ONLINE SUPPLEMENT
Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Contents
TRIAL ORGANIZATION .................................................................................................................. 2
DEFINITIONS.................................................................................................................................. 3
SUPPLEMENTAL METHODS ........................................................................................................... 5
SUPPLEMENTAL RESULTS ............................................................................................................ 7
eFigure I ........................................................................................................................................ 7
eFigure II ....................................................................................................................................... 8
eFigure III ...................................................................................................................................... 9
eFigure IVa .................................................................................................................................... 10
eFigure IVb ................................................................................................................................... 11
eFigure V ...................................................................................................................................... 12
eTable I ......................................................................................................................................... 13
eTable II ......................................................................................................................................... 14
eTable III ....................................................................................................................................... 15
eTable IV ....................................................................................................................................... 16
eTable V ......................................................................................................................................... 17
REFERENCES ............................................................................................................................... 18
TRIAL ORGANIZATION

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**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>Antegrade reperfusion 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 definitions5:
- 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).?

- 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)
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

- IV tPA alone (n=53)

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

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

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

\[
\begin{array}{ccccccc}
\text{ESCAPE}^a & \text{SWIFT PRIME} & \text{EXTEND-IA REVASCAT} & \text{MR CLEAN} & \text{THERAPY} \\
10\% & 9\% & 9\% & 18\% & 19\% & 12\% & 24\% \\
\end{array}
\]

- ESCAPE adjusted analysis p<0.05

- IA+IV
- IV Alone
## 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


