Indications for thrombectomy in acute ischemic stroke from emergent large vessel occlusion (ELVO): report of the SNIS Standards and Guidelines Committee

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INTRODUCTION

This document aims to provide an update on indications for mechanical thrombectomy in acute ischemic stroke (AIS) from emergent large vessel occlusion (ELVO) in the anterior circulation. This reflects new evidence building on the Society of NeuroInterventional Surgery (SNIS) recommendations published in 2015.1 Recommendations herein supersede those of previous SNIS guidelines where overlap exists. Previous publications included an overview of prehospital care, a summary of the role of intravenous (IV) and intra-arterial (IA) therapies, a review of technical aspects of thrombectomy, and initial hospital management.1,3 This guideline focuses on updated indications for thrombectomy of anterior circulation AIS. Evaluation and management of posterior circulation ELVO will be summarized in separate recommendations.

MATERIALS AND METHODS

The Standards and Guidelines Committee of the SNIS, a multidisciplinary society representing the leaders in the field of endovascular therapy for neurovascular disease, prepared this document based on a comprehensive review of the available English language literature relating to the topic. Recommendations follow the American College of Cardiology/American Heart Association (ACC/AHA) classification of recommendation/level of evidence and definition of classes and levels of evidence used in American Heart Association/American Stroke Association (AHA/ASA) recommendations.4 Throughout this document, we will refer to the specific selection criteria from the recent randomized trials and registries of modern thrombectomy approaches, which are summarized in table 1.

INDICATIONS FOR THROMBECTOMY

Defining the criteria to evaluate and select patients with ELVO for endovascular treatment is critically important, since between 3% and 22% of patients with AIS are potentially eligible for mechanical thrombectomy, depending on the specific selection criteria used.3,7 Time of symptom onset (or last known well, magnitude of early ischemic change on initial imaging, clinical severity of stroke symptoms, pre-stroke level of functioning and anatomic location of the ELVO are the most important determinants of candidacy for mechanical thrombectomy.

Time from symptom onset

MR CLEAN,9 EXTEND-IA,9 and SWIFT PRIME10 proved the value of thrombectomy in anterior circulation AIS within the first 6 hours of symptom onset. Specifically, 33% of patients achieved a good clinical outcome (defined as modified Rankin Scale (mRS) score 0–2) with thrombectomy versus 19% with medical therapy in MR CLEAN (with an OR of 1.67). In EXTEND-IA, the respective outcomes were 71% versus 40% (generalized OR=2.0). In SWIFT PRIME, they were 60% versus 35% (calculated risk ratio 1.70). THRACE11 provided additional data for thrombectomy up to 5 hours (53% of patients with thrombectomy achieved a good clinical outcome vs 42% with medical management, OR=1.55). The REVASCAT12 and ESCAPE13 trials provided initial evidence for the benefit of thrombectomy for patients with anterior circulation AIS up to 8 hours (44% with thrombectomy vs 28% with medical management, adjusted OR=2.1) and 12 hours (53% rate of good clinical outcome with thrombectomy versus 29% with medical management, rate ratio 1.8), respectively. A subgroup analysis of 59 patients enrolled within an extended time window ( groin puncture within 6–12 hours) in ESCAPE showed similar treatment effects regardless of early and late windows.14 A treatment effect favoring thrombectomy was seen across all clinical outcomes.

Two recent multicenter randomized controlled trials (RCTs) of mechanical thrombectomy initiated at a later time windows of up to 16 hours (endovascular therapy following imaging evaluation for ischemic stroke 3 [DEFUSE 3]15) and 24 hours from symptom onset (diffusion-weighted imaging [DWI] or CT perfusion [CTP] assessment with clinical mismatch in the triage of wake-up and late presenting strokes undergoing neurointervention with Trevo [DAWN]16) have shown that endovascular therapy is safe and highly effective in carefully selected patients with advanced CTP/magnetic resonance (MR) DWI-PWI imaging in comparison with medical management alone. In DEFUSE 3, 45% of patients achieved good clinical outcome with thrombectomy versus 17% with medical therapy, OR=2.67.15 In DAWN, there was a similar
### Table 1: Randomized trials and registries of modern approaches to thrombectomy

<table>
<thead>
<tr>
<th>Trial</th>
<th>No of patients, total IA (when applicable)</th>
<th>LVO location</th>
<th>Time window for thrombectomy, hours</th>
<th>Stroke severity (NIHSS score)</th>
<th>Imaging criteria</th>
<th>Treatment groups</th>
<th>mRS score=0–2 at 90 days</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Randomized trials: Endovascular vs medical</strong></td>
<td></td>
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<tr>
<td>MR CLEAN³</td>
<td>500/223</td>
<td>ICA, M1, M2, A1, A2</td>
<td>0–6</td>
<td>≥2</td>
<td>No limit</td>
<td>Endovascular arm: stent retrievers in 97% of IA cases; 87% of IA-treated patients received IV rtPA first. Control arm: IV rtPA in 91% of patients.</td>
<td>Endovascular group: 33% Control group: 19% NNT=7.3</td>
</tr>
<tr>
<td>ESCAPE⁴</td>
<td>215/65</td>
<td>ICA, M1, both (all) MDs</td>
<td>0–12</td>
<td>'Disabling' symptoms but no strict NIHSS limit</td>
<td>CT ASPECTS 6–10, moderate-to-good collateral status on mCTA</td>
<td>Endovascular arm: stent retrievers in 86% of all IA cases. 73% of IA-treated patients received IV rtPA first. Control arm: IV rtPA in 79% of patients.</td>
<td>Endovascular group: 53% Control group: 29% NNT=4.2</td>
</tr>
<tr>
<td>EXTEND-IA⁵</td>
<td>70/35</td>
<td>ICA, M1, M2</td>
<td>0–6</td>
<td>No limit</td>
<td>CTP/MRM core &lt;70 mL</td>
<td>Endovascular arm: IV rtPA plus Solitaire stent retriever in all IA cases. Control arm: IV rtPA in all</td>
<td>Endovascular group: 71% Control group: 32% NNT=3.2</td>
</tr>
<tr>
<td>SWIFT PRIME⁶</td>
<td>196/98</td>
<td>ICA, M1</td>
<td>0–6</td>
<td>8–29</td>
<td>CTP/MRM core ≤50 mL, CT/MRI ASPECTS 6–10</td>
<td>Endovascular arm: IV rtPA plus Solitaire stent retriever in all IA cases. Control arm: IV rtPA in all</td>
<td>Endovascular group: 60% Control group: 35% NNT=4</td>
</tr>
<tr>
<td>REVASCAT¹²</td>
<td>206/103</td>
<td>Anterior circulation LVO</td>
<td>0–8</td>
<td>≥6</td>
<td>CT ASPECTS 7–10, MRI DWI ASPECTS 6–10</td>
<td>Endovascular arm: Solitaire stent retriever thrombectomy. 68% of IA-treated patients received IV rtPA first. Control arm: IV rtPA in 78% of patients.</td>
<td>Endovascular group: 44% Control group: 28% NNT=6.3</td>
</tr>
<tr>
<td><strong>Endovascular registries</strong></td>
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<tr>
<td>NASA registry</td>
<td>354</td>
<td>Any LVO</td>
<td>0–8</td>
<td>≥8</td>
<td>Exclusion: CT infarct &gt;1/3 MCA territory</td>
<td>Endovascular arm: IV rtPA + aspiration with traditional penumbra separator/3D stent retriever/Solitaire/Trevo Control arm: IV rtPA in all.</td>
<td>Endovascular group: 57% Control group: 42%</td>
</tr>
<tr>
<td><strong>Randomized trials: comparison of endovascular approaches – aspiration vs stent retriever</strong></td>
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<tr>
<td>ASTER¹¹</td>
<td>381</td>
<td>ICA, M1, M2</td>
<td>0–6</td>
<td>No limit</td>
<td>No limit</td>
<td>Two endovascular arms: direct aspiration (n=192) vs primary stent retriever thrombectomy (n=182)</td>
<td>Direct aspiration: 45% Stent retriever: 50%</td>
</tr>
<tr>
<td>Penumbra Separator 3D⁸</td>
<td>198</td>
<td>Any LVO ≥2.5 mm diameter</td>
<td>0–8</td>
<td>≥8</td>
<td>Exclusion: CT infarct &gt;1/3 MCA territory</td>
<td>Two endovascular arms: 3D stent retriever + aspiration (n=98) vs primary aspiration (n=100)</td>
<td>Direct aspiration: 46% 3D stent retriever: 45%</td>
</tr>
<tr>
<td><strong>Endovascular registries</strong></td>
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<tr>
<td>STRATEGIC registry</td>
<td>984</td>
<td>Any LVO</td>
<td>0–8</td>
<td>8–30</td>
<td>No limit</td>
<td>Solitaire/Mindframe stent retriever in all. 64% patients received IV rtPA first</td>
<td>Endovascular group: 57% Control group: 42%</td>
</tr>
<tr>
<td>NASA registry</td>
<td>354</td>
<td>Any LVO</td>
<td>No limit</td>
<td>No limit</td>
<td>No limit</td>
<td>Solitaire stent retriever in all</td>
<td>Endovascular group: 42%</td>
</tr>
</tbody>
</table>

ASPECTS, Alberta Stroke Programme Early CT Score; BA, basilar artery; CTA, computed tomography; CTA, CT angiography; CTP, CT perfusion; DWI, diffusion-weighted imaging; ICA, internal carotid artery; IV, intravenous; LVO, large vessel occlusion; MCA, middle cerebral artery; MRI, magnetic resonance imaging; MRt, magnetic resonance perfusion; mRS, modified Rankin scale; NIHSS, National Institutes of Health Stroke Scale; NNT, number needed to treat; rtPA, recombinant tissue plasminogen activator.
treatment effect with rates of good clinical outcomes of 49% versus 13%, with an adjusted difference of 33%.16

At first glance, the results of DEFUSE 3 and DAWN suggest a ‘late time window paradox’ where patients treated with thrombectomy at a later time showed the largest absolute difference in good clinical outcome in comparison with earlier randomized thrombectomy trials. This finding seems to contradict the time-dependency effect of thrombectomy in which each 1 hour delay to reperfusion lowers the chances of good clinical outcome observed in HERMES.17 However, a more critical concept illustrated by DEFUSE 3 and DAWN was that collateral flow, in addition to elapsed time, together contribute to duration of tissue viability during ischemia. The use of strict imaging-based selection criteria in DEFUSE 3 and DAWN allowed for the surrogate assessment of collaterals, which now represents an important variable in selection of patients for thrombectomy.

While RCTs are considered ‘the gold standard’ for establishing clinical evidence, their design and applicability to daily clinical practice can be significantly limited by the trials’ selection criteria. Registries provide additional useful information by including a wider range of patients that can potentially serve to validate the findings of RCTs. The TRACK18 and NASA19 registries assessed real-world experience with thrombectomy without any specific restriction in time from symptom onset to treatment.

Both registries showed rates of clinical outcomes comparable to the major RCTs (48% and 42% rates of good clinical outcome in TRACK and NASA, respectively). Combined, 33% of patients from both registries were treated with thrombectomy beyond the first 6 hours, and the safety and efficacy of this treatment was equal to that of treatment performed within 0–6 hours.20 No specific imaging criteria or modalities were required in TRACK and NASA; imaging-based patient selection was left to the discretion of each participating site.

Therefore, there are high-level data from multiple RCTs and registries in support of thrombectomy in appropriately selected patients, up to 24 hours from symptom onset or last known well, including wake-up strokes. There is insufficient evidence to evaluate the safety and efficacy of thrombectomy >24 hours from symptom onset. Presently, only limited experience with thrombectomy of anterior circulation ELVO after 24 hours has been reported.21

**Imaging criteria for thrombectomy**

RCTs have used a number of radiographic selection criteria to determine candidacy for thrombectomy. Specific imaging criteria from these RCTs are summarized in table 1. The primary purpose of imaging in patient selection is to exclude patients unlikely to benefit or for whom thrombectomy may be harmful. Selection criteria for the late-window trials (>6 hours) were more selective than the <6 hours RCTs. For thrombectomy <6 hours, there are insufficient data to establish the superiority of one particular imaging modality. These include non-contrast CT, MR DWI, multiphase CT angiography (mCTA) collateral imaging, and advanced CT/MR perfusion imaging with standardized postprocessing techniques. Various imaging criteria such as the Alberta Stroke Programme Early CT Score (ASPECTS) 6–10, MRI DWI ASPECTS 5–10, moderate-to-good collateral status on mCTA (>50%/middle cerebral artery [MCA] territory), small (<50–70 mL) core infarct volumes, and significant penumbra to core mismatch on perfusion imaging have been used as selection criteria in study subjects with anterior circulation stroke and symptom onset up to 6 hours who qualify for thrombectomy.

In patients 6–24 hours, MR DWI-PWI and CTP imaging are highly accurate in selecting patients for thrombectomy when based on criteria used in DEFUSE 3 and DAWN. However, as discussed earlier, both trials, because of restrictive radiographic selection criteria, limit their generalizability to many patients with ELVO. For example, a single-center study of patients presenting 6–24 hours after last known well showed that 70% of these patients with anterior circulation ELVO were DAWN and/or DEFUSE 3 ineligible.22 Yet, thrombectomy in these patients resulted in rates of good clinical outcomes comparable to those of DAWN and DEFUSE 3 eligible patients.22

Data from the early HERMES collaboration of five RCTs,23 subgroup analyses of THRACE,24 and matched case-control studies indicated that thrombectomy may be beneficial even in patients with ischemic strokes presenting with large core infarct volumes, such as those with CT/MRI ASPECTS 3–5 or MRI DWI and CTP estimated core volumes of >50–70 mL.25–27 The latest HERMES collaboration analysis based on individual patient data from RCTs (MR CLEAN, ESCAPE, EXTEND-IA, SWIFT PRIME, REVASCAT, THRACE, and PISTE) showed that thrombectomy led to better clinical outcomes at 90 days across a broad range of imaging categories, including ASPECTS <6 (OR=1.58 for ASPECTS 5–7 and OR=2.15 for ASPECTS 0–4) and infarcts affecting >1/3 of MCA territory (OR=1.7), supporting the value of thrombectomy in some patients with large infarcts at baseline.28 However, thrombectomy in patients with such unfavorable imaging profiles had higher rates of symptomatic intracranial hemorrhage than in the control group. A separate HERMES collaboration analysis of seven RCTs also confirmed that thrombectomy administered within 0–6 hours of symptom onset remained beneficial in patients with a large (>70 mL) ischemic core measured with CTP or MRI.29

**Location of large vessel occlusion**

The anatomic definition of an ELVO is variable.30 For the purpose of this document, any arterial location or lesion that can be safely selectively catheterized with modern endovascular devices will be referred to as an ELVO. Rigorous clinical trial data support mechanical thrombectomy in patients with intracranial and extracranial occlusions of the internal carotid artery (ICA), including tandem or isolated occlusion of the M1 and M2 segments of the MCA (table 1). Patients with M2 occlusions were also included for thrombectomy in the MR CLEAN, ESCAPE, EXTEND-IA, REVASCAT, and THERAPY trials, although in limited numbers.

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. This is due to a paucity of data representative of this cohort. Although studies indicate that thrombectomy may be safe and effective in patients with distal anterior circulation ELVO, evidence also suggests an increased risk profile with mechanical interventions, such as vessel perforation and vasospasm.31–34 Furthermore, although the natural history of distal occlusions is probably, on average, more favorable than proximal occlusions, the level of disability may still be significant and warrants clarification.

**Stroke severity**

When determining eligibility for thrombectomy, stroke severity should be assessed using the National Institutes of Health Stroke Scale (NIHSS).35 Use of a standardized scale directly quantifies the degree of neurological deficit, facilitates communication, helps to identify patients for thrombolytic or mechanical intervention, allows objective measurement of changing clinical status, and may identify those at higher risk for complications...
such as intracerebral hemorrhage. There was significant variability in the NIHSS score thresholds used for inclusion in recent RCTs for thrombectomy. The MR CLEAN trial had the lowest NIHSS score threshold of 2, ESCAPE and EXTEND-IA set no specific NIHSS score thresholds, but required the symptoms to be ‘disabling’, whereas other trials had variable ranges from an NIHSS score of 6 to 10 (table 1). Because several trials independently validated an NIHSS threshold of 6 (SWIFT PRIME, REVASCAT and DEFUSE 3), an NIHSS score of >6 may serve as a working criterion of clinical severity when considering thrombectomy in anterior circulation AIS. However, patients presenting with anterior circulation ELVO and NIHSS score <6, but with otherwise disabling symptoms such as isolated aphasia, should be considered for thrombectomy. Several studies describe a poor natural history in this cohort, with sometimes eventual worsening of neurologic deficits and functional independence in up to a quarter of patients. More data on this topic are needed (table 2).37-40

### Thrombectomy and intravenous thrombolysis

In recent RCTs of thrombectomy, patients eligible for IV thrombolysis with recombinant tissue plasminogen activator (tPA; alteplase) before thrombectomy received both treatments (table 1). Although there is accumulating evidence suggesting that administering IV tPA in thrombectomy-eligible patients may be futile, there are also data suggesting that it may be beneficial in patients with ELVO.44 This topic is complicated by evidence showing that the efficacy of IV tPA depends on thrombus location; proximal thrombi are less likely to respond to thrombolysis, whereas tPA has a higher likelihood of inducing recanalization at more distally located thrombi.45,46 Thus, future trials comparing thrombectomy with thrombolysis may need to include analysis by thrombus location. A RCT comparing the safety and efficacy of thrombectomy with rtPA versus thrombolysis may need to include analysis by thrombus location. A RCT comparing thrombectomy with rtPA should not delay the initiation of thrombectomy in these patients.

### Age and baseline level of functioning

Significant pre-existing disability often precludes favorable clinical outcomes despite successful thrombectomy. Whether it is due to frailty, poor nutritional status, limited baseline functional capacity, or comorbidities, such patients would, in theory, have almost nothing to gain from thrombectomy. No randomized data exist for thrombectomy in patients with mRS score >1, but this may be a topic of interest for future investigators. On the other hand, multiple studies evaluating thrombectomy in elderly patients have showed mixed but promising results.47-49 The HERMES collaboration analysis of patient-level data of five RCTs showed significant benefit of thrombectomy in patients aged >80 years with a common OR of 3.68.23

### RECOMMENDATIONS

#### Time from symptom onset

- For anterior circulation AIS, thrombectomy is indicated in select patients up to 16 hours from symptom onset or time last known well for unwitnessed strokes, including wake-up strokes [class I, level A], and is indicated in select patients up to 24 hours from last known normal [class IIa, level B]. This replaces the 2015 SNIS guidelines in which thrombectomy recommendations were limited to the first 6 hours of symptom onset.

#### Imaging

- In patients with anterior circulation AIS within the first 6 hours of symptom onset and either CT ASPECTS ≥6, MRI DWI ASPECTS ≥6, or CTP-estimated core infarct volumes, and/or significant penumbral to core mismatch on advanced perfusion imaging (CTP or MRI-DWI-PWI), thrombectomy is indicated [class I, level A].
- Thrombectomy may be reasonable within the first 6 hours of symptom onset in patients with a large core infarct volume such as CT ASPECTS of <6, MRI DWI or CTP-estimated core volume >70 mL [class IIa, level A].
- In patients with anterior circulation AIS due to intracranial ICA and/or M1 occlusion within 6–24 hours of symptom onset who meet the advanced MRI-DWI-PWI or CTP

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**Table 2** Natural history (medical therapy only, no IV tPA) and thrombectomy outcomes in patients with ELVO and mild symptoms

<table>
<thead>
<tr>
<th>Study</th>
<th>Stroke severity</th>
<th>Study groups</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haussen et al, 2016</td>
<td>NIHSS &lt;6</td>
<td>88 Patients with medical therapy, 30 with EVT. Retrospective, matched analysis</td>
<td>▶ EVT predicted favorable NIHSS shift (β = −3.7, 95% CI −6.0 to −1.5, p = 0.02).</td>
</tr>
<tr>
<td>Haussen et al, 2017</td>
<td>NIHSS &lt;6</td>
<td>22 Patients with medical therapy, 10 with EVT</td>
<td>▶ 9/2 (41%) of medically treated patients deteriorated and required thrombectomy.</td>
</tr>
<tr>
<td>Dargazani et al, 2017</td>
<td>NIHSS &lt;8</td>
<td>170 Patients with medical therapy, 131 with EVT</td>
<td>▶ 24/131 (18%) of medically treated patients deteriorated and required EVT.</td>
</tr>
<tr>
<td>Heldner et al, 2015</td>
<td>NIHSS &lt;6</td>
<td>44 Patients treated with medical therapy</td>
<td>▶ Worsening of NIHSS (increase of score ≥1) within the first 24 hours in 10/44 (23%)</td>
</tr>
<tr>
<td>Mokin et al, 2014</td>
<td>NIHSS &lt;8</td>
<td>204 Patients treated with medical therapy</td>
<td>▶ At discharge, 17% of patients with NIHSS 0–4 and 36% with NIHSS 5–7 could not ambulate independently</td>
</tr>
<tr>
<td>Rajajee et al, 2006</td>
<td>NIHSS &lt;5</td>
<td>39 Patients treated with medical therapy</td>
<td>▶ 3/8 (38%) patients with ELVO vs 1/31 (3%) patient without ELVO had early neurologic deterioration with infarct expansion on MRI (OR = 18, 95% CI 1.6 to 209, p = 0.02).</td>
</tr>
</tbody>
</table>

ELVO, emergent large vessel occlusion; EVT, endovascular therapy; IV, intravenous; MRI, magnetic resonance imaging; mRS, modified Rankin scale; NIHSS, National Institutes of Health Stroke Scale; tPA, tissue plasminogen activator.
Thrombectomy is indicated in patients with anterior circulation AIS within 6–24 hours of symptom onset who do not meet imaging criteria for DAWN or DEFUSE 3, thrombectomy is indicated [class I, level B].

▶ Thrombectomy may be indicated in carefully selected patients with anterior circulation AIS within 6–24 hours of symptom onset who do not meet imaging criteria for DAWN or DEFUSE 3 but otherwise have a ‘favorable’ imaging profile such as CT ASPECTS of 6–10, MRI DWI ASPECTS of 6–10, moderate-to-good collateral status on mCTA, or small (<70 mL) core infarct on advanced MRI DWI-PWI or CTP imaging [class IIb, level B-NR (non-randomized)].

Location of ELVO

▶ Thrombectomy is indicated in patients with occlusions of the ICA (including intracranial, cervical segments or tandem occlusion) and M1/M2 MCA [class I, level A]. This replaces the 2015 SNIS guidelines in which thrombectomy recommendations were limited to ICA and MCA M1 LVO locations.

▶ The benefit of thrombectomy in more distal segments, such as MCA M3 or anterior cerebral artery is unclear. Thrombectomy of such patients may be reasonable in some cases and should be considered on a case-by-case basis [class IIb, level B-NR].

Stroke severity

▶ Thrombectomy is indicated in patients with anterior circulation ELVO with NIHSS score ≥6 [class I, level A].

▶ Thrombectomy may be considered in patients with anterior circulation AIS and NIHSS score <6 when associated with disabling symptoms [class IIa, level B-NR]. However, care should be taken when treating these patients to keep complication and hemorrhagic rates below those reported in RCTs.

Age and baseline level of functioning

▶ Age >80 years should not be used as a contraindication for thrombectomy [class IIa, level A].

▶ The benefit of thrombectomy in patients with baseline mRS score >1 is unknown.

Collaborators


Contributors

MM was the primary author and, as such, was responsible for overseeing construction of the document outline, gathering of evidence, and drafting of the manuscript. He also contacted our guest author (MG) as a topic expert, and sought his input. SAA, RAM, and KRB all made major contributions to the manuscript draft, and supplemented entire sections of the text. They also participated in discussions about the outline and organization of the text. MC acted as a consultant for Toshiba (Canon) Medical, Penumbra, and Cerebrotech. MG is a consultant for Medtronic, Styrk, Microvention, and Cerenoveus. He has a licensing agreement with GE Healthcare for systems of stroke diagnosis. Styrk has provided an unrestricted research grant to the University of Calgary. MC is a consultant for Medtronic, Styrk, Penumbra, Genentech, and GE.

Patient consent

Not required.

Provenance and peer review

Not commissioned; internally peer reviewed.

Data sharing statement

Not applicable.

REFERENCES


