Interventionalist Perspective on the New Endovascular Trials

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Abstract—Three recently published trials have conclusively proven the benefit of mechanical endovascular thrombectomy over best medical therapy for patients with acute ischemic stroke and large vessel occlusion. These trials shared some features and differed in others. These similarities and differences in trial design and execution affect the conclusions and recommendations that can be made from the data. We will examine the implications of these studies for neurointerventionists, both for current practice and for future studies. In particular, we will focus on procedural details such as patient selection, devices, adjunctive therapies, treatment time windows, and performance metrics. (Stroke. 2015;46:1440-1446. DOI: 10.1161/STROKEAHA.115.008416.)

Key Words: clinical trial ▪ editorial ▪ stents ▪ stroke

The past 3 months have seen the publication of more positive pivotal clinical trials for the treatment of acute ischemic stroke than the past 20 years combined. This is a once in a generation advance in stroke care. The purpose of this editorial is to carefully review the data from the recently published trials of endovascular treatment (EVT) for acute ischemic stroke, as well as the recent prior failed trials. We will examine the implications of these data for neurointerventionists, both for current practice and for future studies. In particular, we will focus on procedural details such as patient selection, devices, adjunctive therapies, treatment time windows, and performance metrics.

Background

Approximately 20 years ago, the National Institute of Neurological Disorders and Stroke trial proved the benefit of intravenous tissue-type plasminogen activator (tPA) given within 3 hours of symptom onset for patients with ischemic stroke.1 These data, as well as the results from other large trials, including the European Cooperative Acute Stroke Studies (ECASS) extended the window to 4.5 hours and revolutionized stroke care worldwide.2,3 Patients with large vessel occlusions had lower rates of early recanalization and worse outcomes with intravenous tPA compared with patients without large vessel occlusion.4,5 These observations provided the impetus to develop alternative treatments for these patients, including direct infusion of fibrinolytic agents and development of a clot retrieval device.6–8 Pivotal trials based on these early technologies were concluded in 2013 and failed to find an added benefit for catheter-based intervention over intravenous tPA alone or in combination with EVT.9–11

The path was clear after these trials, however.12,13 First, in Interventional Management of Stroke III (IMS III), no imaging screen for large vessel occlusion was used in nearly half of the enrolled patients, leading to the inclusion of many patients who were not candidates for intervention.14 The more recent trials have benefited from wide availability of computed tomographic angiography (CTA). Second, revascularization rates were extremely poor in the failed trials. The past 5 years has seen dramatic improvement in technology, with stentriever and distal access/suction catheters, often in combination, that have provided extremely high revascularization rates.15–17 Finally, the failed trials had long times to revascularization.18 This was largely because of the relative ineffectiveness of early generation endovascular devices and intra-arterial lytic infusion. A strong inverse relationship with outcome and time to reperfusion was found.19

The 3 recently published trials Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands (MR CLEAN),20 Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion With Emphasis on Minimizing CT to Recanalization Times (ESCAPE),21 and Extending the Time for Thrombolysis on Emergency Neurological Deficits (EXTEND-IA),22 the presented but as yet unpublished trial, Solitaire With the Intention for Thrombectomy as Primary Endovascular Treatment for Acute Ischemic Stroke (SWIFT PRIME) and the recent announcement that the French trial Trial and Cost Effectiveness on Evaluation of Intra-Arterial Thrombectomy in Acute Ischemic Stroke (THRACE) was prematurely halted after intermediate analysis showing a positive result, represent dramatic improvement on all 3 of these fronts. These trials all differed in some respects, and a careful analysis of their design, performance, and outcomes is required to translate their findings into practice.
Trial Designs and Protocols

Inclusion/Exclusion Criteria

The trials analyzed in this article were all randomized controlled trials comparing EVT, with intravenous tPA if eligible in all but 1 trial, with medical treatment alone in the management of patients with acute ischemic stroke. Upper age limit ranged from 80 to no limit (Table 1). Baseline National Institutes of Health Stroke Scale (NIHSS) score was variable (Table 1). In all but 2 trials (IMS III and Intra-Arterial Versus Systemic Thrombolysis for Acute Ischemic Stroke [SYNTHESIS]), vascular imaging (CTA or magnetic resonance angiography [MRA]) was used to select patients with large vessel occlusion in the anterior circulation (Table 1). In IMS III, vascular imaging was required after a later protocol amendment.

Intravenous tPA

All but 1 trial (SYNTHESIS) compared EVT plus intravenous recombinant tPA (rt-PA) to intravenous rt-PA alone, if eligible for intravenous tPA (Tables 1 and 2). In most trials (Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy [MR RESCUE], MR CLEAN, ESCAPE, EXTEND-IA, and SWIFT PRIME), patients received standard intravenous rt-PA dose (0.9 mg/kg) ≤ 4.5 hours after the onset of symptoms of acute ischemic stroke. In IMS III, intravenous rt-PA was limited to within 3 hours after symptom onset (also in medical treatment group). Initially the dose was reduced in EVT group to 0.6 mg/kg, but was increased to 0.9 mg/kg after protocol amendment.

In most trials with combination of intravenous rt-PA with EVT, intravenous treatment was started before randomization. In IMS III randomization was accomplished before completion of 40 minutes of the intravenous rt-PA infusion, whereas in MR RESCUE, MR CLEAN, ESCAPE, and SWIFT PRIME patients were eligible if MRA or CTA before or after intravenous treatment showed a persistent target occlusion. In EXTEND-IA, patients were randomized as soon as the inclusion criteria were fulfilled including patients eligible for intravenous rt-PA and large vessel occlusion on CTA or MRA.

Time Window for EVT

The time window for starting EVT after symptom onset ranged from within 5 hours (IMS III with completion of EVT within 7 hours of symptom onset) to within 6 hours (delay for completion of EVT in SYNTHESIS and MR CLEAN and delay from symptom onset to groin puncture in EXTEND-IA and SWIFT PRIME), and within 8 hours (MR RESCUE). In ESCAPE, patients were eligible if symptom onset was within 12 hours.

Exclusions for Core Infarction

Large or moderate/large infarct core was an exclusion criterion in IMS III (defined as more than one-third of the middle cerebral artery territory hypodensity on baseline CT or Alberta Stroke Program Early CT Score [ASPECTS] ≤ 24), ESCAPE, and SWIFT PRIME (defined as ASPECTS < 6 on CT). In EXTEND-IA, the presence of a mismatch on CT or MR was an imaging selection criteria. In MR RESCUE, patients were stratified according to the presence or absence of a favorable penumbral pattern. The status of collateral circulation was used as a selection criterion in ESCAPE, moderate-to-good collateral circulation being defined as the filling of ≥50% of the middle cerebral artery pial arterial circulation on delayed CTA images.

Devices

In 2 negative trials (IMS III and SYNTHESIS), all endovascular techniques were authorized as in a more recent positive trial (MR CLEAN; Table 1). In 2 others (MR RESCUE and ESCAPE), thrombectomy devices were used with a strong recommendation for using stent-retrievers in ESCAPE. Finally in both EXTEND-IA and SWIFT PRIME the stent-retriever Solitaire was the only device that can be used for EVT. The types of guide catheters (including balloon catheters) or distal access/suction catheters used in support of stent-retrievers were not specified or reported for any of these studies.

Table 1. Key Protocol Issues

<table>
<thead>
<tr>
<th>Trial</th>
<th>Age, y</th>
<th>Delay*</th>
<th>NIHSS</th>
<th>rt-PA in EVT† Group</th>
<th>CTA/MRA</th>
<th>EVT†</th>
</tr>
</thead>
<tbody>
<tr>
<td>IMS III</td>
<td>18–82</td>
<td>5 h</td>
<td>≥10</td>
<td>+</td>
<td>Amendment</td>
<td>All</td>
</tr>
<tr>
<td>SYNTHESIS</td>
<td>18–80</td>
<td>6 h</td>
<td>≤25</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>MR RESCUE</td>
<td>18–85</td>
<td>8 h</td>
<td>6–29</td>
<td>+</td>
<td>+</td>
<td>Thrombectomy device</td>
</tr>
<tr>
<td>MR CLEAN</td>
<td>≥18</td>
<td>6 h</td>
<td>≥2</td>
<td>+</td>
<td>+</td>
<td>All</td>
</tr>
<tr>
<td>ESCAPE</td>
<td>≥18</td>
<td>12 h</td>
<td>&gt;5</td>
<td>+</td>
<td>+</td>
<td>Thrombectomy device</td>
</tr>
<tr>
<td>EXTEND IA</td>
<td>≥18</td>
<td>6 h</td>
<td>−</td>
<td>+</td>
<td>+</td>
<td>Solitaire</td>
</tr>
<tr>
<td>SWIFT PRIME</td>
<td>18–80</td>
<td>6 h</td>
<td>8–29</td>
<td>+</td>
<td>+</td>
<td>Solitaire</td>
</tr>
</tbody>
</table>

CTA indicates computed tomographic angiography; ESCAPE, Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion With Emphasis on Minimizing CT to Recanalization Times; EVT, endovascular treatment; EXTEND IA, Extending the Time for Thrombolysis on Emergency Neurological Deficits; IMS III, Interventional Management of Stroke III; MRA, magnetic resonance angiography; MR CLEAN, Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands; MR RESCUE, Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy; NIHSS, National Institutes of Health Stroke Scale; rt-PA, recombinant tissue-type plasminogen activator; SWIFT PRIME, Solitaire With the Intention for Thrombectomy as Primary Endovascular Treatment for Acute Ischemic Stroke; and SYNTHESIS, Intra-Arterial Versus Systemic Thrombolysis for Acute Ischemic Stroke.

*Maximum delay for initiation of IA therapy.
†Endovascular treatment.
Patient Characteristics and Performance Metrics

Details of basic demographic information and time course of study interventions are show in Tables 2 and 3, respectively. Mean age was similar across the trials. As dictated by their protocols, all EVT patients in IMS III, SWIFT PRIME, and EXTEND IA received intravenous tPA. The large majority of patients in ESCAPE and MR CLEAN were treated with intravenous tPA. MR CLEAN and ESCAPE allowed patients with carotid occlusion. In MR CLEAN, 12.7% of patients underwent carotid stenting at the time of EVT. This was discouraged in ESCAPE and the rate of intervention was not reported.

With the exception of the late-window MR RESCUE study, there was remarkable similarity in the time between symptom onset and groin access (Table 3). Most of the studies achieved a median onset to groin time of <4 hours. Time to clot access or first stentriever deployment was similar as well, ≈30 minutes. Time to thrombolysis in cerebral infarction 2B/3 or procedure end was not uniformly reported. The rate of thrombolysis in cerebral infarction 2B/3 increased dramatically during the time frame of these studies, from 44% with IMS III to >80% with studies using stent-retrievers.

Outcomes

The first 3 randomized trials (IMS III, SYNTHESIS, and MR RESCUE) were negative showing no better clinical outcome at 3 months in the EVT group compared with the control group (Table 4). In the most recent trials (MR CLEAN, ESCAPE, EXTEND-IA, and SWIFT PRIME), clinical outcome at 3 months was better in EVT group. All trials, except SYNTHESIS, included patients with a similar clinical severity with a median (or mean) NIHSS around 16 and 17. The 2 main differences between the positive and negative trials were (1) the mandatory use of CTA or MRA for the demonstration of a large vessel occlusion by CTA or MRA (except MR RESCUE, but this trial had a complex design with randomization in 4

Table 2. Baseline Characteristics

<table>
<thead>
<tr>
<th>Trial</th>
<th>Patients (n)</th>
<th>Mean Age, y</th>
<th>NIHSS (Median)</th>
<th>r-tPA, %</th>
<th>M1 Occl., %</th>
<th>Cervical ICA Stenosis/Occlusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>IMS III</td>
<td>434</td>
<td>69*</td>
<td>17</td>
<td>100.0</td>
<td>31.1</td>
<td>NS</td>
</tr>
<tr>
<td>SYNTHESIS</td>
<td>181</td>
<td>66</td>
<td>13</td>
<td>0.0</td>
<td>…</td>
<td>NS</td>
</tr>
<tr>
<td>MR RESCUE</td>
<td>64</td>
<td>65.5</td>
<td>16–19†</td>
<td>43.8</td>
<td>60.9</td>
<td>NS</td>
</tr>
<tr>
<td>MR CLEAN</td>
<td>233</td>
<td>65</td>
<td>17</td>
<td>87.1</td>
<td>66.1</td>
<td>12.9% stented</td>
</tr>
<tr>
<td>ESCAPE</td>
<td>165</td>
<td>71</td>
<td>16</td>
<td>72.7</td>
<td>68.1</td>
<td>12.7</td>
</tr>
<tr>
<td>EXTEND IA</td>
<td>35</td>
<td>68.6</td>
<td>17</td>
<td>100.0</td>
<td>57.1</td>
<td>0</td>
</tr>
<tr>
<td>SWIFT PRIME</td>
<td>98</td>
<td>65.0</td>
<td>17</td>
<td>100.0</td>
<td>67.7</td>
<td>0</td>
</tr>
</tbody>
</table>

ESCAPE indicates Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion With Emphasis on Minimizing CT to Recanalization Times; EXTEND IA, Extending the Time for Thrombolysis on Emergency Neurological Deficits; ICA, internal carotid artery; IMS III, Interventional Management of Stroke III; MR CLEAN, Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands; MR RESCUE, Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy; NIHSS, National Institutes of Health Stroke Scale; r-tPA, recombinant tissue-type plasminogen activator; SWIFT PRIME, Solitaire With the Intention for Thrombectomy as Primary Endovascular Treatment for Acute Ischemic Stroke; and SYNTHESIS, Intra-Arterial Versus Systemic Thrombolysis for Acute Ischemic Stroke.

*Median.
†Penumbral and nonpenumbral groups, respectively.

Table 3. Time and Performance Metrics

<table>
<thead>
<tr>
<th>Trial</th>
<th>Onset to IV tPA Start</th>
<th>IV Start to Groin</th>
<th>Onset to Groin</th>
<th>Groin to First Deployment</th>
<th>Onset to First Deployment/Clot</th>
<th>Onset to Final Reperfusion (Total)</th>
<th>TICI 2b/3</th>
<th>Stent-Retriever, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>IMS III</td>
<td>111</td>
<td>85</td>
<td>196</td>
<td>39</td>
<td>235</td>
<td>316.5 (%)</td>
<td>1.5</td>
<td>1.5</td>
</tr>
<tr>
<td>SYNTHESIS</td>
<td>NA</td>
<td>NA</td>
<td>225</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>23–44*</td>
<td>10.9</td>
</tr>
<tr>
<td>MR RESCUE</td>
<td>NR</td>
<td>NR</td>
<td>330 (onset to enrollment)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>…</td>
<td>0.0</td>
</tr>
<tr>
<td>MR CLEAN</td>
<td>85</td>
<td>175</td>
<td>260</td>
<td>30.0</td>
<td>290</td>
<td>325.8</td>
<td>67†</td>
<td>97.4</td>
</tr>
<tr>
<td>ESCAPE</td>
<td>110</td>
<td>98</td>
<td>208</td>
<td>33.0</td>
<td>241</td>
<td>NR</td>
<td>59</td>
<td>86.1</td>
</tr>
<tr>
<td>EXTEND IA</td>
<td>136</td>
<td>74</td>
<td>210</td>
<td>43.0 (final reperfusion)</td>
<td>253</td>
<td>253</td>
<td>72</td>
<td>100.0</td>
</tr>
<tr>
<td>SWIFT PRIME</td>
<td>110.5</td>
<td>112.5</td>
<td>223</td>
<td>29.0</td>
<td>252</td>
<td>NR</td>
<td>86</td>
<td>100.0</td>
</tr>
</tbody>
</table>

ESCAPE indicates Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion With Emphasis on Minimizing CT to Recanalization Times; EXTEND IA, Extending the Time for Thrombolysis on Emergency Neurological Deficits; IMS III, Interventional Management of Stroke III; IV t-PA, intravenous tissue-type plasminogen activator; MR CLEAN, Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands; MR RESCUE, Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy; NA, not applicable; NR, not reported; SWIFT PRIME, Solitaire With the Intention for Thrombectomy as Primary Endovascular Treatment for Acute Ischemic Stroke; SYNTHESIS, Intra-Arterial Versus Systemic Thrombolysis for Acute Ischemic Stroke; and TICI, thrombolysis in cerebral infarction.

*A total of 38% for an occlusion in the internal carotid artery, 44% for an occlusion in M1, 44% for a single M2 occlusion, and 23% for multiple M2 occlusions.
†2a and 2b/3.
groups and included a limited number of patients) and (2) the use of latest generation devices (stent-retrievers) mandatory in EXTEND-IA, SWIFT PRIME, recommended (ESCAPE) and widely used in MR CLEAN. In ESCAPE and MR CLEAN EVT stent-retrievers were used in 86.1% and 97.4% cases, respectively.

The rate of good clinical outcome in the positive trials was lower in MR CLEAN (32.6%) than in other positive trials (ESCAPE, 53.0%; EXTEND-IA, 71.4%; and SWIFT PRIME, 60.2%). Also, in terms of good clinical outcome (mRS, 0–2), the benefit (in absolute value) of EVT compared with intravenous r-tPA alone is high in all trials (23.7% in ESCAPE, 31.4% in EXTEND-IA, and 24.7% in SWIFT PRIME) compared with MR CLEAN (13.5%). The same phenomenon is observed for mortality. About mortality, all trials except ESCAPE showed no significant differences between EVT and medical groups. In EXTEND-IA (small study population: 70 in total), the mortality rate was not significantly higher in intravenous r-tPA group (20%) than in EVT group (9%). In ESCAPE, mortality rate was significantly (P=0.04) lower in EVT group (10.4%) versus medical group (19.0%). Except in SYNTHESIS that included patient with a lower median NIHSS (13), mortality was relatively homogeneous in the medical arm from the different trials (12.4%–24.1% with a majority of trials around 20%). Inversely in EVT arms, 2 trial groups can be identified (excluding SYNTHESIS): 1 group with high mortality around 20% (IMS III, 20.0%; MR RESCUE, 18.8%; and MR CLEAN, 21%) and 1 group with lower mortality (ESCAPE, 10.4%; EXTEND-IA, 8.6%; and SWIFT PRIME, 9.2%). The high mortality in MR CLEAN is probably related to the broad inclusion criteria of MR CLEAN with relatively limited exclusion criteria and also to the relatively long delay for EVT (median time from stroke onset to groin puncture, 260 minutes).

**Subgroup Analyses**

Given the small number of patients included, no subgroup analysis was conducted in EXTEND-IA. In the other positive trials, subgroup analyses were performed. These subgroup analyses were prespecified, but the numbers of patients in some of these analyses are small, limiting the strength of the conclusions that may be drawn from them.

**Sex and Age**

In both ESCAPE and SWIFT PRIME, the positive effect of mechanical thrombectomy was similar in men and women. The value of mechanical thrombectomy according to age was differently evaluated in SWIFT PRIME with a cutoff at 70 years and in MR CLEAN and ESCAPE with a cutoff at 80. In all trials, the benefit of mechanical thrombectomy was observed, irrespective of the age. Noticeably, the odds ratio (OR) was higher for patients with age ≥80 years in MR CLEAN (3.24 versus 1.60 for patients <80 years). In other trials, OR was relatively similar, irrespective of the age. According to these results, it seems that there is no contraindication for mechanical thrombectomy in elderly patients. It should be noted, however, that all trials excluded patients with baseline functional impairment (mRS <2).

**NIHSS and ASPECTS**

Different NIHSS subgroups were analyzed in the trials (2–15, 16–19, and ≥20 in MR CLEAN, 6–19 and >19 in ESCAPE, and ≤17 and >17 in SWIFT PRIME). In all trials, OR favored mechanical thrombectomy, irrespective of the NIHSS group. In both ESCAPE and SWIFT PRIME, OR was similar in ASPECTS subgroup (which were similar in both trials: 6–7 and 8–10). In MR CLEAN that included patients irrespective of their ASPECTS, OR favored mechanical thrombectomy in subgroups 5 to 7 and 8 to 10 (1.97 and 1.61, respectively), but not in subgroup 0 to 4 (OR, 1.09), suggesting that mechanical thrombectomy has less or no efficacy in patients with large ischemic core.

**Occlusion Location**

The impact of occlusion location was evaluated differently from one trial to another. In MR CLEAN, the benefit of mechanical thrombectomy was higher when internal carotid artery (ICA) terminus occlusion was present (OR, 2.43 versus 1.61 when absent). In ESCAPE, OR showed a similar benefit of mechanical thrombectomy, irrespective of the occlusion (OR, 2.6 for ICA+M1 and 2.7 for M1 or all M2). In SWIFT PRIME, the benefit for M2 was slightly lower (OR, 1.75) compared with ICA/carotid T (OR, 2.96) and M1 (OR, 3.11).

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**Table 4. Outcome**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Good Outcome* EVT, %</th>
<th>Good Outcome* Control, %</th>
<th>Absolute Difference, %</th>
<th>Death EVT, %</th>
<th>Death Control, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>IMS III</td>
<td>40.8</td>
<td>38.7</td>
<td>2.1</td>
<td>20.0</td>
<td>22.4</td>
</tr>
<tr>
<td>SYNTHESIS</td>
<td>42.0</td>
<td>46.4</td>
<td>−4.4</td>
<td>7.7</td>
<td>6.1</td>
</tr>
<tr>
<td>MR RESCUE</td>
<td>18.8</td>
<td>20.4</td>
<td>−1.6</td>
<td>18.8</td>
<td>24.1</td>
</tr>
<tr>
<td>MR CLEAN</td>
<td>32.6</td>
<td>19.1</td>
<td>13.5</td>
<td>21</td>
<td>22</td>
</tr>
<tr>
<td>ESCAPE</td>
<td>53.0</td>
<td>29.3</td>
<td>23.7</td>
<td>10.4</td>
<td>19.0</td>
</tr>
<tr>
<td>EXTEND IA</td>
<td>71.4</td>
<td>40.0</td>
<td>31.4</td>
<td>8.6</td>
<td>20.0</td>
</tr>
<tr>
<td>SWIFT PRIME</td>
<td>60.2</td>
<td>35.5</td>
<td>24.7</td>
<td>9.2</td>
<td>12.4</td>
</tr>
</tbody>
</table>

ESCAPE indicates Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion With Emphasis on Minimizing CT to Recanalization Times; EVT, endovascular treatment; EXTEND IA, Extending the Time for Thrombolysis on Emergency Neurological Deficits; IMS III, Interventional Management of Stroke III; IV t-PA, intravenous tissue-type plasminogen activator; MR CLEAN, Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands; MR RESCUE, Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy; SWIFT PRIME, Solitaire With the Intention for Thrombectomy as Primary Endovascular Treatment for Acute Ischemic Stroke; and SYNTHESIS, Intra-Arterial Versus Systemic Thrombolysis for Acute Ischemic Stroke.

*Modified Rankin Scale 0–2 at 90 days.
Extracranial Carotid Occlusion

Of note, there was still a benefit of mechanical thrombectomy in MR CLEAN when extracranial ICA occlusion was present (OR, 1.43 versus 1.85 when absent) and in ESCAPE OR favoring mechanical thrombectomy was higher when cervical carotid artery occlusion was present (OR, 9.6 versus 2.2 when absent), but the number of patients with cervical carotid occlusion was low (40/315).

Time to EVT

Influence of treatment delay was analyzed in MR CLEAN, ESCAPE, and SWIFT PRIME with the time from onset to randomization with different cutoff value (120, 180, and 188.5 minutes, respectively). In all trials, OR favoring mechanical thrombectomy was similar in both groups. In ESCAPE, where inclusions were possible in a large time window (<12 hours), the number of patients included between 6 and 12 hours is low (49 patients; 15.5%) and analysis of this subgroup is not presented. As mentioned above, many of these patients were wake up strokes.

Intravenous tPA

Finally, in both MR CLEAN and ESCAPE, the OR in favor of mechanical thrombectomy was similar in the subgroups of patients receiving or not receiving intravenous r-tPA. Most of these patients were within the intravenous tPA time window but met medical exclusions for systemic fibrinolysis.

Implications for Current Practice

Eligibility

These data confirm the benefit of early mechanical reperfusion for selected patients with large vessel occlusion and recent ischemic stroke. The strongest evidence is for patients treated with intravenous tPA. Within that group, additional selection criteria should include good functional baseline status, a small completed stroke on baseline CT (ASPECTS >6), and the expectation that the vessel will be opened within 6 hours of symptom onset. There is also good evidence, from MR CLEAN and ESCAPE, for patients who present within the tPA window of 4.5 hours and are ineligible for intravenous tPA for exclusions related to bleeding complications with systemic fibrinolysis. These include recent surgery or anticoagulation within a reasonable range (international normalized ratio <3.0).

Process

As detailed above, these recent trials were positive owing to several important factors related to process improvement and quality. Times to reperfusion were optimized by routine CTA acquisition soon after presentation. Door-to-groin and groin-to-reperfusion times were generally outstanding. Median symptom onset-to-groin times were generally 4 hours. These trials achieved these targets both by working hard to optimize their processes and also by not enrolling patients when it was clear that they would have delays.

Devices/Procedure

IMS III had similar performance metrics as the recent positive trials in all but 1 area: reperfusion rates and time to reperfusion. The data from these trials demonstrate the dramatic technological improvement using Stentrieviers. Although the majority of this is attributable to the use of stentrieviers, some benefit is certainly related to advances guide catheter and distal access/suction catheter technology.

Better results are obtained with stentrieviers if a balloon guide catheter is used rather than a large bore guide catheter in the cervical carotid. This likely limits fragmentation and clot loss during the pull. Nontarget embolization occurred in 5.6% of treated patients in MR CLEAN. In addition, the introduction of large bore suction catheters that can be placed into the origin of the middle cerebral artery also seems to improve recanalization rates. The advantages of this relate to a straight pull of the stentriever into the suction catheter rather than an oblique force pulling the stentriever down into the carotid siphon. In addition, there is less potential loss of clot with a shorter distance into the catheter. Finally, excellent recanalization rates have been reported using suction catheters alone. In summary, these trials were successful because reperfusion was achieved quickly and with high reperfusion rates. Interventionists need to closely monitor these metrics in their own practice to ensure that they are achieving similar performance.

Systems of Care/Implementation

EVT now needs to be implemented into existing systems of care. The organization of primary and comprehensive stroke centers (CSCs) was done with the concept of triage and transfer in mind, analogous to trauma systems. Primary stroke centers will need to develop protocols for the rapid identification (CTA) and transfer of potential EVT patients with CSCs. CSCs will need to develop system-wide networks and internal mechanisms to accommodate rapid transfer. The current supply of neurointerventionists has been projected to be sufficient to provide coverage in the United States. Estimates of manpower needs suggest that a total of 200 to 300 CSCs with at least 3 neurointerventionists on staff will be sufficient to meet the needs in North America.

Implications for Future Studies

Subgroups

More information is required for at least 2 populations not completely evaluated in the present studies. Future studies should evaluate the benefit of EVT for patients presenting outside of the 6-hour window. The data from ESCAPE and EXTEND IA are promising that patients with favorable imaging (small core infarctions and significant tissue at risk) may benefit. This is particularly relevant for intravenous-treated patients who are transferred from primary stroke centers and arrive outside the 6-hour window. Another population with limited data is those with larger amounts of dead tissue at baseline. The 1 trial that did not exclude on this basis, MR CLEAN, showed a trend for benefit even in patients with larger strokes.
Process Improvement
Given the strong impact of reperfusion time, studies investigating the potential of new workflows that trade time for imaging screening will be important. These could include taking patients with a high NIHSS straight to the interventional suite without a CTA. Another emerging workflow involves using the angiosuite as the stroke treatment room: flat panel noncontrast head CT and CTA acquisition followed by intravenous or intravenous/EVT treatment. The use of emergency medical service stroke severity scores to triage patients directly to CSCs should be explored.

New Devices/Technique
Future device and technical development will also be important. We do not have good information on the best method for stentretriever use, and that method may be different for different anatomy (eg, carotid terminus versus distal M1). The present studies provide performance benchmarks for reperfusion rates and times, as well as rates of nontarget embozization. These will all be important technical end points for clinical trials evaluating new devices and methods. For example, randomized studies of balloon guidecatheters versus distal access catheters for stentretrievers should be pursued using the technical end points mentioned above: reperfusion rates, times to reperfusion, and rates of nontarget embozilization. Newer clot retrieval devices will need to be tested in randomized trials against current stentretrievers. The optimal strategy for treating carotid stenosis or occlusion remains to be defined.

The use of general anesthesia seems to be associated with poorer outcomes in stroke intervention. According to the bias encountered in most series, further trials (including randomized) are certainly necessary to evaluate carefully the anesthetic conditions in which mechanical thrombectomy has to be performed.

Pharmacological Adjunctives
Finally, the success of these trials now opens up the opportunity (literally) for the evaluation of pharmacological adjuncts for better reperfusion and neuroprotection. Methods that may mitigate secondary or reperfusion injury can now be tested in a group of patients with well-defined times of reperfusion. Close to half of treated patients in these trials failed to regain independent functional status.

Reimbursement
More data on costs of care for EVT patients needs to be acquired, to determine whether hospital reimbursement and physician fees should change.

Conclusions
EVT with stent-retrievers is now proven effective and is dramatically so, for a well-defined subset of patients with acute ischemic stroke. Current practice needs to incorporate the lessons from the recent trials: careful patient selection and optimizing time to reperfusion and reperfusion rate are critical to providing any benefit to our patients.

Addendum
Since the acceptance of this article, the SWIFT PRIME results referenced as an oral presentation have been published. In addition 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), a 5th positive trial was published. The published results from these two studies do not result in any changes to the content or conclusions of this article.

Disclosures
Dr Pierot has served as a consultant for Blockade, Codman, Covidiem/EV3, Microvention, and Sequent. Dr Derdeyn has served as a consultant for Penumbra (3D separator trial DSMB), Microvention (LVIS trial angio core laboratory), and Silk Road (Roadster trial DSMB). He has equity in Pulse Therapeutics.

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