


# More expansive horizons: a review of endovascular therapy for patients with low NIHSS scores

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## ABSTRACT

While the landmark 2015 stroke trials demonstrated that endovascular therapy (EVT) was superior to medical management for the treatment of acute ischemic stroke due to large vessel occlusion, the efficacy of EVT for patients presenting with a low NIHSS score remains undetermined. We conducted a review of the EVT low National Institutes of Health Stroke Scale (NIHSS) stroke literature, identifying 24 quantitative and six qualitative publications. Details of study designs and outcome were extracted and critically discussed.

All identified qualitative studies were retrospective. There was significant study design heterogeneity, with 18 unique study designs between the 24 identified quantitative manuscripts. Study investigations included low NIHSS EVT feasibility (n=6), EVT versus best medical management (BMM; n=10), EVT versus intravenous therapy (IVT, n=3), and low NIHSS score versus high NIHSS score (n=3). From single-arm EVT feasibility studies, the reported ranges of modified Thrombolysis in Cerebral Infarction and symptomatic intracranial hemorrhage were 78–97% and 0–10%, respectively. The EVT versus BMM literature had heterogeneous results with 40% reporting benefit with EVT and 60% reporting neutral findings. None of the studies comparing EVT with IVT reported a difference between the two revascularization therapies. The four identified meta-analyses had incongruent inclusion criteria and conflicting results. Two randomized trials are currently investigating EVT in patients with a low NIHSS score. Selected meta-analyses do suggest a potential benefit of EVT over BMM; however, current and future randomized clinical trials will better elucidate the efficacy of EVT in this patient population.

## INTRODUCTION

In 2015, multiple randomized controlled clinical trials demonstrated the superiority of endovascular therapy (EVT) over medical management alone for the treatment of acute ischemic stroke (AIS) due to large vessel occlusion (LVO).<sup>1</sup> These results were contrary to previous trials, which showed no additional benefit of EVT over IV tissue plasminogen activator alone. Importantly, these differences were attributed to many considerations, including patient selection, efficient workflow, and higher technical success.<sup>1</sup> An exclusion criterion shared by many of the trials was mild clinical stroke severity, determined by low National Institutes of Health Stroke Scale (NIHSS) score. In trials without this exclusion criterion, patients with AIS and a low

NIHSS score were under-represented, comprising only 5% of the EVT cohorts.<sup>2,3</sup> The efficacy of EVT in patients with AIS-LVO and a low NIHSS score continues to be widely debated, with the literature comprising retrospective investigations that demonstrate conflicting results.<sup>3–12</sup>

Variability in outcomes in patients with AIS and a low NIHSS score highlights the limitations of the NIHSS as a screening tool for treatment eligibility.<sup>13</sup> While the NIHSS is predictive of overall AIS outcome, not all low NIHSS scores are equivalent with regard to clinical outcome.<sup>14,15</sup> Sucharew *et al* used syndromic combination to identify two different low NIHSS profiles with distinct outcomes but both with median NIHSS score of 5. One syndromic profile was characterized by level of consciousness and language, the other by abnormal right motor function. Patients in the latter profile demonstrated better morbidity and mortality, suggesting that the NIHSS may lack the resolution to clinically predict outcomes in low NIHSS score ranges.<sup>15</sup> Discordant outcomes among patients with numerically low NIHSS values increase the variance of the literature-reported outcomes, making it challenging to identify the optimal treatment for these patients. While the routine use of intravenous thrombolysis (IVT) has been the standard of care since 1995, even the role of IVT for patients with a low NIHSS score remains controversial.<sup>16</sup> Increasingly, it is recognized that the variability between patients with a low NIHSS score can be further resolved by classifying the presenting symptoms as disabling versus non-disabling.<sup>16,17</sup>

EVT in patients with a low NIHSS score and LVO is a more nuanced risk–benefit analysis than that for patients with a higher NIHSS score, with potentially smaller clinical benefit at a similar interventional risk. The greatest clinical benefit is garnered in the population subset that further declines, as deficit reversibility in this cohort may not be as feasible even in the setting of exceptional, but delayed, rescue interventional reperfusion. This must be weighed against the risk taken in patients who may recover in the absence of intervention. Investigation into the efficacy of EVT in patients with a low NIHSS score has been limited to retrospective review of prospectively collected data. Furthermore, published studies to date are limited by heterogeneous 'low NIHSS score' definitions, LVO inclusion criteria, and primary endpoints, adding to the already present outcome variability in patients with AIS and a low NIHSS score. Meta-analyses



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attempting to draw conclusions from the heterogeneous literature have consequently yielded conflicting results.<sup>3 12 18 19</sup> In an international survey of 607 practitioners presented with a sample patient with a low NIHSS score, the authors found significant treatment threshold disparity, with 60% deciding to pursue EVT.<sup>20</sup> In one recent study, it was estimated that 11% of patients with LVO AIS undergoing EVT present with mild stroke symptoms.<sup>21</sup> To aid EVT decision-making in this uncertain patient population, we present background on the natural history of patients with AIS and a low NIHSS score, and then review the 'mild stroke' EVT literature.

## NATURAL HISTORY OF PATIENTS WITH AIS AND A LOW NIHSS SCORE

The Safe Implementation of Thrombolysis in Stroke (SITS) International Stroke Thrombolysis and Get with the Guidelines registries report that 21–22% of patients with AIS present with an NIHSS score <6, without LVO specification.<sup>22 23</sup> The SITS registry further reviewed vessel imaging and found that 25% of these patients with stroke and a low NIHSS score were harboring an extracranial or intracranial occlusion, resulting in an overall estimated low NIHSS AIS arterial occlusion incidence of 5%. Documented site-specific arterial occlusion rates were 19% internal carotid artery (ICA) to ICA-terminus (ICA-T), 14.5% M1, 23.1% M2, 2% anterior cerebral artery (ACA), 8% posterior cerebral artery, 5% basilar, and 9.8% vertebral artery.<sup>23</sup> With regard to EVT, the pertinent natural history discussion of low NIHSS AIS encompasses the outcomes in patients treated with conservative management (CM) or best medical management (BMM), including IVT.

Clinical outcomes of patients with AIS and a low NIHSS score treated with CM are superior to those of patients with AIS and a high NIHSS score, but still unfavorable, with a reported 27–35% of patients dependent or dead at hospital discharge.<sup>13 24–26</sup> Nedeltchev *et al* cited a dependency rate of 23%, though they grouped patients with a low NIHSS score with patients with rapidly improving AIS, and these two mild stroke populations may not have similar outcomes.<sup>27</sup> When treated with IVT, the outcomes of patients with a low NIHSS score have been shown to improve if the patient has a coinciding disabling deficit, defined as preventing either basic activities of daily living or returning to work.<sup>16 28–30</sup> The PRISMS trial demonstrated that there was no added benefit of IVT in patients with a low NIHSS score presenting without a disabling deficit.<sup>17</sup>

Although a low NIHSS score is a predictor of good outcome after LVO-AIS, some of these patients may benefit from recanalization therapy.<sup>31</sup> In conservatively managed patients with LVO-AIS and a NIHSS score ≤8 patients, Mokin *et al* retrospectively observed a 38% death or dependence rate. Outcomes did not vary significantly between occlusion location, with vessel-specific death/dependency rates of 37% ICA, 32% M1-M2, 59% basilar, 45% P1-P2.<sup>32</sup> In 378 patients with mild stroke primarily receiving CM, Kim *et al* found that the presence of occlusion was independently associated with early neurologic deterioration (END; OR=2.206, p=0.009).<sup>33</sup> Similarly, Rajasee *et al* found that mild stroke receiving CM in patients with LVO is more susceptible to END (LVO 38% vs non-LVO 3%) and unfavorable functional outcomes (modified Rankin Scale score (mRS) >2 LVO 50% versus non-LVO 3%).<sup>34</sup> In a more recent study, 19.7% of medically managed patients with LVO-AIS experienced END at a median time of 3.6 hours from hospital arrival.<sup>35</sup> Some identified predictors of good outcome (mRS score ≤2) in patients with LVO-AIS and a low NIHSS score include lower NIHSS score (0–3), younger age, reperfusion therapy (IVT, EVT, or both),

absence of hypertension, and absence of hyperglycemia.<sup>9 32 36</sup> Literature for the treatment of patients with LVO-AIS and a low NIHSS score with IVT has yielded conflicting results, probably related to variability in patient exclusion criteria.<sup>9 17 37 38</sup>

## EVT FOR PATIENTS WITH AIS AND A LOW NIHSS SCORE

### Literature review methods

A literature search was conducted on April 15, 2020 by searching the English literature in the Cochrane Library and PubMed. Using the PICO<sup>39</sup> search method, a combination of MeSH terms and free text words were searched: ('mild stroke' OR 'mild large vessel occlusion' OR 'mild ischemic stroke' OR 'low NIHSS' OR 'low National Institutes of Health Stroke Scale') AND ('endovascular' OR 'mechanical thrombectomy' OR '(MeSH) endovascular procedures'). A total of 543 published abstracts or manuscripts were identified. Authors used the Rayyan review app to facilitate a systematic selection of articles.<sup>40</sup> Quantitative manuscripts without a dedicated EVT arm (articles with single arm combined IVT/EVT recanalization groups) were excluded. Non-English literature and abstracts were also excluded.

Each published manuscript that met inclusion criteria and had a discrete EVT treatment group was subjected to data extraction. Owing to significant study heterogeneity and previously published meta-analyses, we did not attempt to combine patient data. Instead, we extracted the study designs and final study conclusions. Study design data points include investigative question, inclusion criteria, NIHSS definition of mild stroke, treatment details, and primary/secondary outcomes. Single-arm EVT studies were labeled as EVT feasibility investigations. Case-control studies without IVT analyses were labeled as EVT versus BMM, whereas those with IVT specification were labeled EVT versus IVT.

### Literature review results

Our literature search yielded 543 results; 30 manuscripts fulfilled our inclusion criterion, 24 quantitative<sup>3–12 21 26 41–52</sup> and six qualitative.<sup>20 53–58</sup> Table 1 displays the identified quantitative studies with EVT treatment of patients with LVO-AIS and a low NIHSS score and their respective inclusion criteria, outcomes, and conclusions. Four meta-analyses were also identified, two of which included their original EVT patient data. There was significant study design heterogeneity, with 18 unique study designs between the 24 identified quantitative manuscripts. The largest points of disparity were study investigation, NIHSS definition of mild stroke, distal vessel exclusion criterion, and primary outcome. Study investigations included low NIHSS EVT feasibility (n=6), EVT versus best medical management (BMM; n=10), EVT versus IVT (n=3), and low NIHSS score versus high NIHSS score (n=3). The most common definitions of mild stroke were NIHSS score ≤5 (n=15, 63%), followed by NIHSS score ≤8 (n=4), and NIHSS score ≤7 (n=3). Studies with parallel investigation and mild stroke definition often had different distal vessel occlusion criteria. The most common vessel criteria used were anterior circulation ICA-terminus, middle cerebral artery (MCA)-M1, or MCA-M2.

### EVT safety and feasibility

Six manuscripts identified were single-arm studies focusing on the feasibility and safety of EVT for patients with LVO-AIS and a low NIHSS score, three (50%) of which defined low NIHSS as NIHSS score ≤5. Among these single-arm trials, the technical feasibility and safety of EVT for patients with LVO-AIS and a low NIHSS score is similar to that of previous stroke trials with reported modified Thrombolysis in Cerebral Infarction (mTICI) ≥2b and symptomatic intracranial hemorrhage (sICH) rates ranging from 78% to 97% and

**Table 1** Identified low NIHSS EVT literature

Date	Author	Investigation	N	NIHSS score	*Vessel criteria*	Primary outcome	Study conclusion
2020	Toth <i>et al</i> <sup>41</sup>	EVT feasibility	20	≤5	Anterior and posterior M2, basilar	mRS ≤1	95% mTICI ≥2b 95% mRS ≤1 0% sICH, 5% SND
2016	Bhogal <i>et al</i> <sup>42</sup>	EVT feasibility	41	≤5	M1 only	mTICI ≥2b	75% mRS ≤2 88% mTICI ≥2b 10% sICH
2018	Kaschner <i>et al</i> <sup>43</sup>	EVT feasibility	30	≤5	M1 only	mRS ≤2	97% mTICI ≥2b 3% sICH
2017	Dargazanli <i>et al</i> <sup>44</sup>	EVT feasibility	138	≤7	Anterior M2, ICA-T	mTICI ≥2b	mTICI ≥2b predictive of FI 81% mTICI ≥2b
2016	Pfaff <i>et al</i> <sup>45</sup>	EVT feasibility	33	≤8	None	mTICI ≥2b	EVT is safe 78% mTICI ≥2b 6% sICH
2018	Bowen <i>et al</i> <sup>46</sup>	EVT feasibility	72	≤8	None	mRS ≤2	EVT is safe 93% mTICI ≥2b 0% sICH
2014	Urra <i>et al</i> <sup>4</sup>	EVT vs BMM	78	≤5	Anterior and posterior M2, A1, basilar, P1	mRS ≤1	NS
2018	Haussen <i>et al</i> <sup>5</sup>	EVT vs BMM	118	≤5	Anterior and posterior M2, ACA, basilar	NIHSS shift	EVT benefit (p=0.03)
2018	Nagel <i>et al</i> <sup>6</sup>	EVT vs BMM	300	≤5	Anterior and posterior M2, ACA, basilar	mRS ≤2	EVT benefit (p=0.03)
2019	†Goyal <i>et al</i> <sup>3</sup>	EVT vs BMM	251	≤5	Anterior M2, ICA-T	mRS ≤2	NS
2017	Haussen <i>et al</i> <sup>7</sup>	EVT vs BMM	32	≤5	Anterior M2, ICA-T	NIHSS shift	EVT benefit (p=0.04)
2018	Sarraj <i>et al</i> <sup>8</sup>	EVT vs BMM	214	≤5	Anterior M4, ACA	mRS ≤1	NS
2020	Saito <i>et al</i> <sup>9</sup>	EVT vs BMM	272	≤5	Anterior and posterior M3, A2, P2	mRS ≤2	NS
2020	Wolman <i>et al</i> <sup>10</sup>	EVT vs BMM	47	≤6	Anterior-none	NIHSS shift	NS
2017	Dargazanli <i>et al</i> <sup>11</sup>	EVT vs BMM	301	≤7	Anterior M2, ICA-T	mRS ≤1	NS
2019	†Shang <i>et al</i> <sup>12</sup>	EVT vs BMM	177	≤8	Anterior M2, ACA	mRS ≤1	EVT benefit (p=0.008)
2019	Manno <i>et al</i> <sup>47</sup>	EVT vs IVT	312	≤5	Anterior M2, ICA-T	mRS ≤1	NS
2017	Messer <i>et al</i> <sup>48</sup>	EVT vs IVT	54	≤5	Anterior M2, ICA-T	mRS ≤1	NS
2018	Kastrup <i>et al</i> <sup>49</sup>	EVT vs IVT	305	≤10	Anterior M2, ICA-T	mRS ≤2	NS
2020	Heldner <i>et al</i> <sup>50</sup>	EVT vs IVT vs CM	185	≤5	Anterior M1, ICA-T	SND	EVT or IVT better than conservative
2018	Shang <i>et al</i> <sup>51</sup>	Extended window	93	≤8	Anterior M2, ACA	mRS ≤1	NS
2019	Goldhoorn <i>et al</i> <sup>26</sup>	Low vs high NIHSS score	71	≤5	Anterior M2, A2	mRS ≤2	Outcomes better patients within low NIHSS score
2019	Kaesmacher <i>et al</i> <sup>52</sup>	Low vs high NIHSS score	193	≤7	Anterior and posterior M3, A2, P2	mRS ≤1	Safety/efficacy similar
2019	Asdaghi <i>et al</i> <sup>21</sup>	Low vs high NIHSS score	446	≤5	None	Patient characteristics	–

\*For vessel imaging criteria the most distal artery of the parent artery is listed. For example, if M4 is listed the study included MCA sections M1, M2, M3, and M4.

†Indicates study also conducted meta-analysis of literature.

ACA, anterior cerebral artery; BMM, best medical management; CM, conservative management; EVT, endovascular therapy; ICA-T, internal carotid artery-terminus; IVT, intravenous therapy; MCA, middle cerebral artery; mRS, modified Rankin Scale; mTICI, modified Thrombolysis in Cerebral Infarction; N, number of patients; NS, no difference in primary outcome; sICH, symptomatic intracranial hemorrhage; SND, symptomatic neurological deficit.

0% to 10%, respectively.<sup>2 41–46</sup> Many studies found that successful recanalization was significantly predictive of favorable clinical outcome.<sup>9 44 46 52</sup> Patients with NIHSS score ≤7 reported excellent outcome (mRS score ≤1); rates for mTICI scores <2b, 2b, and 3 were 35%, 62%, and 79%, respectively.<sup>44</sup> With a NIHSS score ≤5 upper limit, functional independence (mRS score ≤2) rates were 89% in patients with mTICI ≥2b versus 60% in those not recanalized (p<0.05).<sup>9</sup>

### EVT vs best medical management

We identified 10 manuscripts comparing EVT with BMM in patients with LVO-AIS and a low NIHSS score (table 2), six (60%) of which had low NIHSS defined as NIHSS score ≤5.<sup>3–12</sup> Additionally, four meta-analyses were identified (two, NIHSS score ≤5; two, NIHSS

score ≤8).<sup>3 12 18 19</sup> To compare EVT with BMM in mild strokes, the functional benefits of recanalization must be weighed against the added risk of the EVT procedure.

Four of the EVT versus BMM manuscripts concluded that EVT provided clinical benefit.<sup>5–7 12</sup> Outcome endpoints in these investigations were the shift in NIHSS score (discharge NIHSS score minus admission NIHSS score) and mRS score at 90-day follow-up. In 32 patients with LVO-AIS and NIHSS score ≤5, Haussen *et al* observed that immediate EVT resulted in a better discharge NIHSS shift than for those treated with BMM (–2.5 vs 0; p<0.01). However, 90-day functional independence and mortality rates between the two cohorts were the same.<sup>7</sup> Subsequently, Haussen *et al* externally validated and expanded their



**Table 2** Results of studies investigating endovascular therapy versus best medical management

Year	Author	IVT in EVT arm	EVT mRS≤1		EVT mRS≤2		NIHSS shift with EVT		sICH		aICH	
			aOR	P	aOR	P	Shift	P	EVT %	BMM %	EVT %	BMM %
2014	Urra <i>et al</i> <sup>4</sup>	47%	NS	NS	NS	NS	–	–	11.8*	0*	–	–
2018	Haussen <i>et al</i> <sup>5</sup>	31%	–	–	–21%	<0.01	–3.74	0.016	6.7	0	–	–
2018	Nagel <i>et al</i> <sup>6</sup>	51%	NS	NS	3.1	NR*	–	–	5.2	2.6	–	–
2020	*Goyal <i>et al</i> <sup>3</sup>	54%	0.72	0.47	0.73	0.64	–	–	4.4	0.9	22*	3*
2017	Haussen <i>et al</i> <sup>7</sup>	60%	–	–	–	–	–2.5	0.01	0	0	–	–
2018	Sarraj <i>et al</i> <sup>8</sup>	31%	1.3	0.47	0.9	0.77	–	–	5.8*	0*	5.3	10
2020	Saito <i>et al</i> <sup>9</sup>	9.1%	NS	NS	1.65	0.25	–	–	NS	NS	NS	NS
2020	Wolman <i>et al</i> <sup>10</sup>	35%	–	–	–	–	–0.8	0.62	NS	NS	35*	10*
2017	Dargazanli <i>et al</i> <sup>11</sup>	61%	1.15	NS	NS	NS	–	–	NS	NS	16.5*	6.1*
2019	*Shang <i>et al</i> <sup>12</sup>	29%	NS	NS	3.2	0.008	–	–	10*	2*	–	–

– Analysis not performed.

\*Statistically significant ( $p < 0.05$ ) but numbers either not reported or bivariate comparisons.

aICH, any intracranial hemorrhage or in some cases asymptomatic; aOR, adjusted OR without imputation; EVT, endovascular therapy; IVT, intravenous thrombolysis; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; NR, not reported value; NS, not significant with specific number not reported; sICH, symptomatic intracranial hemorrhage.

findings in a multicenter cohort study, in which EVT was an independent predictor of lower discharge NIHSS score ( $p = 0.04$ ), favorable NIHSS shift ( $p = 0.03$ ), and increased independence rates at discharge ( $p = 0.03$ ).<sup>5</sup> While NIHSS shift has been used in non-EVT low NIHSS AIS literature, few EVT low NIHSS investigations used NIHSS shift as a primary endpoint, making it difficult to cross-validate their findings with other studies.<sup>5 7 10 34</sup> Only one other EVT versus BMM study with an NIHSS score  $\leq 5$  criterion detected an EVT benefit. To minimize treatment selection bias, Nagel *et al* matched patients with a low NIHSS score, receiving EVT and BMM, based on age, baseline NIHSS score, and occlusion site. Patients receiving EVT had higher rates of favorable outcome (mRS score  $\leq 2$ , OR = 3.1; 84.4% vs 70.1%;  $p = 0.03$ ).<sup>6</sup> In patients with an NIHSS score  $\leq 8$ , Shang *et al* found that EVT resulted in a significantly higher likelihood of excellent outcome (OR = 3.2,  $p = 0.008$ ); however, the meta-analysis they performed failed to confirm these associations.<sup>12</sup>

Six manuscripts with original patient data failed to detect EVT clinical benefit in patients with a low NIHSS score.<sup>3 4 8–11</sup> Urra *et al* published the first retrospective study of low NIHSS EVT versus BMM in 2014. In 78 patients they observed no EVT benefit; however, IV thrombolysis was predictive of full recovery (OR = 3.7;  $p = 0.015$ ). There was numerically more IVT administration in the BMM group than EVT group, though this was not significant (66% vs 47%;  $p = 0.09$ ).<sup>4</sup> Sarraj *et al* also observed no overall benefit for EVT. However, when stratifying by vessel location, patients with MCA-M1 LVO location trended towards higher rates of excellent outcome (OR = 3.3,  $p = 0.07$ ).<sup>8</sup> Additional EVT versus BMM articles failed to detect clinical benefit for EVT.<sup>9–11</sup> Recently, Goyal *et al* performed a meta-analysis of patients with AIS and NIHSS score  $\leq 5$  with an additional 251 patients from 16 centers.<sup>3</sup> From their original data, patients receiving BMM and EVT had similar rates of 90-day functional outcomes (mRS score  $\leq 2$ , 76.7% vs 85.2%,  $p = 0.12$ ; mRS score  $\leq 1$ , 63.1% vs 70.4%,  $p = 0.26$ ). After adjusting for confounders and using imputation for missing follow-up data, EVT had a lower likelihood of a 90-day mRS score  $\leq 2$  (OR = 0.42,  $p = 0.04$ ). Interestingly, this association disappeared when missing data were not extrapolated (OR = 0.72,  $p = 0.47$ ), highlighting the need for higher-quality data in this patient population.

Hemorrhagic outcomes were closely linked with clinical outcomes, with three of four studies that showed benefit from EVT observing no hemorrhagic differences and five of six studies

without benefit from EVT reporting increased hemorrhage in patients receiving EVT. Three investigations (30%) observed significantly higher rates of sICH in patients receiving EVT (11.8 vs 0%,  $p = 0.03$ ),<sup>4</sup> (5.8% vs 0%;  $p = 0.02$ ),<sup>8</sup> (10% vs 2%;  $p = 0.02$ ).<sup>12</sup> However, the increased sICH risk observed by Shang *et al* was not significant after adjusting for confounders.<sup>12</sup> Three studies (30%) observed increased EVT asymptomatic intracranial hemorrhage (35% vs 10%,  $p = 0.04$ ),<sup>10</sup> (22% vs 3%,  $p = 0.002$ ),<sup>3</sup> (16.5% vs 6.1%,  $p = 0.008$ )<sup>11</sup> but not sICH.<sup>3 10 11</sup> Four investigations (40%) did not detect any difference in hemorrhagic complications between EVT and BMM.<sup>5–7 9</sup>

We identified four meta-analyses for EVT versus BMM, two of which concluded EVT benefit.<sup>3 12 18 19</sup> Unfortunately, these analyses are challenging to compare owing to heterogeneous inclusion criteria and incongruous time of literature review.

## EVT vs IVT

In patients with LVO-AIS and normal NIHSS ranges, EVT with or without IVT is superior to IVT alone, and EVT alone is non-inferior to EVT + IVT, although, the same may not hold true in patients with a low NIHSS score.<sup>2 59</sup> The low NIHSS LVO-AIS literature, with an admixture of revascularization cohorts (EVT or IVT), reports that any reperfusion therapy (IVT, EVT, or both) in patients with LVO-AIS is associated with increased functional independence (OR = 3.1,  $p = 0.030$ ).<sup>36</sup> This suggests that both IVT and EVT play a role in improving outcomes. Our review of the EVT versus BMM literature yielded EVT bridging rates ranging from 9% to 61%, with only one study performing IVT subgroup analyses (table 2).<sup>9</sup> This wide IVT treatment range probably increases interstudy outcome variability. It is essential to compare IVT with EVT  $\pm$  IVT in patients with a low NIHSS score to elucidate the role of EVT bridging therapy in IVT-eligible patients. Our literature review identified four studies that compared EVT with IVT.<sup>47–50</sup>

Two studies had dedicated EVT alone analyses.<sup>47 50</sup> In a propensity matched analysis, Manno *et al* compared patients with LVO-AIS and NIHSS score  $\leq 5$  treated with EVT  $\pm$  IVT with IVT alone; both resulted in comparable mRS  $\leq 1$  rates (63% vs 65.7%, respectively;  $p = 0.840$ ). In vessel-specific subgroup analyses, there remained no difference (ICA/M1  $p = 0.9$ , M2  $p = 0.8$ ). Interestingly, they observed a trend towards higher mortality in patients receiving EVT (9.3% vs 2.8%;  $p = 0.06$ ) even though sICH was rare in both groups (2.8% vs 0%;  $p = 0.997$ ). When

**Table 3** Summary of EVT low NIHSS studies

Total number of studies	24
Low NIHSS definitions	
≤5	15 (63%)
≤7	3 (13%)
≤8	4 (17%)
Other	2 (8%)
EVT feasibility studies (from six studies)	
mTICI ≤2b	78–97%
sICH	0–10%
EVT vs BMM	
Primary outcome showed EVT benefit	4 of 10 studies
sICH EVT risk significant	6 of 10 studies
EVT vs IVT	
Primary outcome showed EVT benefit	0 of 4 studies
sICH EVT risk significant	0 of 4 studies

BMM, best medical management; EVT, endovascular therapy; IVT, intravenous thrombolysis; mTICI, modified Thrombolysis in Cerebral Infarction; NIHSS, National Institutes of Health Stroke Scale; sICH, symptomatic intracranial hemorrhage.

treatment groups were separated into EVT alone, EVT with IVT, and IVT alone, they observed an association between EVT only and mortality (OR 12.75,  $p=0.004$ ), suggesting that EVT alone may incur an additional non-hemorrhagic risk. Retrospective comparisons between these groups are flawed owing to the longer onset to recanalization times in IVT-ineligible patients.<sup>47</sup> Heldner *et al* also observed no difference between patients with LVO and a low NIHSS score treated with EVT alone and IVT alone.<sup>50</sup> Similarly, the two other studies comparing EVT±IVT with IVT alone demonstrated no significant difference in outcomes between treatments.<sup>48,49</sup> It is possible that EVT may be efficacious only in IVT-ineligible patients or that only one thrombolytic treatment is necessary in this patient population.

### EVT patient selection

The importance of patient selection in patients with LVO-AIS has been repeatedly demonstrated in past EVT trials.<sup>12</sup> Based on the conflicting literature results which are summarized in table 3, we hypothesize that EVT is likely beneficial for select patients with a low NIHSS score, although, the challenge will lie in identifying which patients will benefit. Factors of particular consideration include elevated blood pressure on admission, a positive heads-up test, and a large radiographic perfusion deficit, as ideal low NIHSS EVT candidates are those who will develop END. A reported range of 18% to 34.6% of patients with LVO and a low NIHSS score progress to END.<sup>11,60</sup> Unfortunately, delaying EVT until clinical manifestation of END is apparent does not result in favorable outcomes and may incur more risk.<sup>6,7,10,48,50</sup> Nagel *et al* observed that patients who received 'rescue' EVT had worse outcomes than those who received BMM or immediate EVT (54.5% rescue EVT, 71.7% BMM, alone, 85% immediate EVT  $p=0.007$ ).<sup>6</sup>

Patients with LVO-AIS and a low NIHSS score with MCA-M1 or ICA occlusions are more likely to develop END ( $p=0.04$ ), supporting the applicability of distal vessel exclusion criteria.<sup>60</sup> Patients with proximal LVO theoretically have a larger area of brain at risk, and may have a wider EVT benefit margin.<sup>8</sup> Furthermore, distal LVO EVT may incur a higher procedural risk of vessel perforation. A large source of our observed study heterogeneity was due to distal vessel exclusion criteria. A few EVT

feasibility studies claimed that their high revascularization rates were a result of including only MCA-M1 LVO.<sup>44,52</sup> However, these studies were limited by a small sample size. While Sarraj *et al* observed no overall benefit for EVT, a sensitivity analysis demonstrated that EVT trended towards significance for MCA-M1 LVO (mRS score ≤1, OR=3.3,  $p=0.07$ ). Distal LVO did not reflect this trend: M2 (mRS score ≤1, 64.3% EVT vs 72.7% BMM) and M3/M4/ACA (0% EVT vs 53.8% BMM).<sup>8</sup>

Additional patient selection considerations include timing and patient collateral status. Patients who present late from onset of symptoms (>6 hours) have an already narrowed time window in which to develop END, whereas those who present early have a more uncertain clinical course. For patients who are beyond the IVT treatment window, Shang *et al* demonstrated that EVT in patients with a low NIHSS score is feasible up to 24 hours following symptom onset; however, there was no functional improvement observed with EVT.<sup>51</sup> Robust collateral status has been correlated with reduced infarct expansion and favorable outcomes in LVO-AIS.<sup>61</sup> It is likely that low patients with LVO and a low NIHSS score with poor collateral status are more susceptible to END. This requires further investigation, but it highlights the utility of perfusion mapping in this patient population. Ultimately, randomized clinical trials will be essential to elucidate the proper patient selection for EVT in patients with LVO-AIS and a low NIHSS score.

### Ongoing trials

Importantly, the majority of medically managed patients with LVO and a low NIHSS score will not progress to END, making it challenging for future studies to detect EVT efficacy in the entire population. In order to adequately assess EVT efficacy, studies will require either a large sample size or stringent inclusion criteria. Our literature review yielded two ongoing clinical trials investigating the efficacy of EVT in patients with LVO-AIS and a low NIHSS score: "Endovascular Therapy for Low NIHSS Ischemic Strokes" (ENDOLOW) and "Minor Stroke Therapy Evaluation" (MOSTE).<sup>53,54</sup> Both trials are enrolling patients with NIHSS score ≤5 with proximal anterior LVO (ICA, MCA-M1). ENDOLOW is a North American based trial that planned to enroll 200 patients presenting within 8 hours of symptom onset, randomizing to either EVT with EmboTrap II or BMM. MOSTE is a European based trial that planned to recruit 824 patients presenting within 24 hours of symptom onset, randomizing to EVT or BMM. Major endpoints of the trials include mRS shift, mRS score ≤1 rate, mRS score ≤2 rate, sICH, END (increase in NIHSS score of ≥4), and health-related quality of life. The broad inclusion criteria and large enrollment size in the MOSTE trial is probably aimed at specifying which patients will benefit from EVT. The ENDOLOW trial is aimed at quickly determining EVT efficacy in smaller subset of patients.

### Limitations

Our review is comprehensive, but it precludes data synthesis and aggregate calculations. Additionally, our summary of the natural history of patients with a low NIHSS score was not performed systematically.

### CONCLUSION

Our understanding of the role of endovascular therapy in patients with acute ischemic stroke with LVO who present with a low NIHSS score is evolving. Current literature is limited to retrospective reviews that have heterogeneous study

designs and inclusion criteria and report conflicting results. Selected meta-analyses do suggest a potential benefit of EVT over BMM. Selection of patients with a low NIHSS score for EVT will be imperative and may incorporate occlusion location, symptom onset to presentation time, and patient collateral status. Unlike the current literature, ongoing trials have contiguous definitions of low NIHSS scores and outcome measures. Current and future randomized clinical trials will better elucidate the safety and efficacy of endovascular therapy in this patient population.

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