

# Expanding indications for endovascular thrombectomy-how to leave no patient behind

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**Abstract:** Endovascular thrombectomy (EVT) has become standard of care for large vessel occlusion strokes but current guidelines exclude a large proportion of patients from this highly effective treatment. This review therefore focuses on expanding indications for EVT in several borderline indications such as patients in the extended time window, patients with extensive signs of infarction on admission imaging, elderly patients and patients with pre-existing deficits. It also discusses the current knowledge on intravenous thrombolysis as an adjunct to EVT and EVT as primary therapy for distal vessel occlusions, for tandem occlusions, for basilar artery occlusions and in pediatric patients. We provide clear recommendations based on current guidelines and further literature.

**Keywords:** endovascular thrombectomy, ischemic stroke, recanalization therapy

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## Introduction

Since the landmark randomized trials in 2015 resulting in the HERMES meta-analysis in 2016 endovascular thrombectomy (EVT) has become the standard of care for large vessel occlusion (LVO) strokes in the anterior circulation within a time window of 6h after onset of symptoms.<sup>1</sup> Whereas these trials demonstrated that EVT is a very powerful treatment with a number needed to treat of ~2.5, they excluded a large proportion of patients potentially eligible for EVT due to very strict inclusion criteria.<sup>2–5</sup> In this context, redefining the criteria to evaluate and select patients with LVO for endovascular treatment has become more and more important, because 3–22% of patients with ischemic stroke are potentially eligible for this treatment,<sup>6–8</sup> and this percentage may be even greater when including more distal occlusions and occlusions in the posterior circulation.

In this review, we therefore give an update on recent literature of borderline indications in patients who were excluded or underrepresented in the HERMES meta-analysis. Specifically, we present advances concerning patients in the late time

window beyond 6h of symptom onset, of patients with far progressed signs of brain infarction, of patients with vessel occlusions in the posterior circulation and very old patients (nonagenarians) or patients with a pre-existing disability. Further, we discuss the evidence on “bridging” thrombolysis in patients who undergo EVT, of patients with more distal vessel occlusions, milder strokes, tandem occlusion and of pediatric patients in whom etiologies are much different. Finally, we compare the recommendations of the most recent guidelines and give our own recommendation for clinical practice (summarized in Table 1).

## Borderline indications for EVT

### Time from symptom onset

Less than 5% of 1287 patients randomly assigned in five large randomized trials were treated beyond 6h of symptom onset, so that evidence from these trials was scarce.<sup>1–3,5,9</sup> In 2018, the DAWN and DEFUSE-3 randomized trials provided robust evidence that outcomes for disability at 90 days were better with thrombectomy plus standard

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care than with standard care alone in patients in the extended time window of up to 24h after onset of symptoms.<sup>10,11</sup> A key selection criterion for both trials was advanced imaging used to define a mismatch between the infarct core lesion and the tissue at risk (DEFUSE-3)<sup>10</sup> or between core lesion and the clinical deficit (DAWN).<sup>11</sup> However, both trials had restrictive selection criteria meaning that around 70% of patients with anterior circulation LVO assessed between 6 and 24h after onset of symptoms do not comply with the DAWN and/or DEFUSE-3 criteria.<sup>12</sup> There is evidence that EVT in these patients results in a positive treatment effect, even comparable to the effect of DAWN and DEFUSE-3 eligible patients<sup>12</sup> suggesting that further evidence for patients presenting beyond 6h but not fulfilling DAWN and DEFUSE-3 inclusion criteria is warranted. This is currently being addressed by the ongoing MRCLEAN-LATE (ISRCTN19922220) and RESILIENT Extend (NCT02216643) trials investigating whether a simpler imaging paradigm without computed tomographic perfusion (CTP) or magnetic resonance imaging (MRI) could be used for EVT patient selection beyond 6h. In this context, we currently recommend to perform EVT in the late window depending on the degree of potentially salvageable penumbra determined by advanced imaging. This may be the case even later than 24h after onset of symptoms.<sup>13,14</sup>

#### *Extent of infarction*

In four of the five 2015 randomized trials, patients with early ischemic signs seen as an Alberta Stroke Program Early Computed Tomography Scan score (ASPECTS) below 6 or 7 were excluded. Only the MR CLEAN trial allowed for a small number of patients with low ASPECTS. In this trial, there was no treatment effect of EVT in 28 patients with ASPECTS 0–4, while in 92 patients with ASPECTS 5–7 a trend for a treatment benefit of EVT was observed.<sup>3</sup> A 2018 HERMES meta-analysis showed that EVT led to better clinical outcomes at 90 days in patients with ASPECTS <6 [odds ratio (OR)=1.58 for ASPECTS 5–7 and OR=2.15 for ASPECTS 0–4] supporting the value of thrombectomy in some patients with large infarcts at baseline.<sup>15</sup> Likewise, a registry study including 218 patients with a diffusion-weighted imaging (DWI) ASPECTS ≤6 found an increased rate of favorable outcomes and a decreased rate of mortality in patients with successful reperfusion compared to non-reperfused patients.<sup>16</sup> However,

differences in the rate of favorable outcome were not significantly different and mortality increased in patients with a DWI ASPECTS <5. ASPECTS scores determined by DWI will likely differ from those ascertained using computed tomography (CT) due to different sensitivities for early ischemic changes.<sup>17</sup> Nevertheless, a multicentre study with CT-based ASPECTS selection found that successful recanalization in patients with low initial ASPECTS of ≤5 resulted in a significant reduction of edema and was associated with decreased prevalence of malignant infarctions and improvement in clinical outcome.<sup>18</sup> This is in line with a recent meta-analysis suggesting that patients with ASPECTS 0–6 may benefit from EVT. In this analysis successful reperfusion increased the probability functional independence at 3 months without increasing the risk of symptomatic intracerebral hemorrhage. The authors found that even in ASPECTS 4 patients, one in four would be independent, whereas only 14% of patients with ASPECTS 0–3 regained a good functional outcome.<sup>19</sup> In conclusion, there is to date insufficient high-quality evidence to suggest that EVT is both safe and effective in patients with low ASPECTS scores. This was also acknowledged by experts of the European Stroke Organisation, the European Society for Minimally Invasive Neurological Therapy (ESMINT), and the European Society of Neuroradiology in a consensus statement on thrombectomy,<sup>20</sup> leading to the initiation of several randomized controlled trials such as TENSION<sup>21</sup> and RESCUE-Japan LIMIT (ClinicalTrials.gov: NCT03702413). However, we conclude that patients with ASPECTS 4–6 should be treated with EVT and even patients with ASPECTS lower than 3 might benefit in selected cases.

#### *Vertebrobasilar artery occlusions*

Meta-analyses of retrospective studies found high rates of recanalization and functional independence and a good safety profile for patients with basilar artery occlusion.<sup>22,23</sup> However, a recent randomized trial investigating the safety and efficacy of EVT for vertebrobasilar artery occlusions found no significant difference in favorable outcomes of patients receiving endovascular therapy compared with those receiving standard medical therapy alone.<sup>24</sup> However, the authors acknowledged the use of outdated thrombectomy devices for some patients and the fact that loss of equipoise over the course of the trial<sup>25,26</sup> resulted in poor

adherence to the assigned (conservative) treatment, a fact that led to a reduced sample size and early termination of the study.<sup>24</sup> No definite conclusion on EVT in basilar artery occlusion should therefore be drawn from this trial, especially when treating patients with small infarct cores. In contrast, we recommend to perform EVT in patients with vertebrobasilar artery occlusions.

#### *Age and pre-existing disability*

Significant pre-existing disability may preclude favorable clinical outcomes despite successful EVT and most clinical trials excluded chronically disabled patients with the exception of the MR CLEAN trial, leading to 21 patients with modified Rankin Scale (mRS) >1 being included in the analysis.<sup>3</sup> However, no separate analysis has been performed for these patients so that no randomized data exist to date for the potential benefit of thrombectomy in patients with mRS scores >1.

Importantly, there is no concerning safety signal in this population. For patients aged >80 years, a HERMES collaboration analysis showed significant benefit of thrombectomy.<sup>1</sup> Even for nonagenarians multiple studies evaluating thrombectomy have shown promising results.<sup>27,28</sup> In a recent analysis including 124 nonagenarians from the ETIS Registry, patients with successful reperfusion had lower 90-day mRS compared to non-recanalized patients. Moreover, patients with successful reperfusion after one pass had reduced 90-day mortality and increased odds of good outcome (mRS score ≤3).<sup>29</sup> The authors concluded that in case of first-pass failure, terminating the intervention might be an advisable procedural strategy for this fragile subpopulation. This interesting finding emphasizes the high impact of successful reperfusion on favorable outcomes.<sup>29</sup> In 37% (14 of 38) of patients, good outcome was achieved with >1 pass leading to successful reperfusion or even without successful reperfusion. Even more interestingly, in 54% (29 of 53) of all first-pass effect cases, 90-day outcome was neither favorable nor good.<sup>29</sup> Therefore, terminating the procedure after failed first-pass reperfusion of thrombolysis in cerebral infarction (TICI) ≥2b might not be justified. Furthermore, as we become even faster in interventional stroke treatment with new workflow paradigms like the one-stop management, it might be possible to perform multiple thrombectomy maneuvers in the same door-to-reperfusion time as for one try in the past.<sup>30,31</sup> The safety analysis

showed low overall rates of symptomatic cerebral hemorrhage of 4% and no significant difference in complications between successful and unsuccessful reperfusion groups, justifying further thrombectomy attempts.<sup>29</sup> Overall, these findings underline that age itself should not be a criterion to exclude patients from EVT but future studies are warranted to elucidate why very elderly patients with predictors for good outcome still experience poor long-term outcomes.

We conclude that age and pre-existing deficits should not lead to exclusion of these patients from EVT.

#### *Thrombectomy and intravenous thrombolysis*

In the 2015 randomized EVT trials, patients eligible for intravenous (IV) thrombolysis with recombinant tissue plasminogen activator (rtPA; alteplase) received both treatments. Although there is accumulating evidence suggesting that administering IV tPA in thrombectomy-eligible patients may be futile,<sup>32–34</sup> there are also data suggesting that it may be beneficial in patients with LVO.<sup>35</sup> Further complicating the matter, IV tPA efficacy depends on thrombus location meaning that proximal thrombi are less likely to respond to thrombolysis, whereas tPA has a higher likelihood of inducing recanalization at more distally located thrombi.<sup>36,37</sup> The best available evidence comes from a recent randomized trial conducted in China (DIRECT-MT), where EVT alone was non-inferior with regard to functional outcome (within a 20% margin of confidence) to EVT preceded by intravenous alteplase administered within 4.5 h after symptom onset.<sup>38</sup> Future trials comparing thrombectomy with thrombolysis may need to include analyses of thrombus location. Randomized controlled trials comparing the safety and efficacy of thrombectomy with tPA *versus* thrombectomy alone are currently underway (SWIFT DIRECT, ClinicalTrials.gov, NCT 03192332; MR CLEAN-NOIV, ISRCTN 80619088). According to current guidelines, eligible patients with anterior circulation LVO should receive combined therapy but IV tPA should not delay thrombectomy.

#### *Distal occlusions*

The anatomical definition of an anterior circulation LVO may be variable<sup>39</sup> but in recent randomized trials occlusions of the intracranial

internal carotid artery or the first segment of the middle cerebral artery were commonly classified as LVO.<sup>1,10,12</sup> A major reason to withhold EVT in acute ischemic stroke patients are “too” distal occlusions, even in patients with substantial penumbra. According to data from large international registries (for example the STAR, STOP Stroke or Intersect registries), this patient population accounts for up to 30% of all patients with intracranial vessel occlusions.<sup>40</sup> Data for distal occlusions, also named medium vessel occlusions (MeVOs, including the M2, M3 or M4 segments of the middle cerebral artery, the A1, A2 or A3 segments of the anterior cerebral artery and the P1 or P2 segments of the posterior cerebral artery) are comparably sparse because randomized trials focused mainly on LVO. However, some patients (under 10%) with M2 occlusions were also enrolled in the afore-mentioned trials either due to protocol violations or because they were not explicitly excluded from the trial.<sup>1</sup> In 95 patients with isolated M2 occlusions that were finally included in the HERMES meta-analysis (51 were treated with EVT), there was a trend towards positive treatment effect of EVT (OR 1.28 (95% confidence interval (CI) 0.51–3.21)).<sup>1</sup> After including individual patient data from the PISTE and THRACE trials and revisiting the definition of M2 occlusions, the number of patients in a second HERMES meta-analysis increased to 130 (67 treated with EVT) leading to a OR in favor of EVT of 1.68 (95% CI 0.90–3.14).<sup>15</sup> An analysis of these data by Menon *et al.*<sup>41</sup> revealed a significantly higher percentage of functionally independent patients (mRS  $\leq 2$ ) in the EVT group with an absolute difference of 18.5% ( $p=0.04$ ). Nonetheless, guidelines regarding the treatment of M2 occlusions were not changed by the American Stroke Association (ASA)<sup>42</sup> and the European Stroke Organization (ESO) because the data were deemed insufficient to give an evidence-based recommendation in favor or against EVT in M2 occlusions.<sup>43</sup> The main objection was that selection bias could not be ruled out, because 71 patients (54.62%) in the analysis were enrolled despite not being eligible under the primary inclusion criteria. This means that a large proportion of patients were re-classified as M2 occlusions in retrospect even though they were misclassified as having an M1 occlusion at the time of enrollment. This naturally raises concerns about generating a disproportional sample of proximal and large M2 occlusions, limiting the external validity of the data. Conclusively, a large survey among 600

physicians in Europe found that ~40% would not pursue EVT in patients with M2 occlusions.<sup>44</sup> Even in relatively young patients (56 years old) in the early time window (3 h from symptom onset) with incapacitating deficits at presentation (global aphasia) and clear signs of salvageable penumbra only ~56% of the clinicians decided in favor of EVT even under assumed perfect conditions.<sup>44</sup>

The benefit of thrombectomy for more distal MCA occlusions, such as the M3 segments, or anterior cerebral artery occlusions is unclear despite a number of studies evaluating the outcomes of thrombectomy in these patients. Although studies indicate that thrombectomy may be safe and effective in patients with distal anterior circulation LVO, evidence also suggests an increased risk profile with mechanical interventions, such as vessel perforation and vasospasm.<sup>45–48</sup> A recent multicenter study and literature review for isolated posterior cerebral artery occlusions comes to the conclusion that the procedure itself is technically feasible and safe but further studies are needed to investigate safety and long-term functional outcomes with posterior circulation.<sup>49</sup> This is especially important because the natural history of distal occlusions is on average more favorable than of proximal occlusions and therefore EVT should directly be compared with best medical management alone in a randomized trial. We conclude that patients with distal occlusions, and where the target occlusion can be safely reached by EVT, should be treated with EVT in selected cases, where a clinical benefit can be expected.

### Milder strokes

When determining eligibility for thrombectomy, stroke severity should be assessed using the National Institutes of Health Stroke Scale (NIHSS),<sup>50</sup> which objectively measures clinical deficits and may identify those at higher risk for complications. There was significant variability in the NIHSS thresholds used for inclusion in recent randomized controlled trials (RCTs) for thrombectomy. The MR CLEAN trial had the lowest NIHSS threshold of 2, ESCAPE and EXTEND-IA set no specific NIHSS thresholds, but required the symptoms to be ‘disabling’, whereas other trials had variable NIHSS thresholds, ranging from 6 to 10.<sup>1</sup> Because several trials independently validated an NIHSS threshold of 6 (SWIFT PRIME, REVASCAT and DEFUSE 3), an



NIHSS of  $>6$  may serve as a working criterion of clinical severity when considering thrombectomy in anterior circulation stroke. Data for patients presenting with anterior circulation LVO and NIHSS  $<6$  are sparse, with occasional worsening of neurological deficits.<sup>51,52</sup> A large recent multicentre study including a meta-analysis of available data suggested similar outcomes of EVT and best medical treatment in these patients and concluded that clinical equipoise can further be resolved by a randomized clinical trial.<sup>53</sup> Of note, the NIHSS carries its own set of limitations and often does not fully capture functional impairment. Furthermore, even so-called “non-disabling” strokes with low NIHSS can be devastating from a patient perspective: Mild to moderate dysarthria for example results in an NIHSS score of 1 but will prevent teachers, lawyers and doctors from returning back to work. On the other hand, stroke centers may deem that the benefit gained from EVT in mild stroke does not outweigh the risks to the patient from performing the procedure. Moreover, the likelihood of the mild stroke becoming a disabling stroke is less than for more severe strokes so that it is necessary to treat mild strokes on an individual basis taking into account all the risks but also what every individual patient can potentially gain from EVT for continuing his individual life. As a consequence, in milder strokes EVT should only be performed after consideration of the potential risks and benefits.

#### *Tandem occlusions*

In the HERMES meta-analysis (122 of 1254 occlusions) and in THRACE (24 of 196) tandem occlusions were included.<sup>54</sup> In HERMES, there was a heterogeneity of treatment methods for the extracranial carotid occlusion (no revascularization/angioplasty/stenting). A retrospective analysis of pooled data from 18 centers examined 395 patients with tandem occlusions of the anterior circulation who underwent mechanical thrombectomy [TITAN (Thrombectomy in Tandem Lesions)].<sup>55</sup> Successful recanalization (mTICI grade 2b/3) was achieved in ~76% of patients and at 90 days ~52% showed a good functional outcome, whereas ~14% had parenchymal hematoma and mortality was ~13%.<sup>56</sup> Newer techniques of simultaneous thrombectomy and carotid stenosis treatment have emerged and could further increase the recanalization rates while reducing the time of the intervention.<sup>57</sup> Based on this information a randomized trial by the TITAN collaboration is

underway.<sup>58</sup> Based on these preliminary data, we recommend to perform EVT in tandem occlusions with intracranial LVO.

#### *Pediatric strokes*

In children with arterial ischemic stroke with LVO, after several small case series,<sup>59,60</sup> the recently published Save ChildS Study provided multicenter evidence that justifies mechanical thrombectomy as a feasible treatment option.<sup>61</sup> As LVO is a rare event in the pediatric population and not suitable for randomized evaluation, Save ChildS attempted to capture real world treatment regimens in a large retrospective multicenter study design. All pediatric patients ( $<18$  years) with ischemic stroke who underwent endovascular recanalization were screened across 42 stroke centers in Europe and the United States. Thrombectomy performed in 27 centers revealed that most of the children had favorable neurological outcomes and the rate of recanalization and adverse events was comparable to randomized controlled trials in adults.<sup>61</sup> Furthermore, a secondary analysis of this study investigating device selection in different ages and etiologies showed that neurological outcomes are generally good regardless of any specific device selection and suggests that it is important to offer thrombectomy in eligible children regardless of technique or device selection.<sup>62</sup> Data for thrombectomy in children in the extended time window are limited to case reports.<sup>63–67</sup> However, a secondary analysis of the Save ChildS study has recently shown that thrombectomy in an extended time window of up to 24 h after onset of symptoms was safe and neurological outcomes were generally good, if patients were selected by a mismatch between clinical deficit and infarct.<sup>68</sup> The 2019 AHA guidelines were written before this evidence became available.<sup>69</sup> We therefore recommend to perform EVT in pediatric patients with LVO even in the extended time window beyond 6 h after symptom onset. However, caution should be especially applied if an underlying arteriopathy is suspected.

#### **Conclusions**

In conclusion, we recommend to perform EVT patients with vertebrobasilar occlusions and tandem occlusions. In the extended time window EVT should be performed if there is relevant salvageable brain tissue. Moreover, elderly patients,

**Table 1.** Indications for EVT.

Indication	AHA/ASA guidelines	ESO/ESMINT guidelines	Other evidence + recommendation of the authors
Time from symptom onset	In selected patients with AIS within 6–16 h of last known normal who have LVO in the anterior circulation and meet other DAWN or DEFUSE 3 eligibility criteria, mechanical thrombectomy is recommended. Level of evidence A In selected patients with AIS within 16–24 h of last known normal who have LVO in the anterior circulation and meet other DAWN eligibility criteria, mechanical thrombectomy is reasonable. Level of evidence B-R	In adults with anterior circulation large vessel occlusion-related acute ischemic stroke presenting between 6 and 24 h from time last known well and fulfilling the selection criteria of DEFUSE-3 or DAWN, ESO/ESMINT recommends mechanical thrombectomy plus best medical management over best medical management alone to improve functional outcome. Quality of evidence: Moderate ⊕⊕⊕; strength of recommendation: Strong ↑↑	EVT should be performed whenever there is relevant salvageable brain tissue on advanced imaging within
Extent of infarction (ASPECTS) Pre-existing deficits Milder strokes (NIHSS <6)	Although its benefits are uncertain, the use of mechanical thrombectomy with stent retrievers may be reasonable for patients with AIS in whom treatment can be initiated (groin puncture) within 6 h of symptom onset and who have prestroke mRS score >1, ASPECTS <6, or NIHSS score <6, and causative occlusion of the internal carotid artery (ICA) or proximal MCA (M1). Level B-R	ESO/ESMINT recommends that patients with anterior circulation stroke with extensive infarct core (e.g. ASPECTS 70 mL or >100 mL) should be included in randomized controlled trials comparing mechanical thrombectomy plus best medical management with best medical management alone. Quality of evidence: Very low ⊕; strength of recommendation: – ESO/ESMINT recommends that patients with low stroke severity (NIHSS score 0–5) and large vessel occlusion-related acute ischemic stroke within 24 h from time last known well be included in randomized controlled trials comparing mechanical thrombectomy plus best medical management <i>versus</i> best medical management alone. Quality of evidence: Very low ⊕; strength of recommendation: –	HERMES meta-analysis found better clinical outcomes at 90 days in patients with ASPECTS <6 <sup>15</sup> Retrospective studies found increased rates of favorable outcomes and less edema formation in patients with ASPECTS <6 <sup>16,18</sup> We conclude that patients with ASPECTS 4–6 should be treated with EVT and even patients with ASPECTS lower than 3 might benefit in selected cases. We conclude, that pre-existing deficits should not lead to exclusion of these patients from EVT. Meta-analysis found similar outcomes of EVT and best medical treatment for patients with NIHSS <6 <sup>53</sup> We conclude, that in milder strokes EVT should only be performed after careful consideration of the potential risks and benefits.
EVT and intravenous thrombolysis	Patients eligible for IV alteplase should receive IV alteplase even if mechanical thrombectomy is being considered. Level A	In patients with large vessel occlusion-related ischemic stroke eligible for both treatments, ESO/ESMINT recommends intravenous thrombolysis plus mechanical thrombectomy over mechanical thrombectomy alone. Both treatments should be performed as early as possible after hospital arrival. Mechanical thrombectomy should not prevent the initiation of intravenous thrombolysis, and intravenous thrombolysis should not delay mechanical thrombectomy. Quality of evidence: Very low ⊕; strength of recommendation: Strong ↑↑	Randomized trial found EVT alone non-inferior with regard to functional outcome (within a 20% margin of confidence) to EVT preceded by intravenous alteplase administered within 4.5 h after symptom onset <sup>38</sup>

(Continued)

**Table 1.** (Continued)

Indication	AHA/ASA guidelines	ESO/ESMINT guidelines	Other evidence + recommendation of the authors
Distal occlusions Vertebrobasilar artery occlusions	Although the benefits are uncertain, the use of mechanical thrombectomy with stent retrievers may be reasonable for carefully selected patients with AIS in whom treatment can be initiated (groin puncture) within 6 h of symptom onset and who have causative occlusion of the MCA segment 2 (M2) or MCA segment 3 (M3) portion of the MCAs. Level B-R Although the benefits are uncertain, the use of mechanical thrombectomy with stent retrievers may be reasonable for carefully selected patients with AIS in whom treatment can be initiated (groin puncture) within 6 h of symptom onset and who have causative occlusion of the anterior cerebral arteries, vertebral arteries, basilar artery, or posterior cerebral arteries. Level C-LD	Expert opinion on mechanical thrombectomy for M2 occlusion: There is a consensus among the guideline group (11/11 votes) that patients with M2 occlusion fulfilled the inclusion criteria in most randomized trials and therefore mechanical thrombectomy is reasonable in this situation. Expert opinion on mechanical thrombectomy for basilar artery occlusion: There is a consensus among the panel (11/11 votes) that in analogy to anterior circulation large vessel occlusion and with regard to the grim natural course of basilar artery occlusions, the therapeutic approach with intravenous thrombolysis plus mechanical thrombectomy should strongly be considered.	We conclude, that patients with distal occlusions and where the target occlusion can be reached safely, should be treated with EVT in selected cases, where a clinical benefit can be expected. – randomized trial found no difference in favorable outcomes of patients receiving EVT <i>versus</i> medical therapy alone but may be confounded by loss of equipoise over the course of the trial <sup>24</sup> Nonetheless, we recommend to perform EVT in patients with vertebrobasilar artery occlusions.
Tandem occlusions	Treatment of tandem occlusions (both extracranial and intracranial occlusions) when performing mechanical thrombectomy may be reasonable. Level B-R	No recommendation can be provided regarding which treatment modality should be favored in patients with large vessel occlusion-related acute ischemic stroke and associated extracranial carotid artery stenosis or occlusion. ESO/ESMINT recommends the inclusion of such patients in dedicated randomized controlled trials. Quality of evidence: Very low ⊕; strength of recommendation: –	Retrospective study found good rates of successful recanalization (76%) and good functional outcome (52%) but also parenchymal hematoma in 14% and death in 13% <sup>55</sup> We recommend to perform EVT in tandem occlusions with intracranial LVO.
Pediatric strokes	In the absence of pediatric clinical trial data to guide treatment decisions, hyperacute therapies for childhood AIS remain controversial. <sup>69</sup>	–	Retrospective Save ChildS Study found good clinical outcomes and low complication rates regardless of device selection <sup>61,62</sup> We recommend to perform EVT in pediatric patients with LVO but caution should be applied if an underlying arteriopathy is suspected.

The AHA/ASA guideline information is from the 2018 guideline of the American Heart Association/Stroke Association (AHA/ASA) which contains the following general sentence for EVT: "Patients should receive mechanical thrombectomy with a stent retriever if they meet all the following criteria: (1) prestroke mRS score of 0–1; (2) causative occlusion of the internal carotid artery or MCA segment 1 (M1); (3) age ≥18 years; (4) NIHSS score of ≥6; (5) ASPECTS of ≥6; and (6) treatment can be initiated (groin puncture) within 6 h of symptom onset."<sup>70</sup>

The level of evidence in the AHA/ASA guidelines is categorized as follows:

Level A: high-quality evidence from more than one randomized controlled trial (RCT); meta-analyses from the RCTs; one or more RCTs corroborated by high-quality registry studies.

Level B-R (randomized): moderate-quality evidence from one or more RCTs; meta-analyses from the RCTs.

Level C-LD (limited data): randomized or non-randomized observational or registry studies with limitations of design or execution; meta-analyses of such studies; physiological or mechanistic studies in human subjects.

The ESO/ESMINT guideline information is from the 2019 European Stroke Organisation (ESO) – European Society for Minimally Invasive Neurological Therapy (ESMINT) guidelines on mechanical thrombectomy in acute ischaemic stroke endorsed by Stroke Alliance for Europe (SAFE).

The level of evidence and quality of data is from the ESO/ESMINT guidelines.<sup>70</sup>

patients with distal occlusions or with extensive signs of infarction and patients with pre-existing deficits should not be excluded from thrombectomy. Based on the current evidence intravenous thrombolysis should be administered as an adjunct to EVT. Pediatric patients with large vessel occlusions should be treated with EVT but caution should be applied when underlying arteriopathies are suspected.

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