Endovascular Thrombectomy in Acute Ischemic Stroke

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Abstract—Despite several effective strategies of stroke prevention, the stroke epidemic still constitutes the leading cause of permanent disability. The recent series of well-designed, convincingly-positive randomized controlled trials of endovascular thrombectomy in stroke patients with large vessel occlusion launched a paradigm shift and a new era in acute stroke management. The present review provides an overview of the technical aspects of the procedure, discusses patient selection criteria, summarizes the current evidence from randomized trials about its efficacy and safety, and explores its implications in the organization of acute stroke care. (Circ Cardiovasc Interv. 2018;11:e005362. DOI: 10.1161/CIRCINTERVENTIONS.117.005362.)

Key Words: endovascular management ■ stent retriever ■ stroke ■ thrombectomy ■ thrombus aspiration

Nearby 800,000 strokes occur in the United States and 1 million in the European Union each year. Although stroke mortality during the past 10 years has declined, it ranks as the fifth leading cause of death.1 In addition, stroke is the leading cause of permanent disability and one of the most frequent causes of dementia in the developed world.1 Stroke survivors and their families are often burdened with exorbitant rehabilitation costs, lost wages and productivity, and limitations in their daily social activity.2 Most recent estimates place the cost of stroke in the United States in excess of $34 billion per year.

Timely treatment and intervention can minimize long-term disability by salvaging the at-risk penumbra and, consequently, reducing the associated morbidity and mortality. For >20 years, the only proven causal treatment of acute ischemic stroke has been the intravenous thrombolysis (IVT), that is, administration of alteplase, a recombinant tPA (tissue-type plasminogen activator). However, its use has been limited by several factors like the narrow time window after stroke onset and the only moderate recanalization rate especially in the proximal arteries.2 As a result, the implementation of IVT has been low internationally.2–5 Recently, a series of well-designed and well-conducted randomized controlled trials (RCT) concluded convincingly that endovascular thrombectomy (EVT) improves dramatically the outcomes of eligible patients.

The present review provides an overview of the technical aspects of the procedure, discusses patient selection criteria, summarizes the current evidence from randomized trials about its efficacy and safety, and explores its implications in the organization of acute stroke care.

Patient Selection

Important features of the patient’s presentation that bear on EVT decisions include the time of presentation, the clinical status of the patient, and imaging characteristics.

Time of Presentation

The time window for IVT and EVT plays an important role in clinical outcome, as it was shown that their efficacy is time-dependent: in anterior circulation strokes, the impact of successful thrombectomy is greater in the first 3 to 4.5 hours after stroke compared with late recanalization after 5 to 8 hours.6 Although IVT is a treatment option ≤4.5 hours after stroke onset, additional or primary EVT can be performed within a more extended time window: in recent RCTs, only few patients who could not have groin puncture by 6 hours were included. Therefore, the positive results of the trials are driven mainly by the patients treated within 6 hours from symptom onset.7 A meta-analysis of the recent RCTs showed that in patients who achieved substantial reperfusion with EVT, each 1-hour delay to reperfusion was associated with a less favorable degree of disability and less functional independence but no change in mortality.8

Posterior circulation and brain stem strokes caused by vertebro or basilar artery occlusion might be less susceptible to the hemorrhagic complications of reperfusion therapy. Safe recanalization of occluded posterior circulation vessels has been reported ≤24 hours after brain stem infarction.9,10

Clinical Presentation

Patients with significant deficits manifesting National Institutes of Health Stroke Scale scores between 8 and 20 are more likely to benefit from reperfusion with EVT, making them better candidates for treatment. The recent RCTs recruited mainly patients with moderate-to-severe stroke symptoms. Based on these trials, the American Heart Association guidelines provided level 1A evidence for EVT for patients with National Institutes of Health Stroke Scale scores of ≥6.11

However, there is a significant proportion of patients with acute ischemic stroke and large vessel occlusion who...
may present with mild stroke severity (National Institutes of Health Stroke Scale score <8). In these patients, the decision to perform additional EVT is based on the experience of the Stroke Interventionist and the estimated risk of the procedure. Although no related RCT data are available, EVT in patients presenting with minor to mild stroke severity and proximal large vessel occlusion seems to be favorable and safe. However, future RCTs are urgently warranted to guide treatment decisions in these patients.

Imaging

In patients with clinical picture that is suggestive for large vessel occlusion and who could be candidates for EVT, a comprehensive evaluation should be performed with multimodal computed tomography (CT) or multimodal magnetic resonance imaging (MRI) techniques. The major advantages of CT compared with MRI are that CT is widely available and a stroke imaging protocol that consists of noncontrast CT and CT angiography (CTA) can be executed in only a few minutes.

Brain parenchymal imaging, preferably with noncontrast CT or alternatively with MRI, should be used to diagnose intracranial hemorrhage (ICH) or stroke mimics like tumor, infection, and others, which preclude the use of IVT. It is also helpful to measure the extent of early ischemic changes within ischemic brain. The Alberta Stroke Program Early CT Score (ASPECTS) is a systematic approach to detect early CT signs like the insular ribbon sign or obscuration of the lentiform nucleus (Figure 1). Although the ASPECTS score was previously shown to be a strong predictor of functional outcome after IVT, it has now been shown prospectively and successfully to predict also the outcome after EVT: an independent meta-analysis showed that EVT improves outcomes both in patients with CT-based ASPECTS of 8 to 10 (ie, minimal ischemic damage) as well as of 5 to 7 (ie, moderate ischemic damage) (odds ratio 2.1 and 2.04, respectively, for modified Rankin Scale score 0–2 against best medical treatment). On the contrary, patients with a low ASPECTS of 0 to 4 showed no treatment benefit by EVT, suggesting that EVT has little or no efficacy in patients with large ischemic core. However, the interpretation of the ASPECTS is challenging and variable, even between stroke experts. Standardized and automated assessment of ischemic damage could be useful in future clinical practice.

Arterial imaging of the cerebral circulation, preferably with CTA or alternatively with magnetic resonance angiography, is a sine qua non for the assessment of patient eligibility for EVT. CTA is widely available, with fast, thin-section, volumetric spiral CT images acquired during the injection of a time-optimized bolus of contrast material for vessel opacification. The entire region from the aortic arch up to the circle of Willis can be covered in a single data acquisition. CTA confirms the existence of a large vessel occlusion, allows localization of the occluded vessel, and may facilitate the intervention by obviating the need for cerebral angiography of nontarget vessels. Moreover, it may identify collateral circulation and clot length. Collateral circulation likely improves stroke outcome by limiting the extent of brain infarction. A post hoc analysis of MR CLEAN (Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands) neuroimaging data evaluated how the collateral status of the target vessel related to clinical outcome and concluded that baseline CTA collateral status modified the effect of EVT: the benefit of EVT was robust in patients with good collaterals on baseline CTA, whereas treatment benefit could not be established in patients with absent or poor collaterals (Figure 2). However, in everyday clinical practice, collateral status assessment on CTA can be prone to interobserver variability.

Perfusion imaging with perfusion CT or with diffusion-weighted imaging MRI can allow identification and quantification of the ischemic penumbra (ie, ischemic, yet viable tissue at risk that may be salvaged by timely reperfusion) and, therefore, is useful for assessing patient eligibility for EVT in the extended time window. Recently, the DAWN trial (Diffusion Weighted Imaging or Computerized Tomography Perfusion Assessment With Clinical Mismatch in the Triage of Wake Up and Late Presenting Strokes Undergoing Neurointervention) and the DEFUSE 3 trial (Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke 3) reported better outcomes in patients who were treated in the extended time window.
window based on the mismatch principle compared with those who were not treated.21,22

Techniques of Endovascular Thrombectomy
The breakthrough in interventional treatment of acute stroke was achieved in 2008 by the use of stent-like thrombectomy devices which are now called stent retrievers.23,24 The majority of patients in the recent EVT RCTs were treated with these devices; in contrast, previous neutral RCTs of EVT used older devices, something which was considered as one of the causes of failure to identify a beneficial effect of EVT in these trials. The aspiration technique can be used as an alternative method to stent retriever devices.

Stent Retriever Technique
The stent retriever devices allow high recanalization rates with a reduction in the recanalization time and low complication rates.25 Retrievable stents are self-expandable stent-like devices that are fully retrievable. Therefore, these devices combine the advantages of prompt flow restoration and mechanical thrombectomy. Excellent recanalization results can be achieved with this technique with rates of Thrombolysis in Cerebral Infarction (TICI) grade 2a/b or 3 flow as high as 90%. The results of prospective studies showed high rates of favorable clinical outcomes at 3 months.26,27 The improved clinical outcome with flow-restoration devices is because of fast and effective clot removal and the possibility of temporarily restoring flow.23 Moreover, the use of stent retriever devices is associated with low rates of symptomatic ICH and low mortality rates. The low mortality rates reflect the low rate of symptomatic ICH and show the safety of flow-restoration devices compared with thrombectomy devices in the past. This was confirmed in all RCTs.15

At the stent retriever technique, the target vessel is entered with a 0.014-inch guidewire and a suitable microcatheter between 0.018 and 0.027 inch. The thrombus is crossed with the guidewire, and the microcatheter is placed distal to the thrombus. The stent retriever is advanced to the distal end of the microcatheter. Then, the microcatheter is removed to deploy the device under fluoroscopy. A control angiogram is performed after successful unfolding of the device. The sizes of stent retriever devices range from 3.0×15 mm to 6.0×30 mm; however, typically a 6.0-mm device is used. After a short period of time, the device is pulled back with continuous aspiration. The procedure is repeated until a TICI grade of 2b or 3 is reached12 (Figure 3).
Aspiration Technique
Clinical experience has reported situations that are resistant to stent retriever recanalization attempts. These situations include occlusions located in terminal internal carotid artery (ICA) and middle cerebral artery bifurcation and trifurcation thrombi, as well as hard thrombi configuration. For these cases, direct aspiration of the thrombus can be used as an alternative technique. The aspiration technique has been an early hallmark in the history of mechanical thrombectomy, and its use has been demonstrated in a large number of trials and clinical experiences. Over the past few years, new aspiration devices were developed including changes in the distal inner diameters of the catheter; therefore, the aspiration technique is in some centers used as a primary approach for intracranial artery occlusion. Recent studies, including 1 randomized trial, showed that the primary aspiration technique is a safe and effective EVT method with clinical results comparable to those of the stent retriever devices. The main advantages of aspiration technique are the fast procedure time and the high rate of favorable clinical outcome.

When the aspiration technique is used, the thrombus is passed with the microwire and microcatheter, and the aspiration catheter is placed directly in the proximal part of the thrombus. The microwire and the microcatheter are removed. Entrapment of the thrombus is indicated by the absence of backflow. The catheter is then retrieved with constant negative pressure to avoid loss of thrombus. After each retrieval of clot fragments, the procedure is repeated until a TICI grade of ≥2 or 3 was reached (Figure 4).

Tandem Occlusions
Tandem occlusions are a combination of the extracranial segment of the ICA occlusion with a concurrent occlusion of the intracranial segment. Tandem occlusions are not common but represent challenging therapeutic conditions in the setting of acute ischemic stroke. Only few patients with tandem occlusions were included in the recent EVT RCTs. The HERMES meta-analysis (Highly Effective Reperfusion Evaluated in Multiple Endovascular Stroke Trials Collaboration) showed that EVT was beneficial also in this subgroup of patients. Acute occlusion of the extracranial ICA segment resulting in ischemic stroke is different from other forms of acute occlusions of the cerebral vessels. The pathophysiologic process involved in acute occlusion of the extracranial ICA, similar to that observed in acute occlusion of the coronary arteries, is predominantly ruptured atherosclerotic plaque and superimposed thrombus. Therefore, in these patients, acute stenting of the extracranial ICA should be performed to recanalize the vessel. The intervention in patients with tandem occlusions consists of 2 steps: the first step is revascularization of the extracranial ICA segment with stent implantation, as in the treatment of atherosclerotic stenosis. The second step is...
general anesthesia with intubation or under conscious sedation. Some stroke interventionists and stroke physicians prefer general anesthesia with intubation, assuming it may be associated with less pain, anxiety, agitation, movement, and lower risk for aspiration, whereas others favor conscious sedation to save time, evoke less hemodynamic instability, and risk fewer ventilation-associated complications. Up to now, the results of some nonrandomized and a few RCTs showed contradictory results about which method is superior.\textsuperscript{32–34} Thus, the absence of conclusive evidence, whether general anesthesia or conscious sedation is superior, suggests that the stroke team should choose the preferred method on the basis of their experience.\textsuperscript{7}

**Current Evidence From Randomized Studies**
MR CLEAN was the first RCT to report beneficial results for EVT in acute ischemic stroke.\textsuperscript{14} This study was followed by 5 more, positive trials (Table).

**Assessment of Efficacy**
All these RCTs reported an increased rate of successful recanalization, which was defined as a TICI grade of 2b or 3 and varied between 59\% and 88\%. Importantly, this technical success was translated into clinical improvement because it was shown that the likelihood of good outcome increased with better recanalization.\textsuperscript{14,35–39}

In particular, all 6 RCTs showed improved functional outcomes in the EVT group compared with the IVT-alone group. The proportion of patients achieving a favorable clinical outcome with EVT varied between 33\% and 71\%; there was a consistent positive difference across all studies.
with functional independence (defined as a modified Rankin Scale score of 0–2 at 90 days) between the EVT and IVT-alone groups favoring EVT by 14% to 31%. The difference between groups was more pronounced in the trials in which penumbral imaging with perfusion CT was used to guide patient selection. However, even without imaging selection beyond the noncontrast CT, there was a clear benefit in favor of EVT.14,35–39

Meta-analysis of the individual patient data from these RCTs concluded that for every 100 patients treated, 38 will have a less disabled outcome than with IVT and 20 more will achieve functional independence. The number needed to treat for 1 patient to have reduced disability of at least 1 point on modified Rankin Scale was 2.6.15

Recently, the longer-term outcomes of 2 of the aforementioned RCTs were reported showing that the beneficial effect of EVT at 1 to 2 years was similar to that reported at 90 days without any difference in mortality rates.40,41

Assessment of Safety
In all these 6 RCTs, the rates of symptomatic ICH, radiological intracerebral hematoma, and 90-day mortality were similar in the EVT and IVT-alone groups. The rates of ICH in both arms ranged from 0% to 7%. The fact that, in all these RCTs, EVT carried similar bleeding risk and similar 90-day mortality rate compared with IVT alone demonstrates that EVT alone is a safe intervention, and any bleeding risk is associated with the IVT, which may precede. Of importance, the superiority of EVT compared with IVT alone was identified in several subgroups of patients like those aged ≥80 years, those randomized >300 minutes after symptom onset, and those who were not eligible for IVT.14,35–39,42
The recent EVT RCTs made convincingly clear that a paradigm shift in the organization of acute stroke care pathways is urgently needed. Soon after these trials were published, a huge discussion has started about the optimal design of acute stroke care facilities, patient triage, and transfer protocols taken into consideration that 10% to 17% of the ≈795,000 new or recurrent strokes that occur annually in the United States are EVT eligible.1,43

Facilities where EVT is routinely provided in eligible patients are usually called Comprehensive Stroke Centers (mainly in North America) or simply Stroke Units (mainly in Europe)44,45 compared with Primary Stroke Centers (mainly in Europe). Although these 2 acute stroke care structures differ in several aspects, perhaps the most striking difference is the routine availability of EVT.44,45

There are 2 options for the patient transfer protocol in the acute stroke setting: in the first, a patient who is triaged as potentially EVT eligible is transferred directly to a Comprehensive Stroke Center/Stroke Center where EVT could be offered if indeed eligible. In the second option, a patient is transferred initially to a Primary Stroke Center/Stroke Unit where IVT is offered if patient is eligible and then transferred further to a Comprehensive Stroke Center/Stroke Center where EVT may be offered if indicated.46

Each of these approaches has advantages and disadvantages: transferring a patient directly to a Comprehensive Stroke Center/Stroke Center may allow the performance of EVT much earlier (≤129 minutes47), with obvious implications

### Table. Recent Randomized Trials for Endovascular Treatment of Acute Stroke

<table>
<thead>
<tr>
<th>Study Name</th>
<th>Sample Size</th>
<th>Comparison groups</th>
<th>Inclusion Criteria</th>
<th>Primary Outcome</th>
<th>90-d Rankin Scale Score 0–2, %</th>
<th>Symptomatic ICH, %</th>
<th>Mortality, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>MR CLEAN</td>
<td>500</td>
<td>Mechanical treatment, delivery of a thrombolytic agent, or both</td>
<td>Age &gt; 18 y, NIHSS score &gt; 2 at 6 h from onset</td>
<td>Modified Rankin Scale score at 90 d</td>
<td>32.6 vs 19.1</td>
<td>7.7 vs 6.4</td>
<td>21 vs 22</td>
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<td></td>
<td></td>
<td>Conventional therapy</td>
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<tr>
<td>SWIFT-PRIME</td>
<td>196</td>
<td>Intravenous thrombolysis plus retrievable stent</td>
<td>Age, 18–80 y, NIHSS score &gt; 30 and ≤ 30, IV tPA within 4.5 h</td>
<td>Modified Rankin Scale score at 90 d</td>
<td>60 vs 36</td>
<td>1 vs 3.4</td>
<td>9 vs 12</td>
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<td>Intravenous thrombolysis alone</td>
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<tr>
<td>EXTEND-IA</td>
<td>70</td>
<td>Endovascular thrombectomy plus retrievable stent</td>
<td>Age ≥ 18 y, IV tPA within 4.5 h, penumbral imaging using CT or MRI</td>
<td>Reperfusion at 24 h</td>
<td>72 vs 39</td>
<td>0 vs 6</td>
<td>9 vs 20</td>
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<td>Conventional therapy</td>
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<td>ESCAPE</td>
<td>315</td>
<td>Mechanical treatment</td>
<td>Age &gt; 18 y, NIHSS score &gt; 2 at 12 h from onset, groin puncture within 60 min of baseline CT</td>
<td>Modified Rankin Scale score at 90 d</td>
<td>54 vs 29</td>
<td>3.6 vs 2.7</td>
<td>10.4 vs 19</td>
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<td>Conventional therapy</td>
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<tr>
<td>REVASCAT</td>
<td>206</td>
<td>Endovascular thrombectomy plus retrievable stent</td>
<td>Age 18–85 y, NIHSS score &gt; 6 at 8 h from onset</td>
<td>Modified Rankin Scale score at 90 d</td>
<td>43.7 vs 28.1</td>
<td>1.9 vs 1.9</td>
<td>18.4 vs 15.5</td>
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<td>Conventional therapy</td>
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<td>THRACE</td>
<td>414</td>
<td>Intravenous thrombolysis plus mechanical thrombectomy</td>
<td>Age 18–80 y, NIHSS score ≥ 10 and ≤ 25, IV tPA within 4 h</td>
<td>Proportion of patients with functional independence (modified Rankin Scale score 0–2) at 90 d</td>
<td>53 vs 42</td>
<td>2 vs 2</td>
<td>12 vs 13</td>
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<td>Intravenous thrombolysis alone</td>
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CT indicates computed tomography; ESCAPE, Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion With Emphasis on Minimizing CT to Recanalization Times Trial; EXTEND-IA, Extending the Time for Thrombolysis in Emergency Neurological Deficits—Intra-Arterial Trial; MRI, magnetic resonance imaging; MR CLEAN, Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands; NIHSS, National Institutes of Health Stroke Scale; REVASCAT, Randomized Trial of Revascularization With Solitaire FR Device Versus Best Medical Therapy in the Treatment of Acute Stroke due to Anterior Circulation Large Vessel Occlusion Presenting Within Eight Hours of Symptom Onset; SWIFT-PRIME, Solitaire With the Intention for Thrombectomy as Primary Endovascular Treatment Trial; THRACE, Thrombectomie des Artères Cerebrales Trial; and tPA, tissue-type plasminogen activator.
for the outcome of the patients given the time-dependent effect of EVT. On the contrary, a significant proportion of these patients may ultimately be ineligible for EVT and eligible only for IVT, a proportion that could reach ≤41% of all transfers. At a patient level, this would be actually translated into delayed initiation of IVT with obvious implications for the (lower) probability of benefit, whereas at a facility level, it would be translated into higher volumes of patients who could be otherwise treated in Primary Stroke Center/Stroke Units. Obviously, there is no one-size-fits-all approach. The optimal design will depend on several factors like geography and available modes of transportation, the population density, the distribution of available stroke facilities and the distance in-between, reimbursement policies, and patient volumes.

For example, in the United Kingdom, a centralized hub-and-spoke model of acute stroke care reduced mortality and length of hospital stay. Well-designed RCTs are needed to provide further information that may likely inform better the design of more efficient acute stroke pathways.

**Stroke Physicians and Stroke Interventionists**

Stroke is not a disease; it is a syndrome and, actually, a complex one. During the past decades, the stroke community witnessed a dramatic increase in the understanding and knowledge of virtually any aspect of stroke like primary prevention, stroke cause and pathophysiology, diagnostic approach, acute causal treatment, acute stroke management and prevention of acute stroke complications, secondary prevention, and rehabilitation. Nowadays, stroke medicine has evolved so broadly and deeply that now clearly extends horizontally beyond and across the boundaries of the traditional specialties that are typically engaged in the care and management of stroke patients like internists, neurologists, general practitioners, cardiologists, interventional neuroradiologists, physiatrists, and others. Now, more than ever, it becomes obvious that stroke medicine needs to be acknowledged and certified as a distinct, independent subspecialty for medical doctors coming from different related backgrounds who should be rigorously trained, certified, and dedicated toward 2 directions: the stroke physician and the stroke interventionist. In the EVT era, these 2 should form the 2 pillars, which support and lead the specialized multidisciplinary stroke team of any EVT-ready stroke facility.

At present, at an international level, in most cases, the stroke interventionist performing EVT is an interventional neuroradiologist. In North America, the current and projected numbers of interventional neuroradiologists is considered adequate to supply the future need for acute stroke interventions; however, such calculations are lacking for Europe and other parts of the world. Furthermore, it seems highly possible that this may not be the case for healthcare systems relying on limited resources. Still, the major obstacle to offering EVT to all our eligible patients seems to be not the availability but rather the distribution of the interventional neuroradiologists. Indeed, in the United States, most interventional neuroradiologists are concentrated at major medical centers in large cities, whereas nearly half the population resides in less-urban and more-rural areas where access to stroke centers capable to offer EVT is limited. How can this be addressed? Structuring a 24/7 stroke-ready EVT service carries a high cost for infrastructure and for trained and dedicated technical, nursing, and medical staff. This may seem challenging to justify and maintain in areas with lower expected volumes of EVT-eligible patients. In this case, it could be possible to merge facilities and personnel with other interventional disciplines like interventional radiologists and interventional cardiologists. Of course, interventions in the intracranial circulation differ in many aspects from interventions in the coronary circulation: intracranial arteries are more tortuous and carry a higher risk of complication that may necessitate specialized interventions that non-neurointerventionists are not familiar with. Although the technical aspects of EVT may be readily learned, the overall approach in acute stroke management necessitates good knowledge of cerebrovascular anatomy, physiology and pathophysiology, management of potential complications, and the overall acute stroke management pathway. This should require in-depth acute stroke training through fellowships and well-designed demanding curricula.

**Disclosures**

Dr Papanagiotou is a local principal investigator for the Swift Prime Study (Medtronic, Inc) and a consultant for Penumbra Inc, Johnson & Johnson, and Phenox, Inc. Dr Ntaios reports no conflicts.

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Papanagiotou and Ntaios  Endovascular Thrombectomy in Acute Ischemic Stroke


