Aspiration Thrombectomy After Intravenous Alteplase Versus Intravenous Alteplase Alone

J Mocco, MD; Osama O. Zaidat, MD; Rüdiger von Kummer, MD; Albert J. Yoo, MD; Rishi Gupta, MD; Demetrios Lopes, MD; Don Frei, MD; Harish Shownkeen, MD; Ron Budzik, MD; Zahra A. Ajani, MD; Aaron Grossman, MD; Dorethea Altschul, MD; Cameron McDougall, MD; Lindsey Blake, MD; Brian-Fred Fitzsimmons, MD; Dileep Yavagal, MD; John Terry, MD; Jeffrey Farkas, MD; Seon Kyu Lee, MD; Blaise Baxter, MD; Martin Wiesmann, MD; Michael Knauth, MD; Donald Heck, MD; Syed Hussain, MD; David Chiu, MD; Michael J. Alexander, MD; Timothy Malisch, MD; Jawad Kirmani, MD; Laszlo Miskolczi, MD; Pooja Khatri, MD; for the THERAPY Trial Investigators*

Background and Purpose—Thrombectomy, primarily with stent retrievers with or without adjunctive aspiration, provided clinical benefit across multiple prospective randomized trials. Whether this benefit is exclusive to stent retrievers is unclear.

Methods—THERAPY (The Randomized, Concurrent Controlled Trial to Assess the Penumbra System’s Safety and Effectiveness in the Treatment of Acute Stroke; NCT01429350) was an international, multicenter, prospective, randomized (1:1), open label, blinded end point evaluation, concurrent controlled clinical trial of aspiration thrombectomy after intravenous alteplase (IAT) administration compared with intravenous-alteplase alone in patients with large vessel ischemic stroke because of a thrombus length of ≥8 mm. The primary efficacy end point was the percent of patients achieving independence at 90 days (modified Rankin Scale score, 0–2; intention-to-treat analysis). The primary safety end point was the rate of severe adverse events (SAEs) by 90 days (as treated analysis). Patients were randomized 1:1 across 36 centers in 2 countries (United States and Germany).

Results—Enrollment was halted after 108 (55 IAT and 53 intravenous) patients (of 692 planned) because of external evidence of the added benefit of endovascular therapy to intravenous-alteplase alone. Functional independence was achieved in 38% IAT and 30% intravenous intention-to-treat groups (P=0.52). Intention-to-treat ordinal modified Rankin Scale odds ratio was 1.76 (95% confidence interval, 0.86–3.59; P=0.12) in favor of IAT. Secondary efficacy analyses all demonstrated a consistent direction of effect toward benefit of IAT. No differences in symptomatic intracranial hemorrhage rates (9.3% IAT versus 9.7% intravenous, P=1.0) or 90-day mortality (IAT: 12% versus intravenous: 23.9%, P=0.18) were observed.

Conclusions—THERAPY did not achieve its primary end point in this underpowered sample. Directions of effect for all prespecified outcomes were both internally and externally consistent toward benefit. It is possible that an alternate method of thrombectomy, primary aspiration, will benefit selected patients harboring large vessel occlusions. Further study on this topic is indicated.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT01429350.

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From the Mount Sinai Health System, New York, NY (J.M.); St. Vincent Mercy Medical Center, Toledo, OH (O.O.Z.); Universitätsklinikum Carl Gustav Carus, Dresden, Germany (R.v.K.); Texas Stroke Institute, Plano (A.J.Y.); WellStar Health System, Marietta, GA (R.G.); Rush University, Chicago, IL (D.L.); Swedish Medical Center, Denver, CO (D.F.); Central DuPage Hospital, Winfield, IL (H.S.); Riverside Methodist Hospital, Columbus, OH (R.B.); Kaiser Los Angeles, CA (Z.A.A.); St. Joseph’s Regional Medical Center, Paterson, NJ (A.G., D.A.); St. Joseph’s BNI, Phoenix, AZ (C.M.); Sunrise Hospital and Medical Center, Las Vegas, NV (L.B.); Medical College of Wisconsin, Milwaukee (B.-F.F.); University of Miami Health System, FL (D.Y.); Premier Clinical Neuroscience Institute, Dayton, OH (J.T.); Lutheran Medical Center, Brooklyn, NY (J.F.); University of Chicago Medical Center, IL (S.K.L.); Erlanger Health System, Chattanooga, TN (B.B.); Universitätsklinikum Aachen, Germany (M.W.); Universitätsmedizin Göttingen, Germany (M.K.); Forsyth Medical Center, Winston-Salem, NC (D.H.); Sparrow Hospital, Lansing, MI (S.H.); Houston Methodist Hospital, TX (D.C.); Cedars-Sinai Medical Center, Los Angeles, CA (M.J.A.); Alexian Brothers, Elk Grove, IL (T.M.); The Valley Hospital, Ridgewood, NJ (D.A.); JFK Medical Center, Edison, NJ (J.K.); Holy Cross, Fort Lauderdale, FL (L.M.); and University of Cincinnati, OH (P.K.).

* A list of all THERAPY Trial Investigators is given in the Appendix.

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Correspondence to J Mocco, MD, Department of Neurosurgery, Icahn School of Medicine at Mount Sinai, 1 Gustave Levy Place, PO Box 1136, New York, NY 10029. E-mail j.mocco@mountsinai.org

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Until recently, intravenous alteplase was the only proven reperfusion therapy for ischemic stroke.1–5 Five consecutive, prospective, randomized thrombectomy trials have now demonstrated clinical superiority of endovascular therapy to intravenous alteplase alone or best medical care.6–10 THERAPY (The Randomized, Concurrent Controlled Trial to Assess the Penumbra System’s Safety and Effectiveness in the Treatment of Acute Stroke) was designed to evaluate the potential benefit of aspiration thrombectomy for large vessel occlusion patients compared with intravenous tissue-type plasminogen activator (tPA) alone in selected patients. THERAPY hypothesized that aspiration thrombectomy would improve clinical outcomes in intravenous tPA–eligible patients with large vessel occlusion and large clot burden. THERAPY differed from contemporaneous trials in 3 critical ways: (1) thrombectomy was to be achieved by aspiration, whereas all other trials used primarily or exclusively stent retriever thrombectomy, with or without adjunctive aspiration; (2) THERAPY sought to identify the poorest prognosis patients, namely those with a clot burden of ≥28 mm; and (3) unlike all but 2 of the other trials (MR CLEAN [Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands] and 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]), THERAPY did not require advanced perfusion imaging selection8,9 or multiphase computed tomographic (CT) angiography (CTA).7

Single-arm studies have shown aspiration-based thrombectomy to safely facilitate rapid reperfusion in large vessel occlusion stroke patients.15–15 Local aspiration may play an important role when used with stent retrievers for thrombectomy.16 A fundamental question surrounding the recent overwhelming evidence supporting thrombectomy is whether this benefit is exclusive to stent retrievers as the primary approach or may result from other approaches. THERAPY, by testing aspiration thrombectomy, was uniquely positioned to provide insight into this question but was ultimately underpowered.

Materials and Methods

Study Design

THERAPY (NCT01429350) was an international, multicenter, prospective, randomized, open label, blinded end point evaluation, concurrent controlled clinical trial of aspiration thrombectomy after intravenous alteplase administration compared with intravenous alteplase alone in patients with large vessel ischemic stroke because of ≥28 mm thrombus (the full study protocol is provided in the Materials section in the online-only Data Supplement). CT angiography was required to confirm intracranial occlusion and to rule out tandem cervical occlusion that would prevent thrombectomy without treatment. THERAPY was US Food and Drug Administration-approved and each enrolling site obtained appropriate Institutional Review Board or ethics committee approval.

Patients

Eligible patients (18–85 years old) with intracranial internal carotid artery (ICA) or middle cerebral artery occlusion on CT angiography and a National Institute of Health Stroke Scale (NIHSS) score of ≥28 were treated with intravenous–alteplase based on standard eligibility criteria. Enrollment required a nonenhanced thin-section (≤2.5 mm) CT scan demonstrating ≥28 mm clot length. Investigators were trained on clot length identification methodology12 and each site submitted examples before study initiation. Major exclusion criteria included >1 of 3 of the affected middle cerebral artery territory with established infarction, cervical ICA stenosis/occlusion requiring treatment before thrombectomy, and prestroke disability (modified Rankin Scale [mRS] score ≥1). Remaining criteria are outlined in the protocol (Materials section in the online-only Data Supplement). Written informed consent was obtained from all enrolled patients.

Randomization and Masking

Patients were randomized 1:1 to either (1) intravenous–alteplase alone (intravenous group) or (2) intravenous alteplase plus aspiration thrombectomy (intravenous alteplase plus thrombectomy [IAT] group) and stratified according to enrolling center. Both the groups received full dose of intravenous–alteplase (0.9 mg/kg). Randomization was performed through a centralized interactive voice response system.

Procedures

Aspiration thrombectomy was performed with the Penumbra System and included the 3-dimensional (3D) Separator as of December 2012 and the larger bore ACE aspiration catheter as of August 2013. The use of conscious sedation versus general anesthesia and postprocedural neurocritical care was left to the treating physician’s discretion.

Outcomes

The primary efficacy end point was the proportion of patients achieving functional independence by 90 days, defined as mRS score of 0 to 2, in intention-to-treat (ITT) analysis. The primary outcome measure (90-day mRS) was assessed by independent blinded adjudicators (R.E. or E.B.R.). Adjudicators reviewed videotapes of assessments performed by blinded, trained, and certified local investigators. To minimize variability, local investigators performed mRS assessment using the Rankin Focused Assessment Tool.18 Secondary efficacy outcomes included (1) the severity of 90-day disability according to the distribution of scores across the mRS (shift analysis), (2) the proportion of patients with improvement defined as mRS score of 0 to 2 at 30 days, ≥21 point NIHSS improvement from baseline to 24 hours, or NIHSS 0 to 1 at discharge,19 and (3) 24 hours of infarct volume measured using the Alberta Stroke Program Early CT Score (ASPECTS)20 and 24 hours of infarct volume worsening.21 Patients without 90-day mRS data were excluded from primary analyses with additional sensitivity analysis assigning mRS score of 6 (death) to those patients. Efficacy analyses were prespecified for both ITT and per-protocol (PP) population.

The primary safety outcome was the incidence of 90-day serious adverse events (SAEs; see Definitions in the online-only Data Supplement for SAE definition) in an as-treated analysis. Secondary safety outcomes included the rate of symptomatic intracranial hemorrhage (sICH) and mortality at 90 days. sICH was defined as any new hemorrhage identified by the core laboratory with a concomitant ≥4 point worsening in NIHSS as recorded by a blinded, NIHSS-certified assessor.

All baseline and follow-up brain and vessel images and imaging outcome events were assessed by an independent, blinded neuroradiologist (A.Y.). The modified thrombolysis in cerebral ischemia scale21 was used to assess angiographic reperfusion status. ASPECTS was used to evaluate for baseline ischemic change on enrollment CT scans and 24 hours of infarct volume.20,21

Statistical Analysis

A sample size of 692 patients was calculated based on a 2-sided χ² test, with 80% power, an α value of 0.05, and an expected absolute difference in the 90-day mRS score of 0 to 2 rate of 10.6% between the intravenous–alteplase (24.4%) and IAT cohorts (35%). The 24.4% intravenous group estimate was based on a previous estimate of functional independence in intravenous–alteplase–treated patients with persistent large vessel occlusions.22 The 35% rate for the thrombectomy cohort was based on intravenous–alteplase–treated patients with persistent large vessel occlusion treated with IAT in the Penumbra Group.
Table 1. Radiographic Findings

<table>
<thead>
<tr>
<th>Value</th>
<th>Intravenous Alteplase-Thrombectomy</th>
<th>Intravenous Alteplase</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left hemisphere</td>
<td>60% (33/55)</td>
<td>58% (31/53)</td>
<td>1.0</td>
</tr>
<tr>
<td>Site of occlusion</td>
<td></td>
<td></td>
<td>0.44</td>
</tr>
<tr>
<td>Intracranial ICA</td>
<td>33% (18/55)</td>
<td>23% (12/53)</td>
<td></td>
</tr>
<tr>
<td>MCA M1</td>
<td>56% (31/55)</td>
<td>68% (36/53)</td>
<td></td>
</tr>
<tr>
<td>MCA M2</td>
<td>11% (6/55)</td>
<td>9.4% (5/53)</td>
<td></td>
</tr>
<tr>
<td>Clot length, median (IQR)</td>
<td>13 (9.4–22)</td>
<td>14 (10–19)</td>
<td>0.89</td>
</tr>
<tr>
<td>ASPECTS*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASPECTS, 0–4</td>
<td>11% (6/54)</td>
<td>7.5% (4/53)</td>
<td>0.71</td>
</tr>
<tr>
<td>ASPECTS, 5–7</td>
<td>39% (21/54)</td>
<td>36% (19/53)</td>
<td>0.71</td>
</tr>
<tr>
<td>ASPECTS, 8–10</td>
<td>50% (27/54)</td>
<td>57% (30/53)</td>
<td>0.71</td>
</tr>
</tbody>
</table>

ASPECTS indicates Alberta Stroke Program Early CT Score; CT, computed tomography; ICA, internal carotid artery; IQR, interquartile range; and MCA, middle cerebral artery.

*One patient did not have CT imaging available for review.

Pivotal trial. Further details are in the Statistical Analysis Plan (Materials section in the online-only Data Supplement).

Role of the Funding Source

The trial was funded by Penumbra, Inc and designed and led by the steering committee of 5 academic investigators and 2 sponsor representatives. Site investigators gathered study data, with monitoring and database management by the sponsor. The study was monitored by an independent Data Safety and Monitoring Board (DSMB) and Clinical Events Committee (CEC). After termination of the trial, the academic investigators had unrestricted access to the data and led data analyses performed by the study statistician, who was employed by Penumbra Inc. Initial and subsequent drafts of the article were written by the academic steering committee, with input from all coauthors.

Results

Study Termination

Trial enrollment was halted by the steering committee after the presentation of the MR CLEAN study at the World Stroke Congress because of the concern that providing intravenous recombinant-tPA alone would be unethical. Final termination was decided on February 13, 2015 after the presentation and subsequent publication of 3 additional randomized trials that established endovascular therapy, in addition to intravenous recombinant-tPA, as standard of care.

Patient Characteristics

We randomized 108 patients with ischemic stroke (53 intravenous and 55 IAT) between March 2012 and October 2014, across 36 US and German centers. Ninety-day outcome data were available in 96 patients (46 intravenous and 50 IAT; Figure I in the online-only Data Supplement). PP analysis included 78 patients (41 intravenous and 37 IAT; Figure II in the online-only Data Supplement). As-treated analysis included 105 patients (62 intravenous and 43 IAT; Figure III in the online-only Data Supplement). Patients’ baseline characteristics are provided in the Materials section in the online-only Data Supplement. Notable but nonsignificant differences occurred between intravenous-alteplase and thrombectomy cohorts with respect to female sex (57% versus 38%), history of atrial fibrillation (49% versus 33%), smoking history (39% versus 60%), and intracranial ICA occlusions (23% versus 33%). Both cohorts included patients with intermediate to severe early ischemic changes on baseline CT scan: 27 of 54 (50%) IAT patients with ASPECTS of ≤7, with 6 of 54 (11%) being ≤4, and 23 of 53 (44%) intravenous patients with ASPECTS of ≤7, with 4 of 53 (8%) being ≤4 (Table 1).

Intervention Details

Among 55 patients randomized to ITT, traditional separator-based aspiration system (Penumbra) was used in 30 patients (54%), the separator 3D in 14 patients (25%), the ACE catheter (Penumbra) in 15 patients (27%), and either a Solitaire (Covidien) or a Trevo (Stryker) was used in 7 patients (13%). Successful reperfusion (modified thrombolysis in cerebral ischemia 2b/3) was achieved in 30 (70%) of 43 patients treated with only the Penumbra system (95% confidence interval [CI], 54–83) after aspiration thrombectomy alone. Inclusion of thrombectomy attempts with other devices (7 patients) resulted in a final modified thrombolysis in cerebral ischemia 2b/3 in 33 (73%) of 45 patients (95% CI, 58–85); 2 of these 7 stent-retriever patients underwent thrombectomy without attempted aspiration. General anesthesia was used in 29 of 45 (64%) patients who received any thrombectomy procedure. Further procedural details are provided in Table 2.

Table 2. Procedural Details

<table>
<thead>
<tr>
<th>Value</th>
<th>Intravenous Alteplase-Thrombectomy</th>
<th>Intravenous Alteplase</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset to ED (IQR)</td>
<td>64 (40–133)</td>
<td>57 (30–118)</td>
<td>0.4</td>
</tr>
<tr>
<td>Onset to intravenous alteplase (IQR)</td>
<td>108 (86–138)</td>
<td>102 (80–154)</td>
<td>0.76</td>
</tr>
<tr>
<td>Onset to randomization (IQR)</td>
<td>181 (129–221)</td>
<td>169 (132–224)</td>
<td>0.88</td>
</tr>
<tr>
<td>CT to groin puncture (IQR)</td>
<td>123 (80–166)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Onset to groin puncture (IQR)</td>
<td>227 (184–263)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>mTICI 2b/3 after penumbra system</td>
<td>70% (30/43)</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

CT indicates computed tomography; ED, Emergency Department; IQR, interquartile range; mTICI, modified thrombolysis in cerebral ischemia scale; and NA, not applicable.
Primary Outcomes
Rates of functional independence in the thrombectomy and intravenous-alteplase arms were comparable (38% versus 30%; odds ratio [OR], 1.4; 95% CI, 0.6–3.3; \(P=0.44\)) in the ITT analysis (Table 3). Primary safety outcome demonstrated no significant difference in SAE rate as-treated: 42% intravenous-alteplase plus thrombectomy versus 48% intravenous-alteplase alone (No SAE: OR, 1.3; 95% CI, 0.6–2.7; \(P=0.55\)).

Secondary Outcomes
Rates of functional independence in the thrombectomy and intravenous-alteplase arms were also comparable (41% versus 29%; OR, 1.6; 95% CI, 0.6–4.2; \(P=0.30\)) in the PP analysis (Table 3). Overall mRS distributions demonstrated better functional outcome for IAT in the PP analysis (OR, 2.2; 95% CI, 1.0–5.1; \(P=0.047\)) and a trend in the ITT analysis (OR, 2.2; 95% CI, 0.9–5.1; \(P=0.12\); Figure 1). Multivariable adjusted ordinal analyses favored thrombectomy even more robustly (ITT: OR, 2.4; 95% CI, 1.1–5.1; \(P=0.02\) and PP: OR, 2.5; 95% CI, 1.1–5.8; \(P=0.03\); Tables II and III in the online-only Data Supplement). All additional prespecified secondary end points demonstrated consistent directions of effect toward benefit of IAT (Table 3; Figure 2A).

Secondary safety outcomes demonstrated no difference in the rates of sICH; 9 of 43 (20.9%) intravenous-alteplase plus thrombectomy versus 11 of 62 (17.7%) intravenous-alteplase alone (OR, 1.0; 95% CI, 0.3–3.9; Table 3). In addition, we observed comparable mortality rates with the direction of effect favoring aspiration thrombectomy in both ITT (12% thrombectomy versus 24% intravenous-alteplase; OR, 2.3; 95% CI, 0.8–6.8) and PP (7.3% thrombectomy versus 24% intravenous-alteplase; OR, 4.1; 95% CI, 1.0–16) analyses (Figure IVa and IVb in the online-only Data Supplement).

Sensitivity Analysis
When assigning loss-to-follow-up patients with mRS score of 6, or when collapsing mRS score of 5 and 6 into a single ordinal category (Table IV in the online-only Data Supplement), the results remained consistent with the primary efficacy result.

Discussion
THERAPY sought to establish the benefit of aspiration thrombectomy in conjunction with intravenous-alteplase when compared with intravenous-alteplase alone in patients with a large anterior circulation proximal clot burden (≥8 mm), but it was halted early based on external evidence demonstrating the efficacy of thrombectomy.\(^6\)–\(^{10}\) Consequently, THERAPY was not powered to meet its predefined end points. Although the primary end point was not achieved, prespecified secondary end points suggest potential for benefit for aspiration thrombectomy (Figure 2A). In addition, although nonsignificant, the magnitude of potential treatment effect observed for the primary outcome measure is consistent with those of the recent positive thrombectomy trials (Figure 2B). Finally, similar to ESCAPE (The Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion With Emphasis on
Minimizing CT to Recanalization Times) and EXTEND-IA (Extending the Time for Thrombolysis in Emergency Neurological Deficits — Intra-Arterial trial), mortality in the IAT arm of THERAPY was potentially half of that seen in the intravenous arm (Figure V in the online-only Data Supplement).

In contrast to previous positive trials, THERAPY used the alternative thrombectomy technique of aspiration as the primary treatment modality. In MR CLEAN, ESCAPE, EXTEND-IA, SWIFT PRIME (Solitaire With the Intention for Thrombectomy as Primary Endovascular Treatment trial), and REVASCAT stent retrievers were primarily used (81.5%, 86%, 78%, 89%, and 100%, respectively), with or without aspiration, and it remained unclear whether stent retrievers were necessary to realize clinical benefit in this patient population.6–10 Although early termination prevents a definitive answer, THERAPY supports the potential benefit of substantial revascularization from early thrombectomy by other means. Furthermore, the successful reperfusion rate (modified thrombolysis in cerebral ischemia 2b/3) of 73% (95% CI, 58–85) in a ≥8-mm clot burden population is consistent with the recently reported trials of MR CLEAN (59%), ESCAPE (72%), REVASCAT (65.7%), SWIFT PRIME (88%), and EXTEND-IA (86%).6–10 However, aspiration thrombectomy has not directly been compared with stent retrievers, and, after the publication of these findings, only a prospective randomized trial of aspiration therapy versus stent-retriever thrombectomy can definitively answer this question.

Positive trials to date used highly variable approaches to patient selection. MR CLEAN included a broad range of patients and then allowed for clinical judgment to enroll the patient based on the gray area principle.6 REVASCAT required a small, irreversibly injured ischemic core (ie, higher ASPECTS score) for the majority of patients as assessed by standard CT scan (with the exception of older and later presentation patients).10 EXTEND-IA and SWIFT PRIME also selected for the presence of a potentially large salvageable ischemic penumbra.8,9 ESCAPE required the presence of a favorable collateral status.7 These diverse approaches leave the key question of how to best select patients for endovascular therapy. Our findings, when considered along with REVASCAT and possibly MR CLEAN, suggest that noncontrast CT scan may be sufficient for evaluating the brain parenchyma (Table 4).6,10 Advanced imaging such as CT or MR perfusion or multiphasic CT angiography collateral assessment, while selecting patients with favorable physiology, may exclude patients who would
still have a relative benefit from endovascular therapy. Planned prespecified pooled analyses of data from these 3 trials will likely delineate optimal patient selection approaches in a more definitive manner.24 We also look forward to possible future pooled analysis of perfusion selection data from those studies that used perfusion imaging selection. Because THERAPY did not seek to evaluate the contribution of perfusion selection, these data were not collected.

Notably, although we observed no difference in the rate of sICH between the thrombectomy and intravenous-tPA alone cohorts, the overall rate of sICH in both arms was higher in THERAPY than in other recent trials (Table V in the online-only Data Supplement). This likely relates to varying definitions across trials. In THERAPY, sICH definition did not require relatedness to neurological decline, and it was, therefore, more inclusive. When using the published SWIFT PRIME definition, the sICH rate fell to 2.3% in the IAT cohort and 4.8% in the intravenous cohort (Table V in the online-only Data Supplement).

Not surprisingly, our small sample size led to imbalances in baseline characteristics (sex, history of atrial fibrillation, smoking status, and clot location) between the 2 treatment arms, despite randomization. Any and all of these imbalances may have affected outcome. However, most notable is clot location. Fewer intracranial ICA occlusion patients were in the intravenous arm (Table 1), and they experienced only a 10% mRS score of 0 to 2 in the intravenous arm versus a 27% mRS score of 0 to 2 in the IAT arm.

In THERAPY, a large thrombus burden (≥8 mm in length) was a key enrollment criterion. Despite promising early publications suggesting patients with such thrombi to be particularly resistant to intravenous alteplase, our data do not seem to support this hypothesis. The good outcome rate in the intravenous-tPA alone cohort of THERAPY is consistent with estimates from broader cohorts of large vessel occlusion patients. Whether this discrepancy is secondary to limitations in sample size, measurement reliability (despite training), or lack of intravenous-tPA resistance at the 8-mm threshold remains to be elucidated.

<table>
<thead>
<tr>
<th>Table 4. Stroke Trial ASPECTS Scores</th>
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<tbody>
<tr>
<td><strong>Baseline ASPECTS</strong></td>
</tr>
<tr>
<td>-------------</td>
</tr>
<tr>
<td>THERAPY (IQR)</td>
</tr>
<tr>
<td>MR CLEAN (IQR)</td>
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<tr>
<td>ESCAPE (IQR)</td>
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<tr>
<td>EXTEND-IA (IQR)</td>
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<tr>
<td>SWIFT PRIME (IQR)</td>
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<td>REVASCAT (IQR)</td>
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</table>

ASPECTS indicates Alberta Stroke Program Early CT Score; CT, computed tomography; ESCAPE, The Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion With Emphasis on Minimizing CT to Recanlization Times; EXTEND-IA, Extending the Time for Thrombolysis in Emergency Neurological Deficits — Intra-Arterial trial; IA, intravenous alteplase; ITT, intention-to-treat; MR CLEAN, Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands; NR, not reported; 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; SAE, severe adverse events; and SWIFT PRIME, Solitaire With the Intention for Thrombectomy as Primary Endovascular Treatment trial.
multivariable analysis, both ITT and PP analyses of ordinal mRS suggested benefit (Table 3).

THERAPY has several limitations. First, by focusing on a highly selected patient population, generalizability is limited. However, the numerically consistent effect sizes seen across all recent trials suggest potential benefit by varied selection criteria and treatment algorithms. Second, and most significantly, THERAPY was halted early and therefore findings are limited and their interpretations require caution.

In conclusion, THERAPY did not meet its primary endpoint in a limited sample size, but it did demonstrate a direction of effect toward benefit with both internal and external consistencies. It is possible that an alternate method of thrombectomy, primary aspiration, will benefit selected patients harboring large vessel occlusions. Further study on this topic is indicated.

Appendix: THERAPY Investigators

Participating THERAPY Centers with Principal Investigator (PI) in Order of Enrollment (N) US Rush University (9) PI: Demetrius Lopes, MD. Swedish Medical Center (9) PI: Don Frei, MD. CentralDuPage Hospital (6) PI: Harish Showkenne, MD. Riverside Methodist Hospital (5) PI: Ron Budzik, MD. Kaiser Los Angeles (5) PI: Zahra A. Ajani, MD. University of Cincinnati (5) PI: Aaron Grossman, MD. St. Joseph’s Regional Medical Center (5) PI: Dorothea Altschul, MD. St. Joseph’s BNI (4) PI: Cameron McDougall, MD. Vanderbilt (4) PI: J Mocco, MD. Sunrise Hospital and Medical Center (4) PI: Lindsay Blake, MD. Medical College of Wisconsin (3) PI: Brian Fred Fitzsimmons, MD. Jackson Memorial Hospital (3) PI: Dileep Yadav, MD. Miami Valley (3) PI: John Terry, MD. Lutheran Medical Center (3) PI: Jeffrey Farkas, MD. University of Chicago Medical Center (3) PI: Seon Kyu Lee, MD. Erlanger Health System (3) PI: Blaise Baxter, MD. Forsyth Medical Center (2) PI: Don Heck, MD. Sparrow Hospital (2) PI: Seyed Hussain, MD. Methodist Hospital (2) PI: David Chiu, MD. Cedars-Sinai (2) PI: Michael Alexander, MD. Alexian Brothers (2) PI: Tim Malisch, MD. The Valley Hospital (2) PI: Dorothea Altschul, MD. JFK Medical Center (2) PI: Jawad Kirmani, MD. Holy Cross (2) PI: Laszlo Miskolczi, MD. UCSF (1) PI: Alexander Khalessi, MD. Shands at University of Florida (1) PI: Spiros Blackburn, MD. Stony Brook Medical Center (1) PI: Henry Woo, MD. Kalea Health (1) PI: Elad Levy, MD. Lehigh Valley Hospital (1) PI: Christian Schumacher, MD. Abbott Northwestern (1) PI: Josser Delgado, MD. Grady Memorial Hospital (1) PI: Raul Nogueira, MD. WellStar Research Institute (1) PI: Rishi Gupta, MD. University Hospitals of Cleveland (1) PI: Paul Willinsky, MD. University of Cincinnati (1) PI: Rishi Gupta, MD. University of Pittsburgh (1) PI: Alexander Khatri, MD. University of Rochester (1) PI: Rishi Gupta, MD. University of Southern California (1) PI: Scott Hamilton, PhD. Stanford University School of Medicine. Penumbra, Inc: Denise Meyer, MT, CCRP. Hope Buell, MS. Sophia S. Kuo, PhD. Siu Po Sit, PhD. Arani Bose, MD. Submission Preparation: Chesney Oravec.

Acknowledgments

This work was supported by Penumbra, Inc. All coauthors had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Each enrolling site obtained Institutional Review Board or ethics committee approval. Informed consent was obtained for all enrolled patients.

Disclosures

The following investigators report financial associations with the sponsor of this study: Dr. Mocco is a consultant to TSP. Cerebrotech, and Rebound Medical; Dr. Yoo received funding for imaging core laboratory activities; Dr. Gupta is a consultant to Stryker Neurovascular, Medtronic, Rapid Medical, Penumbra, and he received research funding from Stryker Neurovascular, Medtronic, and Penumbra; Dr. Frei received consulting/speaker fees and held stock in Penumbra; Dr. Wiesmann is a consultant to Stryker Neurovascular and received research funding from Stryker Neurovascular, Codman Neurovascular, Medtronic, Penumbra, Microvention, and abmedica; Dr. Knauth received speaker fees; and Dr. Heck is a consultant to Stryker Neurovascular. Vanderbilt University and University of Cincinnati each received salary support to offset the time and effort spent by Drs Khatri and Mocco in their role as principal investigators (PI) of THERAPY. Dr. von Kummer received personal fees from Penumbra, Inc for the submitted work and personal fees from H. Lundbeck A/S, Boehringer Ingelheim, Coviden, BrainGate outside the submitted work. The other authors report no conflicts.

References


Aspiration Thrombectomy After Intravenous Alteplase Versus Intravenous Alteplase Alone


for the THERAPY Trial Investigators*

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The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/47/9/2331

Data Supplement (unedited) at:
http://stroke.ahajournals.org/content/suppl/2016/08/02/STROKEAHA.116.013372.DC1

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TRIAL ORGANIZATION

Steering Committee
J Mocco, MD, MS, Mount Sinai Health System, USA
Pooja Khatri, MD, MSc, University of Cincinnati, USA
Osama Zaidat, MD, MSc, Medical College of Wisconsin, USA
Prof. Dr. med. Rüdiger von Kummer, Universitätsklinikum Carl Gustav Carus Technical University of Dresden, Germany
Rishi Gupta, MD, MBA, Wellstar Health System, USA
Siu Po Sit, PhD, Penumbra Inc.
Arani Bose, MD, Penumbra Inc.

Project Statistician
Hope Buell, MS, Penumbra, USA

DSMB Statistician
Scott Hamilton, PhD, Stanford University School of Medicine, USA

Endpoint Data Analysis CRO
CROS NT, USA
**DEFINITIONS**

**mTICI**
Angiographic revascularization was assessed using the modified Treatment in Cerebral Ischemia (mTICI) scale which ranges from no flow (0) to normal flow (3).\(^1\)\(^2\)

<table>
<thead>
<tr>
<th>mTICI Grade</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No perfusion</td>
</tr>
<tr>
<td>1</td>
<td>Antegradereperfusion past the initial occlusion, but limited distal branch filling with little or slow distal reperfusion</td>
</tr>
<tr>
<td>2a</td>
<td>Antegrade reperfusion of less than half of the occluded target artery previously ischemic territory</td>
</tr>
<tr>
<td>2b</td>
<td>Antegrade reperfusion of more than half of the previously occluded target artery ischemic territory</td>
</tr>
<tr>
<td>3</td>
<td>Complete antegrade reperfusion of the previously occluded target artery ischemic territory, with absence of visualized occlusion in all distal branches</td>
</tr>
</tbody>
</table>

**mRS**
The modified Rankin Scale (mRS) is a measure of functional status and ranges from 0 (no symptoms) to 6 (death).\(^3\)

**ASPECTS**
The Alberta Stroke Program Early CT Score (ASPECTS) is a score from 0 to 10 which grades early ischemic change in specified 10 regions, with lower scores corresponding to larger infarcts.\(^4\)

**ECASS**
A follow-up noncontrast CT scan was performed at 24 ± 12 hours after randomization, and was reviewed to assess hemorrhagic transformation based on ECASS definitions\(^5\):
- HI 1 (small petechiae along the margins of the infarcted area without space-occupying effect),
- HI 2 (more confluent petechiae within the infarcted area but without space-occupying effect),
- PH 1 (hematoma in <30% of the infarcted area with some slight space-occupying effect),
- PH 2 (hematoma in >30% of infarcted area with substantial space-occupying effect).

Based on previous work, only PH2 will be defined as a clinically significant hemorrhage.\(^6\)

In addition, any neurological deterioration should be evaluated by urgent CT scan and other evaluations as indicated according to investigator/hospital best practice.

A symptomatic intracranial hemorrhage will be defined as 24 hour CT evidence of an ECASS defined ICH and a 4-point or more worsening of the NIHSS score.
SWIFT PRIME Symptomatic ICH
Any PH1, PH2, RIH, SAH, or IVH associated with a 4 points or more worsening on the NIHSS within 24 hrs (± 3 hours).7

- PH1: Hematoma within ischemic field with some mild space occupying effect but involving ≤ 30% of the infarcted area.
- PH2: Hematoma within ischemic field with space-occupying effect involving >30% of the infarcted area
- RIH: Any intraparenchymal hemorrhage remote from the ischemic field
- IVH: Intraventricular hemorrhage
- SAH: Subarachnoid hemorrhage

Definition of an SAE
A Serious Adverse Event, a Serious Adverse Device Effect or a Serious Drug Effect is an event that:

a) Led to death
b) Led to a serious deterioration in the health of the patient that:
   - Resulted in life-threatening illness or injury
   - Resulted in permanent impairment of a body structure or a body function
   - Required in-patient hospitalization or prolongation of existing hospitalization
   - Resulted in medical or surgical intervention to arrest permanent impairment to body structure or a body function
   - Led to fetal distress, fetal death or a congenital abnormality or birth defect
SUPPLEMENTAL METHODS

Detailed Inclusion Criteria
- From 18 to 85 years of age
- Present with symptoms consistent with an acute ischemic stroke and eligible for IV rtPA therapy*
- Evidence of a large vessel occlusion in the anterior circulation with a clot length of ≥8mm
- NIH Stroke Scale (NIHSS) score > 8 at presentation
- Signed informed consent

*Patients presenting 3–4.5 hours from symptom onset are not eligible if they are >80 years of age, have a history of stroke and diabetes, anticoagulant use (even if INR is <1.7) and have a NIHSS score >25

Detailed Exclusion Criteria
- History of stroke in the past 3 months.
- Females who are pregnant
- Pre-stroke mRS score >2
- Known severe allergy to contrast media
- Uncontrolled hypertension (defined as systolic blood pressure >185 mmHg or diastolic blood pressure >110 mmHg)
- CT evidence of the following conditions at randomization:
  - Significant mass effect with midline shift
  - Any acute ischemic changes in >1/3 of the affected middle cerebral artery territory
  - Evidence of intracranial hemorrhage
- Angiographic evidence of tandem extracranial occlusion or an arterial stenosis proximal to the occlusion that requires treatment prior to thrombus removal. Moderate stenosis not requiring treatment is not an exclusion.
- Angiographic evidence of preexisting arterial injury
- Rapidly improving neurological status prior to randomization
- Bilateral stroke
- Intracranial tumors
- Known history of cerebral aneurysm or arteriovenous malformation
- Known hemorrhagic diathesis, coagulation deficiency, or on anticoagulant therapy with an International Normalized Ratio (INR) of >1.7
- Baseline platelets <50,000
- Heparin received within 48 hours, resulting in abnormally elevated aPTT greater than the upper limit of normal
- Direct thrombin inhibitors or direct factor Xa inhibitors received within 48 hours
- Pre-treatment glucose <50mg/dL or >300mg/dL
- Life expectancy less than 90 days prior to stroke onset
- Participation in another clinical investigation that could confound the evaluation of the study device

Randomization and Intervention
Patients were randomized 1:1 to monotherapy IV rtPA (control arm) or combined IV rtPA plus IA Penumbra System® treatment (intervention arm). In the IV rtPA arm, subjects were treated by IV infusion of rtPA at 0.9mg/kg to a maximum of 90mg. In the IV rtPA and IA Penumbra System arm, subjects were treated by dual IV rtPA therapy (0.9mg/kg to a maximum of 90mg) and IA adjunctive treatment with the Penumbra System®.

In accordance with the standard practice of the institution, the large vessel occlusion in a patient undergoing IAT was catheterized by a microcatheter following introduction of an aspiration catheter with a 6 F long femoral sheath or an 8 F guide catheter proximal to the thrombus. A Separator 3D (investigational device, Penumbra Inc) could be deployed as an option, then the retained thrombus and retriever were withdrawn into a reperfusion catheter (054, 5MAX, or 5MAX ACE; Penumbra Inc) under continuous aspiration with the MAX pump. The maximum number of times to engage and retrieve the thrombus using the Separator 3D should not exceed 5 attempts. A large bore reperfusion catheter, such as the 5MAX or 5MAX ACE, could be advanced to the thrombus site and direct aspiration applied to remove the clot. Other devices permitted included the 4MAX, 3MAX and 026 catheters (Penumbra Inc). Beyond the Penumbra System, no other adjunctive or rescue therapies were allowed for either treatment group for the sole purpose of reducing the clot burden. Any subject who receives IA rtPA for any purpose will be considered a treatment failure. A post-treatment angiogram was obtained by injecting contrast media through
the guide catheter. Pre-procedure and post-procedure angiograms were sent to an unbiased Core Laboratory for a final determination on TIMI/TICI flow.

**mRS Video Adjudication**
For clinical outcomes, the Core Lab performed independent blinded adjudication of mRS based on video assessments consisting of in-person visits digitally recorded using study camcorders and standard interview questionnaires for data reliability. To minimize interobserver variability, the Rankin Focused Assessment Tool (RFAT) was applied to grade final global disability\(^8\)\(^{-10}\); examinations were HIPAA-compliant.
SUPPLEMENTAL RESULTS

eFigure I
Patient Flow for Randomized Patients (n=108) – Intent to Treat Follow-up

Allocation: Penumbra System + IV tPA (n=55)

90 Day Follow-Up
Final Evaluation n=50:
Final Evaluation not available n=5:
- Lost to follow-up* n=3
- Withdrew consent n=2

Allocation: IV tPA alone (n=53)

90 Day Follow-Up
Final Evaluation n=46:
Final Evaluation not available n=7:
- Lost to follow-up* n=5
- Withdrew consent n=2

*If there is no response after 3 failed attempts to contact the patient, the site mails a certified letter to the patient’s last known address.
eFigure II
Patient Flow for Randomized Patients (n=108) – Per Protocol Follow-up

**Allocation:** Penumbra System + IV tPA (n=55)

- Per-Protocol Enrollment n=39
  - Excluded from Per-Protocol n=16
    - Stenosis proximal to occlusion that requires treatment prior to thrombus removal (n=6)
    - Infarct > 1/3 MCA territory (n=5)
    - Pre-existing neurologic deficit (n=1)
    - Clot length < 8mm (n=3)
    - MCA M4 parietal distal small branch occlusion (n=1)

- 90 Day Follow-Up
  - Final endpoint data available n=37
  - Final endpoint data not available n=2
    - Lost to follow-up (n=2)

**Allocation:** IV tPA alone (n=53)

- Per-Protocol Enrollment n=47
  - Excluded from Per-Protocol n=6
    - Stenosis proximal to occlusion that requires treatment prior to thrombus removal (n=1)
    - Infarct > 1/3 MCA territory (n=4)
    - Pre-existing neurologic deficit (n=1)

- 90 Day Follow-Up
  - Final endpoint data available n=41
  - Final endpoint data not available n=6
    - Lost to follow-up (n=4)
    - Withdrew consent (n=2)
eFigure III
Patient Flow for Randomized Patients (n=108) – Subjects As Treated

Allocation: Penumbra System + IV tPA (n=55)
- Withdrew immediately after randomization n=1
- IV tPA Alone n=9
- IV tPA + Other IA Intervention (No Penumbra System Used) n=2
- Penumbra System + IV tPA n=43

Allocation: IV tPA alone (n=53)
- IV tPA alone n=53

As Treated Analysis:
- Penumbra System + IV tPA (n=43)
- IV tPA alone (n=62)
Figure IVa
Kaplan-Meier for Mortality (ITT)

Log-Rank p-value = 0.1846
Figure IVb
Kaplan-Meier for Mortality (PP)

Treatment Arm (As Randomized)

- Combined IV and IA Penumbra Therapy
- Monotherapy with IV rtPA

Log-Rank p-value = 0.0794
eFigure V
External Consistency Analysis of Mortality

* ESCAPE adjusted analysis p<0.05
### eTable I
**Baseline Characteristics**

<table>
<thead>
<tr>
<th></th>
<th>IV Alteplase+Thrombectomy</th>
<th>IV Alteplase</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (SD)</td>
<td>67 (11)</td>
<td>70 (10)</td>
<td>0.23</td>
</tr>
<tr>
<td>Female (proportion)</td>
<td>38% (21/55)</td>
<td>57% (30/53)</td>
<td>0.08</td>
</tr>
<tr>
<td>Admission NIHSS [IQR]</td>
<td>17 [13,22]</td>
<td>18 [14,22]</td>
<td>0.41</td>
</tr>
<tr>
<td>Glucose [IQR]</td>
<td>111 [99,151]</td>
<td>116 [103,133]</td>
<td>0.93</td>
</tr>
<tr>
<td>Systolic BP (SD)</td>
<td>148 (22)</td>
<td>150 (19)</td>
<td>0.46</td>
</tr>
<tr>
<td>Prior Stroke (proportion)</td>
<td>9.6% (5/52)</td>
<td>7.5% (4/53)</td>
<td>0.74</td>
</tr>
<tr>
<td>Prior TIA (proportion)</td>
<td>6.1% (3/49)</td>
<td>3.8% (2/53)</td>
<td>0.67</td>
</tr>
<tr>
<td>Prior MI (proportion)</td>
<td>8.0% (4/50)</td>
<td>1.9% (1/53)</td>
<td>0.2</td>
</tr>
<tr>
<td>Angina/CAD (proportion)</td>
<td>29% (16/55)</td>
<td>15% (8/53)</td>
<td>0.11</td>
</tr>
<tr>
<td>Hypertension (proportion)</td>
<td>78% (42/54)</td>
<td>79% (41/52)</td>
<td>1.0</td>
</tr>
<tr>
<td>Congestive Heart Failure (proportion)</td>
<td>13% (7/53)</td>
<td>7.7% (4/52)</td>
<td>0.53</td>
</tr>
<tr>
<td>Dyslipidemia (proportion)</td>
<td>43% (23/53)</td>
<td>49% (25/51)</td>
<td>0.69</td>
</tr>
<tr>
<td>Diabetes (proportion)</td>
<td>32% (17/53)</td>
<td>37% (19/51)</td>
<td>0.68</td>
</tr>
<tr>
<td>Atrial Fibrillation (proportion)</td>
<td>33% (18/55)</td>
<td>49% (26/53)</td>
<td>0.12</td>
</tr>
<tr>
<td>Peripheral Artery Disease (proportion)</td>
<td>2.0% (1/50)</td>
<td>3.8% (2/52)</td>
<td>1.0</td>
</tr>
<tr>
<td>Extracranial Cervical Artery Disease (proportion)</td>
<td>8.3% (4/48)</td>
<td>12% (6/52)</td>
<td>0.74</td>
</tr>
<tr>
<td>Current or Former Smoker (proportion)</td>
<td>60% (28/47)</td>
<td>39% (19/49)</td>
<td>0.07</td>
</tr>
</tbody>
</table>
**eTable II**  
**Multivariate Analysis of Ordinal mRS (ITT)**

<table>
<thead>
<tr>
<th>Covariates for Improved Outcome</th>
<th>Odds Ratio</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline NIHSS (per 1 point increase)</td>
<td>0.923</td>
<td>0.0163</td>
</tr>
<tr>
<td>Baseline glucose mg/dL (per 10 point increase)</td>
<td>0.907</td>
<td>0.0434</td>
</tr>
<tr>
<td>Systolic Blood Pressure (per 10 point increase)</td>
<td>0.781</td>
<td>0.0103</td>
</tr>
<tr>
<td>History of Diabetes (vs None)</td>
<td>0.362</td>
<td>0.0299</td>
</tr>
<tr>
<td>ICA target vessel (vs MCA)</td>
<td>0.340</td>
<td>0.0128</td>
</tr>
<tr>
<td>Penumbra System + IV rtPA (vs IV tPA alone)</td>
<td>2.392</td>
<td>0.0229</td>
</tr>
</tbody>
</table>

Final model based on stepwise proportional odds logistic regression for the ordinal outcome of mRS 0-6. All baseline variables with a p-value of <0.20 in the univariate analysis were included as potential covariates. The above final model results in a multivariate adjusted OR of 2.4 with a 95% CI of 1.1, 5.1 (p value of 0.02).
**eTable III**  
**Multivariate Analysis of Ordinal mRS (PP)**

<table>
<thead>
<tr>
<th>Covariates for Improved Outcome</th>
<th>Odds Ratio</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline NIHSS (per 1 point increase)</td>
<td>0.924</td>
<td>0.0251</td>
</tr>
<tr>
<td>History of Hypertension (vs None)</td>
<td>0.282</td>
<td>0.0069</td>
</tr>
<tr>
<td>History of Diabetes (vs None)</td>
<td>0.240</td>
<td>0.0065</td>
</tr>
<tr>
<td>ICA target vessel (vs MCA)</td>
<td>0.304</td>
<td>0.0181</td>
</tr>
<tr>
<td>Penumbra System + IV rtPA (vs IV tPA alone)</td>
<td>2.549</td>
<td>0.0254</td>
</tr>
</tbody>
</table>

Final model based on stepwise proportional odds logistic regression for the ordinal outcome of mRS 0-6. All baseline variables with a p-value of <0.20 in the univariate analysis were included as potential covariates. The above final model results in a multivariate adjusted OR of 2.5 with a 95% CI of 1.1, 5.8 (p value of 0.03).
**eTable IV**  
Unadjusted Analysis of Ordinal mRS (5 and 6 combined)

<table>
<thead>
<tr>
<th>Analysis Population</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intent to Treat (n=96)</td>
<td>1.77</td>
<td>0.86, 3.62</td>
<td>0.12</td>
</tr>
<tr>
<td>Per Protocol (n=78)</td>
<td>2.23</td>
<td>1.00, 4.96</td>
<td>0.05</td>
</tr>
</tbody>
</table>
### eTable V
Stroke Trial Symptomatic ICH Rates

<table>
<thead>
<tr>
<th>Symptomatic ICH</th>
<th>IV Alteplase+ Thrombectomy</th>
<th>IV Alteplase</th>
<th>Reported Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>THERAPY (as prespecified)</td>
<td>9.3%</td>
<td>9.7%</td>
<td>p value = 1.0</td>
</tr>
<tr>
<td>THERAPY (PH1, PH2, RIH, SAH or IVH)*</td>
<td>2.3%</td>
<td>4.8%</td>
<td>p value = 0.64</td>
</tr>
<tr>
<td>MR CLEAN</td>
<td>7.7%</td>
<td>6.4%</td>
<td>Not Reported</td>
</tr>
<tr>
<td>ESCAPE</td>
<td>3.6%</td>
<td>2.7%</td>
<td>RR = 1.4(0.4,4.7)</td>
</tr>
<tr>
<td>EXTEND IA</td>
<td>0%</td>
<td>6%</td>
<td>p value = 0.4</td>
</tr>
<tr>
<td>SWIFT PRIME</td>
<td>0%</td>
<td>3%</td>
<td>p value = 0.12</td>
</tr>
<tr>
<td>REVASCAT</td>
<td>4.9%</td>
<td>1.9%</td>
<td>RR = 2.5 (0.5,13)</td>
</tr>
</tbody>
</table>

*As defined in SWIFT PRIME*
REFERENCES


