Stroke: Vascular and Interventional Neurology

EDITORIAL

How Low Do We Go? NIHSS in Anterior Circulation Thrombectomy Decision-Making

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Since the publication of landmark trials demonstrating the benefit of endovascular therapy (EVT), it has been recommended as the standard of care for patients presenting with acute stroke and a National Institutes of Health Stroke Scale (NIHSS) score of ≥6 who fulfill additional clinical and imaging criteria.[1–8] These criteria were largely derived from randomized clinical trials that demonstrated overwhelming efficacy of EVT. Such trials intentionally excluded patients with mild deficits or low NIHSS scores to augment the chances of intervention success following failed attempts with first-generation trial designs. Without studies specifically designed to include this patient population (those with low NIHSS), how best to treat these high-risk individuals remains uncertain.

Consider the case of a 95-year-old female with a history of atrial fibrillation and baseline modified Rankin Scale (mRS) score of 1 who presented with expressive aphasia. Her initial NIHSS score was 5 for inability to answer questions and complete mutism. Imaging demonstrated subtle loss of gray-white matter differentiation in the anterior left insula and distal occlusion of left middle cerebral artery M1 segment. Perfusion imaging showed regional cerebral blood flow <30% volume of 0 mL, T_{max} >6 seconds volume of 95 mL. She presented out of the window of thrombolytics and due to low NIHSS score, EVT was not pursued. She was eventually discharged to an acute inpatient rehabilitation facility with an NIHSS score of 3 due to dense expressive aphasia, some gait instability related to minor weakness and deconditioning, and an mRS score of 4. Although the patient is expected to continue to experience some recovery of her aphasia, the question remains—would she have had a more rapid or significant recovery of these disabling deficits had she undergone EVT?

Lack of inclusion of patients like this in positive clinical trials who present with low NIHSS scores has limited our ability to answer that question.[1–6] Among the completed randomized clinical trials of EVT for anterior circulation large vessel occlusion, only a few such as the Extending the Time for Thrombolysis in Emergency Neurological Deficits—Intra-Arterial trial[1] permitted the inclusion of patients with any NIHSS. Only 4 patients from the Extending the Time for Thrombolysis in Emergency Neurological Deficits—Intra-Arterial trial had a baseline NIHSS score <6, and the MR CLEAN (Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands), which limited inclusion to patients with a presenting NIHSS ≥2, included only 10 such patients.[5] Although Extending the Time for Thrombolysis in Emergency Neurological Deficits—Intra-Arterial trial and MR CLEAN demonstrated superiority of EVT over medical

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management, they were underpowered to detect differences in outcomes for patients with low NIHSS scores. As a consequence, the overcorrection and intentional exclusion of patients with lower NIHSS scores in most trials have contributed to the ambiguity in treatment recommendations for this population and have likely led to missed treatment opportunities for a considerable number of patients over the past decade.

Due to the inclusion criteria of these trials, the American Heart Association and American Stroke Association[8] and Society of Vascular and Interventional Neurology[9] guidelines support the use of EVT in patients presenting with large vessel occlusions of the anterior circulation with an NIHSS score ≥6. However, in patients with an NIHSS score <6, EVT may be reasonable but benefits are uncertain (Class IIb level evidence). This remains highly controversial, even among experts, with 6 out of 11 Society of Vascular and Interventional Neurology guideline authors supporting the statement that “the effectiveness of EVT [in the late window] compared with medical management is unknown” for these patients.[9] The Society of NeuroInterventional Surgery recommendations are slightly more confident in their 2019 guidelines and recommend EVT be considered in patients with NIHSS score <6 and disabling symptoms (Class IIa evidence).[10]

Because clinical trials have largely excluded patients with low NIHSS scores, cohort studies have been instrumental in improving our understanding of the natural history of this population and outcomes with or without EVT. These trials include significant limitations, such as their retrospective nature, nonrandomized treatment allocation leading to incomplete adjustment for measurable confounders as well as residual confounding, and lack of blinded outcome assessment. Moreover, given the high probability of a good outcome in patients with low NIHSS scores according to the mRS, the mRS may be a poor indicator of clinical improvement after EVT. Few cohort studies including this population have reported any significant improvement in long-term mRS scores associated with EVT. One such analysis of 2 multicenter cohorts reported EVT was associated with lower rates of disability (both at the time of discharge and at 3–6 months).[11] These findings remain strongly contested by the larger analysis of the Recovery by Endovascular Salvage for Cerebral Ultra-Acute Embolism-Japan Registry 2, which found no independent association between EVT and functional independence at 90 days.[12] As there was a trend suggesting benefit with EVT on favorable outcome (odds ratio, 1.65, 95% CI, 0.71–3.88), it is possible Recovery by Endovascular Salvage for Cerebral Ultra-Acute Embolism-Japan Registry 2 was underpowered to identify the small but significant benefit with EVT. In a separate analysis of the Swiss Stroke Registry, when compared to patients treated with intravenous thrombolysis, those treated with EVT and thrombolysis were at no greater odds of 90-day favorable outcome.[13] A meta-analysis of 11 published observational cohort studies including patients with an NIHSS score <6 did not find a significant difference in favorable outcomes with EVT compared to medical management.[14] Of these studies, those that used an intention-to-treat design, by including those who received rescue EVT for clinical decompensation in the control group, did not demonstrate a significant difference between EVT and medically-managed patients. Therefore, we are left to believe if there is any significant benefit of EVT in these patients, it may be small or it may be observed only in particular populations such as those with disabling deficits but low NIHSS scores. The lack of significant association between EVT and a good outcome has been replicated in one analysis of the National Inpatient Sample. In that study, which used propensity score matching to adjust for selection bias in EVT, there was no early benefit with EVT in patients with internal cerebral artery or M1 occlusions and NIHSS score <6 with respect to discharge to home or an acute inpatient rehabilitation facility.[15] The nonrandomized treatment allocation, potential misclassification of diagnosis codes, and lack of validation of acuity in large vessel occlusion abstracted from the National Inpatient Sample remain major limitations of analyses related to this data set.

Further clouding our understanding is the difficulty in applying this data to increasingly complex patients who are now eligible for EVT, such as those with distal or medium vessel occlusions, patients presenting in the late window, or those who are suspected to have concurrent intracranial atherosclerotic disease. As with any procedure, risks and benefits should be considered. These considerations must be taken into account in more distal vessel occlusions, as they are more likely to present with a lower NIHSS score and have higher complication rates for EVT. In a subgroup analysis of M2 occlusions treated with EVT or medical

Nonstandard Abbreviations and Acronyms

EVT	endovascular therapy
NIHSS	National Institutes of Health Stroke Scale
mRS	modified Rankin Scale
MR CLEAN	Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands

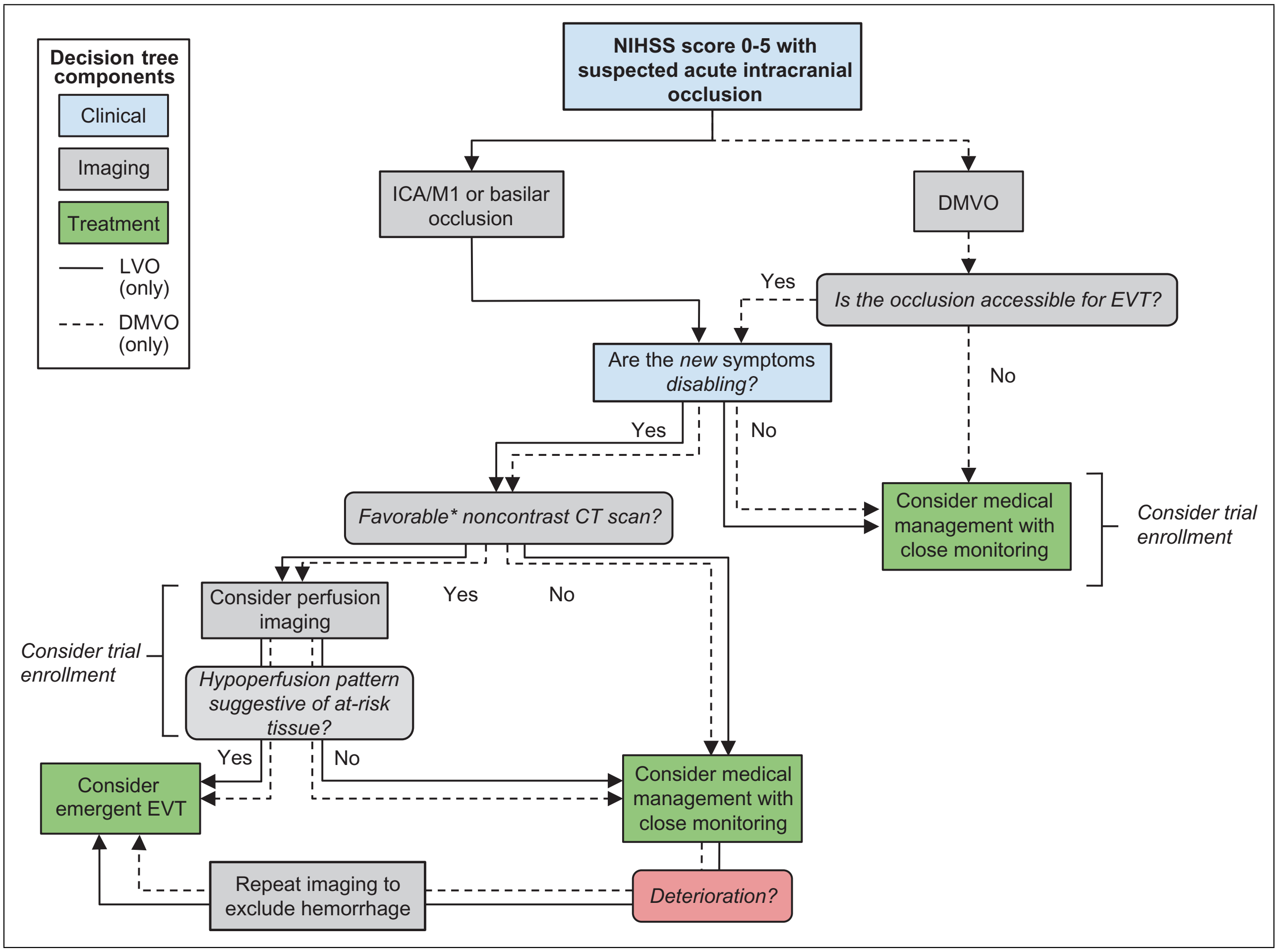

Figure. Proposed decision tree for low NIHSS score. *Favorable noncontrast CT scan in this circumstance is not well defined and should be determined at the discretion of the treating clinician. In general, the imaging would have no evidence of acute intracranial hemorrhage, large region of established infarction, or mass effect (the tissue believed to be at risk of further ischemic injury would be uninjured). These recommendations are only applicable to acute intracranial occlusions, not cervical occlusions or occlusions suspected to be chronic. Not all scenarios are represented in this decision tree, and treatment recommendations should remain personalized according to the discretion of the provider. CT indicates computed tomography; DMVO, distal or medium vessel occlusion; EVT, endovascular therapy; ICA, internal carotid artery; LVO, large vessel occlusion; and NIHSS, National Institutes of Health Stroke Scale.

management in randomized clinical trials, there was a clear benefit of EVT for 90-day functional independence (odds ratio 2.39, 95% CI 1.08–5.28).[16] However, there were too few patients from pooled individual patient data from randomized clinical trials with NIHSS scores 0–6 to power additional subgroup comparisons among patients with M2 occlusions. This benefit must be weighed against the risks of EVT, such as vessel perforation and/or subarachnoid hemorrhage that are more common in distal occlusions, which may contribute to poorer long-term functional outcomes in a patient who originally presented with relatively mild deficits.[17] Following the publication of current guidelines, more recent data from the MR CLEAN-Late arrivals trial have offered new insights into the potential benefit of EVT in patients with low NIHSS who present between 6 and 24 hours after last known well.[18] Of the late window trials, only MR CLEAN-Late trial included patients with NIHSS $\leq$6. In MR CLEAN-Late, 142 patients had NIHSS scores of 1–6 (82 randomized to EVT), and there was a nonsignificant trend favoring EVT for the outcome of favorable shift in the 90-day mRS score (odds ratio 1.79, 95% CI, 0.95–3.37; $P_{interaction} = 0.08$).[18] To date, these remain the most compelling data supporting EVT in mild deficits, and they represent a unique patient population. Other patient subgroups with low NIHSS scores warranting closer evaluation are those with intracranial atherosclerosis. These patients pose unique challenges since those who present with internal carotid artery/M1 occlusions and low NIHSS scores often have intracranial atherosclerotic disease, which typically cannot be differentiated from embolic occlusions without attempted revascularization. These patients may have higher risk of vessel perforation or reocclusion if multiple passes are made during EVT or require emergent stent placement. Despite the high risk of poor outcomes and incomplete revascularization of patients with intracranial atherosclerotic disease as we have seen,[19] the potential procedural complications beg the question as to whether the benefits of attempted revascularization outweigh the risks.[20]

One major limitation inherent to findings from published data pertains to variable selection. Although NIHSS has been used as the primary exposure variable in these circumstances, mRS is invariably selected as the outcome. There is no question NIHSS score correlates strongly with mRS score; however, at the extremes (such as very low or very high NIHSS score) there can be variability in long-term functional outcome according to the mRS. Complete dominant hand paralysis may be captured as an NIHSS score of 0 but leads to significant disability and prevents a patient from returning to employment (mRS of 2). Isolated lower extremity paralysis would also preclude independent ambulation but may only contribute to an NIHSS score of 4 (mRS of 3 or greater). Conversely, a patient with isolated numbness and facial droop may have an NIHSS score of 4 and recover without any lasting disability (mRS 0 or 1). It is practically impossible to compare treatment-related outcomes between these heterogeneous groups despite a numerically equivalent "stroke severity." Furthermore, the generally milder functional disability in patients with low NIHSS scores may be difficult to differentiate using the mRS, which is poorly sensitive for revealing nuances in neurologic deficits. In the absence of high-quality data, we consider several factors in EVT decision making for patients with low NIHSS scores, including the functional disability of the new deficits, location of the occlusion, and imaging findings (Figure).

As Carl Sagan once wrote, "Absence of evidence is not evidence of absence." Although this was not originally expressed to aid in EVT decision-making, we should not succumb to the logical fallacy. Lack of trial *evidence* supporting EVT for patients with low NIHSS scores does not equate to lack of *benefit* with EVT in this population. When stroke symptoms are disabling, despite this lack of evidence, it is unclear if there is equipoise to randomize these patients to best medical management. For patients with acute and disabling symptoms (eg, severe aphasia), even if the measurable deficits as captured by the NIHSS may be small, the long-term outcomes with medical management are likely poor and may justify the risks of EVT at the individual level. These patients are difficult to assess due to poor sensitivity of the NIHSS to capture disability, high rate of early clinical deterioration, and possible concurrent intracranial atherosclerotic disease and distal or medium vessel occlusions, which carry potential increased and unique risks. We eagerly await the results of ongoing clinical trials, including NCT03796468 and NCT04167527, to better understand how to best treat this population.

ARTICLE INFORMATION

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