Safety and Outcome of Endovascular Treatment in Prestroke-Dependent Patients Results From MR CLEAN Registry

Safety and Outcome of Endovascular Treatment in Prestroke-Dependent Patients
Results From MR CLEAN Registry

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Background and Purpose—Prestroke dependence is an exclusion criterion in most trials of endovascular treatment (EVT) for acute ischemic stroke. Little is known about outcomes after EVT in these patients. We compared outcome and safety of EVT between prestroke-dependent and prestroke-independent patients.

Methods—We report patients with an anterior circulation occlusion who were included between March 2014 and June 2016 in the MR CLEAN registry (Multicenter Randomized Clinical Trial of Endovascular Treatment of Acute Ischemic Stroke)—a prospective, multicenter, observational study for stroke intervention centers in the Netherlands. Prestroke dependence was defined as modified Rankin Scale score of 3 to 5 before onset of current stroke. Primary outcome was favorable outcome at 90 days, defined as modified Rankin Scale of 0 to 2 or not worsening of the modified Rankin Scale score. Secondary outcomes included National Institutes of Health Stroke Scale score post-intervention, reperfusion grade, and safety outcomes. Logistic regression analyses (adjusted for age, baseline National Institutes of Health Stroke Scale score, collaterals, time to EVT, and intravenous thrombolysis before EVT) were used to assess the association between prestroke dependence and outcomes.

Results—One thousand four hundred forty-one patients were included in the present study, of whom 157 (11%) were prestroke dependent. Favorable outcome was seen in 27% prestroke-dependent patients, compared with 42% prestroke-independent patients (*P*<0.05). After adjustment, prestroke dependence was not associated with less-favorable outcome ($OR_{adjusted}$, 0.90; 95% CI, 0.58–1.39). The occurrence of symptomatic intracranial hemorrhage and ischemic stroke progression was similar in both groups.

Conclusions—A substantial proportion of prestroke-dependent patients will reach prestroke modified Rankin Scale scores after EVT, and complication rates are comparable with prestroke-independent patients. Therefore, prestroke-dependent patients should not be routinely excluded from EVT. **(*Stroke*. 2018;49:2406-2414. DOI: 10.1161/STROKEAHA.118.022352.)**

Key Words: brain ischemia ■ humans ■ logistic models ■ registries ■ reperfusion

Endovascular treatment (EVT) for acute ischemic stroke has shown to be safe and effective in recently reported trials.[1–8] However, these trials included only few patients who were functionally dependent (modified Rankin Scale [mRS], >2) before current stroke: 21 (4.2%) in MR CLEAN (Multicenter Randomized Clinical Trial of Endovascular Treatment of Acute Ischemic Stroke), 6 (1.9%) in ESCAPE (Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion With Emphasis on Minimizing CT to Recanalization Times), 1 (0.5%) in REVASCAT (Endovascular Revascularization With Solitaire Device Versus Best Medical Therapy in Anterior Circulation Stroke Within 8 Hours), and 3 (1.5%) in SWIFT-PRIME (Solitaire With the Intention for Thrombectomy as Primary Endovascular Treatment for Acute Ischemic Stroke).[9] After implementation of EVT in clinical practice, thrombectomy registries have

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not reported on outcome of prestroke-dependent patients.[10,11] Hence, current data about EVT for acute ischemic stroke in prestroke functionally dependent patients are limited.

Overall, acute ischemic stroke in prestroke-dependent patients is associated with poor outcome and high mortality.[12–15] Although the benefit is uncertain, American Heart Association guidelines state that the use of EVT may be reasonable for prestroke-dependent patients with a causative occlusion of the intracranial internal carotid artery or proximal middle cerebral artery.[16] The aim of the present study is to compare characteristics, outcome, and safety of prestroke-dependent patients with acute ischemic stroke of the anterior circulation who underwent EVT, with those of patients who were independent (mRS, 0–2).

Methods

Patients

We analyzed patients from the MR CLEAN registry who were registered between March 16, 2014, and June 15, 2016. Source data will not be made available because of legislatory issues on patient privacy, but detailed analytic methods and study materials, including log files of statistical analyses, will be made available to other researchers on request to the first author. The MR CLEAN registry is an ongoing multicenter, prospective, observational study in all centers that perform EVT in the Netherlands. Enrollment in the MR CLEAN registry started directly after the final MR CLEAN trial randomization on March 16, 2014. The MR CLEAN registry was approved by the ethics committee of the Erasmus University MC, Rotterdam, the Netherlands (MEC-2014–235). With this approval, it was approved by the research board of each participating center. At University Medical Center Utrecht, approval to participate in the study has been obtained from their own research board and ethics committee.

All patients undergoing EVT (defined as entry into the angiography suite and arterial puncture) for acute ischemic stroke in the anterior or posterior circulation have been registered in the MR CLEAN registry. EVT consisted of arterial catheterization with a microcatheter to the level of the occlusion, followed by mechanical thrombectomy or thrombus aspiration, with or without delivery of a thrombolytic agent. The method of EVT for each patient was left to the discretion of the treating physicians.

For the present study, we used the following selection criteria for analysis: groin puncture within 6.5 hours after symptom onset; age of ≥18 years; and intracranial proximal arterial occlusion of the anterior circulation (intracranial carotid artery or middle [M1/M2] or anterior [A1/A2] cerebral artery), demonstrated by computed tomographic angiography. Prestroke functional status was estimated according to the mRS score[17] and was reported by local investigators on the basis of information provided by patients, their families, or information derived from medical records. Patients were excluded when prestroke mRS score was missing. Prestroke dependence was defined as prestroke mRS score of 3 to 5. Local investigators reported the cause of prestroke dependence, and if the cause was not reported, it was extracted from medical records. Two researchers (R.-J.B.G. and M.V.) categorized the causes of prestroke dependence by consensus. The cause was classified as unknown when medical records did not provide sufficient information.

ASPECTS (Alberta Stroke Program Early CT Score) on baseline noncontrast computed tomography and collateral status on computed tomographic angiography were scored by an independent core laboratory using internationally accepted definitions.[18,19]

Outcome Measures

The primary outcome is functional outcome according to the mRS at 90 days (investigators were instructed to assess the mRS score at 90±14 days). To compare functional outcome between prestroke-dependent and prestroke-independent patients, we report favorable outcome. Favorable outcome was defined as mRS of 0 to 2 or not worsening of the mRS score, in concordance with definitions used in previous studies investigating acute ischemic stroke in prestroke functionally dependent patients.[14,15] Secondary outcomes were National Institutes of Health Stroke Scale (NIHSS) score post-intervention,[20] reperfusion grade, and safety outcomes. An independent core lab, blinded for clinical outcome, assessed all digital subtraction angiographies. Reperfusion was scored by the extended Thrombolysis in Cerebral Ischemic (eTICI) score,[21] which ranges from grade 0 (no reperfusion) to grade 3 (complete reperfusion). Successful reperfusion was defined as eTICI 2B or higher. When a bidirectional view on final digital subtraction angiographies was not available (missing lateral or anterior view), the maximum eTICI score was 2A. Safety outcomes were occurrence of symptomatic intracranial hemorrhage, ischemic stroke progression, and mortality at 90 days. Intracranial hemorrhage was considered symptomatic if the patient had died or had deteriorated neurologically (a decline of at least 4 points on the NIHSS) and the hemorrhage was related to the clinical deterioration (according to Heidelberg criteria).[22] Symptomatic intracranial hemorrhage was assessed by the adverse events committee after evaluation of medical reports and imaging assessment.

Statistical Analysis

Baseline characteristics and outcomes were analyzed for patients with and without prestroke dependence, defined as mRS of 3 to 5. For analyzing differences in baseline characteristics between the groups, we used standard statistics. Unadjusted and adjusted (for age, baseline NIHSS score, collateral status, time from onset to EVT, and intravenous thrombolysis [IVT] before EVT) logistic regression analyses were used to determine the association between prestroke dependence and outcomes. To assess the statistical significance of interaction between reperfusion status and prestroke functional status on functional outcome, we added a multiplicative term to the regression model.

Missing NIHSS scores were retrospectively scored with a standardized score chart based on information from the reported neurological examination. If successful reperfusion was not achieved during EVT, the time of last contrast bolus injection was used as a proxy for time of reperfusion. Any follow-up mRS score of 0 to 5 assessed within 30 days was considered missing. Missing mRS scores at 90 days were replaced by mRS scores derived from multiple imputation.[23] Multiple imputation was performed with Stata/SE 14.1 (StataCorp, TX) with the following variables: age, sex, baseline NIHSS score, diabetes mellitus, previous myocardial infarction, previous stroke, atrial fibrillation, IVT before EVT, systolic blood pressure, baseline ASPECTS, occlusion segment, computed tomographic angiography collateral status, time from symptom onset to start of EVT, time from symptom onset to successful reperfusion, eTICI score at the end of the intervention, and NIHSS score after 24 to 48 hours. All descriptive analyses include patients with complete data, whereas all regression models include all patients with imputed data. Statistical analyses were performed with Stata/SE 14.1 (StataCorp, TX).

Results

Patient Characteristics

In the MR CLEAN registry, 1627 patients were registered until June 15, 2016. Of these, 187 patients did not meet the inclusion criteria for this study (Figure I in the online-only Data Supplement), of whom 27 because of missing prestroke mRS score and 20 because of discrepancy between reported prestroke mRS score and description of prestroke functional status in medical records. Table 1 shows the baseline characteristics of the remaining 1441 patients of whom 1284 patients (89%) were functionally independent before the current stroke (mRS, 0–2) and 157 patients (11%) who were functionally dependent (mRS, 3–5). Prestroke-dependent patients were significantly older and had more comorbidity. Left hemispheric stroke was

Table 1. Baseline Characteristics

	Prestroke mRS, 0–2 (n=1284)	Prestroke mRS, 3–5 (n=157)	*P* Value	Missings (n)
Age, y; median (IQR)	69 (59–78)	80 (71–86)	<0.05	0
Male sex, n (%)	706 (55)	64 (41)	<0.05	0
NIHSS, median (IQR)	16 (11–20)	17 (13–20)	0.24	27
Clinical localization: left hemisphere, n (%)	683 (53)	91 (58)	<0.05	0
Systolic blood pressure, mean mm Hg (SD)	150 (24)	149 (26)	0.70	39
Intravenous alteplase treatment, n (%)	1023 (80)	100 (64)	<0.05	2
Medical history				
Atrial fibrillation, n (%)	262 (20)	58 (37)	<0.05	20
Hypertension, n (%)	618 (48)	97 (62)	<0.05	17
Diabetes mellitus, n (%)	197 (15)	46 (29)	<0.05	9
Hypercholesterolemia, n (%)	351 (27)	59 (38)	<0.05	46
Myocardial infarction, n (%)	170 (13)	45 (29)	<0.05	25
Peripheral artery disease, n (%)	109 (8)	23 (15)	<0.05	25
Ischemic stroke, n (%)	183 (14)	52 (33)	<0.05	8
Medication and intoxications				
Current smoking, n (%)	297 (23)	30 (19)	0.34	14
Statin use, n (%)	435 (34)	66 (42)	0.06	25
Antiplatelet use, n (%)	400 (31)	70 (45)	<0.05	18
Coumarine use, n (%)	145 (11)	40 (25)	<0.05	11
Imaging				
Level of occlusion on noninvasive vessel imaging, n (%)			<0.05	72
ICA	75 (6)	5 (3)		
ICA-T	273 (21)	29 (18)		
M1	704 (55)	98 (62)		
M2	154 (12)	15(10)		
Other: M3/anterior	11 (1)	5 (3)		
ASPECTS, median (IQR)	9 (7–10)	9 (8–10)	0.76	62
ASPECTS subgroups, n (%)			0.27	
0–4	79 (6)	7 (4)		
5–7	302 (24)	31 (20)		
8–10	845 (66)	115 (73)		
Collaterals, n (%)			0.87	105
Grade 0	85 (7)	9 (6)		
Grade 1	393 (31)	53 (34)		
Grade 2	463 (36)	58 (37)		
Grade 3	247 (19)	28 (18)		
Workflow				
Transfer from primary stroke center, %	706 (55)	72 (46)	<0.05	0
Onset to EVT start, min; median (IQR)	205 (160–265)	220 (165–270)	0.06	0
Onset to reperfusion/last contrast bolus, min; median (IQR)	266 (216–330)	291 (222–338)	0.13	82
Median duration of interventional procedure, min; median (IQR)	64 (40–90)	61 (45–85)	0.75	140

ASPECTS indicates Alberta Stroke Program Early CT Score; EVT, endovascular treatment; ICA, intracranial carotid artery; ICA-T, intracranial carotid artery terminus; IQR, interquartile range; mRS, modified Rankin Scale; and NIHSS, National Institutes of Health Stroke Scale.

significantly more frequent in prestroke-dependent patients, they were less often treated with intravenous thrombolytics, and were less often transferred from a primary stroke center.

Prestroke-dependent patients had more often intracranial carotid artery and ICA-T occlusions and less M1 occlusions, but differences were minimal. ASPECTS and collateral scores were not significantly different.

Intervention Characteristics

Prestroke-dependent patients in whom an attempt was made for thrombus retrieval, successful reperfusion (eTICI 2B or higher) was achieved in 80 of 134 (60%) patients, which was not different in prestroke-independent patients: 655 of 1109 (59%; P=0.89; Table I in the online-only Data Supplement).

Clinical Outcomes

Functional Outcome

An mRS score at 90 days was available for 1320 patients (Figure 1). Favorable outcome was less frequent in prestroke-dependent patients (40 of 147 [27%] versus 491 of 1173 [42%] in prestroke-dependent patients; P<0.05; Table 2). After adjustments, prestroke dependence was not associated with a reduced likelihood of favorable outcome ($OR_{adjusted}$, 0.90; 95% CI, 0.58–1.39; Table 3). In the group of patients with prestroke dependence, better reperfusion status on eTICI was associated with higher chances of favorable outcome ($OR_{adjusted}$, 1.36; 95% CI, 1.03–1.79; Figure 2), and the effect of successful reperfusion (eTICI 2B–3) on favorable outcome was not different between prestroke-dependent and prestroke-independent patients ($P_{interaction}$, 0.14; Figure IIA in the online-only Data Supplement).

Early Clinical Outcome

Twenty-four to 48 hours post-intervention, the NIHSS score was higher for prestroke-dependent patients compared with prestroke-independent patients (Table 2). In prestroke-dependent patients, postintervention improvement of ≥4 points on the NIHSS was substantial (43%) yet lower than in prestroke-independent patients (54%; P<0.05).

Safety Outcomes

Death occurred in 79 of 157 (50%) patients with prestroke mRS of 3 to 5, compared with 302 of 1284 (24%) patients with prestroke mRS of 0 to 2. Prestroke dependence was associated with a higher mortality rate compared with prestroke independence ($OR_{adjusted}$, 2.07; 95% CI, 1.40–3.04). Nevertheless, the rate of symptomatic intracranial hemorrhage (8% versus 6%; P=0.28) and progression of ischemic stroke (11% versus 9%; P=0.55) were similar between the groups.

Better reperfusion status on eTICI was associated with lower mortality rate in prestroke-dependent patients ($OR_{adjusted}$, 0.79; 95% CI, 0.62–1.02). The effect of successful reperfusion (eTICI 2B–3) on mortality was not different between prestroke-dependent and prestroke-independent patients ($P_{interaction}$, 0.99; Figure IIB in the online-only Data Supplement). Causes of death in successfully reperfused prestroke-dependent patients were intracranial hemorrhage (19.4%), ischemic stroke progression or new ischemic stroke (11.1%), pneumonia (16.7%), cardiac arrest (8.3%), withdrawal of treatment because of persisting neurological deficit or refractory cardiopulmonary symptoms (13.9%), and unknown (30.6%).

Cause of Prestroke Dependence

The causes of prestroke dependence were heterogeneous, the most frequent being previous stroke and cardiopulmonary disease (Table V in the online-only Data Supplement). Mortality was the highest in patients who had had recent surgery (75%) and was the lowest in patients with a previous ocular disorder (25%).

Discussion

We presented data of a relatively large group of prestroke-dependent patients, multicenter, prospectively collected, and representative of current clinical practice. In our registry, 11% of patients with ischemic stroke because of an intracranial proximal arterial occlusion of the anterior circulation who underwent EVT were prestroke functionally dependent. In more than a quarter of prestroke-dependent patients, the mRS score at 3 months was not higher than the prestroke mRS score. Prestroke dependence was associated with increased mortality rate, without increased rate of treatment-related complications. In prestroke-dependent patients, better reperfusion was associated with favorable functional outcome, which suggests a positive effect of EVT.

Previous studies of IVT in prestroke-dependent patients showed prestroke dependence in 2% to 7%, considerably lower than in our study,[14,15] probably as a result of more strict exclusion criteria for IVT compared with EVT. In the IVT studies, prestroke-dependent patients were older and had more vascular risk factors, as was the case in our study. Death within 3 months occurred in 38% to 48% in the previous IVT

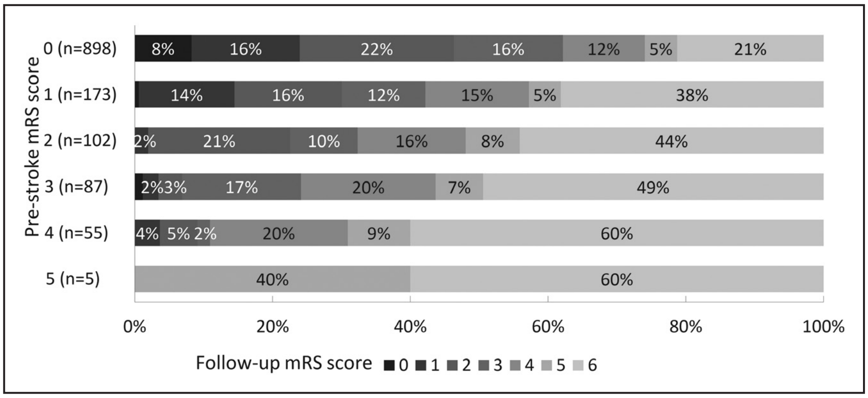

Figure 1. Distribution of the modified Rankin Scale (mRS) at 90 d for prestroke mRS subgroups (n=1320).

Table 2. Primary and Secondary Outcomes

	Prestroke mRS, 0–2 (n=1284)	Prestroke mRS, 3–5 (n=157)	*P* Value
mRS at 90 d, median (IQR)*	3 (2–5)	6 (4–6)	<0.05
Favorable outcome, n (%)*	491 (42)	40 (27)	<0.05
Return to at least preexistent mRS, n (%)*	122 (10)	40 (27)	<0.05
sICH, n (%)	71 (6)	12 (8)	0.28
Ischemic stroke progression, n (%)	120 (9)	17 (11)	0.55
Death within 90 d, n (%)	302 (24)	79 (50)	<0.05
Improvement on NIHSS of ≥4 points, n (%)	622 (48)	57 (36)	<0.05
Deterioration on NIHSS of ≥4 points, n (%)	146 (11)	20 (13)	0.61
NIHSS postintervention, 24 h; median (IQR)†	10 (4–18)	14 (8–20)	<0.05

IQR indicates interquartile range; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; and sICH, symptomatic intracranial hemorrhage.

*n=1320 (mRS score at 90 d was missing for 121 patients); favorable outcome was defined as mRS score of 0 to 2 or not worsening mRS score.

†n=1283 (baseline, postintervention NIHSS score, or both were missing for 158 patients).

studies, and return to the prestroke mRS score was observed in 34% to 40%, which is higher than in our study. However, it should be noted that in our study, in contrast to IVT studies, a proximal intracranial artery occlusion on computed tomographic angiography was present in all patients with consequently a higher median NIHSS score.

The cause of prestroke dependence in patients with acute ischemic stroke was reported in one of the previous IVT studies.[15] Dementia was the most frequent cause (34%), whereas in our study, cognitive impairment was the cause for only 9% of patients. Possibly, the invasive nature of EVT might have led to a higher threshold in providing treatment for the cognitively impaired.

Only 1 single-center observational study investigated EVT in prestroke-dependent patients, which included 23 patients with an intracranial proximal artery occlusion of the anterior circulation.[24] Similar to our study, patients were older and more often had a previous stroke than independent patients, and occurrence of symptomatic intracranial hemorrhage could not be held responsible for the high mortality rate. Death occurred in 35% of prestroke-dependent patients, which was lower than in our study. However, in contrast with our study, patients with limited life expectancy were excluded, and the distribution of prestroke mRS score was not reported.

This study has certain limitations. First, the mRS score might not be an appropriate way to determine functional outcome in prestroke functionally dependent patients. With higher mRS scores, the score is less discriminative for neurological deficit. Second, because functional outcome is influenced by preexistent disability in prestroke-dependent patients, the value of comparison of functional outcome with prestroke-independent patients is limited. Nevertheless,

Table 3. Comparison of Primary and Secondary Outcomes Between Patients Who Were Dependent (mRS, 3–5) Versus Independent (mRS, 0–2) Before Current Ischemic Stroke

	Unadjusted Odds Ratio (95% CI)	Adjusted Odds Ratio (95% CI)
mRS at 90 d, median (IQR)*	0.31 (0.22–0.44)†	0.34 (0.25–0.48)†
Favorable outcome, n (%)*	0.57 (0.39–0.84)	0.90 (0.58–1.39)
Return to at least preexistent mRS, n (%)*	3.55 (2.34–5.39)	5.10 (3.12–8.34)
sICH, n (%)	1.41 (0.75–2.67)	1.36 (0.71–2.64)
Ischemic stroke progression, n (%)	1.18 (0.69–2.02)	1.16 (0.66–2.03)
Mortality at 90 d, n (%)	3.17 (2.25–4.68)	2.07 (1.40–3.04)
Postintervention ≥4 improvement on NIHSS, n (%)‡	0.60 (0.42–0.85)	0.70 (0.47–1.03)
Postintervention deterioration of ≥4 on NIHSS, n (%)‡	1.14 (0.69–1.88)	1.10 (0.65–1.85)
NIHSS post-intervention (24 h), median (IQR)‡	β, 2.60 (1.01–4.19)	β, 1.29 (−0.18 to 2.76)

Odds ratios estimated with logistic regression analyses. Adjustments were made for age, time from onset to EVT, baseline NIHSS score, collateral score, and IVT before EVT. EVT indicates endovascular treatment; IQR, interquartile range; IVT, intravenous thrombolysis; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; and sICH, symptomatic intracranial hemorrhage.

*n=1320 (mRS score at 90 d was missing for 121 patients).

†Common odds ratio.

‡n=1283 (baseline, postintervention NIHSS score, or both were missing for 158 patients).

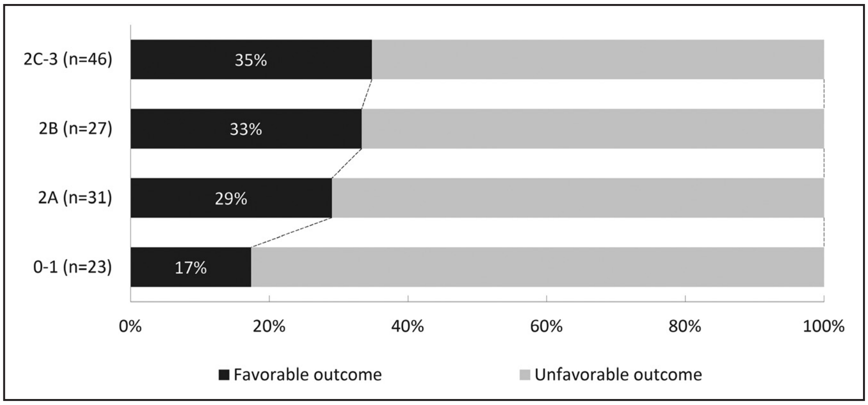

Figure 2. Favorable outcome of prestroke-dependent patients according to extended Thrombolysis in Cerebral Ischemic (eTICI) score.* *Patients in whom an attempt for thrombectomy was performed, and both modified Rankin Scale score at 90 d and postintervention eTICI score were available (n=127).

our definition of favorable outcome is consistent with previous studies, which investigated acute ischemic stroke in prestroke functionally dependent patients,[14,15] and takes into account the low threshold of negatively shifting on the lower range of the mRS. Because reaching functional independence (mRS, 0–2) is generally considered favorable outcome for prestroke-independent patients, our definition of favorable outcome confines overreporting of poor functional outcome in prestroke-independent patients. Third, the prestroke mRS score was estimated by local investigators on the basis of patient information and medical records and was not assessed according to a standardized method, such as the assessment of the mRS score at 90 days. To minimize information bias, medical records of prestroke-dependent patients were checked for misinterpretation of the prestroke mRS score. Fourth, we were not able to identify patients with a prestroke mRS that was caused by a transient disease, such as an adequately treated infection, bone fracture, or heart condition. Future research should focus on this group of patients because they likely have a different prognosis compared with patients with other, more permanent pathogeneses for preexisting disability. Finally, we only presented patients who underwent EVT, so we cannot rule out some selection bias, and we are unable to determine treatment effect because we lacked a control group. Nevertheless, because data about outcome and safety of EVT in prestroke-dependent patients are scarce, the results of our study may be able to support decision-making in daily practice.

Conclusions

A substantial proportion of prestroke-dependent patients who underwent EVT will recover to their prestroke functional status. In these patients, neurological deficits may be substantially reduced, and the intervention-related complication rate is comparable with prestroke-independent patients. Furthermore, the chance of achieving good functional outcome was positively affected by better reperfusion status. Prestroke-dependent patients might, therefore, benefit from EVT and should not be routinely excluded from this treatment. Nevertheless, prestroke-dependent patients have a high mortality rate; therefore, the decision to perform EVT in prestroke-dependent patients should be made with caution, especially when prognosis of comorbidity likely supersedes a possible effect of EVT.

Appendix

MR CLEAN registry (Multicenter Randomized Clinical Trial of Endovascular Treatment of Acute Ischemic Stroke) investigators are as follows. Executive committee: Diederik W.J. Dippel (Department of Neurology, Erasmus MC University Medical Center, Rotterdam), Aad van der Lugt (Department of Radiology, Erasmus MC University Medical Center, Rotterdam), Charles B.L.M. Majoie (Department of Radiology, Academic Medical Center, Amsterdam), Yvo B.W.E.M. Roos (Department of Neurology, Academic Medical Center, Amsterdam), Robert J. van Oostenbrugge (Department of Neurology, Cardiovascular Research Institute Maastricht, Maastricht University Medical Center), Wim H. van Zwam (Department of Radiology, Cardiovascular Research Institute Maastricht, Maastricht University Medical Center), Jelis Boiten (Department of Neurology, Haaglanden MC, The Hague), Jan-Albert Vos (Department of Radiology, Sint Antonius Hospital, Nieuwegein). Study coordinators: Ivo G.H. 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