A review of endovascular treatment for medium vessel occlusion stroke

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ABSTRACT

Medium vessel occlusions (MeVOs), that is, occlusions of the M2/3 middle cerebral artery, A2/3 anterior cerebral artery, and P2/3 posterior cerebral artery segments, account for 25%–40% of all acute ischemic stroke cases. Clinical outcomes of MeVO stroke with intravenous thrombolysis, which is the current standard of care, are moderate at best. With improving imaging technologies and a growing literature, MeVOS are increasingly recognized as a target for endovascular treatment (EVT). For the time being, there is limited but promising evidence for the safety and efficacy of MeVO EVT, and many neurointerventionists are already routinely offering EVT for MeVO stroke, despite the lack of clear guideline recommendations. In this article, we review the evidence on endovascular treatment for MeVO stroke and summarize the available literature on current imaging techniques, commonly used EVT selection criteria, EVT outcomes of MeVO strokes are better compared to LVO, while 25%–40% are caused by medium-vessel occlusions (MeVOS). Although it is commonly assumed that outcomes of MeVO strokes are better compared with LVO strokes, due to the more distal occlusion location and less extensive ischemia, cohort studies suggest that outcomes are frequently poor, despite best medical management. Over the past few years, several randomized trials have proven the safety and efficacy of endovascular treatment (EVT) in LVO stroke, while for patients with MeVOS, there is currently no high-level evidence for EVT. But given the high efficacy of EVT in LVO stroke and the substantial morbidity associated with MeVO, EVT is now increasingly performed for MeVO stroke.

DEFINITION OF MEDIUM-VESSEL OCCLUSIONS

In a recent publication, MeVOS have been defined as occlusions of the M2, M3, A2, A3, P2, or P3 segment. That being said, the distinction between LVOs and MVOs is often challenging. For example, there are various ways to define the border between the M1 segment, which is considered a “large vessel”, and the M2 segment of the middle cerebral artery. Furthermore, because M2 occlusions, particularly those affecting the dominant branch, can cause clinical symptoms identical to M1 occlusions, some authors include M2 occlusions in their definition of LVO. Given the variability in anatomy and clinical symptoms, a multidimensional definition based on morphological features (ie, vessel anatomy and size) and clinical deficits (ie, symptoms that are commensurate with the occluded vessel) may be preferred over a purely anatomical definition.

PRIMARY AND SECONDARY MEVOS

Not all MeVOS are the same: MeVOS can be classified based on their underlying mechanism as either primary or secondary MeVOS. “Primary” MeVOS occur de novo, with etiologies similar to LVOs. “Secondary” MeVOS occur when clot migration or fragmentation of a LVO occurs. This can happen spontaneously or iatrogenically, after intravenous thrombolysis or during EVT. Secondary MeVOS either represent embolization to new territory, that is, MeVOS that occur simultaneously with other occlusions. They are likely part of an “embolic shower” or could be due to fragmentation of a more proximal occlusion.

PREVALENCE AND CLINICAL COURSE OF MEVO STROKE

Although it is commonly assumed that outcomes of MeVO strokes are better compared with LVO strokes, due to the more distal occlusion location and less extensive ischemia, a recent analysis from the INTERRSeCT and PRove-IT cohort studies has shown that one out of four patients with MeVO stroke does not achieve functional independence (modified Rankin Scale (mRS) 0–2) at 90 days with current best management, including intravenous thrombolysis if indicated. An excellent outcome (mRS 0–1) is only achieved by half of the patients with MeVO stroke (online supplemental figure 1). These somewhat sobering results emphasize the need for a more effective therapy. Given the overwhelming efficacy of endovascular treatment (EVT) in LVO strokes, it might seem obvious to expand this treatment to MeVO patients as well. Many neurointerventionists already routinely offer EVT in MeVO strokes, particularly in the case of M2.
occlusions⁷–¹⁰ but there is no randomized evidence for MeVO EVT, and it is possible that due to the smaller vessel size, MeVO EVT may yield an increased risk of procedural complications.¹¹ Therefore, the question whether EVT is truly beneficial in the setting of MeVO stroke or not, remains to be answered. Furthermore, the smaller vessel caliber and more distal occlusion location of MeVOS compared with LVOs warrant changes in EVT technique and technology.

In the following, we review the existing literature on treatment indications, imaging selection criteria, and treatment techniques for MeVO EVT as well as clinical outcomes following MeVO EVT. We conclude with an outlook on open questions and ongoing developments.

SEARCH STRATEGY
We searched the electronic databases Medline/PubMed, Google Scholar, and EMBASE using the search terms stroke, thrombectomy, endovascular, aspiration, mechanical, small, distal, medium, M2, M3, A2, A3, P2, and P3. We included original research studies, systematic reviews, and meta-analyses which: reported angiographic and/or clinical outcomes of patients with MeVO stroke treated with EVT; included at least five patients; and were published in English. Bibliographies of identified manuscripts were screened for additional relevant studies. The literature search is up-to-date as of 23 November 2020. Tables 1 and 2 provide an overview of the studies and systematic reviews that were identified during the literature search.

IMAGING PROTOCOLS – HOW TO IMAGE MEVO STROKE?
Baseline imaging can facilitate EVT treatment decision making in MeVO stroke, or enrolment in a randomized EVT MeVO trial for that matter, by answering the following questions:
1. Is there evidence of intracranial hemorrhage? Just as with LVO stroke, hemorrhagic stroke needs to be ruled out prior to treatment.
2. Is there an acute MeVO? EVT can only be initiated if a target occlusion is visualized.
3. Does that MeVO explain the patient’s deficit (clinical-anatomical correlation, particularly important for secondary MeVOS and concurrent MeVOS in the setting of multiple occlusions)? Right-sided hemiparesis, for example, can be well-explained by a left-sided M2 occlusion, while left-sided hemi-paresis cannot.
4. Is the occlusion likely to recanalize with intravenous thrombolysis? Smaller, permeable thrombi may resolve with intravenous thrombolysis which may influence EVT decision-making.
5. Is the MeVO amenable to safe and fast recanalization using EVT? How technically challenging an operator perceives EVT for a certain MeVO and the availability of dedicated EVT tools designed for MeVOS will also influence the treatment decision and help to set the expectations of the patient and the medical team right.

Since EVT has been established as standard of care in 2015,⁶ non-invasive neurovascular imaging (CTA or less frequently MR angiography) is recommended for all acute ischemic stroke patients,²² and should thus be obtained in all MeVO patients. In the past, detection of MeVOS on non-invasive imaging has been challenging, but innovative imaging techniques such as multiphase CTA (including color-coded mCTA maps) and CT perfusion have rendered fast and reliable MeVO detection possible²³–²⁵ (online supplemental figure 2). Determining the presence of salvageable brain tissue is more challenging in MeVOS compared with LVOs. Established EVT imaging selection criteria that are currently used in LVO stroke, namely Alberta Stroke Program Early CT Score (ASPECTS)≥6,⁶ intermediate to good collateral,¹⁶ ¹⁷ and currently established perfusion mismatch/core criteria (eg, ischemic core on rCBF maps)¹⁸–²¹ will likely be of little use in MeVO stroke. Due to the more distal occlusion, the ischemic territory will be smaller, and as such, ASPECTS will be generally higher and areas with severe hypoperfusion (“core”) smaller. When assessing collateral status, one would have to assess collaterals solely within the affected territory downstream to the MeVO, which can be challenging, especially in the ACA and PCA territory. So far, no standardized methodology has yet been established. Due to the relative insensitivity and high inter-rater reliability of NCCT in detecting early ischemic changes, and because detecting MeVOS on conventional CTA/MRA images is difficult at times, advanced imaging protocols (CTP and MRI) are often used.

However, accurately determining infarct core and penumbra in MeVO stroke may be challenging or not possible at all, as recent literature suggests that we currently lack the ability to precisely delineate infarct “core” with routinely used imaging methods.²² More importantly, delineating ischemic core and penumbra may not even be necessary, as past early time window LVO trials failed to show any volume cut-off below which EVT was no longer beneficial, and current EVT guidelines for LVO patients in the early time window therefore exclusively rely on NCCT ASPECTS to estimate the degree of irreversible tissue damage.⁶ That being said, using ASPECTS in MeVO stroke may be problematic, since the anterior and posterior cerebral artery territories are not represented at all, and even in middle cerebral artery MeVOS, the ASPECTS range will be relatively small, since the internal capsule, lentiform, and caudate are unlikely to be affected, and of the cortical 6 regions, only few will be affected. Thus, for a typical M3 occlusion, ASPECTS may be either 8, 9, or 10.

Most of the MeVO EVT studies we identified used a CT-based imaging protocol, and approximately half of them included CT perfusion as part of the standard protocol, regardless of the time frame, and some reported MRI-based protocols with DWI±PWI sequences (table 2). Studies that relied on NCCT and single-phase CTA were mostly subgroup analyses from randomized LVO trials and LVO registries,²³ ²⁴ that is, M2 occlusions were a small minority of all cases. Many studies simply transferred the perfusion thresholds,²⁵ and ASPECTS²⁶ ²⁷ cut-offs that are used for LVO strokes to their MeVO patient sample, which may be suboptimal for MeVO patient selection. Only a few studies adapted imaging selection criteria and used, for example, a higher ASPECTS cut-off.²⁸ ²⁹ Table 3 provides an overview of different MeVO imaging paradigms. Future studies should aim to develop MeVO-specific imaging selection criteria for EVT.

CLINICAL EVT SELECTION CRITERIA FOR MEVO EVT
Just as there are no uniform imaging criteria for EVT patient selection in MeVO strokes, there is also no consensus on clinical selection criteria. Several MeVO EVT studies used an NIHSS threshold of ≥6,²³–²⁶ as it is currently recommended for LVO strokes.⁶ However, a recent analysis from prospective cohort studies has shown that 1/3 of MeVO stroke patients have a baseline NIHSS <6. One study specifically stated that they included patients “with NIHSS ≥6 or disabling deficit”,³⁰ and another one lowered the NIHSS cut-off of 5 instead of 6,²⁹ which seems more appropriate, considering that one out of three patients with untreated supposedly “mild” strokes (NIHSS <5) will not be functionally independent at 90 days.³¹ Indeed, in a recent survey, most physicians stated that they would offer EVT for...
<table>
<thead>
<tr>
<th>First Author Year</th>
<th>Study type</th>
<th>N with MeVO (median/mean)</th>
<th>NIHSS (median/mean)</th>
<th>ASPECTS (median/mean)</th>
<th>Imaging modality used</th>
<th>Treatment criteria</th>
<th>MeVO type</th>
<th>Technique used</th>
<th>Anesthesia</th>
<th>Angiographic outcome</th>
<th>Clinical outcome</th>
<th>sICH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Romano et al 2020</td>
<td>MC</td>
<td>44 10</td>
<td>9</td>
<td>NCCT+CTA (±DWI if onset unknown)</td>
<td>NIHSS ≥6</td>
<td>Pre-stroke mRS 0–2</td>
<td>ASPECTS ≥6</td>
<td>M2, M2/M3</td>
<td>DA</td>
<td>GA, CS</td>
<td>TICI 2b: 91%</td>
<td>mRS 0–2: 71%</td>
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<tr>
<td>Haussen et al 2020</td>
<td>SC</td>
<td>137 8/9</td>
<td>8</td>
<td>NCCT+CTA+CTP</td>
<td>--</td>
<td>M2, M3</td>
<td>Any ACA</td>
<td>DA, SR</td>
<td>--</td>
<td>--</td>
<td>TICI 2b: 84% (SR) vs 69% (DA)</td>
<td>TICI 3: 58% (SR) vs 46% (DA)</td>
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<tr>
<td>Ardhaneyasskul et al 2020</td>
<td>MC</td>
<td>197 15/17</td>
<td>9</td>
<td>NCCT+CTA</td>
<td>ICA occluded MeVO (absence of concurrent LVO)</td>
<td>M2</td>
<td>DA, SR</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>TICI 2b: 90% (SR) vs 77% (DA)</td>
<td>mRS 0–2: 52% (SR) vs 37% (DA)</td>
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<tr>
<td>Jiang et al 2019</td>
<td>SC</td>
<td>37 15</td>
<td>10</td>
<td>NCCT+CTA+CTP</td>
<td>Symptom onset ≤24 hour NIHSS ≥6</td>
<td>Pre-stroke mRS 0–1 ASPECTS ≥6</td>
<td>Absence of large infarction CTP mismatch ratio&gt;1.8</td>
<td>M2</td>
<td>SR</td>
<td>CS, GA</td>
<td>TICI 2b: 95%</td>
<td>TICI 3: 76%</td>
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<td>Compagne et al 2019</td>
<td>MC</td>
<td>244 14</td>
<td>9</td>
<td>NCCT+CTA</td>
<td>Symptom onset ≤6 hour</td>
<td>NIHSS ≥6</td>
<td>Pre-stroke mRS 0–1 ASPECTS ≥6</td>
<td>M2</td>
<td>DA, SR, IA tPA</td>
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<td>TICI 2b: 57%</td>
<td>mRS 0–2: 46% mRS 0–1: 26% mRS 0: 7%</td>
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<td>Gory et al 2018</td>
<td>RCT</td>
<td>79 13.4</td>
<td>8</td>
<td>NCCT+CTA</td>
<td>--</td>
<td>M2</td>
<td>DA, SR</td>
<td>CS, GA</td>
<td>--</td>
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<td>TICI 2b: 84% (SR) vs 90% (DA)</td>
<td>TICI 2: 55% (SR) vs 54% (DA)</td>
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<td>Qureshi et al 2017</td>
<td>RCT</td>
<td>34 16</td>
<td>--</td>
<td>NCCT+CTA</td>
<td>Age 18–82y ICA eligibility</td>
<td>NIHSS ≥5</td>
<td>ASPECTS ≥8</td>
<td>M2, M3, M2, P2, A2</td>
<td>DA</td>
<td>TICI 2b: 97%</td>
<td>TICI 2: 83%</td>
<td>TICI 3: 43%</td>
</tr>
<tr>
<td>Vargas et al 2017</td>
<td>SC</td>
<td>35 14.1</td>
<td>--</td>
<td>NCCT+CTA+CTP</td>
<td>Contraindication to IV tPA</td>
<td>M2, A2</td>
<td>DA</td>
<td>SR, IA tPA</td>
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<td>--</td>
<td>TICI 2b: 78%</td>
<td>mRS 0–2: 63% mRS 0–1: 36% mRS 0: 14%</td>
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<td>Sarraj et al 2016</td>
<td>MC</td>
<td>288 16</td>
<td>9</td>
<td>NCCT+CTA</td>
<td>Symptom onset ≤8 hour</td>
<td>NIHSS ≥6</td>
<td>ASPECTS ≥8</td>
<td>M2, M3, P2, A2</td>
<td>DA, CS and GMC</td>
<td>TICI 2b: 100%</td>
<td>TICI 3: 83%</td>
<td>mRS 02: 100% mRS 0–1: 60% mRS 0: 20%</td>
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<tr>
<td>Naik et al 2016</td>
<td>SC</td>
<td>6 12.5</td>
<td>--</td>
<td>NCCT+CTA+CTP</td>
<td>NIHSS ≥6</td>
<td>ASPECTS ≥8</td>
<td>M2, M3, P2, A2</td>
<td>DA, CS and GMC</td>
<td>TICI 2b: 100%</td>
<td>TICI 3: 83%</td>
<td>mRS 02: 100% mRS 0–1: 60% mRS 0: 20%</td>
<td>0%</td>
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<tr>
<td>Menon et al 2019</td>
<td>RCT</td>
<td>67 14</td>
<td>9</td>
<td>NCCT+CTA (±CTP/PMR)</td>
<td>--</td>
<td>M2</td>
<td>SR</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>TICI 2b: 59%</td>
<td>mRS 0–2: 58% mRS 0–1: 37% mRS 0: 19%</td>
</tr>
<tr>
<td>Coutinho et al 2016</td>
<td>MC</td>
<td>50 13</td>
<td>9</td>
<td>NCCT+CTA (±CTP/PMR)</td>
<td>--</td>
<td>M2</td>
<td>SR</td>
<td>CS, GA</td>
<td>--</td>
<td>--</td>
<td>TICI 2b: 85%</td>
<td>mRS 0–2: 60% mRS 0–1: 50%</td>
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<tr>
<td>Grossberg et al 2018</td>
<td>SC</td>
<td>69 18.1</td>
<td>8</td>
<td>NCCT+CTA+CTP</td>
<td>Persisting disabling deficits despite IV ICA</td>
<td>M2, M3, P2, A2</td>
<td>DA, CS and GMC</td>
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<td>Any ACA</td>
<td>Any PCA</td>
<td>TICI 2b: 83%</td>
<td>TICI 3: 45%</td>
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<th>N with tEVT</th>
<th>NIHSS (median/mean)</th>
<th>ASPECTS (median/mean)</th>
<th>Imaging modality used</th>
<th>Treatment criteria</th>
<th>MeVO type</th>
<th>Technique used</th>
<th>Anesthesia</th>
<th>Angiographic outcome</th>
<th>Clinical outcome</th>
<th>sICH</th>
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<tr>
<td>Nakano et al 2020</td>
<td>MC</td>
<td>51</td>
<td>17</td>
<td>8</td>
<td>–</td>
<td>–</td>
<td>M2</td>
<td>DA, SR</td>
<td>–</td>
<td>TICI 2b/3: 84%</td>
<td>mRS 0–2: 49%</td>
<td>3%</td>
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<td>Altenbernd et al 2018</td>
<td>SC</td>
<td>58</td>
<td>15</td>
<td>9</td>
<td>NCCT+CTA+CTP</td>
<td>Age ≥18 NIHSS ≥6 ASPECTS ≥8</td>
<td>M2, M3</td>
<td>DA, GA</td>
<td>–</td>
<td>TICI 2b/3: 100%</td>
<td>mRS 0–2: 93%</td>
<td>0%</td>
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<tr>
<td>Crockett et al 2019</td>
<td>SC</td>
<td>14</td>
<td>8</td>
<td>9</td>
<td>–</td>
<td>–</td>
<td>A2, A3, P2, M3, SCA</td>
<td>DA</td>
<td>–</td>
<td>TICI 2b/3: 100%</td>
<td>mRS 0–2: 63% mRS 0–1: 50% mRS 0: 43%</td>
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<td>Bhogal et al 2017</td>
<td>SC</td>
<td>106</td>
<td>12</td>
<td>9</td>
<td>NCCT+CTA or MRI</td>
<td>–</td>
<td>M2</td>
<td>SR</td>
<td>–</td>
<td>TICI 2b/3: 91%</td>
<td>mRS 0–2: 55% mRS 0–1: 45% mRS 0: 24%</td>
<td>5%</td>
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<td>de Castro Afonso et al 2019</td>
<td>SC</td>
<td>30</td>
<td>16</td>
<td>9</td>
<td>NCCT+CTA</td>
<td>Symptom onset ≤6 hour or CTP mismatch if symptom onset 6–24 hour NIHSS ≥6 ASPECTS ≥6</td>
<td>M2</td>
<td>DA, SR, combination</td>
<td>CS, GA</td>
<td>TICI 2b/3: 90%</td>
<td>mRS 0–2: 50% mRS 0–1: 23% mRS 0: 17%</td>
<td>7%</td>
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<tr>
<td>Grieb et al 2019</td>
<td>SC</td>
<td>52</td>
<td>12</td>
<td>–</td>
<td>NCCT+CTA</td>
<td>NIHSS ≥6 or aphasia Absence of large infarction</td>
<td>M2</td>
<td>DA, GA</td>
<td>–</td>
<td>TICI 2b/3: 91%</td>
<td>mRS 0–2: 56%</td>
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<tr>
<td>Pérez-García et al 2020</td>
<td>SC</td>
<td>102</td>
<td>16</td>
<td>9</td>
<td>–</td>
<td>–</td>
<td>M2, M3, Any ACA Any PCA</td>
<td>SR, combination</td>
<td>CS, GA</td>
<td>TICI 2b/3: 50% (SR)</td>
<td>mRS 0–2: 53 (SR) vs 51% (combination)</td>
<td>13% (SR) vs 2% (combination)</td>
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<tr>
<td>Haussen et al 2020</td>
<td>SC</td>
<td>52</td>
<td>17</td>
<td>8</td>
<td>–</td>
<td>–</td>
<td>M2</td>
<td>Combination</td>
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<td>mRS 0–2: 40%</td>
<td>–</td>
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<tr>
<td>Pfiff et al 2016</td>
<td>SC</td>
<td>30</td>
<td>18</td>
<td>9</td>
<td>DWI+MR A+ PWI or NCCT+CTA+CTP</td>
<td>Symptom onset ≤8 hour NIHSS ≥8 ASPECTS ≥6</td>
<td>A2, A3, A4</td>
<td>SR</td>
<td>CS, GA</td>
<td>TICI 2b/3: 73%</td>
<td>mRS 0–2: 37%</td>
<td>0%</td>
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<tr>
<td>Stuckon et al 2020</td>
<td>MC</td>
<td>15</td>
<td>13</td>
<td>10 (pCASPECTS)</td>
<td>–</td>
<td>–</td>
<td>SCA, AICA, PICA</td>
<td>SR, DA, combination</td>
<td>IA tPA</td>
<td>TICI 2b/3: 88%</td>
<td>mRS 0–2: 50% mRS 0–1: 29% mRS 0: 7%</td>
<td>–</td>
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</table>

Note: MC = multi center, SC = single center, EVT = endovascular treatment, MeVO = medium vessel occlusion stroke, NIHSS = National Institutes of Health Stroke Scale, pCASPECTS = (posterior circulation) Alberta Stroke Program Early CT Score, CTA = CT angiography, NCCT = non-contrast head CT, DWI = diffusion weighted imaging, CTP = CT perfusion, DA = direct aspiration, SR = stent retriever, IA 9A = intra-arterial alteplase, CS = conscious sedation, GA = general anesthesia, SCA = superior cerebellar artery, AICA = anterior inferior cerebellar artery, PICA = posterior inferior cerebellar artery, TICI = Thrombolysis in Cerebral Infarction Score, mRS = modified Rankin Score, sICH = symptomatic intracranial hemorrhage.
LVO patients with low NIHSS.32 Whether a patient is eligible for intravenous thrombolysis or not also seems to play an important role in MeVO EVT decision-making. More than 50% of physicians would perform EVT in M3, A2, and P2 occlusions if the patient is ineligible for intravenous thrombolysis, but when intravenous thrombolysis can be safely administered, the willingness to proceed with EVT is substantially lower.7 For now, until randomized trial data become available, the decision to treat or not to treat a MeVO will remain a subjective one that is influenced by many factors, including patient preferences, eligibility for intravenous thrombolysis, and operator skills. Treatment decision-making is further complicated by the variety of clinical symptoms MeVO patients can present with, which are dependent on the eloquence of the affected area.3 A patient with a right-sided small branch anterior M2 occlusion, for example, may barely suffer from any deficits, but another patient suffering from a similar sized left-sided M2 occlusion may present with severe aphasia. Furthermore, new thrombolytic agents such as Tenecteplase32 and neuroprotectants such as Nerinetide17 could improve the prognosis of MeVO stroke with conservative management and thereby also influence treatment decision-making in MeVO EVT.

**THROMBECTOMY TECHNIQUE – HOW TO PERFORM EVT IN MEVO STROKE?**

Several challenges emerge when performing EVT for MeVOSs. For the time being, we don’t know how high the risk of vasospasm and dissection is when the catheter size matches or exceeds the vessel diameter, which can happen with large-bore aspiration catheters in MeVOS. Medium-sized vessels can be too small to harbor a regular-sized distal access catheter (DAC), as most of the currently used DACs are 5–6F in diameter. Another problem is the DAC often gets stuck at the ledge of a bifurcation point such, such as the M1 bifurcation, but there are wedge-shaped microcatheters available to overcome this ledge effect. Furthermore, using a primary combined approach (ie, the combination of stent retriever, DAC, and balloon guide catheter), and advancing the system in a tri-axial manner, as it is commonly done for LVOs, may not be possible because of insufficient catheter length and diameter discrepancies. For example, using a longer DAC to access an M3 occlusion may not allow for a small enough and long enough microcatheter capable of deploying a stent. Thus, currently, the microwire and microcatheter are often introduced without a DAC. Once the microcatheter is in place, the stent can be deployed and the microcatheter removed before the distal access catheter is navigated to the site of occlusion (so-called “blind exchange mini-pinning technique”).34 35 However, this is probably a transient problem, as many of the newer stent retrievers can be deployed through a stent, and thus, the microcatheter may be a slight inconvenience for the operator, but the benefits of EVT remain unchanged.

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### Table 2 Systematic reviews and meta-analyses that were identified during the literature search

<table>
<thead>
<tr>
<th>First Author Year</th>
<th>Study type</th>
<th>Research question</th>
<th>Main findings</th>
<th>N of studies</th>
<th>N with MeVO EVT</th>
<th>NIHSS (median/mean)</th>
<th>MeVO Technique used</th>
<th>Angiographic outcome</th>
<th>Clinical outcome</th>
<th>sICH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phan et al 201838</td>
<td>MA</td>
<td>What are the repurification rates in M2 occlusions treated with SR vs DA?</td>
<td>Both SR and DA are effective in recanalizing M2 occlusions. The literature is skewed by DA being performed sooner after onset of stroke compared with SR EVT.</td>
<td>12</td>
<td>835 14</td>
<td>9</td>
<td>Modify M2</td>
<td>TICI 2b/2c: 81% (SR) vs 87% (DA)</td>
<td>mRS 0–2: 60% (SR) vs 75% (DA)</td>
<td>6% (SR) vs 3% (DA) (I2=40%)</td>
</tr>
<tr>
<td>Saber et al 201842</td>
<td>MA</td>
<td>What are the angiographic results and functional outcome after M2 EVT and how do they compare to EVT for LVO?</td>
<td>M2 EVT is technically feasible and safe with high functional independence. There may be a slightly increased risk of ICH.</td>
<td>12</td>
<td>1000 14</td>
<td>–</td>
<td>M2 SR, DA</td>
<td>TICI 2b/2c: 81% (DA)</td>
<td>mRS 0–2: 59% (I2=61%)</td>
<td>19% (I2=75%)</td>
</tr>
<tr>
<td>Kim et al 2019</td>
<td>MA</td>
<td>What are the angiographic results and functional outcome after M2 EVT and how do they compare to EVT for M1 occlusions?</td>
<td>M2 EVT is technically feasible. Further studies are needed to better characterize the effect of EVT in M2 occlusions.</td>
<td>8</td>
<td>650 –</td>
<td>–</td>
<td>M2 –</td>
<td>TICI 2b/2c: 69% (I2 not provided)</td>
<td>mRS 0–2: 59% (I2 not provided)</td>
<td>6% (I2 not provided)</td>
</tr>
</tbody>
</table>

Note: MA = meta-analysis, SR = stent retriever, DA = direct aspiration, EVT = endovascular treatment, sICH = symptomatic intracranial hemorrhage, TICI = Thrombolysis in Cerebral Infarction Score, mRS = modified Rankin Score.
data from the HERMES collaboration\textsuperscript{40} and individual EVT trials\textsuperscript{41} show worse outcomes with GA. It is possible that the use of GA will substantially increase when performing MeVO EVT, given the need for an excellent roadmap to get access to the relatively distally located clot. In addition, the anatomical variability is much higher in distal vessels. Sometimes, the MeVO may be right at the origin of a vessel branch, which requires the operator to blindly explore the site of the occlusion very gently in order to find the relevant vessel origin, which is much easier under GA, when patient movement is completely eliminated. Thus, the impact of an increased use of GA on functional outcome will need to be better understood.

**OUTCOME ASSESSMENT IN MEVO EVT**

**Clinical outcomes**

In MeVO strokes the area that is affected by ischemia is smaller than in LVO strokes. Thus, one would intuitively expect clinical outcomes to be better. Most studies that were identified in the literature search reported “good outcome”, defined as mRS 0–2 at 90 days, as primary outcome (table 1). Given the overall better prognosis, it seems however worthwhile to consider a more restrictive outcome measure such as “excellent outcome”, i.e., mRS 0–1, or mRS shift analysis. Indeed, this has been recognized by several authors, who reported mRS 0–1 or proportions of patients in each mRS category in addition to mRS 0–2 (table 1).

It is important to note that deficits such as isolated abulia (due to A2/3 occlusion), alexia and agraphia (due to M2/3 occlusions), or quadrantopia (due to P2/3 occlusion) are not well captured in the NIHSS and mRS. Not only are those scales limited in their granularity, they are also heavily focused on motor function and thus unable to capture the more subtle personality changes and domain-specific impairment that often play a dominant role in MeVO stroke-related disability.

**Angiographic outcomes**

In most MeVO EVT studies, angiographic outcomes are reported as “successful reperfusion”, that is, TICI 2b/3, analogous to reperfusion assessment in LVO stroke, although several studies reported TICI 3 and/or TICI 2c/3 reperfusion in addition to TICI 2b/3 rates (table 1). Reporting successful reperfusion (TICI 2b/3) only is problematic, given that MeVOS in the anterior and posterior cerebral artery territory are not reflected in TICI at all, and patients with distal M2 or M3 occlusions will frequently have TICI 2b at baseline. There is currently no satisfactory reperfusion grading system tailored to MeVO stroke. Crockett et al made an interesting attempt in this regard: in addition to the “regular” TICI, they used a modified TICI, which focused solely on the territory affected by the MeVO, with a scoring system identical to the standard TICI system (1, 2a, 2b, 2c, 3).\textsuperscript{42} Figure 1 shows a proposed modified eTICI scoring system for MeVO.
Ischemic stroke

anterior, middle, and posterior cerebral artery MeVOs. The key difference to the conventional eTICI score is hereby the “denominator”, that is, only the affected territory downstream to the MeVO, rather than the entire middle cerebral artery territory, is used as a comparator.

Safety outcomes
Accurate and consistent reporting of safety outcomes is crucial when performing MeVO EVT, since the risk of complications is probably higher compared with LVOs, due to the relatively smaller vessel size and more distal occlusion location. Symptomatic intracranial hemorrhage (sICH) was the most consistently reported complication type in MeVO EVT studies (table 1), although many reported asymptomatic hemorrhage, vasospasm, and extracranial complications as well. In two studies, sICH rates ranged from 10%–11%,25 42 while the prevalence in other studies was below 8%, which is only slightly higher compared with LVOs.5

OUTCOMES FOR EVT IN PRIMARY VS. SECONDARY MEVOS
Most of the literature published on MeVO EVT does not distinguish between primary and secondary MeVOs. But in particular the effect of “rescue” EVT in procedure-related secondary MeVOs is of great interest for neurointerventionalists, since peri-procedural embolization of clot fragments is a common phenomenon. Embolization causing anterior cerebral artery occlusion, for example, has been observed in more than 10% of LVO EVT procedures,45 especially in cases with terminal ICA occlusion, in which the clot segment extending into the ACA might get “guillotined off” by the distal aspiration catheter or stent retriever.44 Since the infarcted area will often be larger in secondary MeVOs, one would assume clinical outcomes to be worse compared with primary MeVO strokes. However, Grossberg et al, who reported post-EVT outcomes for primary and iatrogenic (EVT-induced) secondary MeVOs separately, found similar recanalization results and even slightly better clinical outcomes in patients with secondary MeVOs, despite more severe symptoms at baseline.45 Future studies on MeVO EVT should aim to capture information on MeVO types, and report results stratified for primary vs secondary MeVOs.

CONCLUSION AND OUTLOOK
With improving imaging technologies and a growing body of literature, MeVOs are being increasingly recognized as a target for EVT. Outcomes with intravenous thrombolysis, which is the current standard of care, are moderate at best and many patients are not eligible for thrombolytic treatment at all. At the present time, there is limited but promising evidence for the safety and efficacy of MeVO EVT. Many interventionists are already routinely treating primary as well as secondary MeVOs, that is, emboli into distal vessels during EVT for LVO stroke. However, standardized imaging protocols, treatment indication criteria, and unbiased comparisons of different EVT techniques for MeVOs are lacking. At the same time, imaging tools and particularly MeVO EVT techniques are rapidly evolving. A randomized controlled trial seems unavoidable in order to establish MeVO EVT as standard of care.

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Acknowledgements The authors want to thank Basti Uhlmann for his help in designing the figure.

Contributors Both authors were involved in drafting and critical revisions of the manuscript.

Figure 1 Suggested modified eTICI classification for MeVOs in the anterior (MeVO-A-TICI: A), middle (MeVO-M-TICI: B) and posterior (MeVO-P-TICI: C) cerebral artery. Blue overlays in (A1), (B1), and (C1) indicate the “denominator”, that is, the territory downstream of the occlusion that serves as a comparator. Complete reperfusion of the territory marked in blue would correspond to an eTICI score of 3. Reperfusion contained to territory marked with red overlays in (A2), (B2), and (C2) would indicate a MeVO-A-TICI, MeVO-M-TICI, and MeVO-P-TICI score of 2A, that is, reperfusion of less than 50% of the initially affected territory. Reperfusion contained to territory marked with yellow overlays in (A3), (B3), and (C3) would indicate an MeVO-A-TICI, MeVO-M-TICI, and MeVO-P-TICI score of 2B, that is, reperfusion of 50%–90% of the initially affected territory. Reperfusion contained to territory marked with red overlays in (A4), (B4), and (C4) would indicate an MeVO-A-TICI, MeVO-M-TICI, and MeVO-P-TICI score of 2C, that is, near-complete reperfusion/ reperfusion of less than 90%–99% of the initially affected territory.
REFERENCES


### SUPPLEMENTARY MATERIAL

**A Review of Endovascular Treatment for Medium Vessel Occlusion Stroke**

![Graph showing mRS distribution](image)

<table>
<thead>
<tr>
<th></th>
<th>90 day mRS (n = 258)</th>
<th>90 day mRS without prox. M2 occlusions (n = 184)</th>
<th>90 day mRS baseline NIHSS &lt; 12 only (n = 196)</th>
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<tr>
<td></td>
<td>25.6</td>
<td>29.9</td>
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<td>24.4</td>
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<tr>
<td></td>
<td>8.9</td>
<td>6.5</td>
<td>3.3</td>
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</table>

**Suppl. figure 1**: Distribution of 90 day mRS in patients with MeVO strokes (data from the PRove-IT and INTERRSeCT studies, published with permission from AHA, 2020) \(^1\) \(^2\) (A). mRS categories are shown in ascending order from left to right. Numbers indicate the percentage of patients in one category of the mRS. The mRS distribution was similar after excluding patients with proximal M2 occlusions (B), and after excluding patients with baseline NIHSS > 12 (C).
Figure 2 (published with permission from ASNR, 2020): Patient with acute left-hemispheric symptoms (weakness of the right arm and aphasia). Multiphase CTA (arterial phase shown in A, peak-venous and late-venous phases shown in B and C) show delayed contrast washout in the left perisylvian region, which raises the suspicion of a medium vessel occlusion. On single phase CTA (D), it is very challenging to see the occlusion or any difference in collateral filling. Color-coded time variant mCTA summation maps facilitate the diagnosis further, as the abrupt change in vessel color on the mCTA summation map is more obvious than changes in enhancement on greyscale images (color-coded mCTA summation map (GE FastStrokeTM) shown in E: vessels with maximum enhancement in the arterial phase are shown in red, those enhancing in the peak-venous and late-venous phases are shown in green and blue). The time-to-peak map (courtesy: Wu Qiu, PhD) that is derived from mCTA (F) shows a clear change of color in the affected parenchyma and are another possibility to fast and reliably detect MeVOS.
References

