Received: 30 April 2023 | Accepted: 27 July 2023

DOI: 10.1111/ene.16009

european journal of neurology
the official journal of the european academy of neurology

ORIGINAL ARTICLE

Relevance of National Institutes of Health Stroke Scale subitems for best revascularization therapy in minor stroke patients with large vessel occlusion: An observational multicentric study

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Abstract

Background and purpose: The best management of acute ischemic stroke patients with a minor stroke and large vessel occlusion is still uncertain. Specific clinical and radiological data may help to select patients who would benefit from endovascular therapy (EVT). We aimed to evaluate the relevance of National Institutes of Health Stroke Scale (NIHSS) subitems for predicting the potential benefit of providing EVT after intravenous thrombolysis (IVT; "bridging treatment") versus IVT alone.

Methods: We extracted demographic, clinical, risk factor, radiological, revascularization and outcome data of consecutive patients with M1 or proximal M2 middle cerebral artery occlusion and admission NIHSS scores of 0–5 points, treated with IVT ± EVT between May 2005 and March 2021, from nine prospectively constructed stroke registries at

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seven French and two Swiss comprehensive stroke centers. Adjusted interaction analyses were performed between admission NIHSS subitems and revascularization modality for two primary outcomes at 3 months: non-excellent functional outcome (modified Rankin Scale score 2–6) and difference in NIHSS score between 3 months and admission.

Results: Of the 533 patients included (median age 68.2 years, 46% women, median admission NIHSS score 3), 136 (25.5%) initially received bridging therapy and 397 (74.5%) received IVT alone. Adjusted interaction analysis revealed that only facial palsy on admission was more frequently associated with excellent outcome in patients treated by IVT alone versus bridging therapy (odds ratio 0.47, 95% confidence interval 0.24–0.91; $p = 0.013$). Regarding NIHSS difference at 3 months, no single NIHSS subitem interacted with type of revascularization.

Conclusions: This retrospective multicenter analysis found that NIHSS subitems at admission had little value in predicting patients who might benefit from bridging therapy as opposed to IVT alone. Further research is needed to identify better markers for selecting EVT responders with minor strokes.

KEYWORDS
acute ischemic stroke, acute stroke management, mild symptoms

INTRODUCTION

Although endovascular therapy (EVT) combined with intravenous thrombolysis (IVT) has become the standard of care for patients with acute ischemic stroke (AIS) with large vessel occlusion (LVO) in the anterior circulation and moderate-to-severe neurological symptoms, the best management of patients with AIS with LVO and minor stroke severity has not yet been determined. On the one hand, approximately 15%–30% of such patients receiving medical treatment alone develop early neurological deterioration and are likely to have unfavorable outcomes, especially in cases of persistent LVO [1–3]. On the other hand, the potential risks may eliminate the gain that patients with mild symptoms can expect to derive from EVT. Unfortunately, in randomized clinical trials of EVT, only MR CLEAN and EXTEND-IA included patients with National Institutes of Health Stroke Scale (NIHSS) scores of ≤5, and the number of patients was small, precluding definite conclusions [4].

Given these uncertainties, more data on the efficacy and safety of EVT in patients with minor strokes are needed to ensure the quality of the current practice of treating such patients in stroke centers. In particular, having clinical and radiological criteria to help select those minor stroke patients who may benefit from EVT could be useful. We therefore aimed to evaluate the relevance of NIHSS subitems for predicting the potential benefit of EVT in AIS patients with M1 or proximal M2 middle cerebral artery (MCA) occlusion and admission NIHSS scores ≤5 points pretreated with IVT ("bridging treatment") versus IVT alone.

METHODS

We conducted an observational multicenter study of consecutive AIS patients with proximal MCA occlusions and low NIHSS scores who received IVT with or without subsequent EVT. Inclusion criteria were: AIS defined as acute onset of a clinical hemispheric stroke syndrome; acute M1 or proximal M2 MCA occlusion corresponding to the clinical deficit, with or without extracranial or intracranial internal carotid artery (ICA) stenosis or occlusion (tandem pathology) on acute computed tomography (CT) and/or magnetic resonance (MR) arteriography; admission NIHSS score ≤5 points; and revascularization treatment with IVT (alteplase only) alone or followed by EVT (bridging treatment). The decision to perform IVT and/or EVT was up to the treating physicians at the time of the acute assessment. Some patients received delayed EVT due to early neurological deterioration of at least 4 NIHSS points <24 h after admission ("rescue EVT"); these were included in the group of patients treated with IVT alone [5].

Exclusion criteria were unavailability of NIHSS subitem scores on admission and insufficient baseline CT and/or MR arteriography data for classification of vessel occlusion location.

We analyzed consecutive patients fulfilling all inclusion criteria between May 2005 and March 2021 from nine prospectively constructed stroke registries at seven French and two Swiss comprehensive stroke centers. We noted baseline characteristics routinely recorded in all registries, including age, sex, pre-stroke modified Rankin Scale (mRS) score, vascular risk factors, pre-stroke anti-thrombotic medication and time from symptom onset to start of IVT. For patients receiving EVT, we also recorded time from symptom onset to groin puncture and from groin puncture to reperfusion.

Clinical evaluation and NIHSS score on admission were performed by a NIHSS-certified stroke neurologist, or by a neurology resident, with the initial NIHSS score being discussed and corrected (if needed) by a NIHSS-certified neurologist on the next working day. At the 3-month outpatient visit, a NIHSS-certified stroke neurologist performed the NIHSS assessment. We used the standard 15-item version of the NIHSS [6].

In addition, we assessed the mRS score at 3 months in person or via a structured telephone interview [7] by non-blinded Rankin-certified personnel.

All included patients underwent either CT arteriography or MR arteriography before IVT, and follow-up CT or magnetic resonance imaging (MRI) approximately 12–24 h following admission, and additionally in cases of secondary neurological worsening. We collected imaging variables including the occlusion site from one of the following categories: ICA "T" occlusion (defined as distal internal carotid occlusion with simultaneous occlusion of the origin of the M1 and the A1), or ICA "L" occlusion (defined as distal internal carotid occlusion with simultaneous occlusion of the origin of the M1; ICA-T/L) [8], proximal M1 (±tandem cervical ICA), distal M1 (±tandem cervical ICA) and M2 (±tandem cervical ICA) occlusion. The M1 segment was defined as the first portion of the MCA up to the main bifurcation, dichotomized as proximal or distal based on MCA origin-to-clot interface distance <10 and ≥10 mm, respectively. In addition, we recorded: thrombus length, measured by MRI (i.e., susceptibility vessel sign), CT (hyperdense MCA sign), or CT arteriography [9–11]; infarct extent, evaluated by the Alberta Stroke Program Early CT Score (ASPECTS) [12] or diffusion-weighted imaging (DWI)-ASPECTS [13], respectively; recanalization, measured by the arterial occlusive lesion (AOL) score at 24 h after revascularization therapy [14]; and intracerebral hemorrhage according to the European-Australasian Acute Stroke Study (ECASS) II criteria [15].

Statistical analysis

We first performed a univariable analysis. For categorical variables, we used the χ^2 test or Fisher's exact test, as appropriate, and for continuous and ordinal variables, we used one-way analysis of variance or the Mann–Whitney *U*-test, as appropriate, to compare baseline characteristics, demographic data, vascular risk factors, baseline imaging findings, therapy details and outcome variables between patients treated by bridging treatment and IVT alone.

For the multivariable analysis, all variables significant at the $p<0.05$ level in the univariable analysis were included.

Before assessing interaction, the influence of treatment modality on 3-month Rankin-shift, on the difference in NIHSS at 3 months, and the differences in each NIHSS subitem score between 3 months and admission were evaluated with stepwise ordinal regression analyses. We also assessed the influence of treatment modality on successful recanalization (AOL 2/3) at 24 h, and hemorrhagic transformation (graded according to ECASS II) [16] by stepwise multivariable binary logistic regression analyses. To avoid overfitting, the maximum number of potential confounders in the models was restricted to up to one-tenth of the size of the smallest number of the outcome categories, and we did not adjust for intermediate variables on a causal path from exposure to outcome.

We finally performed an adjusted interaction analysis between the ordinal admission NIHSS subitem scores and therapy modality for the two primary outcomes at 3 months: (i) non-excellent functional outcome (mRS score 2–6) at 3 months by multivariable binary logistic regression analysis; (ii) difference in the total NIHSS score between 3 months and admission (NIHSS difference at 3 months) by ordinal regression analysis. In both analyses, we removed all non-significant NIHSS subitems stepwise to reach the final model. For the two primary outcomes, we applied a Bonferroni correction, resulting in a *p* value of 0.025 being considered as significant.

We performed sensitivity analyses for the two primary outcomes for patients with M2 occlusions and patients admitted from 2015.

We performed statistical analysis using SPSS 25.0 (SPSS Inc.).

Ethical considerations, patient consent and data sharing

The participating stroke registries had local ethics committee approval for quality control and research. Patients were informed about the registries and the potential use of their data for research.

For patients from Lausanne, ethics committee approval and patient consent were not required for this study according to the Swiss Federal Act on Research involving Human Beings from 2011 (HRA, Art. 3) as all data were anonymized and the project assessed quality, safety and outcome of routine AIS management. For French patients, in accordance with French law, those who refused the use of their data for research were excluded from the analysis. We also excluded patients from Bern who did not consent to potential use of their data for research from the study. This study complied with the Declaration of Helsinki and all data analysis followed Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines [17].

RESULTS

After excluding 25 patients due to ≥1 missing admission NIHSS subitem, absence of good quality CT or MR arteriography, or both criteria (Figure S1), we analyzed 533 patients (median age 68.2 years, interquartile range 59.2–79, $n=245$ women (46%), median admission NIHSS score 3, interquartile range 2–4). MRI with MR arteriography as the primary imaging modality was performed in 376 patients (71%) and CT with CT arteriography as the primary imaging modality was performed in the remaining patients. A total of 136 patients (25.5%) received bridging therapy and 397 (74.5%) were treated by IVT alone (of whom 29 later received a rescue EVT, but remained in the IVT group for further analysis; Table 1).

The bridging therapy group had more occlusions that were proximal and more right-side thrombus location compared to the IVT-alone group. MRI-based imaging was less frequently performed in the bridging group, and the majority of bridging treatments (93.4%) were performed after 2015. Otherwise, the two groups had similar

TABLE 1 Baseline characteristics of the overall cohort.

	IVT group (*n* = 397)		Bridging group (*n* = 136)		
	Value	Missing values	Value	Missing values	*p* value
Age, median (range) years	70 (18–96)	0	70 (19–96)	0	0.537
Women, *n* (%)	187 (47.1)	0	58 (42.6)	0	0.368
Pre-stroke mRS score, median, (range)	0 (0–4)	60	0 (0–4)	11	0.357
Included since year 2015, *n* (%)	231 (58.2)	0	127 (93.4)	0	<0.0001
Vascular risk factor, *n* (%)					
Arterial hypertension	228 (57.6)	1	76 (55.9)	0	0.731
Diabetes mellitus	61 (15.4)	1	20 (14.7)	0	0.845
Current smoking	80 (20.3)	3	33 (24.4)	1	0.311
Previous stroke	33 (8.3)	0	17 (12.5)	0	0.148
Coronary artery disease	63 (15.9)	1	22 (16.2)	0	0.941
Antithrombotics		0		0	
Antiplatelets	114 (28.7)		41 (30.1)		0.751
Anticoagulation	19 (4.8)		6 (4.4)		1.000
MRI-based imaging, *n* (%)	294 (74.1)	0	82 (60.3)	0	0.002
Location of acute vessel occlusion on acute non-invasive imaging where available, *n* (%)		0		0	0.003
ICA T or L occlusion	5 (1.3)		2 (1.5)		
Proximal M1 segment (±ICA tandem)	26 (6.5)		14 (10.3)		
Distal M1 segment (±ICA tandem)	89 (22.4)		49 (36)		
M2 segment (±ICA tandem)	277 (69.8)		71 (52.2)		
Tandem occlusions	45 (11.3)		11 (8.1)		
Right-sided stroke	197 (49.6)	0	93 (68.4)	0	<0.0001
ASPECTS	9 (2–10)	1	9 (6–10)	0	0.142
Thrombus length < 9 mm	201 (56.6)	42	64 (50)	8	0.197
Rescue EVT	29 (7.3)	0	0	0	<0.0001
Delays, median (range) min					
From stroke discovery to IVT	160 (25–450)	2	150 (47–559)	1	
From stroke discovery to groin puncture of primary EVT	NA	NA	214 (105–600)	2	0.107
From stroke discovery to groin puncture of rescue EVT	334 (130–1550)	0	NA	NA	
Admission NIHSS total, median, (range)	4 (0–5)	0	4 (0–5)	0	0.206
NIHSS subitems, *n* (%)					
1a. Admission level of consciousness					1.000
1 point	2 (0.5)		0		
1b. Admission level of consciousness questions					0.401
1 point	45 (11.3)		20 (14.7)		
2 points	38 (9.6)		16 (11.8)		
1c. Admission level of consciousness commands					0.341
1 point	22 (5.5)		12 (8.8)		

TABLE 1 (Continued)

	IVT group (*n* = 397)		Bridging group (*n* = 136)		
	Value	Missing values	Value	Missing values	*p* value
2 points	1 (0.3)		0		
2. Admission best gaze					0.312
1 point	11 (2.8)		1 (0.7)		
2 points	0		0		
3. Admission visual					0.881
1 point	25 (6.3)		9 (6.6)		
2 points	16 (4)		7 (5.1)		
3 points	1 (0.3)		0		
4. Admission facial palsy					0.376
1 point	166 (41.8)		66 (48.5)		
2 points	47 (11.8)		13 (9.6)		
5a. Admission motor left arm					0.941
1 point	57 (14.4)		20 (14.7)		
2 points	7 (1.8)		3 (2.2)		
5b. Admission motor right arm					0.085
1 point	27 (6.8)		7 (5.1)		
2 points	0		2 (1.5)		
3 points	1 (0.3)		0		
6a. Admission motor left leg					0.312
1 point	32 (8.1)		11 (8.1)		
2 points	1 (0.3)		1 (0.7)		
3 points	0		1 (0.7)		
6b. Admission motor right leg					0.529
1 point	12 (3)		6 (4.4)		
2 points	2 (0.5)		0		
7. Admission limb ataxia					0.425
1 point	32 (8.1)		11 (8.1)		
2 points	9 (2.3)		6 (4.4)		
8. Admission sensory					0.600
1 point	67 (16.9)		22 (16.2)		
2 points	12 (3)		2 (1.5)		
9. Admission best language					0.735
1 point	96 (24.2)		39 (28.7)		
2 points	75 (18.9)		22 (16.2)		
3 points	3 (0.8)		1 (0.7)		
10. Admission dysarthria					0.390
1 point	155 (39)		60 (44.1)		
2 points	8 (2)		1 (0.7)		
11. Admission extinction and inattention					0.004
1 point	48 (12.1)		10 (7.4)		
2 points	19 (4.8)		17 (12.5)		

Abbreviations: ASPECTS, Alberta Stroke Program Early CT Score; EVT, endovascular therapy; ICA, internal carotid artery, IVT, intravenous thrombolysis; MRI, magnetic resonance imaging; NA, not applicable; NIHSS, National Institutes of Health Stroke Scale.

baseline clinical and radiological characteristics; including pre-stroke mRS score and admission NIHSS total score (Table 1). Most admission NIHSS subitem scores were similar as well; only admission neglect and inattention subscore was more severe in the bridging group. mRS score was available for 515 patients, while NIHSS difference at 3 months was analyzed only in the 467 of 533 patients for whom NIHSS score was evaluated in person in the outpatient clinic. Good quality CTA or MRA at 24 h was available for 411 out of 533 patients.

In the multivariable analyses assessing influence of treatment modality on the two main outcomes, patients in the bridging therapy group had a significant shift toward a lower/better 3-month mRS score ($p=0.006$), and a better NIHSS difference at 3 months ($p=0.025$) than the IVT-only group (Table 2). We did not observe a significant difference in hemorrhagic transformation between the two groups ($p=0.073$), but successful recanalization at 24 h was significantly higher in the bridging group (odds ratio [OR] 0.14, 95% confidence interval [CI] 0.05–0.36; $p<0.0001$). Bridging was associated with a greater improvement in NIHSS disorientation ($p=0.019$) and aphasia ($p=0.001$) subitem scores (Table 2; Table S1) at 3 months.

Regarding the adjusted interaction analysis for the two primary outcomes, non-excellent functional 3-month outcome (mRS score 2–6) and individual NIHSS subitems did not show a significant interaction with treatment type. The subitem "facial palsy" at admission was inversely associated with non-excellent outcome after bridging therapy ($p=0.013$; OR 0.47, 95% CI 0.24–0.91; Table 3). In other words, a facial palsy on admission predicted better outcome if a patient only received IVT, without added EVT.

We found no NIHSS subitem interaction with type of revascularization therapy with respect to the second primary outcome, NIHSS difference at 3 months.

In the sensitivity analysis of patients with M2 occlusions, we did not reveal any differences in outcome between the revascularization therapies (Tables S2 and S3). However, adjusted interaction analysis revealed that the admission NIHSS subitem "right side leg motor paresis" score less frequently predicted NIHSS difference at 3 months in patients treated by bridging therapy versus IVT alone ($p=0.018$; estimate = −1.41 [−2.73–0.09]; Table S4).

In the second sensitivity analysis of patients admitted from 2015, there were differences in outcome analysis between the IVT and bridging groups, mostly in favor of the bridging therapy group (Table S6). Further, the adjusted interaction analysis revealed that the admission NIHSS subitem "aphasia" score more frequently predicted non-excellent 3-month outcome in patients treated by IVT alone versus bridging therapy ($p=0.017$; OR 2.06, 95% CI 1.06–4.01 [Tables S5–S7]).

DISCUSSION

The main findings of our study were that there was an overall benefit of adding EVT to IVT in patients with minor stroke due to MCA occlusion, but that individual NIHSS subitems at admission had little value in identifying potential responders to bridging therapy. Considering the Bonferroni correction for multiple outcomes, only the facial palsy subitem predicted a possibly less favorable response to EVT.

We did find an overall benefit on outcome of adding EVT to IVT in this minor stroke cohort. Some of the other retrospective studies that have investigated this also found a benefit in minor stroke patients with MCA occlusions [18–21], whereas a previous analysis from our group found slightly worse outcomes [22]. This discordance between our previous study and the current analysis may be related to the inclusion of different patients, given that in the current study we considered only patients with available NIHSS subitems data; furthermore, new patients were added to the databases of participating centers.

When performing rescue (late) EVT after worsening in minor stroke patients with LVO, one study found a benefit of adding EVT [23], whereas another reported a worse outcome [21].

A potential effect of EVT in minor stroke still needs to be proven in randomized clinical trials, particularly in view of the neutral result in the (underpowered) thrombolysis trial of stroke with non-disabling neurological deficits [24]. Given that an effect of EVT in these patients may only exist in selected patients, in contrast to patients with moderate to severe strokes with proximal occlusions [4], there is a strong need for clinical and/or radiological criteria that may help in selecting mild AIS patients for EVT. Concerning radiological predictors, a multicenter international observational study recently found that minor strokes due to M2 occlusions have a particularly poor outcome after EVT [23]; on the other hand, minor stroke patients with proximal M1 ± ICA occlusions seemed to benefit [23]. Regarding perfusion imaging, the same group found that the baseline mismatch volume modified the effect of EVT, predicting worse outcome after EVT in patients with mismatch volumes of ≤40 mL [22].

In patients with distal occlusions but moderate deficits, the effect of EVT may be better, as shown in a few retrospective case series [25–27]; here again, perfusion imaging may be useful in determining EVT responders [25]. Overall, both the clinical stroke severity and radiological features (occlusion site, mismatch profile) may be useful to select the revascularization strategy, whereas the evidence for using single clinical features remains insufficient.

This is the first study, to our knowledge, that has focused on potential associations of NIHSS subitems with EVT response. With our mostly negative findings, we cannot recommend using NIHSS subitems to select in favor of or against EVT on top of IVT in minor stroke patients with MCA occlusions. We found that paresis, that is, facial palsy in the overall group and right leg weakness in the M2-occlusion sensitivity analysis, predicted poorer EVT response; this finding could be explained pathophysiologically by the fact that hemispheric deficits (aphasia, hemineglect, visual fields) have larger brain volumes that, when only partially being saved by EVT, can better compensate for the initial deficits than the more dense pyramidal structures.

Our findings should be interpreted in the context of the current uncertainty of EVT benefit in such patients and considering the substantial rate of early neurological deterioration in these patients treated with IVT alone [3].

TABLE 2 Clinical and radiological outcomes of the overall cohort, comparing the intravenous thrombolysis and bridging patients. Unadjusted and adjusted *p* value results are shown. In the lower part of the table (National Institutes of Health Stroke Scale [NIHSS] subitems), we show changes from admission to 3 months for each NIHSS subitem for the 467 patients included in this analysis.

At follow-up	IVT group (n = 397)	Bridging group (n = 136)	p values of unadjusted analysis	p values of adjusted analysis
mRS score at 3 months (mRS shift analysis) median value (with IQR)	1 (0–2)	1 (0–2)	0.074	0.006
0	126 (33.1%)	58 (43.3%)		
1	110 (28.9%)	34 (25.4%)		
2	68 (17.8%)	17 (12.7%)		
3	49 (12.9%)	12 (9%)		
4	8 (2.1%)	8 (6%)		
5	1 (0.3%)	0		
6	19 (5%)	5 (3.7%)		
NIHSS difference at 3 months, median (range)				
Total median value, with (IQR)	0 (0–1)	0 (0–1)	$p = 0.215$	$p = 0.192$
Change from admission (delta-NIHSS)	−2 (−5–42)	−3 (−5–41)	$p = 0.058$	$p = 0.025$
Intracerebral hemorrhage (ECASS II)			$p = 0.133$	$p = 0.073$
None	327 (84.3%)	122 (89.7%)		
HI1	31 (8%)	6 (4.4%)		
HI2	18 (4.6%)	4 (2.9%)		
PH1	5 (1.3%)	2 (1.5%)		
PH2	7 (1.8%)	2 (1.5%)		
Successful recanalization at 24 h (AOL 2/3)	222 (76.6%)	116 (95.9%)	Unadjusted OR (95% CI) 0.14 (0.56–0.36), 0.001	Adjusted OR (95% CI) 0.14 (0.05–0.36), <0.0001
NIHSS subitems				
1a. 3-month level of consciousness				
Change from admission	0 (−1–3)	0 (0–3)	0.560	0.895
1.b 3-month level of consciousness questions				
Change from admission	0 (−2–2)	0 (−2–2)	0.289	0.019
1c. 3-month level of consciousness commands				
Change from admission	0 (−2–2)	0 (−1–2)	0.330	0.069
2. 3-month best gaze				
Change from admission	0 (−1–2)	0 (0–2)	0.540	0.952
3. 3-month visual				
Change from admission	0 (−2–3)	0 (−2–3)	0.275	0.612
4. 3-month facial palsy				
Change from admission	0 (−2–3)	0 (−2–3)	0.328	0.473
5a. 3-month motor left arm				
Change from admission	0 (−2–4)	0 (−2–4)	0.775	0.199
5b. 3-month motor right arm				
Change from admission	0 (−2–4)	0 (−2–4)	0.630	0.793
6a. 3-month motor left leg				
Change from admission	0 (−2–4)	0 (−2–4)	0.504	0.491
6b. 3-month motor right leg				
Change from admission	0 (−2–4)	0 (−1–4)	0.305	0.172

(Continues)

TABLE 2 (Continued)

At follow-up	IVT group (n = 397)	Bridging group (n = 136)	p values of unadjusted analysis	p values of adjusted analysis
7. 3-month limb ataxia				
Change from admission	0 (−2–2)	0 (−2–2)	0.283	0.848
8. 3-month sensory				
Change from admission	0 (−2–2)	0 (−2–2)	0.998	0.624
9. 3-month best language				
Change from admission	0 (−2–3)	0 (−3–3)	0.335	0.001
10. 3-month dysarthria				
Change from admission	0 (−2–2)	0 (−2–2)	0.132	0.198
11. 3-month extinction and inattention				
Change from admission	0 (−2–2)	0 (−2–2)	0.063	0.195 (0.561)

Abbreviation: CI, confidence interval; IQR, interquartile range; IVT, intravenous thrombolysis; mRS, modified Rankin scale; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio.

Note: Values are given as numbers with percentages, unless otherwise stated. Results adjusted according to inclusion before versus after 2015, location of acute vessel occlusion, occlusion side, magnetic resonance versus computed tomography-based imaging and admission NIHSS subitems (if different at a $p < 0.05$ level in univariable comparison).

TABLE 3 Adjusted interaction analysis between admission National Institutes of Health Stroke Scale (NIHSS) subitems and revascularization type (bridging therapy vs. intravenous thrombolysis) regarding 3-month non-excellent outcome (modified Rankin Scale score 2–6) and NIHSS difference at 3 months.

Main analysis	Non-excellent outcome (mRS score 2–6)	NIHSS difference at 3 months
Interaction between therapy and total NIHSS score	p = 0.489; OR = 1 (95% CI 0.75–1.35)	NA
Interaction between therapy and level of consciousness	NA	NA
Interaction between therapy and level of consciousness questions	p = 0.199; OR = 1.32 (95% CI 0.70–2.51)	p = 0.453; estimate = 0.03 (95% CI −0.53–0.60)
Interaction between therapy and level of consciousness commands	p = 0.249; OR = 1.86 (95% CI 0.31–11.14)	p = 0.433; estimate = 0.12 (−1.21–1.44)
Interaction between therapy and best gaze	p = 0.500	NA
Interaction between therapy and visual fields	p = 0.079; OR = 1.89 (95% CI 0.78–4.57)	p = 0.208; estimate = −0.31 (95% CI −1.07–0.44)
Interaction between therapy and facial palsy	p = 0.013; OR = 0.47 (95% CI 0.24–0.91)	p = 0.239; estimate = −0.20 (95% CI −0.77–0.36)
Interaction between therapy and motor left arm	p = 0.098; OR = 0.54 (95% CI 0.21–1.38)	p = 0.116; estimate = −0.51 (95% CI −1.36–0.33)
Interaction between therapy and motor right arm	p = 0.408; OR = 0.86 (95% CI 0.23–3.20)	p = 0.321; estimate = −0.27 (95% CI −1.41–0.87)
Interaction between therapy and motor left leg	p = 0.100; OR = 0.46 (95% CI 0.14–1.51)	p = 0.136; estimate = −0.61 (95% CI −1.68–0.47)
Interaction between therapy and motor right leg	p = 0.358; OR = 0.70 (95% CI 0.10–4.74)	p = 0.191; estimate = −0.76 (95% CI −2.44–0.93)
Interaction between therapy and limb ataxia	p = 0.438; OR = 1.09 (95% CI 0.39–3.06)	p = 0.343; estimate = −0.17 (95% CI −0.99–0.65)
Interaction between therapy and sensory deficit	p = 0.165; OR = 1.66 (95% CI 0.60–4.60)	p = 0.371; estimate = −0.14 (95% CI −0.99–0.71)
Interaction between therapy and best language	p = 0.071; OR = 1.54 (95% CI 0.87–2.72)	p = 0.378; estimate = 0.08 (95% CI −0.40–0.56)
Interaction between therapy and dysarthria	p = 0.416; OR = 0.92 (95% CI 0.41–2.07)	p = 0.345; estimate = −0.145 (95% CI −0.86–0.57)
Interaction between therapy and extinction and inattention	p = 0.355; OR = 0.87 (95% CI 0.42–1.81)	p = 0.296; estimate = −1.62 (95% CI −0.75–0.43)

Abbreviations: CI, confidence interval; IVT, intravenous thrombolysis; mRS, modified Rankin scale; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio.

The aforementioned results and our data should not change the current European Stroke Organization (ESO)/ European Society for Minimally Invasive Neurological Therapy (ESMINT) guidelines whereby the experts' opinion states that "mechanical thrombectomy [...] may be reasonable in patients with deficits that appear disabling at presentation and/or in case of clinical worsening despite intravenous thrombolysis" [28]. With or without EVT, the current ESO thrombolysis consensus statement suggests that IVT should be given in minor disabling stroke with LVO [29].

Our study has several limitations. First, it was a retrospective, observational, non-controlled, non-randomized study with potential selection bias, in particular, concerning the decision to perform IVT and/or EVT. Second, some of the initial NIHSS evaluations were not performed by NIHSS-certified neurology residents, potentially making them less reliable. However, these admission NIHSS scores were discussed for each patient with a NIHSS-certified stroke neurologist the following day and were retrospectively corrected if needed. Third, 7.3% of patients intended for treatment with IVT only received rescue EVT due to early neurological deterioration. Fourth, as the study was a quality assurance project conducted by the participating stroke centers, it may not be applicable to other institutions or patient cohorts, in particular, not to non-White elderly patients. Finally, although we present new data in patients with minor stroke and LVO in the anterior circulation eligible for IVT ± EVT, our study does not inform us whether bridging therapy is superior to IVT alone, even in the subgroup of patients with specific NIHSS subitems. This will need to be verified in randomized trials that also consider other clinical and radiological prognostic markers.

In conclusion, our retrospective study demonstrated that NIHSS subitems at admission had little predictive value as to which mild stroke patients with MCA occlusion might respond to bridging therapy compared to IVT alone. These results need to be corroborated by other multicentric observations and ongoing randomized trials to identify better markers to be used as EVT selection criteria in patients with minor strokes.

AUTHOR CONTRIBUTIONS

Paola Palazzo, Giovanna Padlina, Tomas Dobrocky, Patrik Michel and Mirjam R. Heldner had full access to all the data and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Mirjam R. Heldner. Study supervision: Patrik Michel and Mirjam R. Heldner. Acquisition of data: All co-authors. Extraction of data: All co-authors. Statistical analysis: Mirjam R. Heldner. Analysis and interpretation: Paola Palazzo, Patrik Michel and Mirjam R. Heldner. Drafting of the manuscript: Paola Palazzo, Patrik Michel and Mirjam R. Heldner. Critical revision of the manuscript for important intellectual content: All co-authors.

ACKNOWLEDGMENTS

We thank Mattia Branca, PhD, for statistical advice and Mrs Melanie Price Hirt, PhD, for English language correction and editing. We are grateful to all the stroke teams who contributed to this study. Open access funding provided by Inselspital Universitatsspital Bern.

FUNDING INFORMATION

Mirjam R. Heldner reports a grant from the Bangerter Foundation, directly related to this project and grants from the Swiss National Science Foundation, SITEM-Insel Support Funds and from the Swiss Heart Foundation, all outside of the submitted work. Kateryna Antonenko reports a grant from the Swiss National Science Foundation.

CONFLICT OF INTEREST STATEMENT

Mirjam R. Heldner reports a grant from the Bangerter Foundation, directly related to this project and grants from the Swiss National Science Foundation, SITEM-Insel Support Funds and from the Swiss Heart Foundation, all outside of the submitted work. Kateryna Antonenko reports a grant from the Swiss National Science Foundation. All other co-authors report no conflict of interest.

DATA AVAILABILITY STATEMENT

The raw, anonymized data that support the findings of this study are available from the corresponding author upon reasonable request, and after local ethics committee clearance and signing a data transfer and use agreement. If the data are then used for a publication, the methods should be communicated, and internationally recognized authorship rules should apply.

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REFERENCES

1. Nedeltchev K, Schwegler B, Haefeli T, et al. Outcome of stroke with mild or rapidly improving symptoms. *Stroke*. 2007;38(9):2531-2535.
2. Heldner MR, Jung S, Zubler C, et al. Outcome of patients with occlusions of the internal carotid artery or the main stem of the middle cerebral artery with NIHSS score of less than 5: comparison between thrombolysed and non-thrombolysed patients. *J Neurol Neurosurg Psychiatry*. 2015;86(7):755-760.
3. Seners P, Ben Hassen W, Lapergue B, et al. Prediction of early neurological deterioration in individuals with minor stroke and large vessel occlusion intended for intravenous thrombolysis alone. *JAMA Neurol*. 2021;78(3):321-328.
4. 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(10029):1723-1731.
5. Nagel S, Haussen DC, Nogueira RG. Importance of the intention-to-treat principle. *JAMA Neurol*. 2020;77(7):905-906.
6. Lyden P, Brott T, Tilley B, et al. Improved reliability of the NIH stroke scale using video training. NINDS TPA Stroke Study Group. *Stroke*. 1994;25(11):2220-2226.
7. Wilson JT, Hareendran A, Grant M, et al. Improving the assessment of outcomes in stroke: use of a structured interview to assign grades on the modified Rankin scale. *Stroke*. 2002;33(9):2243-2246.
8. Liebeskind DS, Flint AC, Budzik RF, et al. Carotid I's, L's and T's: collaterals shape the outcome of intracranial carotid occlusion in acute ischemic stroke. *J Neurointerv Surg*. 2015;7(6):402-407.

9. Naggara O, Raymond J, Domingo Ayllon M, et al. T2* "susceptibility vessel sign" demonstrates clot location and length in acute ischemic stroke. *PloS One*. 2013;8(10):e76727.
10. Rohan V, Baxa J, Tupy R, et al. Length of occlusion predicts recanalization and outcome after intravenous thrombolysis in middle cerebral artery stroke. *Stroke*. 2014;45(7):2010-2017.
11. Riedel CH, Jensen U, Rohr A, et al. Assessment of thrombus in acute middle cerebral artery occlusion using thin-slice nonenhanced computed tomography reconstructions. *Stroke*. 2010;41(8):1659-1664.
12. Barber PA, Demchuk AM, Zhang J, Buchan AM. 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(9216):1670-1674.
13. Nezu T, Koga M, Nakagawara J, et al. Early ischemic change on CT versus diffusion-weighted imaging for patients with stroke receiving intravenous recombinant tissue-type plasminogen activator therapy: stroke acute management with urgent risk-factor assessment and improvement (SAMURAI) rt-PA registry. *Stroke*. 2011;42(8):2196-2200.
14. Khatri P, Neff J, Broderick JP, Khoury JC, Carrozzella J, Tomsick T. Revascularization end points in stroke interventional trials: recanalization versus reperfusion in IMS-I. *Stroke*. 2005;36(11):2400-2403.
15. Larrue V, von Kummer RR, Müller A, Bluhmki E. Risk factors for severe hemorrhagic transformation in ischemic stroke patients treated with recombinant tissue plasminogen activator: a secondary analysis of the European-Australasian acute stroke study (ECASS II). *Stroke*. 2001;32(2):438-441.
16. Hacke W, Kaste M, Fieschi C, et al. Randomised double-blind placebo-controlled trial of thrombolytic therapy with intravenous alteplase in acute ischaemic stroke (ECASS II). Second European-Australasian acute stroke study investigators. *Lancet*. 1998;352(9136):1245-1251.
17. von Elm E, Altman DG, Egger M, et al. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. *Lancet*. 2007;370(9596):1453-1457.
18. 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 Neurointerv Surg*. 2017;9(10):917-921.
19. Haussen DC, Lima FO, Bouslama M, et al. Thrombectomy versus medical management for large vessel occlusion strokes with minimal symptoms: an analysis from STOPStroke and GESTOR cohorts. *J Neurointerv Surg*. 2018;10(4):325-329.
20. Griessenauer CJ, Medin C, Maingard J, et al. Endovascular mechanical Thrombectomy in large-vessel occlusion ischemic stroke presenting with low National Institutes of Health stroke scale: systematic review and meta-analysis. *World Neurosurg*. 2018;110:263-269.
21. Heldner MR, Chaloulos-Iakovidis P, Panos L, et al. Outcome of patients with large vessel occlusion in the anterior circulation and low NIHSS score. *J Neurol*. 2020;267(6):1651-1662.
22. Seners P, Arquizan C, Fontaine L, et al. Perfusion imaging and clinical outcome in acute minor stroke with large vessel occlusion. *Stroke*. 2022;53:3429-3438.
23. Seners P, Perrin C, Lapergue B, et al. Bridging therapy or IV thrombolysis in minor stroke with large vessel occlusion. *Ann Neurol*. 2020;88(1):160-169.
24. Khatri P, Kleindorfer DO, Devlin T, et al. Effect of Alteplase vs aspirin on functional outcome for patients with acute ischemic stroke and minor nondisabling neurologic deficits: the PRISMS randomized clinical trial. *JAMA*. 2018;320(2):156-166.
25. Sarraj A, Parsons M, Bivard A, et al. Endovascular Thrombectomy versus medical management in isolated M2 occlusions: pooled patient-level analysis from the EXTEND-IA trials, INSPIRE, and SELECT studies. *Ann Neurol*. 2022;91(5):629-639.
26. Menon BK, Hill MD, Davalos A, et al. Efficacy of endovascular thrombectomy in patients with M2 segment middle cerebral artery occlusions: meta-analysis of data from the HERMES collaboration. *J Neurointerv Surg*. 2019;11(11):1065-1069.
27. Dobrocky T, Piechowiak EI, Volbers B, et al. Treatment and outcome in stroke patients with acute M2 occlusion and minor neurological deficits. *Stroke*. 2021;52(3):802-810.
28. Turc G, Bhogal P, Fischer U, et al. European stroke organisation (ESO) – European Society for Minimally Invasive Neurological Therapy (ESMINT) guidelines on mechanical Thrombectomy in acute ischemic stroke. *J Neurointerv Surg*. 2019;11:535-538.
29. Berge E, Whiteley W, Audebert H, et al. European stroke organisation (ESO) guidelines on intravenous thrombolysis for acute ischaemic stroke. *Eur Stroke J*. 2021;6(1):I-LXII.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Palazzo P, Padlina G, Dobrocky T, et al. Relevance of National Institutes of Health Stroke Scale subitems for best revascularization therapy in minor stroke patients with large vessel occlusion: An observational multicentric study. *Eur J Neurol*. 2023;30:3741-3750. doi:10.1111/ene.16009