# Benefit of successful reperfusion achieved by endovascular thrombectomy for patients with ischemic stroke and moderate pre-stroke disability (mRS 3) results from the MR CLEAN Registry

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Original research

# Benefit of successful reperfusion achieved by endovascular thrombectomy for patients with ischemic stroke and moderate pre-stroke disability (mRS 3): results from the MR CLEAN Registry

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## ABSTRACT

**Background** Pre-stroke dependent patients (modified Rankin Scale score (mRS) ≥3) were excluded from most trials on endovascular treatment (EVT) for acute ischemic stroke (AIS) in the anterior circulation. Therefore, little evidence exists for EVT in those patients. We aimed to investigate the safety and benefit of EVT in pre-stroke patients with mRS score 3.

**Methods** We used data from the Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic stroke in the Netherlands (MR CLEAN) Registry. All patients treated with EVT for anterior circulation AIS with pre-stroke mRS 3 were included. We assessed causes for dependence and compared patients with successful reperfusion (defined as expanded Thrombolysis in Cerebral Ischemia scale (eTICI) 2b–3) to patients without successful reperfusion. We used regression analyses with pre-specified adjustments. Our primary outcome was 90-day mRS 0–3 (functional improvement or return to baseline).

**Results** A total of 192 patients were included, of whom 82 (43%) had eTICI <2b and 108 (56%) eTICI ≥2b. The median age was 80 years (IQR 73–87). Fifty-one of the 192 patients (27%) suffered from previous stroke and 36/192 (19%) had cardiopulmonary disease. Patients with eTICI ≥2b more often returned to their baseline functional state or improved (n=26 (26%) vs n=15 (19%); adjusted odds ratio (aOR) 2.91 (95% CI 1.08 to 7.82)) and had lower mortality rates (n=49 (49%) vs n=50 (64%); aOR 0.42 (95% CI 0.19 to 0.93)) compared with patients with eTICI <2b.

**Conclusions** Although patients with AIS with pre-stroke mRS 3 comprise a heterogenous group of disability causes, we observed improved outcomes when patients achieved successful reperfusion after EVT.

### Key messages

**What is already known on this topic?**

⇒ Available literature on the efficacy and safety of EVT in pre-stroke disabled patients is not unambiguous and includes mostly the whole range of mRS score disabilities (mRS 3–5) and/or is compared to EVT in pre-stroke independent patients (mRS 0–2). We think that the equipoise in this comparison is limited and that analyzing the benefit of EVT in the same patient population (regarding pre-stroke functional state) is the more relevant question to ask.

**What does this study add?**

⇒ In this study we were able to show that (1) the pre-stroke functional state was not always reported accurately and, since pre-stroke patients with mRS 3 could have 90-day mRS 0–2, falsely high mRS scores were not uncommon; (2) a quarter of successfully treated pre-stroke patients with mRS 3 did not worsen to a 90-day mRS score >3; and (3) mortality decreased by 15% and the odds of having symptomatic intracranial hemorrhage decreased from 11% to 6%.

**How does this study affect research, practice, or policy?**

⇒ This study shows that successfully treating pre-stroke patients with mRS 3 is beneficial and safe. We hypothesize that in the future (1) an increasing number of EVT-eligible patients will have some pre-morbid disabilities/comorbidities and (2) EVT techniques/stroke care will continue to improve, further improving patient outcomes. This could outdate current criteria for EVT eligibility (pre-stroke mRS 0–1) and could change the selection practice of patients with AIS with some pre-stroke disability.

## INTRODUCTION

Several randomized trials have proved the benefit of endovascular treatment (EVT) for acute ischemic stroke (AIS).[1–7] Pre-stroke functional dependence was an exclusion criterion in most trials and, as such, current guidelines restrict their recommendations for EVT to patients with a pre-stroke modified Rankin Scale (mRS) score of 0–1.[8] However, in clinical practice, patients with AIS and

pre-stroke mRS 0–2 are routinely offered EVT.[9] Furthermore, most evidence for EVT in patients with pre-stroke mRS 3–5 has been gathered from observational studies.[10–13] In these studies, pre-stroke dependent patients with the full range of dependence (mRS 3–5) were included and compared with pre-stroke independent patients (mRS 0–2), showing that the latter fare better than the former.[13–15] The clinical interpretability of such aggregate comparisons is, however, limited by the fact that patients in the mRS 3–5 group are highly heterogeneous and the degree of equipoise with treating a patient with pre-stroke mRS 3 is very different from that with mRS 5. Besides, comparing the outcomes of these patients to those without pre-stroke disability tells us little about the treatment effect in the former group. As such, it is quite unclear whether the outcome of patients with pre-stroke mRS 3 would improve with achieving reperfusion via EVT. Since EVT itself is not always successful, comparing outcomes with the achievement of successful reperfusion via EVT versus unsuccessful reperfusion could serve as a proxy to evaluate the treatment effect of EVT in this challenging group in a registry setting. Therefore, we aimed to investigate the benefit of successful reperfusion, as a proxy for EVT, in patients with moderate pre-stroke disability (mRS 3). Furthermore, we explored the association of different causes of pre-stroke dependence with clinical outcome.

## METHODS

### Patient selection and study design

We included patients from the MR CLEAN Registry, a multicenter prospective observational registry including all patients treated with EVT in the Netherlands after the last recruitment in the MR CLEAN trial[1] (16 March 2014) up to the last inclusion for Parts I and II (1 November 2017). All patients without contraindications received IV alteplase prior to EVT.[16] The MR CLEAN Registry protocol was approved by the ethics committee of the Erasmus University MC, Rotterdam, the Netherlands (MEC-2014–235). Further details on the objectives and full design of the Registry were reported by Jansen *et al*.[9] Due to privacy and data safety regulations, original data are not available for this study. Analysis results and statistical codes are available from the corresponding author on reasonable request.

For the current study, we included MR CLEAN Registry patients with anterior circulation AIS (occlusion in the internal carotid artery (ICA), internal carotid artery terminus (ICA-T), middle cerebral artery (M1 or M2 segments) or anterior cerebral artery (A1 or A2 segments)) up to 1 November 2017, aged ≥18 years, who were treated in a MR CLEAN trial center within 6.5 hours of symptom onset and had a pre-stroke mRS score of 3. Patients with a temporary cause of pre-stroke dependence (defined as a disability that was expected to return to independence within 1 month after the stroke; n=12) were excluded because this subgroup would likely have returned to independence (mRS 0–2) had they not suffered from a stroke and could therefore be considered pre-stroke independent.

### Data collection

Imaging and clinical data were centrally collected for the MR CLEAN Registry at baseline, during EVT, at 24–48 hours after EVT, and at 90 days after stroke. The 90-day mRS score was assessed by clinical or research nurses through a telephone interview 90 days after the index stroke. Imaging data were centrally adjudicated by a core laboratory, blinded to all clinical information except symptom side.[9] Reperfusion during EVT was graded by the expanded Thrombolysis in Cerebral Ischemia (eTICI) score,[17] ranging from 0 (no reperfusion) to 3 (complete reperfusion). Successful reperfusion was defined as an eTICI score of 2b or higher.

Pre-stroke functional status was estimated according to the mRS[18] and reported by local investigators based on information provided by patients, their families, or information derived from medical records. Local investigators also reported the cause of stroke dependence. Additional details and non-reported causes were extracted from medical records by the first author (FB) if available.

The causes of pre-stroke dependence were categorized into previous stroke, cardiopulmonary disease, cognitive impairment, musculoskeletal disease, neurological disorder other than stroke and dementia, other causes, need for assistance due to unspecified comorbidities and unknown causes (see online supplemental table 1 for further details). In case of multiple causes, the first author (FB) checked medical records and estimated which comorbidity had the highest impact. If it was not possible to identify a single contributor with the largest impact, the cause was classified as 'need for assistance due to unspecified comorbidities'. If no data on the dependence cause were available, it was classified as unknown.

### Outcome measures

The primary outcome was 90-day mRS score 0–3, indicating return to baseline or functional improvement compared with baseline. The latter could have occurred in case of a reason for disability that resolved within the 90-day assessment period or in case of an erroneous falsely high measurement of the pre-stroke mRS score. Secondary outcomes were change in 90-day mRS (ie, ΔmRS; mRS at 90 days minus baseline mRS). Safety outcomes were 30-day mortality, 90-day mortality and symptomatic intracranial hemorrhage (sICH). The latter was defined as neurological deterioration (≥4 points decline on the National Institutes of Health Stroke Scale (NIHSS)) or death and intracranial hemorrhage on CT related to the clinical deterioration (scored according to the Heidelberg criteria).[19]

### Statistical analyses

Baseline characteristics and outcomes were reported and compared based on patients' reperfusion status, with numbers and percentages or medians and interquartile ranges (IQR) appropriate to the type of data. For categorical variables we used $\chi^2$ tests when expected counts were >5 and Fisher's exact tests when the expected counts were <5. For continuous variables we used the Mann–Whitney U test.

Unadjusted and adjusted logistic regression analyses were used to determine the association between successful reperfusion and outcome resulting in adjusted and unadjusted (common) odds ratios (a[c]OR and u[c]OR, respectively) with 95% CIs. Binary and ordinal logistic regression was used for dichotomous and ordinal outcomes, respectively. Because the MR CLEAN Registry only includes patients who underwent EVT, we used successful reperfusion as an independent variable of interest (as proxy for EVT). This method was used previously.[10 20 21] Furthermore, since first-pass effect (FPE) reperfusions have been shown to be an important predictor for good clinical outcome after EVT,[22–24] we performed additional analyses (see online supplemental table 3) using FPE as an independent variable. We defined FPE as eTICI 2b–3 achieved with one attempt and non-FPE as any other post-eTICI achieved or an eTICI 2b–3 achieved with multiple attempts. Pre-specified adjustments were made for age,

baseline NIHSS score, collateral status, atrial fibrillation, baseline systolic blood pressure, stroke onset-to-groin puncture time, and IV alteplase treatment. Missing data in the regression analyses were imputed by using 'flong' multiple imputations models. Descriptive tables and figures were presented as crude unimputed data.

The effect of the cause of pre-stroke dependence on the outcome was assessed in a descriptive exploratory fashion only, since patient numbers per category were low. Statistical analyses were performed with IBM SPSS Statistics v25. P values <0.05 were considered statistically significant.

## RESULTS

### Patient characteristics

Of 3637 patients, 204 (5.6%) had a pre-stroke mRS score of 3. Twelve patients had a temporary cause of dependence, leaving 192 patients for the analyses (online supplemental figure 1). Table 1 shows the baseline characteristics of the included patients, stratified by reperfusion status. This revealed no significant differences between patients with and patients without successful reperfusion (eTICI ≥2b and eTICI <2b, respectively); two patients were excluded for not having post-eTICI scores

**Table 1** Baseline characteristics of included patients, stratified by reperfusion status (n=190)

| | Non-reperfused eTICI <2b (n=82) | Reperfused eTICI ≥2b (n=108) | P value | Missing (n) |
|---|---|---|---|---|
| Age (years), median (IQR) | 81 (70–87) | 80 (73–87) | 0.92 | 0 |
| Male sex, n (%) | 26 (32) | 35 (32) | 0.99 | 0 |
| IV alteplase treatment, n (%) | 53 (65) | 76 (70) | 0.44 | 0 |
| Smoking, n (%) | 11 (13) | 26 (24) | 0.08 | 54 |
| Atrial fibrillation, n (%) | 28 (34) | 42 (39) | 0.65 | 1 |
| Hypertension, n (%) | 48 (59) | 77 (71) | 0.06 | 6 |
| Diabetes mellitus, n (%) | 21 (26) | 28 (29) | 0.62 | 3 |
| Myocardial infarction, n (%) | 12 (14) | 25 (23) | 0.19 | 6 |
| NIHSS at baseline, median (IQR) | 15 (12–21) | 16 (13–22) | 0.47 | 3 |
| Systolic blood pressure (mmHg), median (IQR) | 153 (134–170) | 150 (130–164) | 0.16 | 3 |
| Left-sided occlusion, n (%) | 38 (46) | 43 (40) | 0.19 | 4 |
| Level of occlusion on CTA, n (%) | | | 0.66 | 1 |
| Intracranial ICA | 1 (1) | 3 (3) | | |
| ICA-T | 11 (11) | 21 (19) | | |
| M1 | 53 (64) | 66 (61) | | |
| M2 | 15 (18) | 14 (13) | | |
| Other (eg, M3, anterior cerebral artery) | 2 (2) | 3 (3) | | |
| Baseline collateral status*, n (%) | | | 0.91 | 6 |
| Grade 0 | 7 (9) | 9 (8) | | |
| Grade 1 | 31 (38) | 36 (33) | | |
| Grade 2 | 30 (37) | 44 (41) | | |
| Grade 3 | 12 (15) | 15 (14) | | |
| Baseline ASPECTS, n (%) | | | 0.41 | 3 |
| 0–4 | 3 (4) | 7 (6) | | |
| 5–7 | 10 (12) | 16 (15) | | |
| 8–10 | 69 (84) | 82 (76) | | |
| Causes of pre-stroke dependence, n (%) | | | 0.67 | 27 |
| Previous stroke | 19 (23) | 31 (29) | | |
| Cardiopulmonary disease | 14 (17) | 21 (19) | | |
| Cognitive impairment | 9 (11) | 8 (7) | | |
| Musculoskeletal disease † | 3 (4) | 3 (3) | | |
| Neurological disorder other than stroke and dementia | 6 (7) | 7 (6) | | |
| Other ‡ | 4 (5) | 11 (10) | | |
| Need for assistance due to multiple unspecified comorbidities | 12 (15) | 15 (14) | | |
| Unknown § | 15 (18) | 12 (11) | | |

Total n=190/192; data on reperfusion status were missing for two patients.
*Collateral score according to Tan *et al*.[34]
†Including rheumatoid arthritis (n=3), osteoarthritis (n=1), and amputation (n=2).
‡Including malignancy (n=10), alcohol/drug abuse (n=3), glaucoma (n=1), peripheral artery disease (n=1).
§No relevant information regarding dependence available in discharge letters, hence depicted as unknown causes (n=27). Full dependence causes are shown in online supplemental table 1.
ASPECTS, Alberta Stroke Program Early CT Score; CTA, computed tomography angiography; eTICI, expanded Thrombolysis In Cerebral Ischemia; ICA, internal carotid artery; M1/M2/M3, first/second/third segment of middle cerebral artery; NIHSS, National Institutes of Health Stroke Scale.

**Table 2** Primary and secondary outcome measures by reperfusion grade (n=190)

| | Non-reperfused eTICI <2b (n=82) | Reperfused eTICI ≥2b (n=108) | P value | Missing (n) | Unadjusted OR (95% CI) | Adjusted OR* (95% CI) |
|---|---|---|---|---|---|---|
| 90-day mRS 0–3, n (%) | 15/78 (19) | 26/99 (26) | 0.28 | 13 | 1.53 (0.76 to 3.09) | **2.91 (1.08 to 7.82)** |
| ΔmRS, median (IQR) | 3 (1–3) | 2 (0–3) | 0.07 | 13 | 0.59 (0.33 to 1.06) | **0.41 (0.21 to 0.80)** |
| 90-day mortality, n (%) | 50/78 (64) | 49/99 (49) | 0.05 | 13 | 0.56 (0.31 to 1.03) | **0.42 (0.19 to 0.93)** |
| 30-day mortality, n (%) | 45/49 (92) | 40/49 (82) | 0.14 | 1 | 0.39 (0.11 to 1.38) | 0.41 (0.11 to 1.58) |
| sICH, n (%) | 9/82 (11) | 6/108 (6) | 0.17 | 0 | 0.43 (0.15 to 1.24) | 0.42 (0.14 to 1.24) |

Total n=190/192; data on reperfusion status were missing for two patients.
*Adjustments were made for age, baseline NIHSS score, collateral status, atrial fibrillation, baseline systolic blood pressure, stroke onset-to-groin puncture time, and intravenous alteplase treatment.
eTICI, expanded Thrombolysis In Cerebral Ischemia; mRS, modified Rankin Scale; sICH, symptomatic intracranial hemorrhage.

available. Most of the patients were female (129/192; 67%) and the median age was 80 years (IQR 73–87). Most occlusions were in the M1 segment of the middle cerebral artery (119/192; 62%). The cause of pre-stroke dependence was reported in 165/192 (84%) patients. In 51/192 (27%), pre-stroke dependence was due to a previous stroke, in 36/192 (19%) it was due to cardiopulmonary pathology, and in 27/192 (14%) it was due to multiple unspecified comorbidities. Less common causes of dependence were musculoskeletal diseases (6/192; 3%) and neurological disorders other than stroke and dementia (13/192; 7%).

### Benefit of reperfusion

For 13/192 (7%) patients, 90-day mRS scores were missing and 2/192 (1%) had missing data on angiographic reperfusion. Patients with successful reperfusion more often achieved 90-day mRS 0–3 (26/99, 26%) than those with unsuccessful reperfusion (15/78, 19%), although this difference was not statistically significant (p=0.28). Patients with successful reperfusion showed numerically less deterioration in ΔmRS (2 (IQR 0–3) vs 3 (IQR 1–3) points; p=0.07). With successful reperfusion, 90-day mortality decreased from 50/78 (64%) to 49/99 (49%) (p=0.05). The occurrence of sICH and 30-day mortality did not differ significantly between patients with or without reperfusion (p=0.17 and p=0.14, respectively; table 2). The entire range of 90-day mRS scores stratified by EVT reperfusion status is shown in figure 1.

The regression analyses (table 2) show that 90-day mRS 0–3 was achieved significantly more often with successful reperfusion (adjusted OR (aOR) 2.91 (95% CI 1.08 to 7.82)) compared with unsuccessful reperfusion. The odds of 90-day mortality and ΔmRS decreased significantly with successful reperfusion (aOR 0.42 (95% CI 0.19 to 0.93) and cOR 0.41 (95% CI 0.21 to 0.80), respectively). There was no significant association for sICH or 30-day mortality.

When we compared FPE patients (n=44) with non-FPE patients (n=124) we observed the same effect trends (see online supplemental table 3), but the effect magnitude increased. The latter is mainly observed in the 90-day mRS 0–3 outcome (aOR 4.33 (95% CI 1.40 to 13.43) compared with aOR 2.91 (95% CI 1.08 to 7.82)).

### Role of cause of pre-stroke dependence

The rate of achieving 90-day mRS 0–3 was highest among patients with cardiopulmonary disease (12/36; 33%) and patients with an unknown cause for dependence (9/27; 33%), followed by other causes (4/15; 27%), cognitive impairment (3/17; 18%), and patients who previously suffered from a stroke (8/51; 16%). Mortality rates were highest in patients with musculoskeletal diseases (4/6; 67%) and in patients with disabilities due to cardiopulmonary disease (22/36; 61%, table 3). The 90-day mRS scores per cause of dependence are shown in online supplemental figure 2.

## DISCUSSION

Successful reperfusion in pre-stroke patients with mRS 3 was associated with higher chances of returning to baseline functional

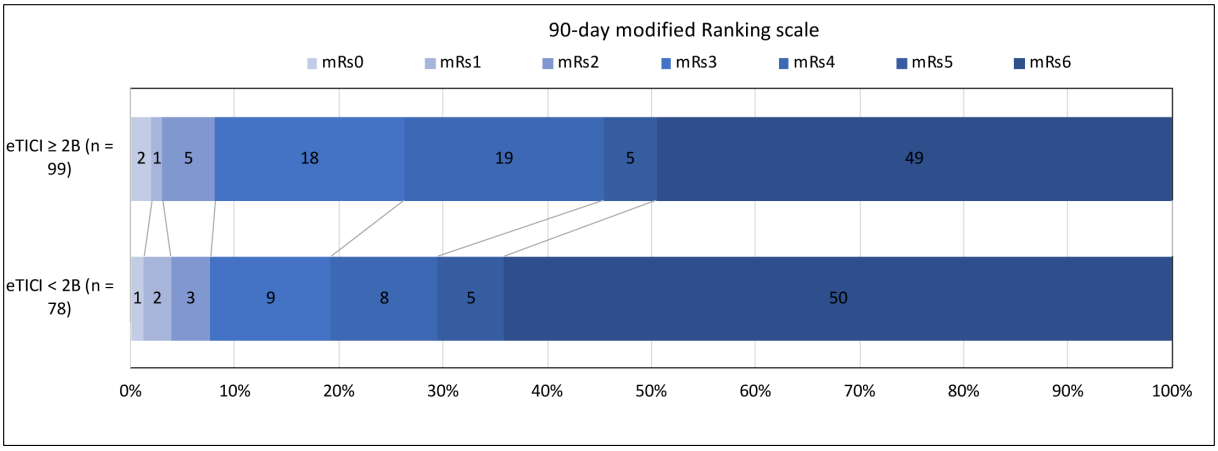


**Figure 1** 90-day mRS score, stratified by successful reperfusion (eTICI ≥2b vs eTICI <2b). Total n=177/192, 13 missing cases of 90-day mRS (n=4 in eTICI <2b group and n=9 in eTICI ≥2b group) and two missing cases of post-eTICI. Numbers in bars represent counts. mRS, modified Rankin Scale; eTICI, expanded Thrombolysis in Cerebral Ischemia.

**Table 3** Causes of pre-stroke dependence and 90-day outcome (n=179)

| | Patients | Favorable outcome* | Mortality | Missing |
|---|---|---|---|---|
| Previous stroke, n (%) | 51 (28) | 8 (16) | 26 (52) | 4 (8) |
| Cardiopulmonary disease, n (%) | 36 (20) | 12 (33) | 22 (61) | 2 (6) |
| Cognitive impairment, n (%) | 17 (9) | 3 (18) | 7 (41) | 3 (18) |
| Musculoskeletal disease†, n (%) | 6 (3) | 0 (0) | 4 (67) | 0 (0) |
| Neurological disorder other than stroke and dementia, n (%) | 13 (7) | 2 (15) | 7 (54) | 1 (8) |
| Other‡, n (%) | 15 (8) | 4 (27) | 8 (53) | 0 (0) |
| Need for assistance due to unspecified comorbidities, n (%) | 27 (15) | 3 (11) | 15 (56) | 2 (7) |
| Unknown§, n (%) | 27 (15) | 9 (33) | 11 (41) | 1 (4) |

90-day mRS scores were not available in 13 patients.
*Favorable outcome is defined as achieving an mRS of 0–3.
†Including rheumatoid arthritis (n=3), osteoarthritis (n=1), and amputation (n=2).
‡Including malignancy (n=10), alcohol/drug abuse (n=3), glaucoma (n=1), peripheral artery disease (n=1).
§No relevant information regarding dependence available in discharge letters, hence depicted as unknown causes (n=27).

status (or better), lower mortality, and less deterioration in their functional state when compared with unsuccessful reperfusion. Almost one-fifth of successfully treated pre-stroke patients with mRS 3 returned to their pre-stroke functional state (mRS 3), and almost one-tenth even improved to an independent functional state (mRS 0–2). Improvement from pre-stroke mRS 3 to pre-stroke mRS 0–2 could indicate that (1) the pre-stroke mRS score was erroneously reported by local investigators at baseline or 90 days follow-up or (2) the cause of dependence was transient against expectations, and the patient recovered within the 90-day assessment time period (even after we excluded all 'temporary' cases, this might still be a possibility). Human error in measuring the pre-stroke mRS score is not infrequently encountered, especially in the acute setting. Prakapenia *et al*,[25] for example, showed an initial misjudgment rate depicting the correct pre-stroke mRS score of 33.6%, which of course could influence the actual benefit of EVT in this dependent patient group.

A recently published paper[26] analyzing pooled data of the HERMES database compared the outcome of EVT in patients without pre-stroke dependence (mRS 0) to patients with mild pre-stroke dependence (mRS 1–2) and showed that the latter had a worse outcome than the former. However, they failed to show any interaction between this mild disability and the effect of EVT on outcome, proving that pre-stroke mRS 1–2 disability is a prognostic (outcome) but not a predictive (response to therapy) variable in EVT. On the other hand, the study recently published by Van de Graaf *et al*[27] using the MR CLEAN registry data showed that pre-stroke disability is the most important predictor of futile successful reperfusion (after baseline NIHSS and post-procedural factors such as sICH and pneumonia). The discrepancy in the results of these two papers could be due to the selection of the specific pre-stroke mRS range, where the former only included mRS 1–2 and the latter included the whole range of mRS scores.

When analyzing the benefit of EVT in moderate pre-stroke dependent patients (mRS 3), we also noticed that the available literature[10 12–15] mainly focuses on the comparison with pre-stroke independent patients and/or those with more severe disabilities (eg, mRS 4 and mRS 5). For example, Oesh *et al*[13] investigated a large cohort of over 1200 pre-stroke dependent patients (mRS 3–5) and looked at the rate of good outcome (which was defined as mRS 0–3 for pre-stroke dependent patients and mRS 0–2 for pre-stroke independent patients), the occurrence of sICH, and the mortality rate at 3 months compared with pre-stroke independent patients (mRS 0–2). They found that dependent patients less often had a good clinical outcome and had a higher mortality risk than independent patients (26.2% vs 44.4% and 46.4% vs 25.5%, respectively). However, this effect disappeared when adjusting for confounding factors, suggesting that the difference in outcome may have been caused by differences in specific patient baseline characteristics and comorbidities rather than the pre-stroke level of functioning itself—even though the two are, naturally, related.

The results of these papers make intuitive sense: pre-stroke dependent patients do worse after EVT than pre-stroke independent patients (eg, due to more pre-existing comorbidities or disabilities).[28–30] However, a more relevant question to ask could be: "What are the benefits of successful EVT in patients with moderate pre-stroke disability (mRS 3)?" This is only done in additional analyses in some of the previous published literature[10 14] by using non-successful EVT as a control group.

The paper by Salwi *et al*,[10] for example, shows that succesful EVT was associated with a higher trend towards excellent outcome (defined as mRS 0–1 or no disability accumulated) in minimally to moderately disabled patients (mRS 0–1 and mRS 2–3) compared with non-successful EVT (29% vs 15%). This is similar to our study where we show a favorable outcome (mRS 0–3) rate of 26% versus 19%, respectively, although we included only moderately disabled patients (mRS 3) which may have made our outcome more favorable.

Goldhoorn *et al*[14] showed in a previous paper using the MR CLEAN Registry cohort that successful reperfusion in the pre-stroke disability group (including the whole range of pre-stroke mRS 3–5) was associated with higher chances of achieving a favorable outcome than unsuccessful reperfusion (45/127; 20% vs 13/127; 10%) and that this association was comparable to the pre-stroke independent patient group ($P_{interaction}$=0.14). These numbers are slightly lower than our results, which could be explained by (1) the inclusion of more severe disabilities (mRS 4 and mRS 5) and/or (2) the inclusion of older data at baseline (2015–2016 vs 2015–2017), for example, 'better' outcome of patients after 2016 due to improved EVT techniques.

In addition, we found that one-third of the patients with cardiopulmonary disease and almost one-third of the patients with 'other causes' (ie, malignancy, alchohol abuse, peripheral artery disease and glaucoma) returned to an mRS score of 0–3. Of all patients with musculoskeletal disease, cardiopulmonary disease and patients with disabilities due to mulitiple unspecified comorbidities, more than 60% died. However, these results have to be interpreted with caution as the sample size was small (eg, musculoskeletal disease: n=6). A previously published paper by

Goldhoorn *et al*[14] showed that patients with psychiatric disorders and ocular disorders had the highest chance of achieving a good outcome, while patients with recent surgery and those with malignancies had the highest rate of mortality. This discrepancy could be due to the different inclusion criteria of the studies (eg, mRS 3–5 vs mRS 3, as mentioned above).

The strength of this paper is that we used a large multicenter dataset and, to our knowledge, are the first to focus on one specific patient group (with pre-stroke mRS 3 disability), investigating the role of EVT within this group in terms of functional outcome, mortality, and the rate of sICH (by comparing successful reperfusion with unsuccessful reperfusion). This study, however, also has some limitations. First, although we used a large dataset of 3637 patients available, only 192 (from a single country) were included and they all received EVT. Selection based on other favorable baseline characteristics may have occurred, so our results may not be fully generalizable to the general pre-stroke mRS 3 population. Second, since all patients in the MR CLEAN Registry underwent EVT, we had to use successful reperfusion as a surrogate for EVT and could not truly investigate the EVT effect itself. Ideally, future studies would randomize pre-stroke dependent patients to EVT versus best medical management to assess the benefit of EVT reliably and definitively. Third, the pre-stroke mRS score was estimated by local investigators based on available information and medical records. Although all causes of dependence were checked for misinterpretations, information bias can still not be excluded. In addition, a fine line exists between pre-stroke mRS 2 and pre-stroke mRS 3,[31–33] and accurately distinguishing mRS 2 from mRS 3 is not always possible in an emergency setting.[25] Finally, since the number of patients who returned to their pre-stroke functional state and had a defined cause of dependence was low, analyses on the association between dependence causes and outcomes were only exploratory.

In our cohort (including patients treated from 2014 to 2017), more than a quarter of successfully treated patients with a pre-stroke mRS score of 3 returned to their baseline functional state (or better). We hypothesize that, in the future, an increasing number of EVT-eligible patients will have some pre-morbid disabilities/comorbidities (due to population ageing) and EVT techniques and stroke care will continue to improve, further improving patient outcomes. This could outdate current criteria for EVT eligibility (pre-stroke mRS 0–1). Before the guideline recommendations can be re-evaluated, however, randomized data are needed to confirm the observational data acquired to date.

## CONCLUSIONS

Although patients with AIS with a pre-stroke mRS score of 3 comprise a heterogenous group with respect to cause of disability, we observed favorable outcomes when successful reperfusion was achieved after EVT. This could suggest that EVT may be beneficial in patients with a moderate pre-stroke functional status, although randomized data are needed to confirm these observations.

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**Contributors** FB collected and analyzed the data and wrote the manuscript. MK analyzed the data and revised the manuscript. JO, AG and RVM revised the manuscript. MG and WHvZ created the hypothesis and research question. All co-authors assisted in revising the manuscript. MG is the guarantor.

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