test, the latter when the expected counts were <5. For

ordinal and continuous variables we used the Mann–Whitney U test.

The effect of pre-stroke mRS on the ΔmRS was estimated using a multiple regression model. To identify possible predictors of ΔmRS, two multiple regression models were fitted with the ΔmRS as dependent variable and two sets of baseline variables as predictors. In the first model we forced as predictors all the variables included in the MR PREDICTS decision tool (age, baseline NIHSS score, pre-stroke mRS, diabetes mellitus, systolic blood pressure, glycemia, IV thrombolysis, baseline Alberta Stroke Program Early CT Score, site of occlusion, collateral score, onset to recanalization time),[20] which represents the most reliable model for determining the benefit of EVT for AIS.[21] In a second model, we added two variables related to EVT (eTICI and any HT) which are well recognized to be predictors of the benefit of EVT. Standardized β and p values were reported for all models.

Additionally, we performed a partial correlation between pre-stroke mRS and ΔmRS, controlling for variables selected by the multiple regression analysis, to measure the relationship between the two variables while eliminating the effect of potential confounders previously identified.

To evaluate the role of the continuous variable(s) selected by multiple regression as potential mediator(s) of the relationship between pre-stroke mRS and ΔmRS, a mediation analysis was performed with ΔmRS as dependent variable, selected variable(s) as the mediator(s) (see Results section) and pre-stroke mRS as predictor. To this aim, we used the PROCESS version 4.2 beta release for SPSS.[22]

Normality of distribution was assessed with the Shapiro–Wilks test. In case of non-normal distribution, data were log-transformed. A p value <0.05 was considered significant.

Missing data

Primary and secondary outcomes contained a percentage of missing values <5% that were handled by a listwise deletion automatically performed by the statistical program. Covariates containing a percentage of missing values ≥5% (arterial hypertension, hypercholesterolemia, diabetes mellitus, smoking habit, systolic and diastolic blood pressure, door to reperfusion time, and procedural duration) were replaced according to a multiple imputation model assuming a missing at random mechanism. Multiple imputations with a fully conditional specification method were performed in SPSS 26.0 and five imputed datasets were generated.

RESULTS

Population

We enrolled 180 patients (90 patients in each of Groups 1 and 2), comprising 127 women (70.6%), median age 84 years (IQR 76–88), and a median NIHSS score of 17 (IQR 12–21). The distribution of patients among the five different recruiting centers is shown in online supplemental table 1.

Clinical and neuroradiological characteristics as well as treatment details are reported in online supplemental table 2. No differences were found between the two groups except for a higher diastolic blood pressure at baseline in Group 1 than in Group 2 (median value 83 (IQR 76–87) mmHg vs 84 (IQR 76–88) mmHg, p=0.049) (see online supplemental table 2).

A description of the reason for disability is provided in online supplemental table 3.

Primary outcomes

No differences were found in the bivariate comparison between Group 1 and Group 2 regarding the three primary outcomes (figure 1): (1) 3-month good outcome: 26.6% vs 25.5%, χ^2=0.001, p=0.974; (2) any HT: 26.6% vs 22%, χ^2=0.117, p=0.733; and (3) symptomatic HT: 8.9% vs 4.4%, χ^2=1.429, p=0.232. No differences were found in the bivariate comparison between Groups 1 and 2 concerning the type of HT according to ECASS-III criteria (online supplemental table 4). By contrast, the ΔmRS was significantly smaller in Group 2 than in Group 1 (mean value 1.64 vs 2.97, U=−4.547, p<0.001) (figure 2).

Secondary outcomes

No differences in secondary outcomes were found between the two groups: (1) successful reperfusion: 84.4% vs 78.9%, χ^2=0.928, p=0.335; (2) complete reperfusion (63.3% vs 55.6%, χ^2=1.129, p=0.288); (3) death at 3 months (38.9% vs 44.4%, χ^2=1.210, p=0.271) (figure 1).

Additional analyses

Predictors of ΔmRS

ΔmRS was positively associated with baseline NIHSS score (β=0.458, p<0.001) and glycemia (β=0.224, P=0.047) and negatively associated with pre-stroke mRS (β=−0.404, p<0.001) in model 1. ΔmRS was positively associated with baseline NIHSS (β=0.443, p<0.001) and any HT (β=0.226, p=0.020) and negatively associated with pre-stroke mRS (β=−0.518, p<0.001) and eTICI (β=−0.314, p<0.001) in model 2. Unadjusted and adjusted results for the regression analysis are shown in table 1.

Partial correlation

The pre-stroke mRS score was negatively correlated with the ΔmRS (ρ=−0.381, p<0.001). The correlation became stronger (ρ=−0.490, p<0.001) when the analysis was controlled for the confounders selected based on the results of the regression analysis using model 2 (baseline NIHSS, eTICI and any HT). This choice was based on the fact that model 2 explained more variance than model 1 (R^2=0.624 vs R^2=0.478 for models 2 and 1, respectively) and yielded more predictors, thus allowing control for more variables in the following partial correlation.

Mediation analysis

There was a significant total indirect effect of pre-stroke mRS on ΔmRS through eTICI and baseline NIHSS, although the effect size was small (*b*=0.05, 95% BCa CI 0.01 to 0.10) (figure 3). There was a significant and robust direct effect of pre-stroke mRS on ΔmRS with a negative correlation (*b*=−0.74, p<0.001) (figure 3).

DISCUSSION

When comparing patients with AIS with pre-stroke mRS 0–2 and mRS 3 who underwent EVT for LVO of the anterior circulation in the extended time frame, we did not find any differences in our primary (3-month good outcome, any HT, symptomatic HT) or secondary (successful reperfusion, complete reperfusion, death at 3 months) outcomes.

By contrast, when considering ΔmRS, both groups worsened at 3 months, but patients with moderate disability (Group 2) did so less than those with no or slight disability (Group 1), with a between-group difference in the score of 1.33. However, this latter finding must be cautiously interpreted because of the following several limits of measuring outcome through mRS.

The mRS is an ordinal scale in which each step does not have the same weight in clinical practice. For instance, the difference between a score of 1 and 2 or 2 and 3 does not have the same

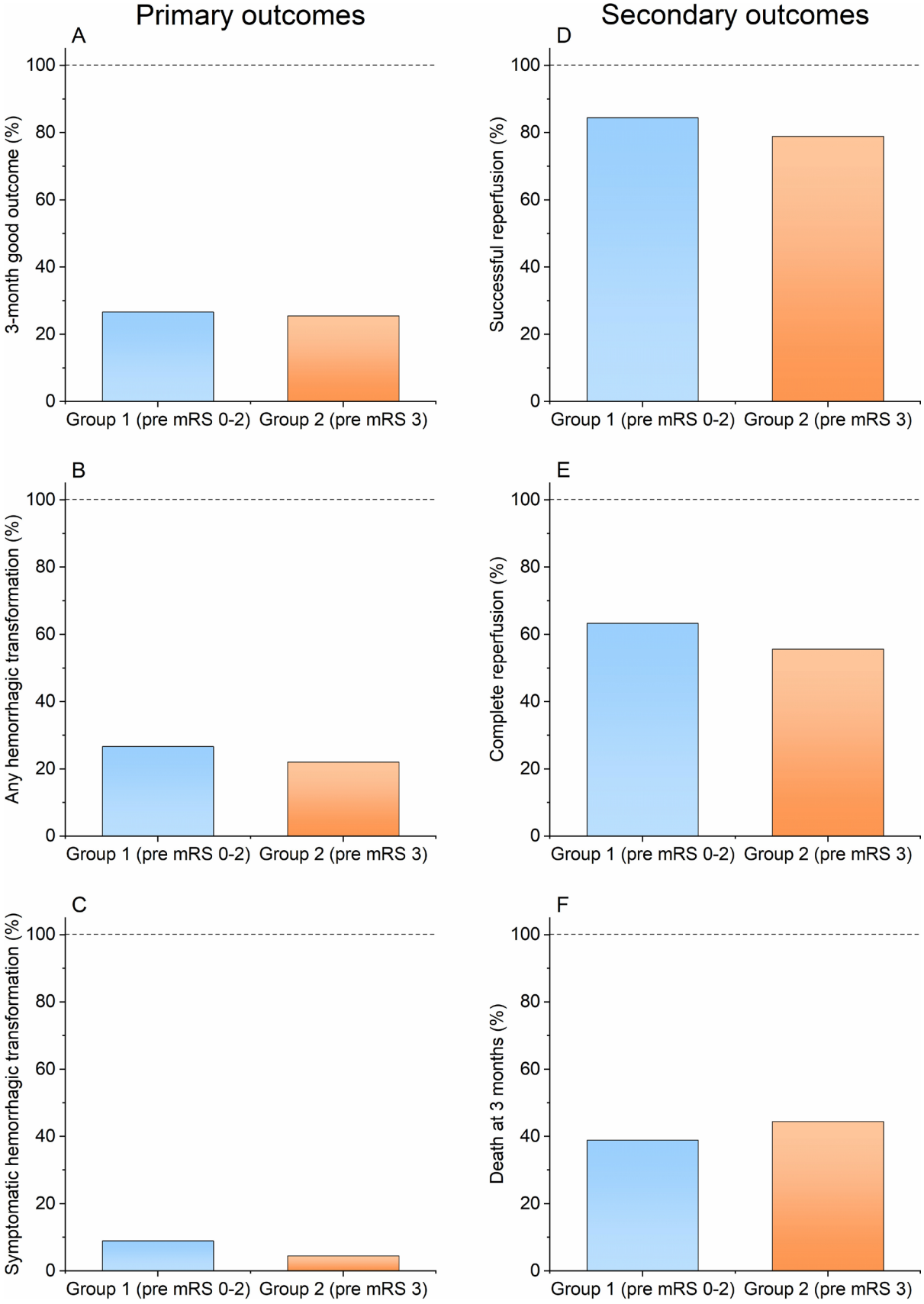

Figure 1 Bivariate comparison of percentage between Group 1 (pre-stroke mRS 0–2) and Group 2 (pre-stroke mRS 3) according to the three different primary outcomes: (A) 3-month good outcome; (B) any hemorrhagic transformation; (C) symptomatic hemorrhagic transformation, and secondary outcomes: (D) successful reperfusion (eTICI 2b–3); (E) complete reperfusion (eTICI 2c–3]; (F) death at 3 months. No statistical differences were detected between the two groups for any of the outcome measures. eTICI, expanded Thrombolysis in Cerebral Ischemia; mRS, modified Rankin Scale.

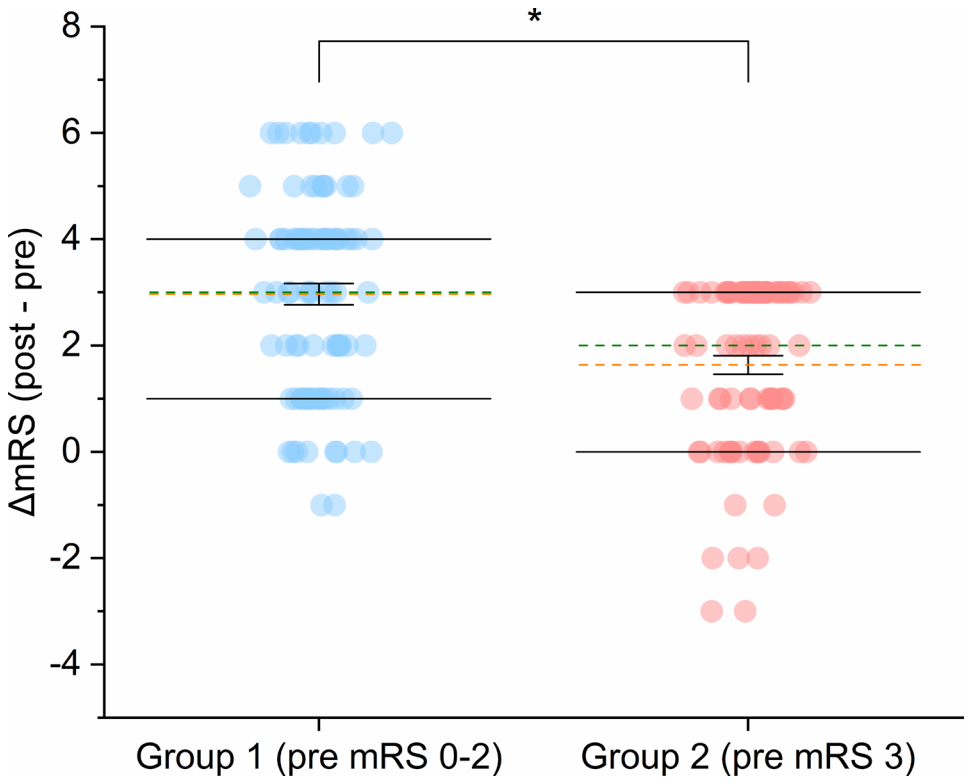

Figure 2 Bivariate comparison of ΔmRS at 3 months, defined as mRS at 3 months minus baseline mRS, between Group 1 (pre-stroke mRS 0–2) and Group 2 (pre-stroke mRS 3). Group 2 has a smaller ΔmRS at 3 months compared with Group 1 (P<0.001). Asterisks indicate statistically significant difference (P<0.05). Each transparent circle represents one observation. The dashed orange line represents the median value (3 and 2 for Groups 1 and 2, respectively), the dashed green line is the mean value (2.97 and 1.64 for Groups 1 and 2, respectively), the solid black lines indicate the interquartile ranges, and the whiskers depict the SE of the mean. mRS, modified Rankin Scale.

individual and social implications compared with a difference between 3 and 4. Therefore, on the one hand, more inclusive dichotomous outcomes such as return to pre-stroke mRS (or corrected mRS at 3 months in our case) should be considered more appropriate than the simple assessment of mRS at 3 months.[7 23] On the other hand, sometimes patients may show a functional improvement compared with pre-stroke status. For this reason, measuring clinical outcome as an ordinal variable (ΔmRS in our case) which captures the change in mRS score due to stroke may be better suited to account for different scenarios found in clinical practice.[16] Second, the mRS emphasizes physical disability more than cognitive disability and mixes the construct of disability with impairment and handicap.[24] Although this scale is the gold standard for measuring the functional outcome after stroke, it seems not to be completely reliable in the acute stroke setting and does not inform on the nature of disability. Even though it was originally intended for post-stroke measurement, it is widely used in the acute stroke setting when access to reliable information is limited due to the unavailability of caregivers and due to the inability of patients with stroke to communicate,[25] sometimes resulting in an approximate evaluation, particularly for prior cognitive impairment, where a formal assessment is missing.[26 27] Therefore, the use of scores assessing and balancing comorbidities of the pre-stroke status in the acute care setting should be encouraged. In this way, pre-stroke frailty has been found in over a quarter of patients with AIS otherwise eligible for mechanical thrombectomy.[28] A pre-stroke cumulative deficit frailty index of ≥0.24, adjusted for age, baseline NIHSS, and eventual treatment by IV thrombolysis, was associated with a poor clinical outcome at 3 months (death: OR 3.12 (95% CI 1.32 to 7.4); mRS 3–5: OR 3.04 (95% CI 1.10 to 8.44)) after EVT.[28]

Nevertheless, taken together, these results suggest that there is no evidence to withhold EVT in the ET in routine practice for patients presenting with pre-stroke mRS 3 since there are no differences in outcomes and safety compared with patients with pre-stroke mRS 0–2. Our results are in line with those from the pooled analysis of the CLEAR and RESCUE-Japan Registry 2 studies, which found higher odds for return to pre-stroke status (adjusted OR 3.68, 95% CI 1.97 to 6.87) in patients with pre-morbid mRS 4 treated by EVT in the ET compared with those not treated.[13] In this study, 205 patients had a pre-stroke mRS score of 3, 84.4% of whom were treated by EVT and the remainder by medical therapy. There are some differences in the design limiting the comparison with our study: (1) the control group was represented by patients treated with medical management; (2) a wider range of disability was evaluated (mRS 2–4) with fewer patients having a more severe pre-stroke disability; and (3) the primary outcome measure was defined as the return to pre-stroke mRS at 3 months. A similar result was also found in terms of mortality rate, since a non-significant slight reduction in mortality was found at 3 months with EVT versus medical management,[13] in line with the absence of difference in the mortality rate in our study. Of note, a similar mortality of ~40% was found in both groups in our study so we can probably assume mortality to be increased due to ET, considering that the rate was higher regardless of the acute treatment (EVT or not) or the presence of pre-stroke disability.

The percentage of symptomatic HT in our study was in line with that reported by the sub-analysis of the MR CLEAN study,

Table 1 Results of the multiple regression analyses for the change in mRS at 3 months (ΔmRS), defined as mRS at 3 months minus baseline mRS

	Unadjusted		Adjusted (model 1)		Adjusted (model 2)	
Variables	**β value**	**p value**	**β value**	**p value**	**β value**	**p value**
Age	0.003	0.964	0.004	0.970	0.012	0.893
Baseline NIHSS score	0.385	**<0.001**	0.458	**<0.001**	0.443	**<0.001**
Pre-stroke mRS	−0.381	**<0.001**	−0.404	**<0.001**	−0.518	**<0.001**
Diabetes mellitus	−0.144	0.144	−0.222	0.055	−0.132	0.199
Systolic blood pressure	0.066	0.406	0.064	0.539	0.058	0.523
Glycemia	0.158	**0.022**	0.224	**0.047**	0.104	0.298
IV thrombolysis	0.121	0.112	−0.037	0.714	0.018	0.839
Baseline ASPECTS score	−0.201	**0.010**	−0.074	0.517	−0.061	0.541
M1 occlusion	−0.055	0.484	−0.235	0.609	−0.265	0.506
M2 occlusion	−0.248	**0.001**	−0.187	0.628	−0.165	0.621
Intracranial ICA occlusion	0.278	**<0.001**	−0.127	0.711	−0.260	0.384
Tandem occlusion	0.078	0.319	−0.068	0.785	−0.118	0.587
Collateral score	−0.076	0.472	−0.129	0.218	−0.163	0.074
Onset to recanalization time	−0.066	0.505	−0.062	0.538	−0.123	0.173
eTICI	−0.116	0.127	–	–	−0.314	**<0.001**
Any HT	0.303	**<0.001**	–	–	0.226	**0.020**

Model 1 adjusted for all variables of the MR PREDICTS decision tool. Model 2 adjusted for all variables of the MR PREDICTS decision tool plus two variables related to endovascular treatment (the reperfusion score (eTICI) and the presence of any hemorrhagic transformation). Model 1: R^2=0.478, p<0.001; model 2: R^2=0.624, p<0.001.
Bold type denotes statistical significance at p<0.05 level.
ASPECTS, Alberta Stroke Program Early Computed Tomography Score; eTICI, expanded Thrombolysis in Cerebral Ischemia; HT, hemorrhagic transformation; ICA, internal carotid artery; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale.

focusing on patients with pre-stroke mRS 3 treated in the early time window, which varied from 6% in patients who underwent complete reperfusion to 11% in patients who did not.[16] The rate of asymptomatic HT was lower than that described in the Endovascular Treatment in Ischemic Stroke (ETIS) study, which reported ~43% of asymptomatic HT in patients treated by EVT in the early time window.[29] However, as underlined by the partial correlation in our study, controlling for the significant confounders including the occurrence of any HT did not affect the effect of the pre-stroke status on ΔmRS, partially in contrast with the result highlighted by this study.[16]

Strengths and limitations of the study

Although our study is not the only one to assess the effect of pre-stroke mRS 3 on safety and outcomes of EVT for LVO of the anterior circulation in the ET, it provides some novel information. First, the MR PREDICTS decision tool[20] was confirmed to be a reliable tool even for patients with AIS treated in the ET. Indeed, in our study the regression analysis using model 1 explained 48% of the variance of ΔmRS and selected as predictors, beyond the pre-stroke mRS, the baseline NIHSS with a moderate prediction and glycemia with a weak prediction. Moreover, the addition of the reperfusion rate and the occurrence of any HT in model 2 increased the variance of ΔmRS explained (ie, 62%) and selected as predictors, beyond the pre-stroke mRS, baseline NIHSS, eTICI, and any HT. The role of baseline NIHSS, baseline glycemia, and reperfusion rate[16] as predictors of good outcome at 3 months is well recognized and in line with current literature. Second, we observed a positive association between pre-stroke mRS and ΔmRS between baseline and 3-month values, even after eliminating the effect of possible confounders and mediators, as suggested by our partial correlation and mediation analysis.

Another strength of the study is the multicenter design, which reflects different systems of care and different populations in a real-world setting, and by the comparison with a control group of patients with pre-stroke mRS 0–2.

There are several limitations in our study, including its retrospective design with selection bias. We did not control for patients with pre-stroke mRS 3 who were not treated by EVT. Another limitation of our study is that the reason for the disability was unknown for around 30% of patients. One could hypothesize that disability from prior strokes or comorbidities versus orthopaedic causes may have different implications, the latter having better outcomes than the former. However, this has not been evaluated in the literature. A sub-analysis of the MR CLEAN data focusing on patients with pre-stroke mRS 3 found that the rate of mRS 0–3 at 3 months was highest among patients with cardiopulmonary disease (12/36; 33%) and unknown cause for dependence (9/27; 33%), followed by other causes (4/15;

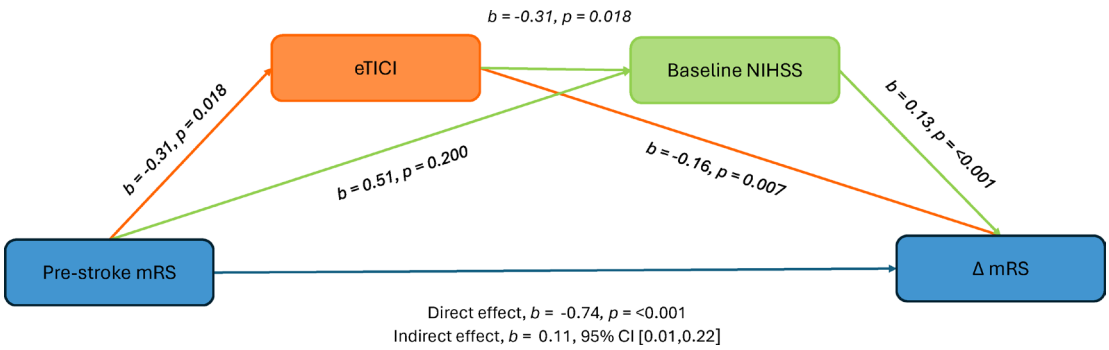

Figure 3 Model of pre-stroke mRS as a predictor of ΔmRS at 3 months, mediated by eTICI and baseline NIHSS. The CI for the indirect effect is a BCa bootstrapped CI based on 5000 samples. mRS, modified Rankin Scale; eTICI, expanded Thrombolysis in Cerebral Ischemia; NIHSS, National Institutes of Health Stroke Scale.

27%).[16] Unfortunately, a subgroup analysis in our study was not possible due to the high rate of missing data/unknown causes.

Another limitation was the limited sample size due to the scarcity of patients with pre-stroke mRS 3 undergoing EVT, especially in the ET, considering that these patients are currently off label according to current guidelines since they were excluded by randomised controlled trials.[1 2 30]

CONCLUSION

Patients with a moderate pre-stroke disability (mRS 3) are likely to have similar outcomes after EVT in the ET to patients with slight or no pre-stroke disability (mRS 0–2), with no differences in safety. Therefore, our results support the use of EVT in the ET in patients with pre-stroke mRS 3.

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Contributors IM and VDR researched literature and conceived the study. All authors were involved in patient recruitment and data analysis. IM and LR performed the statistical analyses and wrote the first draft of the paper. IM, LR, and VDR interpreted data. All authors reviewed and edited the manuscript and approved the final version and IM is the guarantor.

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Patient consent for publication Not applicable.

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Supplementary Table 1. Distribution of patient enrollment among the five centers. Group 1 (patients with pre-stroke mRS 0-2) and Group 2 (patients with pre-stroke mRS 3).

	Group 1 (n = 90)	Group 2 (n = 90)	
Rome Tor Vergata	26 (28.9)	19 (21.1)	
Barcelona	36 (40.0)	36 (40.0)	
Boston Medical Center	22 (22.4)	22 (22.4)	p value = 0.088
Rome Gemelli	6 (6.7)	6 (6.7)	
Padua	-	7 (7.8)	

Values are number of patients (%).

	All (n=180)	Group 1 (n=90)	Group 2 (n=90)	p value
Demographic characteristics and vascular risk factors				
Age [a]	84 (76-88)	83 (76-87)	84 (76-88)	0.380
Male	54 (30)	27 (30)	27 (30)	0.870
Arterial hypertension	155 (86)	75 (83)	80 (89)	0.404
Hypercholesterolemia	95 (52)	46 (51)	47 (52)	0.999
Diabetes mellitus	45 (25)	16 (18)	28 (31)	0.120
Smoking habit	41 (23)	22 (24)	16 (18)	0.481
Ongoing antiplatelet therapy	29 (16)	15 (17)	14 (15)	0.978
Ongoing anticoagulant therapy	30 (17)	14 (15)	16 (18)	
Clinical presentation at baseline				
NIH Stroke Scale score [a]	17 (12-21)	17 (11-20)	16 (12-22)	0.470
SBP, mmHg [a]	150 (138-170)	150 (138-170)	150 (136-175)	0.831
DBP, mmHg [a]	80 (70-90)	82 (70-98)	80 (68-86)	**0.049**
Glycemia, mg/dl [a]	123 (104-146)	117 (103-138)	125 (105-160)	0.332
TOAST classification				0.867
Undetermined origin	22 (12)	10 (11)	12 (13)	
Cardioembolic	67 (37)	33 (37)	34 (38)	
Atherosclerosis	17 (9)	10 (11)	7 (8)	
Other	2 (1)	1 (1)	1 (1)	
Neuroradiological features				
Baseline ASPECTS [a]	8 (7-10)	9 (7-10)	8 (7-10)	0.676
Left side of occlusion	112 (62)	82 (61)	58 (63)	0.880
Site of occlusion				0.374
Isolated MCA – M1	85 (47.)	40 (44)	45 (50)	
Isolated MCA – M2	43 (24)	21 (23)	22 (24)	
Isolated ACA	2 (1)	0 (0)	2 (2)	
Tandem	8 (4)	5 (6)	3 (3)	
Terminal ICA T-type	32 (18)	18 (20)	14 (16)	
ICA extra	3 (2)	3 (3)	0 (0)	
Revascularization treatment				
Rt-PA	36 (20.0)	19 (21.1)	17 (18.9)	0.737
Onset-to-door time, min [a]	459 (367-695)	480 (379-712)	427 (360-689)	0.147
Onset-to-recanalization time, min [a]	552 (421-738)	552 (451-741)	556 (387-735)	0.815
Procedural duration, min [a]	37 (25-60)	37 (27-56)	37 (22-62)	0.637
Device passages, nr [a]	2 (1-3)	2 (1-3)	2 (1-3)	0.203
Intraprocedural complications	20 (11)	12 (13)	8 (9)	0.881

Procedural sedation				0.380
General anesthesia	25 (14)	14 (15)	11 (12)	
Continous sedation	110 (61)	52 (58)	61 (68)	
None	45 (25)	24 (27)	18 (20)	

Supplementary Table 2. Comparison between Group 1 (patients with pre-stroke mRS 0-2) and Group 2 (patients with pre-stroke mRS 3) according to baseline and treatment characteristics of the study population. SBP = systolic blood pressure, DBP = diastolic blood pressure, ASPECTS = Alberta stroke program early CT score, MCA = middle cerebral artery, ACA = anterior cerebral artery, ICA = internal cerebral artery. Unless specified, values are number of patients (%). [a] Median (interquartile range). Bold values denote statistical significance ($p < 0.05$).

	Group 2 (n = 90)	
Cognitive impairment	17 (18.9)	
Previous stroke	2 (2.2)	
Cardiopulmonary disease	7 (7.8)	
Musculoskeletal disease	22 (24.4)	p value = 0.306
Other neurological disorder	5 (2.8)	
Other causes	5 (2.8)	
Need for assistance due to multiple unspecified comorbidities	5 (2.8)	
Unknown/Missing	27 (30.0)	

Supplementary Table 3. Description of the reason for disability of patients with a pre-stroke mRS score of 3 (Group 2). Values represent percentages of patients.

Supplementary Table 4. Comparison of the type of hemorrhagic transformation according to ECASS-III criteria between Group 1 (patients with pre-stroke mRS 0-2) and Group 2 (patients with pre-stroke mRS 3).

	Group 1 (n = 90)	Group 2 (n = 90)	
HI1	8 (8.9)	7 (7.8)	
HI2	6 (6.7)	8 (8.9)	
PH1	4 (4.4)	3 (3.3)	p value = 0.868
PH2	6 (6.7)	3 (3.3)	
SAH	1 (1.1)	2 (2.2)	

Values are number of patients (%). HI = Hemorrhagic Infarction, PH = Parenchymal Hematoma, SAH = subarachnoid hemorrhagic transformation