Safety and Outcome of Endovascular Treatment for Minor Ischemic Stroke

Safety and Outcome of Endovascular Treatment for Minor Ischemic Stroke: Results From the Multicenter Clinical Registry of Endovascular Treatment of Acute Ischemic Stroke in the Netherlands

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Goal: Insufficient data is available about safety and efficacy of endovascular treatment (EVT) in patients with minor stroke symptoms because these patients were excluded from most randomized trials. We aimed to compare characteristics, functional outcome, and complications in patients with minor ischemic stroke National Institutes of Health Stroke Scale score ≤5 (NIHSS score ≤5) and moderate to severe ischemic stroke (NIHSS score ≥6) due to intracranial proximal artery occlusion of the anterior circulation who underwent EVT. *Materials and Methods:* We report patients with an anterior circulation occlusion who were included between March 2014 and June 2016 in the multicenter randomized clinical trial of EVT of acute ischemic stroke in the Netherlands Registry, a prospective, multicenter, observational study for stroke centers that perform EVT in the Netherlands. Minor ischemic stroke was defined as baseline NIHSS score of 5 or less. Primary outcome is the modified Rankin Scale (mRS) score at 90 days. Secondary outcomes include symptomatic intracranial hemorrhage (sICH) and mortality. *Findings:* Seventy-one (5.5%) patients had a NIHSS score of 5 or less. Functional independence (mRS 0-2 at 90 days) was reached in 75% of these patients, compared to 40% of patients with NIHSS score of 6 or more. sICH occurred in 4% of patients, of which 1% occurred peri-interventionally. Death occurred in 6% of patients. *Conclusions:* Patients with

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minor ischemic stroke with an intracranial proximal arterial occlusion of the anterior circulation who underwent EVT have a high chance of favorable outcome and appear to have low occurrence of treatment-related sICH. Therefore, our results encourage the use of EVT for minor ischemic stroke in the absence of effect estimates from controlled studies.

Key Words: Ischemic stroke—endovascular treatment—minor symptoms—large vessel oclusion

Introduction

Endovascular treatment (EVT) for acute ischemic stroke due to an intracranial proximal arterial occlusion of the anterior circulation was shown to be safe and effective in recently performed randomized controlled trials.[1] Ischemic stroke with minor symptoms can be caused by a large intracranial arterial occlusion.[2,3] Presence of such a lesion is associated with unfavorable outcome.[4-8] Only the Multicenter Clinical Registry of Endovascular Treatment of Acute Ischemic Stroke in the Netherlands (MR CLEAN) and the Extending the Time for Thrombolysis in Emergency Neurological Deficits−Intra−Arterial (EXTEND-IA) included patients with NIHSS score of 5 or less: 10 of 500 (2%) in MR CLEAN and 4 of 70 (6%) in EXTEND IA.[9,10] Therefore, insufficient information is available about EVT in patients with minor stroke symptoms, and, as a consequence, the benefit of EVT is considered uncertain in patients presenting with baseline NIHSS score of 5 or less according to American Heart Association (AHA) guidelines.[11]

In the absence of knowledge about treatment effect from controlled studies, observational data about safety and outcome might guide treatment decisions. In the present study, we describe characteristics, outcome, and safety of patients with minor ischemic stroke (NIHSS score ≤5) with an intracranial proximal arterial occlusion of the anterior circulation treated with EVT in the MR CLEAN Registry.

Methods

Patients

We analyzed patients from the MR CLEAN Registry who were registered from the start (16 March 2014) until 15 June 2016. The MR CLEAN Registry is a multicenter, prospective, observational study for all stroke intervention centers in the Netherlands (trial protocol: https://www.mrclean-trial.org/docs/latestprotocol.pdf).

All patients undergoing EVT (arterial puncture with the intention to perform arterial catheterization with a micro catheter to the level of the occlusion, followed by mechanical thrombectomy and/or thrombus aspiration, with or without delivery of a thrombolytic agent) for acute ischemic stroke have been enrolled in the MR CLEAN Registry. The method of EVT was left to the discretion of the treating physicians.

We used the following selection criteria for analysis: groin puncture within 6.5 hours after symptom onset (we chose to extend the time window by half an hour compared to the MR CLEAN trial to be compatible with the MR CLEAN trial inclusion criterion of intended treatment within 6 hours); age of 18 years and older; prestroke modified Rankin Scale (mRS)[12] score of 2 or less; intracranial proximal arterial occlusion of the anterior circulation (intracranial carotid artery (ICA, ICA-T or middle [M1/M2; definition in supplementary data] or anterior [A1/A2] cerebral artery), demonstrated by baseline computed tomography angiography (CTA). Stroke severity was assessed by NIHSS at baseline.[13] Minor ischemic stroke was defined as baseline NIHSS score of 5 or less. Alberta Stroke Programme early CT (ASPECT) score on baseline non contrast computed tomography (CT) and collateral status on CTA were scored by an independent core lab using definitions described in previous literature.[14,15]

Outcome Measures

The primary outcome was the mRS score at 90 days (investigators were instructed to assess the mRS score at 90+/−14 days). The mRS is a 7-point scale ranging from 0 (no symptoms) to 6 (death). Functional outcomes were defined as excellent (mRS of 0-1), good (mRS of 0-2), or favorable (mRS of 0-3). Other outcomes were NIHSS score postintervention, successful reperfusion postintervention digital subtraction angiography (DSA; assessed by an independent core lab blinded for clinical outcome), and safety outcomes. Reperfusion was scored by the extended Thrombolysis in Cerebral Ischemia (eTICI) score,[16] which ranges from grade 0 (no reperfusion) to grade 3 (complete reperfusion). Successful reperfusion was defined as eTICI 2B or higher. In the case 2- directional view on final DSA was not available (missing lateral or anterior view), the maximum eTICI score was 2A. An independent core lab, blinded for clinical outcome, assessed all DSAs. Safety outcomes were occurrence of symptomatic intracranial hemorrhage (sICH), ischemic stroke progression, and mortality at 90 days. Intracranial hemorrhage was considered symptomatic if the patient had died or had declined at least 4 points on the NIHSS, and the hemorrhage was related to the clinical deterioration (Heidelberg criteria).[17] SICH was assessed by the complication committee after evaluation of medical reports and imaging assessment. Ischemic stroke progression was defined as neurological deterioration of at least 4 points on the NIHSS, in which

an intracranial hemorrhage was excluded as the cause of the deterioration with CT. Ischemic stroke progression was assessed by the complication committee on the basis of medical reports.

Statistical Analysis

Baseline characteristics of patients with minor ischemic stroke (NIHSS score ≤5), and moderate to severe ischemic stroke (NIHSS score ≥6), were analyzed using standard statistics. Unadjusted and adjusted (for age, collateral status, and time from onset to start of EVT [arterial puncture]) logistic regression analyses were used to determine the association between outcomes and minor ischemic stroke (NIHSS score ≤5), compared to moderate to severe ischemic stroke (NIHSS score ≥6). To assess the statistical significance of interaction between reperfusion status and baseline clinical stroke severity on functional outcome, we added a multiplicative term to the regression model.

We performed a sensitivity analysis on functional and safety outcomes excluding those patients that did not have a target occlusion on DSA and in whom no attempt for clot retrieval was made.

In the case NIHSS scores were not available, we scored these retrospectively according to a standardized chart with information from the reported physical examination in medical reports. If successful reperfusion was not reached during EVT, the time of last contrast bolus injection was used as a proxy for time of reperfusion. Any follow-up mRS score of 0-5 assessed within 30 days was considered missing. Missing mRS scores at 90 days were replaced by mRS scores derived from multiple imputation.[18] 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, prestroke mRS score, atrial fibrillation, intravenous thrombolysis prior to EVT, systolic blood pressure, baseline ASPECTS, occlusion segment, CTA 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 24-48 hours after EVT. All descriptive analyses include patients with complete data, while 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, 1628 patients were registered until June 15th, 2016. We included 1292 patients for the present study (Fig S1). Seventy-one (5.5%) patients presented with minor ischemic stroke (NIHSS score ≤5; range 2-5) and 1221 (94.5%) patients with moderate to severe ischemic stroke (NIHSS score ≥6) (Table 1). Minor ischemic stroke patients were younger, although the difference was not statistically significant. Facial paresis was the most frequent symptom on baseline, both for minor and moderate to severe ischemic stroke (Table S1). Occlusion site on baseline CTA was significantly different: ICA-T occlusions were more often present in patients with baseline NIHSS score of 6 or more (23% versus 3%), and M2 occlusions were more often present in patients with baseline NIHSS score of 5 or less (21% versus 11%). ASPECT score on baseline CT, and collateral status on CTA were higher in minor ischemic stroke patients, with collateral score 3 (maximum score) present in 38% of patients with NIHSS score of 5 or less, compared to 18% of patients with baseline NIHSS score of 6 or more.

Intervention Characteristics

In patients in whom an attempt for thrombus retrieval was made, successful reperfusion (eTICI 2B or higher) was present in 35 of 54 patients (65%) with baseline NIHSS score of 5 or less, and 627 of 1060 (59%) with baseline NIHSS score of 6 or more (Table S2). In 13 of 71 patients (18%) with minor ischemic stroke, no target occlusion was present on DSA, and no intracranial intervention was performed. In 11 of 13 (85%) of these patients, alteplase was administered intravenously prior to EVT, and in the majority of patients a distal occlusion of M1, or an occlusion of M2 segment was present on CTA (n = 9; 69%). For comparison, absence of a target occlusion on DSA in patients with baseline NIHSS score of 6 or more occurred in 91 patients (7%; $P < .05$). Anesthetic management during the procedure was not significantly different in both groups.

Clinical Outcomes

Functional Outcome

The score on the mRS at 90 days was available for 1179 patients. Functional outcome was better in patients with minor ischemic stroke (Fig 1). Excellent functional outcome was seen in 28 of 60 patients (47%), and good functional outcome was seen in 45 of 60 patients (75%) with baseline NIHSS score of 5 or less, compared to 221 of 1119 (20%) and 450 of 1119 patients (40%) with baseline NIHSS score of 6 or more. There was no significant interaction between baseline clinical stroke severity and successful reperfusion on good functional outcome (Fig S2; $P_{interaction} = .82$).

Safety Outcomes

SICH occurred in 3 of 71 patients with minor stroke (4%) of which one occurred peri-interventionally (1%). Ischemic stroke progression occurred in 5 of 71 patients (7%) with minor ischemic stroke (Table 2). Four patients (6%) died during the 90 days follow-up: 1 patient due to

Table 1. *Baseline characteristics*

	NIHSS ≤5 (n = 71)	NIHSS ≥6 (n = 1221)	*P* value	Missings (n)
Age - median (IQR)	65 (55-77)	70 (59-78)	.10	0
Male sex - n. (%)	38 (54)	672 (55)	.80	0
NIHSS - median (range; IQR)	4 (2-5; 3-5)	16 (6-42; 12-20)		0
Clinical localization: left hemisphere - n. (%)	38 (54)	647 (53)	.58	0
Systolic blood pressure - mean mm Hg (SD)	153 ± 21	149 ± 25	.91	35
Intravenous alteplase treatment - n. (%)	61 (86)	972 (80)	.42	2
Medical history				
Atrial fibrillation - n. (%)	11 (15)	250 (20)	.28	20
Hypertension - n. (%)	36 (51)	590 (48)	.69	18
Diabetes mellitus - n. (%)	8 (11)	197 (16)	.27	7
Hypercholesterolemia - n. (%)	18 (25)	338 (28)	.59	46
Current smoking - n. (%)	20 (28)	280 (23)	.58	13
Ischemic stroke - n. (%)	10 (14)	181 (15)	.85	8
Pre-stroke modified Rankin Scale score - n. (%)			.87	24
0	55 (77)	923 (76)		
1	9 (13)	175 (14)		
2	5 (7)	101 (8)		
Imaging				
Level of occlusion on noninvasive vessel imaging (CTA) - n. (%)			.00	69
ICA (intracranial)	7 (10)	68 (6)		
ICA-T	2 (3)	278 (23)		
M1	42 (59)	666 (55)		
M2	15 (21)	135 (11)		
Other: M3 and ACA	1 (1)	9 (1)		
Missing	4 (6)	65 (5)		
ASPECTS subgroups			.01	60
0-4 - n (%)	2 (3)	81 (7)		
5-7 - n (%)	7 (10)	291 (24)		
8-10 - n (%)	59 (83)	792 (65)		
Missing	3 (4)	57 (5)		
Collaterals			.00	96
Grade 0 - n (%)	1 (1)	87 (7)		
Grade 1 - n (%)	9 (13)	387 (32)		
Grade 2 - n (%)	30 (42)	432 (35)		
Grade 3 - n (%)	27 (38)	223 (18)		
Transfer from primary stroke center - n (%)	38 (54)	684 (56)	.68	
Onset to start of EVT (min) - median (IQR)	225 (170-270)	205 (158-265)	.23	

CTA, computed tomography angiography; NIHSS, National Institutes of Health Stroke Scale; ASPECT, Alberta Stroke Programme early computed tomography; CT, computed tomography; EVT, endovascular treatment; ICA, intracranial carotid artery, IQR, interquartile range.

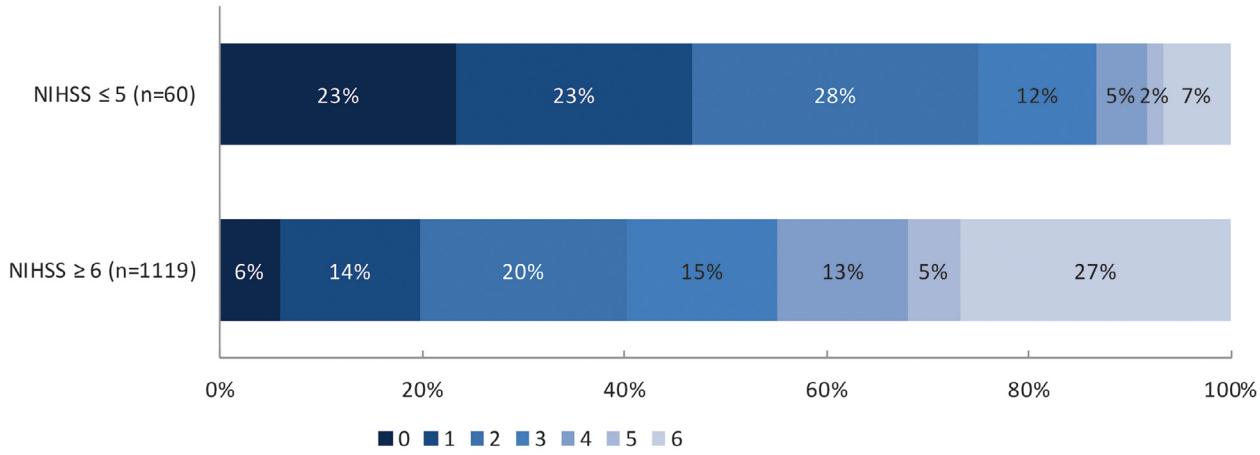

Figure 1. *Distribution of the modified Rankin Scale (mRS) score at 90 days (n = 1179; mRS score at 90 days was missing for 113 patients).*

Table 2. *Primary and secondary outcomes. Comparison between patients with baseline NIHSS score of 5 or less and NIHSS score of 6 or more*

	NIHSS ≤5 (n = 71)	NIHSS ≥6 (n = 1221)	Unadjusted common odds ratio	Adjusted common odds ratio
mRS at 90 d - median (IQR)*	2 (1-2)	3 (2-6)	5.62 (95% CI: 2.02-15.65)	3.37 (95% CI: 2.08-5.46)
mRS 0-1 at 90 d - n. (%)*	28 (47)	221 (20)	3.65 (95% CI: 2.20-6.05)	2.93 (95% CI: 1.74-4.95)
mRS 0-2 at 90 d - n. (%)*	45 (75)	450 (40)	4.78 (95% CI: 2.64-8.66)	3.89 (95% CI: 2.07-7.33)
mRS 0-3 at 90 d - n. (%)*	53 (88)	617 (55)	5.46 (95% CI: 2.60-11.47)	4.52 (95% CI: 2.08-9.83)
sICH - n. (%)	3 (4)	69 (6)	0.74 (95% CI: 0.23-2.40)	0.76 (95% CI: 0.23-2.52)
Ischemic stroke progression - n. (%)	5 (7)	116 (10)	0.72 (95% CI: 0.29-1.83)	0.98 (95% CI: 0.38-2.53)
Mortality at 90 d - n. (%)	4 (6)	300 (25)	0.18 (95% CI: 0.06-0.50)	0.24 (95% CI: 0.08-0.68)
NIHSS post intervention (24 h) - median (IQR)	2 (0-4)	11 (4-18)	β −8.16 (95% CI: −10.31 to −6.01)	β −6.55 (95% CI: −8.61 to −4.50)

Regression models include all patients with imputed data. Regression analyses without the use of multiple imputation are presented in Table S3. Adjustments were made for age, collateral score, and time to start of EVT.

*n = 1179 (mRS score at +/−90 d was missing for 113 patients).

sICH, 1 patient 2 weeks after occurrence of a new ischemic stroke, and 2 patients with unknown cause during follow-up. Mortality was significantly higher (n = 300; 25%) in patients with baseline NIHSS score of 6 or more.

Sensitivity Analysis

We repeated the analysis on functional and safety outcomes excluding those patients that did not have a target occlusion on DSA and in whom no attempt for clot retrieval was made. Results were similar (Table S4).

Discussion

In the MR CLEAN Registry, 5.5% of patients with ischemic stroke due to an intracranial proximal arterial occlusion of the anterior circulation who underwent EVT had a minor stroke (NIHSS score ≤5). In these patients, we found more M2 occlusions, higher ASPECT score on baseline CT, and more often good collateral status on baseline CTA. Almost half of these patients reached excellent functional outcome (mRS 0-1), 3 quarters reached good functional outcome (mRS 0-2), and peri-interventional complication rate was low.

Previous studies have shown lower median NIHSS scores in patients with M2 occlusions compared to patients with M1 occlusions (median 13-14 versus 17).[19,20] The high frequency of M2 occlusions among patients with a low baseline NIHSS score in our study is in line with these findings, although neurological deficit resulting from M2 occlusions can be heterogeneous. In MR CLEAN, baseline NIHSS score was found lower when collateral score was higher,[21] in line with the high percentage of good collateral status in our minor ischemic stroke cohort. This is clinically plausible because in M2 occlusions, or in the presence of good collateral flow, a smaller part of the brain would be deprived from blood supply.

Patients with minor ischemic stroke due to a large vessel occlusion generally achieve favorable outcomes, even in the absence of acute revascularization therapy.[5,7,22] However, these patients can have unfavorable outcomes. One study showed early neurological deterioration in 38% of patients, and 50% of patients did not reach functional independency at discharge.[5] Another observational study reports an independent ambulatory status at discharge in 65% (comparable with mRS 0-3) of patients with an anterior circulation occlusion.[7] In our study, functional outcome exceeded functional outcome reported in these previous studies that described functional outcome in the absence of acute recanalization therapy. However, comparison with these studies should be considered with caution, because of heterogeneity of investigated patients, primarily concerning differences in baseline NIHSS score cut-off values defining minor ischemic stroke.

When treated with intravenous thrombolysis, in the presence of a proximal intracranial arterial occlusion in the anterior circulation, a recently published study

showed that patients with NIHSS score of 5 or less have a 9%-30% chance of early neurological deterioration, depending on occlusion site.[8] Early neurological deterioration was strongly associated with functional dependence or death within 3 months. Additional endovascular therapy might improve functional outcome in these patients.

Five earlier observational studies reported EVT in ischemic stroke with baseline NIHSS score of 5 or less. Three studies reported single center data of 41, 10, and 30 patients respectively.[22-24] Excellent functional outcome ranged from 67%-70%, good functional outcome (mRS 0-2) from 75%-100%, and parenchymal hemorrhage or sICH occurred in 0.0%-6.7% of the patients. In 2 of these studies EVT was compared with medical therapy, and both favored EVT in terms of functional outcome at 3 months.[23,24] However, in both studies occlusion site was heterogeneous (posterior circulation in 20.0%-23.3%). In one of these studies, treatment allocation occurred on the basis of careful discussion between treating physicians, and patients or their families, which probably resulted in selection bias. Furthermore, no firm conclusions could be made because of single center design and small sample size.

Two multicenter studies reported 34, and 113 patients with NIHSS score of 5 or less, who underwent EVT.[25,26] In these studies, no significant differences in functional outcome were found between patients who underwent EVT and patients who were treated medically. However, in the first study, occlusion site was heterogeneous, with a posterior circulation occlusion in more than one-third of the patients, and primary EVT was mainly performed in the late time window (4.5-6.0 hours after symptom onset), whereas primary intravenous thrombolysis (IVT) was mainly performed for less than 4.5 hours after symptom onset. Moreover, patients were included between 2009 and 2012, in the period that EVT was an experimental treatment option.[25] In the second study, the medical control group originated from 1, different center than the patients treated endovascularly. Approximately one-fifth of the patients primarily treated medically, underwent rescue EVT, which might have influenced the comparison between EVT and best medical treatment.[26] In our study, we presented data of a large group of patients with minor stroke, that was multicenter collected and representative of current clinical practice.

"In acute ischemic stroke, presence of minor to mild symptoms generally results in better functional outcome compared to when moderate to severe symptoms are present at baseline.[27] Therefore, returning to excellent functional outcome (mRS 0-1) may be a more adequate representation of a successful result in minor ischemic stroke. Past studies report excellent outcome in 59-70% of the patients with NIHSS score $\leq$ 5 with a large vessel occlusion who underwent EVT, which is higher than in our study (47%).[22-26] Possible explanations could be the presence of lower rates of pre-stroke mRS score $\geq$ 1 (5-17% versus 20% in our study), and higher rates of successful reperfusion (82-100% versus 65% in our study) that were achieved in these studies."

The effect of reperfusion on functional outcome was presented by 1 previous study, in which minor to mild stroke was defined as NIHSS score of less than 8.[28] The patients underwent EVT for an intracranial proximal artery occlusion of the anterior circulation, and, as in our study, good functional outcome was more frequent in successfully reperfused (ie, $\geq$TICI 2B) patients. These findings could substantiate the pursuit of recanalization by mechanical thrombectomy in minor ischemic stroke due to an intracranial proximal artery occlusion.

This study has limitations. First, selection bias was probably present, because EVT was not standard of treatment for minor ischemic stroke, and we were unaware of the patients who did not undergo EVT. Second, the sample size of patients with minor deficits is small. Nevertheless, we present a large cohort compared to previous studies describing patients with NIHSS score of 5 or less. Finally, as only results of patients who underwent EVT are reported, we were not able to determine treatment effect. To gain information on treatment effect, initiatives for a multicenter randomized controlled trial on EVT of acute stroke patients with minor deficits (NIHSS score $\leq$5) with a large vessel occlusion in the anterior circulation have been presented (In Extremis trial, presented at SLICE Live Course 2017, Nice, France).

The strength of our study is that it reflects results from EVT in daily clinical practice captured in a nationwide registry. Moreover, core lab assessment was applied for imaging and complications. In the absence of randomized controlled trials investigating EVT in minor ischemic stroke patients, our study provides information which can contribute to decision making in daily practice.

Conclusion

Patients with minor ischemic stroke with an intracranial proximal arterial occlusion of the anterior circulation who underwent EVT have a high chance of favorable outcome and appear to have low occurrence of treatment related sICH. Therefore, our results encourage the use of EVT for minor ischemic stroke in the absence of effect estimates from controlled studies.

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Supplementary Materials

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References

1. Goyal M, Menon BK, van Zwam WH, et al. Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials. Lancet 2016;387:1723-1731.
2. Maas MB, Furie KL, Lev MH, et al. National Institutes of Health Stroke Scale score is poorly predictive of proximal occlusion in acute cerebral ischemia. Stroke 2009;40: 2988-2993.
3. Smith WS, Tsao JW, Billings ME, et al. Prognostic significance of angiographically confirmed large vessel intracranial occlusion in patients presenting with acute brain ischemia. Neurocrit Care 2006;4:14-17.
4. Kim J-T, Park MS, Chang J, et al. Proximal arterial occlusion in acute ischemic stroke with low NIHSS scores should not be considered as mild stroke. PLOS One 2013;8(8):e70996:1-7.
5. Rajajee V, Kidwell C, Starkman S, et al. Early MRI and outcomes of untreated patients with mild or improving ischemic stroke. Neurology 2006;67:980-984.
6. Sato S, Uehara T, Ohara T, et al. Factors associated with unfavorable outcome in minor ischemic stroke. Neurology 2014;83:174-181.
7. Mokin M, Masud MW, Dumont TM, et al. Outcomes in patients with acute ischemic stroke from proximal intracranial vessel occlusion and NIHSS score below 8. J NeuroIntervent Surg 2014;6:413-417.
8. Mazya MV, Cooray C, Lees KR, et al. Minor stroke due to large artery occlusion. When is intravenous thrombolysis not enough? Results from the SITS International Stroke Thrombolysis Register. Eur Stroke J 2017;0:1-10.
9. Berkhemer OA, Fransen PSS, Beumer D, et al. A randomized trial of intra-arterial treatment for acute ischemic stroke. N Engl J Med 2015;372:11-20.
10. Campbell BC, Mitchell PJ, Kleinig TJ, et al. Endovascular therapy for ischemic stroke with perfusion-imaging selection. N Engl J Med 2015;372:1009-1018.
11. Powers WJ, Derdeyn CP, Biller J, et al. 2015 American Heart Association/American Stroke Association focused update of the 2013 guidelines for the early management of patients with acute ischemic stroke regarding endovascular treatment: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2015;46:3020-3035.
12. Swieten van JC, Koudstaal PJ, Visser MC, et al. Interobserver agreement for the assessment of handicap in stroke patients. Stroke 1988;19:604-607.
13. Brott T, Adams Jr. HP, Olinger CP, et al. Measurements of acute cerebral infarction: a clinical examination scale. Stroke 1989;20:864-870.
14. Barber PA, Demchuk AM, Zhang J, et al. Validity and reliability of a quantitative computed tomography score in predicting outcome of hyperacute stroke before thrombolytic therapy. ASPECTS Study Group. Alberta Stroke Programme Early CT score. Lancet 2000;355:1670-1674.
15. Tan IY, Demchuk AM, Hopyan J, et al. CT angiography clot burden score and collateral score: correlation with clinical and radiologic outcomes in acute middle cerebral artery infarct. Am J Neuroradiol 2009;30:525-531.
16. Noser EA, Shaltoni HM, Hall CE, et al. Aggressive mechanical clot disruption: a safe adjunct to thrombolytic therapy in acute stroke? Stroke 2005;36:292-296.
17. Kummer von R, Broderick JP, Campbell BC, et al. The heidelberg bleeding classification: classification of bleeding events after ischemic stroke and reperfusion therapy. Stroke 2015;46:2981-2986.
18. Donders AR, van der Heijden GJ, Stijnen T, et al. Review: a gentle introduction to imputation of missing values. J Clin Epidemiol 2006;59:1087-1091.
19. Coutinho JM, Liebeskind DS, Slater LA, et al. Mechanical thrombectomy for isolated M2 occlusions: a post hoc analysis of the STAR, SWIFT, and SWIFT PRIME Studies. Ame J Neuroradiol 2016: 667-672.
20. Sarraj A, Sangha N, Hussain MS, et al. Endovascular therapy for acute ischemic stroke with occlusion of the middle cerebral artery M2 segment. JAMA Neurol 2016;73: 1291-1296.
21. Berkhemer OA, Jansen IGH, Beumer D, et al. Collateral status on baseline computed tomographic angiography and intra-arterial treatment effect in patients with proximal anterior circulation stroke. Stroke 2016;47: 768-776.
22. Haussen DC, Lima FO, Bouslama M, et al. Thrombectomy versus medical management for large vessel occlusion stroke with minimal symptoms: an anlaysis from STOPStroke and GESTOR cohorts. J NeuroIntervent Surg 2017;0:1-5.
23. Bhogal P, Bü cke P, Ganslandt O, et al. Mechanical thrombectomy in patients with M1 occlusion and NIHSS score $\leq$ 5: a single-centre experience. Stroke Vasc Neurol 2016;1:165-171.
24. Haussen DC, Bouslama M, Grossberg JA, et al. Too good to intervene? Thrombectomy for large vessel occlusion strokes with minimal symptoms: an intention to treat analysis. J NeuroInt Surg 2016;0:1-5.
25. Urra X, San Román L, Gil F, et al. Medical and endovascular treatment of patients with large vessel occlusion presenting with mild symptoms: an observational multicenter study. Cerebrovasc Dis 2014;38:418-424.
26. Dargazanli C, Arquizan C, Gory B, et al. Mechanical thrombectomy for minor and mild stroke patients harboring large vessel occlusion in the anterior circulation. A multicenter cohort study. Stroke 2017;48:3274-3281.
27. Adams HP, Davis PH, Leira EC, et al. Baseline NIH Stroke Scale score strongly predicts outcome after stroke. Neurology 1999;53:126. https://doi.org/10.1212/WNL.53.1.126.
28. Dargazanli C, Consoli A, Gory B, et al. Is reperfusion useful in ischaemic stroke patients presenting with a low national institutes of health stroke scale and a proximal large vessel occlusion of the anterior circulation? Cerebrovasc Dis 2017;43:305-312.