Evolution of Practice During the Interventional Management of Stroke III Trial and Implications for Ongoing Trials

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Background and Purpose—We explored changes in the patient population and practice of endovascular therapy during the course of the Interventional Management of Stroke (IMS) III Trial.

Methods—Changes in baseline characteristics, use of baseline CT angiography, treatment times and specifics, and outcomes were compared between the first 4 protocols and the fifth and final protocol.

Results—Compared with subjects treated in the first 4 protocol versions (n=610), subjects treated in fifth and final protocol (n=46) were older (75 versus 68 years, \(P<0.0002\)) and less likely to have a pretreatment Rankin of 0 (76% versus 89%, \(P=0.009\)), had quicker median times in the endovascular arm from onset to start of intra-arterial therapy (209 versus 250 minutes, \(P=0.002\)) and to reperfusion (269 versus 344 minutes, \(P<0.0001\)), had a higher mean dose of total tissue-type plasminogen activator in the endovascular arm (74.0 versus 63.7 mg, \(P<0.0001\)), and were less likely to receive intra-arterial tissue-type plasminogen activator as part of the endovascular procedure (16% versus 44%, \(P=0.015\)). There were no significant differences in functional and safety outcomes between subjects treated in the 2 treatments arms in either the first 4 protocols or fifth protocol although the small sample size in the fifth protocol provided limited power.

Conclusions—Endovascular technology and diagnostic approaches to acute stroke patients changed substantially during the IMS III Trial. Efforts to decrease the time to delivery of endovascular therapy were successful. (Stroke. 2014;45:3606-3611.)

Key Words: clinical trial ■ therapeutic thrombolysis ■ tissue-type plasminogen activator

The Interventional Management of Stroke (IMS) III Trial was a phase III, randomized, international trial designed to test the approach of intravenous (IV) tissue-type plasminogen activator (tPA) followed by protocol-approved endovascular treatment compared with IV tPA alone for the treatment of acute ischemic stroke.1 At the beginning of the trial, intra-arterial (IA) tPA was the standard of practice for endovascular therapy, and the only US Food and Drug Administration (FDA)-cleared thrombectomy device was still undergoing National Institutes of Health (NIH)-funded research evaluation.2-4 The Trial leadership recognized that endovascular technology would continue to improve and evolve. To keep the trial clinically relevant and to provide the best opportunity for the endovascular approach to be successful, the trial

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allowed for the inclusion of additional devices as they became cleared for clinical use by the FDA and the regulatory authorities of participating countries, as well as approved by the IMS III Trial Executive Committee.

CT angiography (CTA) was used sparingly when the trial was first submitted for review, and thus, we did not require CTA before treatment with IV tPA. The use of a National Institutes of Health Stroke Scale (NIHSS) score of 10 or more had been demonstrated in prior studies to be associated with a high likelihood of an intracranial occlusion at intracerebral angiography after IV tPA.6–8 CTA use dramatically increased at IMS III centers during the course of the trial, prompting us to incorporate its use into the design of the trial; however, it was not required because about half of the centers still did not use CTA as standard of care in the later years of the trial.

The paradigm of IV tPA followed by endovascular therapy had been tested in Emergency Management of Stroke (EMS), IMS I and II Trials using an IV dose of 0.6 mg/kg of tPA before endovascular therapy.6–8 This kept the total tPA dose for a given patient near the dose demonstrated to be safe and efficacious in the National Institute of Neurologic Diseases and Stroke (NINDS) tPA Stroke Trial and European Cooperative Acute Stroke (ECASS) II Trial. At the time, there was limited published safety data about the use of the standard 0.9 mg/kg dose of IV tPA in patients who subsequently were treated with IA tPA. These data became available as the use of standard dose IV tPA before endovascular therapy became increasingly common as part of endovascular therapy in the larger stroke community as IMS III progressed.11

Finally, limiting the time to treatment with IV tPA and time to start of endovascular therapy were major goals of the trial. However, the drip and ship paradigm at some of our centers substantially increased the time from onset to endovascular therapy.

Thus, at the time when IMS III was stopped for futility in April 2012, the study protocol had changed significantly from its beginning in 2005, which mirrored changes in endovascular practice worldwide. Subjects treated as part of the fifth protocol were similar in many ways to subjects treated in the currently ongoing randomized trials of endovascular therapy. The goals of these analyses were to document the changes in the patient population and practice of endovascular therapy during the course of the trial and to examine treatment responses in patients treated in the first 4 protocol versions compared with those in the fifth protocol. Our hypothesis was that substantial changes had occurred between the original trial protocol and the final protocol version and that these changes may be associated with differences in treatment response.

Table 2. Baseline Characteristics, Treatment Times, and Type of Endovascular Treatment in Protocols 1 to 4 vs Protocol 5

<table>
<thead>
<tr>
<th>Protocol</th>
<th>n</th>
<th>%</th>
<th>Treatment Arm</th>
<th>Endovascular</th>
<th>IV tPA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protocols 1–4</td>
<td>610</td>
<td>222</td>
<td>All randomized</td>
<td>434</td>
<td>100.00</td>
</tr>
<tr>
<td>Protocols 1–4</td>
<td>610</td>
<td>122</td>
<td>Randomized under protocol amendment</td>
<td>123</td>
<td>28.34</td>
</tr>
<tr>
<td>Protocols 1–4</td>
<td>610</td>
<td>63</td>
<td>Amendment 1: August 2007</td>
<td>67</td>
<td>15.44</td>
</tr>
<tr>
<td>Protocols 1–4</td>
<td>610</td>
<td>31</td>
<td>Amendment 1: August 2007</td>
<td>67</td>
<td>15.44</td>
</tr>
<tr>
<td>Protocols 1–4</td>
<td>610</td>
<td>54</td>
<td>Amendment 2: January 2009</td>
<td>54</td>
<td>12.44</td>
</tr>
<tr>
<td>Protocols 1–4</td>
<td>610</td>
<td>27</td>
<td>Amendment 2: January 2009</td>
<td>54</td>
<td>12.44</td>
</tr>
<tr>
<td>Protocols 1–4</td>
<td>610</td>
<td>164</td>
<td>Amendment 3: June 2009</td>
<td>164</td>
<td>37.79</td>
</tr>
<tr>
<td>Protocols 1–4</td>
<td>610</td>
<td>81</td>
<td>Amendment 3: June 2009</td>
<td>164</td>
<td>37.79</td>
</tr>
<tr>
<td>Protocols 1–4</td>
<td>610</td>
<td>26</td>
<td>Amendment 4: June 2011</td>
<td>26</td>
<td>5.99</td>
</tr>
<tr>
<td>Protocols 1–4</td>
<td>610</td>
<td>20</td>
<td>Amendment 4: June 2011</td>
<td>26</td>
<td>5.99</td>
</tr>
<tr>
<td>Protocols 5</td>
<td>46</td>
<td>44</td>
<td>Use of IA tPA alone for endovascular therapy</td>
<td>44</td>
<td>16.5</td>
</tr>
</tbody>
</table>


tPA indicates tissue-type plasminogen activator.

CTA indicates CT angiography; IA, intra-arterial; IMS, Interventional Management of Stroke; IV, intravenous; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; and tPA, tissue-type plasminogen activator.

Table 1. IMS III Trial Original Protocol and 4 Subsequent Protocol Amendments

<table>
<thead>
<tr>
<th>Treatment Arm</th>
<th>n</th>
<th>%</th>
<th>Pretreatment modified Rankin Scale of 0, %</th>
<th>0.08</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protocols 1–4</td>
<td>610</td>
<td>35</td>
<td>Current statin use, %</td>
<td>8.08</td>
</tr>
<tr>
<td>Protocols 1–4</td>
<td>610</td>
<td>76</td>
<td>Total dose of IV and IA tPA in endovascular arm, mg, mean (SD)</td>
<td>74.0 (14.6)</td>
</tr>
<tr>
<td>Protocols 1–4</td>
<td>610</td>
<td>114</td>
<td>Time from stroke onset to IV tPA initiation, min, median (range)</td>
<td>120 (25–200)</td>
</tr>
<tr>
<td>Protocols 1–4</td>
<td>610</td>
<td>209</td>
<td>Time from stroke onset to start of endovascular therapy, min, median (range)</td>
<td>250 (135–430)</td>
</tr>
<tr>
<td>Protocols 1–4</td>
<td>610</td>
<td>269</td>
<td>Time from stroke onset to last angiography, min, median (range)</td>
<td>344 (144–481)</td>
</tr>
<tr>
<td>Protocols 1–4</td>
<td>610</td>
<td>20</td>
<td>Drip-and-ship/ship-and-drip in endovascular arm, %</td>
<td>0.61</td>
</tr>
<tr>
<td>Protocols 1–4</td>
<td>610</td>
<td>16</td>
<td>Use of IA tPA alone for endovascular therapy, %</td>
<td>0.015</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Protocol</th>
<th>n</th>
<th>%</th>
<th>Pretreatment modified Rankin Scale of 0, %</th>
<th>0.08</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protocol 5</td>
<td>46</td>
<td>48</td>
<td>Current statin use, %</td>
<td>8.08</td>
</tr>
<tr>
<td>Protocol 5</td>
<td>46</td>
<td>74.0 (14.6)</td>
<td>Total dose of IV and IA tPA in endovascular arm, mg, mean (SD)</td>
<td>74.0 (14.6)</td>
</tr>
</tbody>
</table>
Methods

The methodology of the IMS III Trial has been previously reported.1,12 There were 4 amendments to the Trial after the initial protocol. We have labeled these protocols 1 to 5 throughout the article. Table 1 lists the original protocol and subsequent 4 protocol amendments, the respective changes in the trial conduct, and the number of subjects enrolled under each protocol version. Time from onset to groin puncture was considered time to start of endovascular therapy. Time from onset to time of last angiographic image was used to represent time to reperfusion.

We compared the changes in baseline subject characteristics, treatment times, use of CTA, and outcomes between the 2 treatment arms by protocol version. Subjects treated as part of the fifth and final protocol were compared statistically to subjects treated under the first 3 protocols and the fourth and fifth protocol. We also performed a similar comparison for subjects, treated in the 2 treatments arms in either the first 4 protocol versions or protocol 5 (Table 3), although the small sample in protocol 5 provides limited power. Subjects in protocol 5 had numerically greater differences in the percentage of mRS≤2 at 3 months between the endovascular and the IV tPA groups, a higher percentage of procedural complications, and a greater percentage of asymptomatic intracerebral hemorrhages (ICHs). These differences are likely explained, in part, by differences in age and baseline NIHSS as shown in Table 4.

Table 3. Comparison of Outcomes in 2 Treatment Arms Between Protocols 1 to 4 vs Protocol 5

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Protocols 1–4 (n=610)</th>
<th>Percent Difference (99% CI)</th>
<th>Protocol 5 (n=46)</th>
<th>Risk Difference (99% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death within 90 days, endovascular/tPA arms</td>
<td>19%/21%</td>
<td>−2% (−11%, 7%)</td>
<td>19%/30%</td>
<td>−11% (−44%, 22%)</td>
</tr>
<tr>
<td>sICH rate, endovascular/tPA arms</td>
<td>6%/6%</td>
<td>0% (−5%, 5%)</td>
<td>4%/0%</td>
<td>4% (−6%, 14%)</td>
</tr>
<tr>
<td>aSICH rate, endovascular/tPA arms</td>
<td>27%/18%</td>
<td>9% (−1%, 17%)</td>
<td>39%/25%</td>
<td>14% (−22%, 48%)</td>
</tr>
<tr>
<td>Device or procedural complications</td>
<td>15%</td>
<td>na</td>
<td>27%</td>
<td>na</td>
</tr>
<tr>
<td>Reperfusion (TICI 2b/3 by angiogram) in endovascular arm</td>
<td>40%</td>
<td>na</td>
<td>42%</td>
<td>na</td>
</tr>
<tr>
<td>Recanalization (partial or complete) by 24-hr CTA</td>
<td>84%/59%*</td>
<td>25% (7%, 44%)</td>
<td>100%/73%*</td>
<td>27% (−7%, 62%)</td>
</tr>
<tr>
<td>mRS≤2 at 90 days, endovascular/tPA arms</td>
<td>40%/39%</td>
<td>1% (−10%, 12%)</td>
<td>46%/35%</td>
<td>11% (−26%, 48%)</td>
</tr>
</tbody>
</table>

aSICH indicates asymptomatic ICH; ICH, intracerebral hemorrhage; mRS, modified Rankin Scale; na, not applicable; sICH, symptomatic ICH; TICI, Thrombolysis in Cerebral Infarction score; and tPA, tissue-type plasminogen activator.

Comparison of Outcomes in 2 Treatment Arms Between Protocols 1 to 4 vs Protocol 5

Discussion

The IMS III Trial chronicles the rapidly changing practice of the diagnosis and treatment of patients with moderate to severe ischemic stroke who were eligible for IV tPA treatment within 3 hours of onset during the conduct of IMS III from 2005 to 2012. Because we were testing the approach of a pretreatment CTA, had quicker times from onset to start of endovascular therapy and reperfusion in the endovascular arm, had a higher dose of total tPA in the endovascular arm, and were less likely to receive IA tPA as part of the endovascular procedure. The Figure demonstrates changes in use of CTA, use of IA treatment alone, and treatment times over the course of all 5 protocol versions. Of the 26 subjects randomized to the endovascular arm under protocol 5, 5 were treated with the Solitaire stent retriever and 3 were treated with a stent retriever off protocol (2 subjects treated with both Solitaire and Penumbra devices and 1 subject with Trevo stent retriever that was not approved for use in the Trial).

With the exception of recanalization rate differences between the treatment groups observed by the 24-hour CTA in the first 4 protocol versions, there were no significant differences in functional and safety outcomes between subjects treated in the 2 treatments arms in either the first 4 protocol versions or protocol 5 (Table 3), although the small sample in protocol 5 provides limited power. Subjects in protocol 5 had numerically greater differences in the percentage of mRS≤2 at 3 months between the endovascular and the IV tPA groups, a higher percentage of procedural complications, and a greater percentage of asymptomatic intracerebral hemorrhages (ICHs). These differences are likely explained, in part, by differences in age and baseline NIHSS as shown in Table 4. Table 5 illustrates the changes in mRS outcomes across all protocol versions. Table 1 in the online-only Data Supplement details the changes in use of endovascular approaches across the 5 protocol versions. Finally, in the supplemental materials, we compare subjects in protocols 1 to 3 and protocols 4 to 5 as another suggested comparison point between earlier and later parts of the trial (Tables II–IV in the online-only Data Supplement).
Table 4. Comparison of Age and Baseline NIHSS in the 2 Treatment Groups in Protocols 1 to 4 vs Protocol 5

<table>
<thead>
<tr>
<th></th>
<th>Protocols 1–4</th>
<th>Protocol 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (range)</td>
<td>70 (23–89)</td>
<td>74 (39–83)</td>
</tr>
<tr>
<td>Baseline NIHSS, median (range)</td>
<td>17 (7–40)</td>
<td>18 (7–25)</td>
</tr>
</tbody>
</table>

None of the comparisons are statistically significant at α=0.01. IV indicates intravenous; NIHSS, National Institutes of Health Stroke Scale; and tPA, tissue-type plasminogen activator.

Combined IV tPA followed by endovascular therapy, rather than a given device, we were able to add changes in technology as the Trial progressed, although the Trial was stopped prematurely before stent retriever technology could be used except for a handful of patients. The overall Thrombolysis in Cerebral Infarction (TICI) score 2b-3 rates in protocol 5 were still lower than those reported for randomized trials of stent retrievers.13 However, examining changes in baseline variables, processes, and outcomes in relationship to changes in the protocol and practice is informative for the conduct and potential success of ongoing trials.

The choice of endovascular treatment changed substantially during the study. In the first 4 protocol versions, 44% of subjects in the endovascular arm were treated with IA tPA alone compared with only 16% of subjects in protocol 5. Most of this change occurred during protocol 4 (when the Penumbra aspiration system was added) and protocol 5 (when the Solitaire stent retriever was added; Figure). However, the increase in use of mechanical thrombectomy was accompanied by a nonsignificant trend in the increase in device or procedural complications from 15% to 27%. The symptomatic ICH rate for subjects in the endovascular arm in protocol 5 was similar to those in the first 4 protocol versions, whereas the asymptomatic ICH rate was nonsignificantly higher. Despite numerically higher rates of procedural complications in protocol 5, the difference in mRS between the endovascular and the IV tPA arm was 11% in favor of endovascular therapy, although the number of subjects in protocol 5 is small. Much of this difference is likely driven by a lower rate of mRS ≤2 in the IV tPA arm (35%) in protocol 5 compared with the first 4 protocol versions (39%), which reflects differences in age and baseline NIHSS in the IV tPA group (Table 4).

One of the major improvements during the conduct of the trial was the time from stroke onset to initiation of endovascular therapy and time to completion of angiography, which was used as a measure of maximum reperfusion. Time from stroke onset to start of endovascular therapy in IMS III in the early years of the Trial was longer than that in the IMS I and II pilot trials.1,8,10 Thus, improving the time from stroke onset to initiation of endovascular therapy was a major focus of our trial leadership that prompted travel awards to the international stroke meetings to share best practices with other IMS III investigators. In 2010, we also initiated an IMS III guideline of time from start of IV tPA to groin puncture of 90 minutes, which predated subsequent adoption of this time standard at the STAIR VII conference.14 IMS I, II, III, and other endovascular trials clearly demonstrate the strong relationship between the time from stroke onset to reperfusion and a good functional outcome, and the faster times to reperfusion in protocol 5 subjects may have also contributed to better outcomes in the endovascular group.15–18 IMS III demonstrates that attempts to minimize the time to endovascular therapy are achievable and may increase the possibility of positive outcomes in ongoing and future endovascular trials.

The use of pretreatment CTA considerably increased during the conduct of IMS III. Post hoc analyses of treatment effect by location of intracranial arterial occlusion in IMS III demonstrated that endovascular therapy is most likely to be of benefit in patients with occlusions of the terminal ICA with or without MCA occlusions, whereas there was no evidence of benefit in patients with M1 occlusions.19 A post hoc analysis of all patients with a pretreatment CTA-positive occlusion demonstrated a borderline significant benefit in favor of endovascular therapy using an ordinal analysis (P=0.01).19 These data indicate that CTA or other intracranial vascular imaging will be important to assess the best use of endovascular therapy in ongoing trials. Yet, it should be noted that only 65% of subjects in protocol 5 had a pretreatment CTA, indicating that its use, while much more widespread, was not uniform at the completion of the trial, even at tertiary and busy regional centers.

Change in the age criteria was made to help recruitment and to extend generalizability of the Trial. This change resulted in an increase in the age of the study population, as well as a decrease in the percentage of subjects with a pretreatment mRS of 0.

The use of the standard dose IV tPA before endovascular therapy in protocol 5 was not associated with an increase in symptomatic ICH although the number of subjects is small and the proportion of asymptomatic ICH was numerically greater. However, the total mean dose in protocol 5 subjects compared with the first 4 protocol versions was less than expected with the increase in IV tPA dose because the proportion of endovascular subjects who received IA tPA was much

Table 5. Three-Month mRS ≤2 for 2 Treatment Groups in 5 Protocols

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Endovascular</td>
<td>40% (n=123)</td>
<td>36% (n=67)</td>
<td>48% (n=54)</td>
<td>40% (n=164)</td>
<td>46% (n=26)</td>
</tr>
<tr>
<td>IV tPA</td>
<td>43% (n=63)</td>
<td>32% (n=31)</td>
<td>30% (n=27)</td>
<td>42% (n=81)</td>
<td>35% (n=20)</td>
</tr>
<tr>
<td>Overall</td>
<td>41% (n=186)</td>
<td>35% (n=98)</td>
<td>42% (n=81)</td>
<td>41% (n=245)</td>
<td>41% (n=46)</td>
</tr>
</tbody>
</table>

n in the parenthesis are the denominators; missing or out of window cases are imputed with mRS>2. IV indicates intravenous; mRS, modified Rankin Scale; and tPA, tissue-type plasminogen activator.
less. Given the use of current technology that minimizes use of IA tPA and the safety data in IMS III and earlier studies, use of the standard IV tPA dose before endovascular therapy seems safe.

Even general management and treatments that are not specified in the trial design can change during the course of a treatment trial. Statin use increased from 35% in the first 4 protocols versions to 48% in protocol 5 although this difference was not statistically significant. This likely reflects the increasing use of statin in the general population, as well as patients with prior stroke or transient ischemic attacks. Statin agents are currently being investigated as a treatment for acute stroke and could be a treatment modifier if they are shown to have a positive biological effect in patients with acute ischemic stroke.

Summary

Endovascular technology and diagnostic approaches to acute stroke patients changed substantially during the course of the IMS III Trial. We have demonstrated that decreasing the time from hospital arrival to delivery of endovascular therapy during the conduct of a large multicenter clinical trial is doable with appropriate efforts. We were not able to demonstrate differences in outcomes seen with the evolution in the trial protocols but had limited power because of the small number of patients. The evolution of technology and clinical practice are likely to continue to evolve during ongoing and future acute ischemic stroke trials. Such change should be expected and monitored and its effect measured, particularly in trials that last >2 to 3 years.

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Disclosures

Dr Broderick is awarded research monies to Department of Neurology from Genentech for PRISMS Trial; travel to Australian stroke conference paid for by Boehringer Ingelheim. Study medication from Genentech for IMS III Trial. Dr Palesch is awarded research monies to her department for role as DSMB member for the Biogen and Brainsgate trials. Dr Demchuk received honoraria for CME and unrestricted grant to support the ESCAPE trial from Covidien. Dr Yeatts is awarded research monies from Genentech for statistical role in PRISMS Trial. Dr Khatri’s Department of Neurology receives research support from Genentech, Inc for her role as Lead PI of the PRISMS trial, Penumbra, Inc. for her role as Neurology PI of the THERAPY trial, and Biogen, Inc. for her role as DSMB member. Dr Goyal received honoraria for teaching engagements as a consultant from Covidien; partial funding for ESCAPE trial provided by Covidien through an unrestricted grant to the institution; stockholder in NoNo inc, Calgary Scientific. Dr Mazighi received funding for travel from Covidien, Boehringer Ingelheim, and Bayer. Dr Yan received research funding from Codman (Johnson Johnson), speaker’s honorarium from Stryker and Bio CSL, and educational grant from Bayer. Dr von Kummer received personal fees from Synarc. Dr Hill received consulting fees from Vernalis Group; grant support from Hoffmann–La Roche Canada; lecture fees from Hoffmann–La Roche Canada, Servier Canada, Bristol-Myers Squibb Canada; stock options from Calgary Scientific; financial support from Heart and Stroke Foundation of Alberta, Northwest Territories, and Nunavut and Alberta Innovates–Health Solutions. Dr Jauch is awarded research monies to Division of Emergency Medicine from Penumbra for Therapy Trial and from Covidien, Stryker for POSITIVE Study, and from Genentech for PRISMS Solutions. Dr Jovin is a consultant and owner, Genentech, Sanofi-aventis, and Shire plc; he has served on scientific advisory boards for Bayer, Boehringer Ingelheim, Bristol-Myers-Squibb, and Pfizer. He has received research support from the Kaethe-Zingg-Schwichtenberg-Fonds of the Swiss Academy of Medical Sciences, the Swiss Heart Foundation, and Swiss National Science Foundation. The other authors report no conflicts.

References


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for the Interventional Management of Stroke III Investigators

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Supplemental Materials

Evolution of Practice during the IMS III Trial and Implications for Ongoing Trials
Supplemental Table I: Use of intra-arterial t-PA and devices by protocol version

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>No Endovascular Therapy</td>
<td></td>
<td>26 (21%)</td>
<td>19 (28%)</td>
<td>12 (22%)</td>
<td>36 (22%)</td>
<td>7 (27%)</td>
<td>100</td>
</tr>
<tr>
<td>IA t-PA with standard micro-catheter</td>
<td></td>
<td>50 (41%)</td>
<td>22 (33%)</td>
<td>21 (39%)</td>
<td>46 (28%)</td>
<td>3 (12%)</td>
<td>142</td>
</tr>
<tr>
<td>EKOS</td>
<td></td>
<td>13 (11%)</td>
<td>6 (9%)</td>
<td>1 (2%)</td>
<td>2 (1%)</td>
<td>0 (0%)</td>
<td>22</td>
</tr>
<tr>
<td>MERCI</td>
<td></td>
<td>33 (27%)</td>
<td>16 (24%)</td>
<td>15 (28%)</td>
<td>25 (15%)</td>
<td>6 (23%)</td>
<td>95</td>
</tr>
<tr>
<td>PENUMBRA</td>
<td></td>
<td>0.00 (0%)</td>
<td>1 (1%)</td>
<td>4 (7%)</td>
<td>48 (29%)</td>
<td>1 (4%)</td>
<td>54</td>
</tr>
<tr>
<td>SOLITAIRE</td>
<td></td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>5 (19%)</td>
<td>5</td>
</tr>
<tr>
<td>OTHER (including multiple devices)*</td>
<td></td>
<td>1 (1%)</td>
<td>3 (4%)</td>
<td>1 (2%)</td>
<td>7 (4%)</td>
<td>4 (15%)</td>
<td>16</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>123</td>
<td>67</td>
<td>54</td>
<td>164</td>
<td>26</td>
<td>434</td>
</tr>
</tbody>
</table>

"Other" includes 16 subjects treated with endovascular treatments outside of defined protocol: Solitaire, Penumbra, and intra-arterial t-PA (4), Solitaire and Penumbra (2), Solitaire and Merci (1), Trevo and intra-arterial t-PA (1), Penumbra, Trevo and intra-arterial t-PA (1), Penumbra, Merci and intra-arterial t-PA (2), Penumbra system followed by Merci Retriever (1), Merci, intra-arterial t-PA, and aspiration through catheter (1), EKOS and Penumbra (1), intra-arterial t-PA and Penumbra catheter with manual suction (1), and intra-arterial t-PA and then Merci (1).

IA – intra-arterial
### Supplemental Table II. Baseline characteristics, treatment times, and type of endovascular treatment in Protocols 1-3 and Protocols 4-5

<table>
<thead>
<tr>
<th></th>
<th>Protocols 1-3 N=365 (endovascular 244, t-PA 121)</th>
<th>Protocols 4-5 N=291 (endovascular 190, t-PA 101)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr): median (range)</td>
<td>67 (23-89)</td>
<td>70 (31-84)</td>
<td>0.004</td>
</tr>
<tr>
<td>NIHSS score: median (range)</td>
<td>17 (8-39)</td>
<td>17 (7-40)*</td>
<td>0.81</td>
</tr>
<tr>
<td>ASPECTS 8-10: (%)</td>
<td>55%**</td>
<td>62%**</td>
<td>0.07</td>
</tr>
<tr>
<td>Subjects with baseline CTAs (%)</td>
<td>42%</td>
<td>53%</td>
<td>0.007</td>
</tr>
<tr>
<td>Atrial fibrillation: (%)</td>
<td>33%</td>
<td>35%</td>
<td>0.50</td>
</tr>
<tr>
<td>Pretreatment Modified Rankin Scale of 0: (%)</td>
<td>91%</td>
<td>84%</td>
<td>0.01</td>
</tr>
<tr>
<td>Current statin use: (%)</td>
<td>35%</td>
<td>37%</td>
<td>0.71</td>
</tr>
<tr>
<td>Total dose of IV and IA t-PA in endovascular arm (mg): mean (sd)</td>
<td>60.0 (14.6)***</td>
<td>60.5 (13.6)***</td>
<td>0.88</td>
</tr>
<tr>
<td>Time from stroke onset to IV t-PA initiation (min): median (range)</td>
<td>120 (29-200)†</td>
<td>119 (25-194)†</td>
<td>0.49</td>
</tr>
<tr>
<td>Time from stroke onset to start of endovascular therapy (min): median (range)</td>
<td>255 (150-430)‡</td>
<td>236 (135-391)‡</td>
<td>0.005</td>
</tr>
<tr>
<td>Time from stroke onset to last angio image (min): median (range)</td>
<td>352 (208-481)††</td>
<td>312 (144-453)††</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Drip-and-ship/ship-and-drip in endovascular arm (%)</td>
<td>23%‡‡</td>
<td>16%‡‡</td>
<td>0.11</td>
</tr>
<tr>
<td>Use of IA t-PA alone for endovascular therapy (%)</td>
<td>50%§</td>
<td>33%§</td>
<td>0.003</td>
</tr>
</tbody>
</table>

* Based on N=289
** Based on N=361 in the first three protocol versions and N=288 in Protocols 4-5.
*** Based on N=243 in the first three protocol versions and N=190 in Protocols 4-5.
† Based on N=364.
‡ Based on N=182 in the first three protocol versions and N=142 in Protocols 4-5.
†† Based on N=185 in first three protocol versions and N=142 in Protocols 4-5, and the time is from symptom onset to end of last angiogram.
‡‡ Based on N=242 in first three protocol versions and N=188 in Protocols 4-5.
§ Based on N=187 in first three protocol versions and N=147 in Protocols 4-5.

Endo - endovascular
Supplemental Table III. Comparison of outcomes in two treatment arms between Protocols 1-3 and Protocols 4-5.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Protocols 1-3 N=365 (endovascular 244, t-PA 121)</th>
<th>Percent Difference (99% CI)</th>
<th>Protocols 4-5 N=291 (endovascular 190, t-PA 101)</th>
<th>Percent Difference (99% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death within 90 days – endovascular/t-PA arms</td>
<td>21% / 20%</td>
<td>1% (-10%,13%)</td>
<td>17% / 24%</td>
<td>-7% (-20%, 6%)</td>
</tr>
<tr>
<td>sICH rate – endovascular/t-PA arms</td>
<td>7% / 7%</td>
<td>0% (-8%, 7%)</td>
<td>6% / 4%</td>
<td>2% (-5%, 8%)</td>
</tr>
<tr>
<td>aSICH rate – endovascular/t-PA arms</td>
<td>27% / 17%</td>
<td>10% (-1%, 22%)</td>
<td>27% / 21%</td>
<td>6% (-7%, 20%)</td>
</tr>
<tr>
<td>Device or procedural complications in endovascular arm</td>
<td>17%</td>
<td>Na</td>
<td>15%</td>
<td>Na</td>
</tr>
<tr>
<td>Reperfusion (TICI 2b/3 by angiogram) in endovascular arm</td>
<td>38%</td>
<td>Na</td>
<td>42%</td>
<td>Na</td>
</tr>
<tr>
<td>Recanalization (partial or complete) by 24-hr CTA</td>
<td>85% / 58%*</td>
<td>27% (2%, 51%)</td>
<td>86% / 64%*</td>
<td>22% (-1%, 46%)</td>
</tr>
<tr>
<td>mRS ≤ 2 at 90 days - endovascular/t-PA arms</td>
<td>41% / 37%</td>
<td>4% (-11%, 17%)</td>
<td>41% / 41%</td>
<td>0% (-15%, 16%)</td>
</tr>
</tbody>
</table>

* Based on first three protocol versions: N=66 in endovascular and N=36 in t-PA arm; Protocols 4-5: N=81 in endovascular and N=33 in t-PA groups, due to either missing baseline or missing 24-hour CTA.
Endo – endovascular, sICH – symptomatic ICH, aSICH – asymptomatic ICH, TICI - thrombolysis in cerebral infarction score
Supplemental Table IV. Comparison of age and baseline NIHSS in the two treatment groups in Protocols 1-3 and Protocol 4-5

<table>
<thead>
<tr>
<th></th>
<th>Protocols 1-3</th>
<th>Protocols 4-5</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Endovascular</td>
<td>IV t-PA</td>
</tr>
<tr>
<td>Age: median (range)</td>
<td>68 (23-89)</td>
<td>65 (23-81)</td>
</tr>
<tr>
<td>Baseline NIHSS: median (range)</td>
<td>17 (10-39)</td>
<td>16 (8-30)</td>
</tr>
</tbody>
</table>

None of the comparisons are statistically significant at alpha=0.01