Special Report

State of Acute Endovascular Therapy
Report From the 12th Thrombolysis, Thrombectomy, and Acute Stroke Therapy Conference

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Acute endovascular therapy for ischemic stroke is at a pivotal juncture. Until recently, on the basis of randomized trials comparing devices, we knew that endovascular treatment options were effective in quickly restoring blood flow and that successful early recanalization was associated with better functional outcome when compared with sustained occlusion.1,2 We did not have randomized evidence that available acute endovascular therapy improved patient outcomes; the initial randomized controlled trials of endovascular recanalization treatment published in February of 2013—the Phase II Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy (MR RESCUE), Phase III Interventional Management of Stroke (IMS) III, and Local Versus Systemic Thrombolysis for Acute Ischemic Stroke (SYNTHESIS) trials—failed to demonstrate improved clinical outcomes.3–5

Many factors may have contributed to the failure of these 3 initial trials to show endovascular benefits. These trials were performed during a period of rapid evolution of imaging and treatment options, and used intra-arterial thrombolysis, or first-generation device therapies at best, with little use of newer generation devices, such as stent retrievers, demonstrated to achieve significantly higher rates of recanalization.1,2 Patients with mild or moderate stroke severity may have been less likely to benefit from endovascular reperfusion based on IMS III and Prolyse in Acute Cerebral Thromboembolism (PROACT) II post hoc analyses and others.6,7 The power of these trials was diluted by

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including subjects without intracranial vessel occlusions, and post hoc analyses of IMS III suggested a potential treatment effect among stroke patients with baseline computed tomographic (CT) angiographic occlusions.8 Larger vessel occlusions, which are more resistant to recanalization by intravenous recombinant tissue-type plasminogen activator (r-tPA), such as intracranial internal carotid artery (ICA) location or occlusions >8 mm, may have been more likely to show a treatment effect of endovascular therapy supplementing intravenous r-tPA.8,9 Faster angiographic reperfusion could lead to better outcomes in the endovascular arm and thereby increase treatment effect.10 Patients with substantial ischemic burden on baseline imaging (Alberta Stroke Program Early CT Score [ASPECTS], ≤4) may have poor prognoses regardless of treatment, and their exclusion could have increased trial power.11 It was suggested that patients with significant perfusion–diffusion mismatch or other criteria for penumbral selection might represent an enriched, responder population.12 On the basis of the experiences of these 3 clinical trials with broad inclusion criteria, the field shifted toward designing and implementing proof-of-principle trials among the most promising patient cohorts.

On October 25, 2014, at the World Stroke Congress, the first Phase III, randomized trial demonstrating benefit of endovascular device therapy was announced—the Dutch Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands (MR CLEAN) trial. Berkhemer and colleagues15 reported robust clinical benefit of endovascular therapy in a predominantly intravenous r-tPA–treated 500-subject cohort of ischemic stroke patients with intracranial thrombi. Within 2 weeks, 2 additional trials—the international Endovascular Treatment for Small Core and Proximal Occlusion Ischemic Stroke (ESCAPE) and the Australian Extending the Time for Thrombolysis in Emergency Neurological Deficits-Intra-Arterial (EXTEND-IA)—announced overwhelming efficacy at interim analyses of 316 and 70 patients, respectively, using protocol-prespecified thresholds. Subsequently, at the International Stroke Conference on February 11, 2015, the Covidien-sponsored Solitaire FR as Primary Treatment for Acute Ischemic Stroke (SWIFT-PRIME) trial announced overwhelming efficacy at interim analysis of 196 enrolled patients. Most recently, on March 3, 2015, the French Trial and Cost Effectiveness Evaluation of Intravenous Thrombectomy in Acute Ischemic Stroke (THRACE) trial announced a positive treatment effect of endovascular therapy based on interim review of clinical outcomes of the first 395 subjects. Results are pending from additional trials as well, including the Spanish Endovascular Revascularization With Solitaire Device Versus Best Medical Therapy in Anterior Circulation Stroke Within 8 Hours (REVASCAT) trial, which was halted after a prespecified interim analysis of 174 subjects, and the Penumbra-sponsored Assess the Penumbra System in the Treatment of Acute Stroke (THERAPY) trial, which was prematurely halted after enrolling 108 subjects based on the new state of evidence for endovascular therapy; results from these trials are anticipated at the European Stroke Organisation Conference in April, 2015.

Immediately before these announcements of the first positive trials of thrombectomy, on October 18, 2014, the Virtual International Stroke Trials Archive (VISTA)-Endovascular Collaboration convened in Mannheim as an adjunct to the biennial 12th Thrombolysis, Thrombectomy, and Acute Stroke Therapy conference to plan pooled analyses of major endovascular trials. It was understood that, given the diversity of clinical trial designs and the relatively small sample sizes of recent clinical trials, no single trial would be able to answer many of the critical questions in the field. A detailed inventory of ongoing acute stroke trials was undertaken at the Thrombolysis, Thrombectomy, and Acute Stroke Therapy conference, and plans to pool data were proposed. Here, we provide this timely summary of ongoing endovascular acute stroke trials and incorporate recent developments. We also present our plans for prespecified pooled analyses of endovascular trials of intravenous r-tPA–treated patients.

Ongoing and Recently Completed Randomized Controlled Trials

As of March 5, 2015, we were aware of 13 recently completed, early halted, or ongoing randomized controlled trials testing endovascular therapy (versus either intravenous r-tPA or supportive care). These 13 trials enrolled 1707 subjects with 7535 subjects originally planned. Among these 13 trials, 10 trials included intravenous r-tPA–treated subjects and 7 trials included intravenous r-tPA–ineligible cohorts (Table 1); 4 of these trials consisted of both intravenous r-tPA and r-tPA–ineligible cohorts. Five trials, including 3 with intravenous r-tPA–treated cohorts, were continuing to enroll subjects.

Beyond the requirement for a symptomatic intracranial occlusion, trial eligibility criteria varied in terms of locations of intracranial occlusions, endovascular devices permitted, allowance of extracranial high-grade stenosis/occlusions, ranges of stroke severity (baseline National Institutes of Health Stroke Scale [NIHSS]), time limits for enrollment, and multimodal imaging parameters (Table 2).

Designs of Recently Completed Randomized Controlled Trials

Five recently announced trials—MR CLEAN, ESCAPE, EXTEND-IA, and SWIFT-PRIME, and THRACE—have reported a benefit of endovascular therapy in intravenous r-tPA–treated patients (Table 3; MR CLEAN, ESCAPE, and EXTEND-IA results).

The MR CLEAN trial13 enrolled 500 subjects using a pragmatic design that had broad entry criteria, with the final enrollment decision based on clinical judgment. Specifically, subjects were potentially eligible if they had an intracranial artery occlusion of diverse degree (including as distal as the A2 segment of the anterior cerebral artery) and almost any stroke severity (including NIHSS as low as 2), and intravenous r-tPA eligibility/treatment was not required; there were no additional imaging selection criteria and no upper age limit. Patients who met these eligibility criteria were then offered the trial based on the clinical impression of the enrolling investigators that the benefit of endovascular therapy was uncertain for the given patient; this was referred to as the grey area principle and stemmed from the uncertainty principle.13,24 Ultimately, despite a broadly eligible population, enrolled subjects
consisted of relatively severe strokes (median NIHSS, 18) and primarily middle cerebral artery and internal carotid artery occlusions (92%). The majority of the cohort was treated with intravenous r-tPA (89%), and a great preponderance randomized to the endovascular arm was treated with stent retriever devices (82%). Recruitment was rapid, occurring >40 months in a country of 16 million inhabitants, possibly due in part to reimbursement for mechanical embolectomy being limited to patients enrolled in the trial. A robustly positive effect of endovascular therapy was demonstrated (Table 3).  

The ESCAPE trial16 enrolled 316 planned subjects and had aimed to enroll 500 consecutively eligible patients based on the trial’s defined population. Eligible patients were to be within 12 hours of stroke onset (including wake up strokes) with an NIHSS of >5 and age of ≥18 years. From this group, imaging was performed to select subjects with a major proximal intracranial occlusion (ICA T/L, M1-middle cerebral artery with or without ICA T/L, or both/all M2s) and to exclude those with any of the following: (1) unfavorable CT scan defining a moderate to large ischemic core, indexed by ASPECTS <6; (2) poor collateral circulation defined on single/multiphase CTA; or (3) CT perfusion imaging (cerebral blood volume ASPECTS, <6) if performed. Arterial puncture was intended to be within 60 minutes of first-slice baseline noncontrast CT, and first reperfusion was to be achieved within 90 minutes of the first-slice baseline CT. Any off-the-shelf thrombectomy device was permissible, but, in practice, newer generation retrievable stent devices were used. The majority of enrolled subjects (≈75%) were treated with intravenous r-tPA. The trial was stopped on the advice of the Data and Safety Monitoring Board after an interim analysis using protocol-prespecified thresholds showed overwhelming efficacy, and final published results were also robustly positive (Table 3).  

The EXTEND-IA trial18 was a Phase II trial that enrolled 70 of 100 planned subjects. Patients were eligible if they were ≥18 years old, had ICA, M1, or M2 occlusions treated with intravenous r-tPA within 4.5 hours of stroke onset, could achieve arterial puncture for endovascular therapy within 6 hours of onset, and met multimodal imaging criteria. A key difference was the use of automated CT perfusion using Rapid Processing of Perfusion and Diffusion (RAPID)19 software for patient selection. Imaging criteria involved CT perfusion imaging evidence of salvageable tissue and ischemic core <70 mL. This trial was also stopped based on an interim analysis showing overwhelming efficacy for the coprimary efficacy end point. Unlike the other 3 trials, the primary end point was a combined tissue and clinical end point—reperfusion on 24-hour perfusion imaging and early neurological improvement (8-point reduction in NIHSS score between baseline and day 3 or reaching NIHSS 0–1 at day 3). There was also a major and statistically
significant benefit in 90-day functional outcome, despite the smaller sample size (Table 3).20

The SWIFT-PRIME trial21 was a Phase III trial that enrolled 196 of 833 planned subjects on being halted by their Data Safety and Monitoring Board after demonstrating overwhelming efficacy. Patients were eligible if they were 18 to 85 years old, treated with intravenous r-TPA, and could start endovascular therapy within 6 hours. Similar to EXTEND-IA, the trial initially required the presence of penumbral as assessed by RAPID software for inclusion and then expanded eligibility to allow for investigator judgment of imaging evidence for benefit of endovascular therapy. Preliminary results were robust and positive as presented at the 2015 International Stroke Conference, and the publication of final results is pending.

Finally, the Phase III THRACE trial22 was halted on March 3, 2015, on the advice of their Data Safety and Monitoring Board after enrolling 412 of 480 planned subjects. This trial has announced a positive treatment effect of endovascular therapy based on interim review of clinical outcomes of the first 395 subjects. Patients were eligible for the THRACE trial if they had intracranial occlusion of ICA, M1, or distal basilar arteries, had an NIHSS between 10 and 25, and could start endovascular therapy within 5 hours. Unlike the previous positive trials, there were no proscribed imaging selection criteria and they allowed a large range of endovascular devices. Final outcomes, including the remaining 17 subjects enrolled, will be available by June, 2015. Further details and final results of the THRACE trial are anticipated at the 2016 International Stroke Conference.

### Table 2. Designs of Endovascular Randomized Controlled Trials Testing the Efficacy of Endovascular Therapy

<table>
<thead>
<tr>
<th>Trials</th>
<th>Device</th>
<th>Thrombus</th>
<th>Endovascular Start</th>
<th>NIHSS</th>
<th>Advanced Imaging Selection Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>BASICS</td>
<td>All available options</td>
<td>Basilar</td>
<td>≤6 h</td>
<td>NIHSS≥10</td>
<td>No</td>
</tr>
<tr>
<td>DAWN</td>
<td>TREVO</td>
<td>ICA/M1</td>
<td>Randomized at 6–24 h</td>
<td>NIHSS≥10</td>
<td>Core and penumbra*</td>
</tr>
<tr>
<td>ESCAPE</td>
<td>Available choices since 2013</td>
<td>ICA/M1/M1 equivalent (2 M2s)</td>
<td>≤12 h</td>
<td>NIHSS&gt;5</td>
<td>Core, collaterals, or penumbra†</td>
</tr>
<tr>
<td>EXTEND-IA</td>
<td>Solitaire</td>
<td>ICA/M1/M2</td>
<td>≤6 h</td>
<td>N/A</td>
<td>Core and penumbra‡</td>
</tr>
<tr>
<td>MR CLEAN</td>
<td>All CE marked devices</td>
<td>ICA/M1/M2/A1/A2</td>
<td>≤6 h</td>
<td>NIHSS≥2</td>
<td>No</td>
</tr>
<tr>
<td>PISTE</td>
<td>All CE marked since 2013</td>
<td>ICA/M1/M2</td>
<td>≤5.5 h</td>
<td>NIHSS≥6</td>
<td>No</td>
</tr>
<tr>
<td>POSITIVE</td>
<td>Penumbra, Solitaire, and TREVO</td>
<td>ICA/M1</td>
<td>≤12 h</td>
<td>NIHSS≥8</td>
<td>Core and penumbra§</td>
</tr>
<tr>
<td>RESILIENT</td>
<td>Solitaire</td>
<td>ICA/M1</td>
<td>≤7.5 h</td>
<td>NIHSS≥10</td>
<td>Core</td>
</tr>
<tr>
<td>REVASCAT</td>
<td>Solitaire</td>
<td>ICA/M1</td>
<td>≤8 h</td>
<td>NIHSS≥6</td>
<td>Core#</td>
</tr>
<tr>
<td>SWIFT-PRIME</td>
<td>Solitaire</td>
<td>ICA/M1</td>
<td>≤6 h</td>
<td>NIHSS≥10, NIHSS≤30</td>
<td>Core+Penumbra**</td>
</tr>
<tr>
<td>THERAPY</td>
<td>Penumbra</td>
<td>ICA/M1/M2</td>
<td>≤5 h</td>
<td>NIHSS≥8</td>
<td>Core, clot ≥8 mm††</td>
</tr>
<tr>
<td>THRACE</td>
<td>MERC, Catch, Penumbra, Solitaire, Trevo, Revive, Penumbra 3d Separator and ACE, Mindframe Capture and Flow, rPRecet</td>
<td>ICA/M1/basilar-distal</td>
<td>≤5 h</td>
<td>NIHSS≥10 and ≤25</td>
<td>No</td>
</tr>
<tr>
<td>THRILL</td>
<td>Solitaire or TREVO</td>
<td>ICA/M1</td>
<td>≤3 h</td>
<td>NIHSS&gt;7 and ≤26</td>
<td>Core‡‡</td>
</tr>
</tbody>
</table>

*ASPECTS indicates Alberta Stroke Program Early CT Score; BASICS, Basilar Artery International Cooperation Study; CE, Conformité Européenne (or European Conformity); CTP, computed tomographic perfusion; CTA-SI, CT angiography source images; DAWN, Trevo and Medical Management Versus Medical Management Alone in Wake Up and Late Presenting Strokes; ESCAPE, Endovascular Treatment for Small Core and Proximal Occlusion Ischemic Stroke; DWI, diffusion weighted imaging; EXTEND-IA, Extending the Time for Thrombolyis in Emergency Neurological Deficits-Intra-Arterial; ICA, internal carotid artery; IV r-TPA, intravenous recombinant tissue-type plasminogen activator; MCA, middle cerebral artery; MR CLEAN, Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands; NIHSS, National Institutes of Health Stroke Scale; PISTE, Pragmatic Ischaemic Stroke Thrombectomy Evaluation; POSITIVE, Perfusion Imaging Selection of Ischemic Stroke Patients for Endovascular Therapy; rCBV, regional cerebral blood volume; RESILIENT, Endovascular Treatment With Solitaire FR as Best Medical Therapy in Acute Ischemic Stroke; REVASCAT, Endovascular Revascularization With Solitaire Device Versus Best Medical Therapy In Anterior Circulation Stroke Within 8 Hours; SWIFT-PRIME, Solitaire FR as Primary Treatment for Acute Ischemic Stroke; THERAPY, Assess the Penumbra System in the Treatment of Acute Stroke; THRACE, Trial and Cost Effectiveness Evaluation of Intra-Arterial Thrombectomy in Acute Ischemic Stroke; and THRILL, Comparison of Thrombectomy and Standard Care for Ischemic Stroke in Patients Ineligibility for Tissue Plasminogen Activator Treatment.

†Less than 1/3 MCA territory involved. Clinical imaging mismatch defined as one of the following on Rapid Processing of Perfusion and Diffusion (RAPID) MR-DWI or CTP-rCBF maps: (1) 0–20 cc ischemic core and NIHSS≥10 (and age, ≥80 y), (2) 0–30 cc ischemic core and NIHSS≥10 (and age, <80 y), or (3) >30 cc to ≤5 cc ischemic core and NIHSS≥20 (and age, <80 y).
†Baseline ASPECTS 6–10 on CT with confirmatory evidence of ASPECTS 6–10 on either CT angiography collateral or perfusion imaging.
‡CT perfusion demonstrating a penumbra (Tmax>6 s) vs ischemic core (rCBF<30%) mismatch ratio>1.2, absolute mismatch>10 cc, and an ischemic core <70 cc.
§Absence of large (>1/3 of the middle cerebral artery) regions of clear hypodensity on the baseline CT scan or ASPECTS of <7. The presence of an associated large penumbra as defined by physiological imaging according to the standard of practice at the participating institution.
||ASPECTS score of <7 on CT or CTA-SI or <6 on DWI magnetic resonance imaging.
#ASPECTS >6 on CT or CTA-SI or >5 on DWI magnetic resonance imaging.
**CT hypodensity or MR hyperintensity of <1/3 of the MCA or in other territories, ≤100 cc of tissue, baseline ASPECTS 6–10, and absence of imaging evidence that suggests, in the opinion of the investigator, the subject is not appropriate for mechanical thrombectomy intervention.
††Large infarct region (ex: >1/3 of the middle cerebral artery territory) and thin-slice reconstruction CT with thrombus ≥8 mm.
‡‡ASPECTS, 7–10.
Thus, over a landmark 5-month period, 4 successive, randomized trials have together unequivocally shown the benefit of endovascular therapy for selected patients with acute ischemic stroke, and a fifth trial has been announced. Patients enrolled in the 4 resulted trials had intracranial occlusions of larger arteries, smaller ischemic cores, and rapid angiographic reperfusion, and their endovascular treatments generally consisted of modern devices. In addition to these key principles, each also required something else: (1) the grey area principle for MR CLEAN, (2) a favorable collateral profile for ESCAPE, (3) significant penumbral tissue for EXTEND-IA, and (4) optional selection by penumbral imaging for SWIFT-PRIME. With their disparate design features, the challenge for the clinician will be to determine how to optimally operationalize patient selection for endovascular therapy in a given region and center.

Future Directions—Pooled Analysis Plans

The recently presented and published trial results allow the field to progress from asking whether endovascular therapy is clinically beneficial to asking who will benefit from endovascular therapy. Furthermore, we need to determine the generalizability of these recent trial findings, including how to apply them in varied healthcare structures across the world while maintaining similar or better risk-benefit ratios. Pooled analyses will play a critical role in advancing the field.

In addition to pooling the trials that have reported results to date, there is the opportunity to learn from the additional trials that have halted early. Some will likely be underpowered to demonstrate efficacy of the endovascular approach. None, whether completed as planned or aborted early or still ongoing, will be individually powered to give definitive guidance about more granular aspects of patient selection. These questions are generally best answered using a large mega-trial or patient-level analysis of pooled data from a group of trials.

The 3 previously completed (IMS III, SYNTHESIS, and MR RESCUE) and all 13 recently completed or ongoing endovascular trials with intravenous r-tPA-treated subjects (Table 1) have committed to a retrospective patient-level pooled analysis of randomized trials testing combined intravenous r-tPA/endovascular versus intravenous r-tPA alone, entitled the Thrombectomy and tPA (TREAT) analysis. The TREAT proposal will be performed within the VISTA-Endovascular consortium. It is anticipated that each completed trial will publish primary results and key secondary results before proceeding with the TREAT/VISTA collaboration.

The primary data pool for TREAT will consist of subjects enrolled in prospective, randomized trials with newer generation devices (direct aspiration catheters or stent retrievers) comprising at least 85% of treated cases, and sensitivity analyses will be performed by including trials using older generation devices. Full inclusion criteria are listed in Table 4. As of March 5, 2014, >1700 subjects were enrolled in ongoing and recently completed TREAT-eligible trials.

The TREAT analysis will test whether key patient selection criteria modify treatment effect. Specifically, we will test whether the following variables modify treatment effect: location of intracranial arterial occlusion (intracranial ICA versus M1 versus M2 versus A1/A2), stroke severity (baseline NIHSS), time to initiation of intravenous r-tPA and randomization, early ischemic changes on baseline neuroimaging, and age. Among cases with available data, we will also assess treatment effect modification based on the presence of collaterals on baseline computed tomographic angiography/MRA and evidence of mismatch between thresholded perfusion and evidence of mismatch between thresholded perfusion.

Table 3. Baseline Demographics and Results of the Recent Randomized Randomized Controlled Trials of Endovascular Therapy

<table>
<thead>
<tr>
<th>Trials</th>
<th>Age (median, y)</th>
<th>Baseline NIHSS (median)</th>
<th>IV r-tPA Treatment Rate</th>
<th>Endovascular Only</th>
<th>Endovascular vs Control Arm 90 d Clinical Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>mTICI 2b/3</td>
<td>mRS Common</td>
</tr>
<tr>
<td>MR CLEAN</td>
<td>65</td>
<td>18</td>
<td>89%</td>
<td>59%</td>
<td>1.7 (1.2–2.3) 33 vs 19 21 vs 22</td>
</tr>
<tr>
<td>ESCAPE</td>
<td>71</td>
<td>17</td>
<td>76%</td>
<td>72%</td>
<td>2.6 (1.7–3.8) 54 vs 29 10 vs 19</td>
</tr>
<tr>
<td>EXTEND-IA†</td>
<td>71.5</td>
<td>15</td>
<td>100%</td>
<td>86%</td>
<td>2.0 (1.2–3.8) 71 vs 40 9 vs 20</td>
</tr>
</tbody>
</table>

ESCAPE indicates Endovascular Treatment for Small Core and Proximal Occlusion Ischemic Stroke; EXTEND-IA, Extending the Time for Thrombolysis in Emergency Neurological Deficits-Intra-Arterial; IV r-tPA, intravenous recombinant tissue-type plasminogen activator; mRS, modified Rankin Scale; mTICI, modified thrombolysis in cerebral infarction; NIHSS, National Institutes of Health Stroke Scale; and OR, odds ratio.

*Common OR for mRS was calculated with different statistical methods for each trial.
†The EXTEND-IA primary outcome measure was a combined end point of tissue reperfusion at 24 h and early neurological improvement at day 3 (ie, 8-point reduction in NIHSS score from baseline or reaching NIHSS 0–1).

Table 4. Requirements for Datasets Included in the Thrombectomy and tPA (TREAT) Pooled Analysis

<table>
<thead>
<tr>
<th>Minimum data set of 20 subjects</th>
<th>Prospectve and randomized data set of combined IV tPA with endovascular therapy versus IV tPA alone</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV tPA initiated within 3 or 4.5 h</td>
<td>Documented entry criteria</td>
</tr>
<tr>
<td>Documented consent after local IRB-approved procedure</td>
<td>Documented treatment times (IV r-tPA start, IA arterial access start time)</td>
</tr>
<tr>
<td>Baseline NIHSS, age, sex, glucose, and side (right vs left) of brain ischemia recorded</td>
<td>Documented treatment times (IV r-tPA start, IA arterial access start time)</td>
</tr>
<tr>
<td>Blinded modified Rankin Score assessment at 90 days</td>
<td>Registered with clinicaltrials.gov or comparable governmental Web site</td>
</tr>
</tbody>
</table>

IA indicates intra-arterial; IRB, institutional review board; IV r-tPA, intravenous recombinant tissue-type plasminogen activator; and NIHSS, National Institutes of Health Stroke Scale.
Table 5. Primary and Secondary Clinical Outcomes for the Thrombectomy and t-PA (TREAT) Pooled Analysis

<table>
<thead>
<tr>
<th>Primary outcome</th>
<th>mRS distribution at 90 days, adjusted*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Secondary outcomes</td>
<td>mRS distribution at 90 days, unadjusted</td>
</tr>
<tr>
<td></td>
<td>mRS 0–2 at 90 days, adjusted*</td>
</tr>
<tr>
<td>Symptomatic intracranial hemorrhage†</td>
<td></td>
</tr>
<tr>
<td>Mortality at 90 days</td>
<td></td>
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</tbody>
</table>

†IV r-PA indicates intravenous recombinant tissue-type plasminogen activator; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; and SITS-MOST, Safe Implementation of Thrombolysis in Stroke-Monitoring Study.

*Adjusted for age, baseline NIHSS, baseline glucose, time to IV r-PA, and side of brain ischemia.

†SITS-MOST registry definition.

Imaging and ischemic core. An effort to pool the raw imaging data from all of these trials through the Stroke Imaging Repository Consortium is underway to allow analyses beyond the prespecified standard imaging variables recorded in the individual trials. Furthermore, we will explore the effects of general anesthesia, the presence of ipsilateral extracranial carotid occlusion, time to start of endovascular treatment, and time to angiographic reperfusion on clinical outcome. Planned primary and secondary clinical outcome measures are listed in Table 5.

We will initiate the TREAT project once ≥2 of the trials have available data. If a meta-analysis is conducted repeatedly without any allowance for multiplicity, the overall risk of a false-positive finding will increase with the number of meta-analyses performed. Because the sample available to answer each of the prespecified questions is not yet known and will accumulate incrementally as each trial completes, we will use sequential meta-analysis techniques to handle the multiple testing and will formally declare results only once a threshold has been crossed for efficacy or futility. Sequential meta-analysis techniques are a more robust approach than traditional cumulative meta-analysis techniques as the point and interval estimates are adjusted for multiple testing. In addition, the power can be quantified, stopping for futility is an option, and gains in efficiency can be achieved. For each prespecified analysis, we will use the triangular testing procedure of Whitehead, with a target effect size of 10% improvement in the ordered categories of modified Rankin Scale and a 1-sided value of 0.005 (representing a 2-sided \( P \) value of 0.01). The full statistical analysis plan will be published in advance of conducting the analyses.

Future pooled analyses will also be planned for trials with intravenous r-PA–ineligible subjects. Subject accrual is too low for performing such an analysis in the near future.

In conclusion, we now have evidence that mechanical thrombectomy can improve patient outcomes from successive, independent, randomized trials with different selection paradigms. With >1700 intravenous r-PA–treated subjects enrolled in these and additional endovascular trials, we look forward to initiating patient-level pooled analyses through a large-scale, international collaboration. These analyses will advance our understanding of optimal patient selection criteria for endovascular therapy in daily clinical practice and will allow us to plan future clinical trials to further enhance outcomes after acute ischemic stroke.

Sources of Funding

Dr Saver’s services as a scientific consultant to Covidien, Stryker, and Codman for Pragmatic Ischaemic Stroke Thrombectomy Evaluation (PISTE). Drs Goyal, Hill, and Davis were supported by unrestricted grant to University of Calgary from Covidien, and active/in-kind support consortium of public/charitable sources (Heart & Stroke Foundation, Alberta Innovates Health Solutions, and Alberta Health Services) and the University of Calgary (Hotchkiss Brain Institute, Departments of Clinical Neurosciences and Radiology, and Calgary Stroke Program) for Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) trial. Drs Jauch and Turk were supported by Covidien, Stryker, and Penumbra grants for Perfusion Imaging Selection of Ischemic Stroke Patients for Endovascular Therapy (POSITIVE) trial. Dr Ciccone was supported by Italian Medicines Agency for Local Versus Systemic Thrombolysis for Acute Ischemic Stroke (SYNTHESIS) and SYNTHESIS-Expansion trials. Dr Nogueira was supported by Stryker Neurovascular for Trevo-2 and Trevo and Medical Management Versus Medical Management Alone in Wake Up and Late Presenting Strokes (DAWN) trials. Drs Nogueira, Saver, and Goyal were supported by Covidien for SWIFT and Solitaire FR as Primary Treatment for Acute Ischemic Stroke (SWIFT-PRIME) trials.

Disclosures

Dr Khatri received financial support to Department for research roles from Genentech (lead principal investigator [PI] of Prevention of Relapses and Disability by Interferon β-1a Subcutaneously in Multiple Sclerosis [PRISMS] trial), Penumbra (neurology PI of Assess the Penumbra System in the Treatment of Acute Stroke [THERAPY] trial), and Biogen (Data and Safety Monitoring Board [DSMB] member). Dr Hacke is a steering committee member for Solitaire FR as Primary Treatment for Acute Ischemic Stroke (SWIFT-PRIME) and the Chair of Virtual International Stroke Trials Archive (VISTA)-Endovascular. Dr Fiehler received funding from DFG, SFB 936 Multi-site Communication in the Brain and BMBF for Airchill Research Project. He received consultant/lecturer fees from Acandis, Bayer, Boehringer Ingelheim, Codman, Covidien, MicroVention, Penumbra, Philips, Sequent, Siemens, and Stryker. Dr Saver is an employee of the University of California (UC). UC Regents received funding for Dr Saver’s services as a scientific consultant to Covidien, Stryker,BrainsGate, Pfizer, and St. Jude Medical. He is an unpaid site investigator in multicenter trials run by Lundbeck for which the UC Regents received payments for enrollment of subjects. He is also an unpaid consultant to Genentech for PRISMS trial. UC has patent rights in...
retrieval devices for stroke. Dr Diener received honoraria for participation in clinical trials, contribution to advisory boards, or oral presentations from Abbott, Allergan, AstraZeneca, Bayer Vital, BMS, Boehringer Ingelheim, CoAxia, Corinnum, Coviden, Daiichi-Sankyo, D-Pharm, Fresenius, GlaxoSmithKline, Janssen-Cilag, Johnson & Johnson, Knoll, Lilly, MSD, Medtronic, MindFrame, Neurobiological Technologies, Novartis, Nordisk, Paion, Parke-Davis, Pfizer, Sanofi-Aventis, Schering-Plough, Servier, Solvay, Syngis, Teleciris, Thrombogenics, WebMD Global, Wyeth, and Yamanouchi. He received financial support for research projects from AstraZeneca, GSK, Boehringer Ingelheim, Lundbeck, Novartis, Janssen-Cilag, Sanofi-Aventis, Syngis, and Teleciris. The department received research grants from DFG, BMBF, European Union, National Institutes of Health (NIH), Bertelsmann Foundation and Heinz-Nixdorf Foundation. He is also an editor of Aktuelle Neurologie, Arzneimittellheather, Kopfschmerzneues, and guidelines of the German Neurological Society; coeditor of Cephalalgia, editorial board of Lancet Neurology, Stroke, European Neurology, and Cerebrovascular Disorders.

Dr Bendszus is a PI of Comparison of Thrombectomy and Standard Care for Ischemic Stroke in Patients Ineligible for Tissue Plasminogen Activator Treatment [THRIIL; uncompensated] and received consultant/lecture fees from Codman, Guerbet, Novartis, Vascular Dynamics, and Roche. Dr Bracard received grant from French Ministry of Health for Trial and Cost Effectiveness Evaluation of Intraluminal Device [Stent System in the Treatment of Intracranial Aneurysms (FRED) trial. Dr Broderick received research monies to department from Genentech (PRISMS SC); travel to conference payment from Boehringer Ingelheim. Dr Ciccone received consultant/lecture fees from Boehringer Ingelheim and Teva. Dr Dávalos received honoraria from Medtronic. Dr Davis is a consultant to Boehringer Ingelheim and received travel grants from BMS Pfizer, Allergan, Coviden, and Ever Neuropharma. Dr Dippel received nominal unrestricted grants from AngioCare, Coviden/ev3, Medac/Lamepro, and Penumbra. Dr Fiorella royalties and consulting fees from Codman/JnJ; consulting fees and research support from Penumbra; research support from Microvention/Terumo, Siemens Medical Imaging, and Sequent Medical; and consulting fees from ev3. Dr Goyal is a consultant to Coviden (educational engagements). Dr Hill received research grant from Hoffman La Roche, and he is a consultant to Merck (adjudication committee for clinical trial). Dr Jauch received research grants from Genentech (Executive Committee PRISMS Trial). Dr Jovin is a consultant to Silk Road Medical and an unpaid consultant to Coviden Vascular, and Stryker Neurovascular. Dr Lieberskind is a consultant to Stryker and Coviden and an employee of UC, which holds a patent on retriever devices for stroke, at the time of this work. Dr Majooie received payment for lecture to institution from Stryker. Dr Mocco is a PI of THERAPY, Perfusion Imaging Selection of Ischemic Stroke Patients for Endovascular Therapy (POSITIVE), Large Aneurysm Randomized Trial: Flow Division Versus Traditional Endovascular Coiling Therapy (LARGE), Framing Eighteen Coils in Cerebral Aneurysms Trial (FEAT) Trial, and Barrel Study; he is a consultant to Medina Medical, Edge Therapeutics, Pulsar, and Lazarus Effect; he is a science advisory board member for Codman Neurovascular; and he is an investor of Blockade Medical and Medina Medical. Dr Muir is an advisory board member for Coviden in 2011. Dr Nogueira received support from Coviden (Study of Tamofoxifen andRaloxifene [STAR] Trial angiographic Core Laboratory—significant), Penumbra (3D Separator Trial Executive Committee—no payment), and Rapid Medical (Stroke Trial [DSMB—modest]. Dr Siddiqui received financial interests from Hotspur, Intratech Medical, StimSom, Valor Medical, Blockade Medical, Lazarus Effect, Pulsar Vascular, and Medina Medical. He is a consultant to Codman & Shurtleff, Coviden Vascular Therapies, GuidePoint Global Consulting, Penumbra, Stryker, Pulsar Vascular, Microvention, Lazarus Effect, Blockade Medical, and Reverse Medical. He is a National Steering Committee member of Penumbra, 3D Separator trial; Coviden, for SWIFT-PRIME trial; Microvention, for Pivotal Study of the FRED [FlowRedirection Intraluminal Device] Stent System in the Treatment of Intracranial Aneurysms (FRED) trial. He is also a member of speakers’ bureaus for Codman & Shurtleff and an advisory board member for Codman & Shurtleff, Coviden Neurovascular, ICAVL, and Medina Medical, and he received honoraria from Abbott Vascular, Codman & Shurtleff, and Penumbra. Dr Thomalla is a neurological principal investigator of THRILL and received consultant/lecture fees from Bayer Healthcare, Bristol-Myers-Squibb/Pfizer, Boehringer Ingelheim, and Coviden. Dr Tomick is a coprincipal investigator of the NIH-funded Interventional Management of Stroke (IMS) II trial. Dr Turk received research grants from Toshiba. He is a consultant to Penumbra, Stryker, Lazarus Effect, and Siemens, and he is a member of the speakers’ Bureau for Penumbra. Dr White is an educational consultant to Codman and Microvention, and he received research grant from Microvention for Stroke: An Evaluation of Thrombectomy in the Aging Brain (STABILISE) Trial and travel support from Microvention. Dr Zaidat is a consultant/speaker for Penumbra, Stryker, and Coviden. Dr Lees plays a leadership role in VISTA, a DMC member for REVASCAT, and a scientific committee member for SITS and SITS-OPEN. He is also the president of ESO that receives sponsorship from companies.

References


Kév Woros: clinical trial ■ thrombectomy ■ thrombolysis therapy
State of Acute Endovascular Therapy: Report From the 12th Thrombolysis, Thrombectomy, and Acute Stroke Therapy Conference


on behalf of the VISTA-Endovascular Collaboration

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제12회 혈전유해, 혈전제거 및 급성뇌졸중치료 회의 보고서

State of Acute Endovascular Therapy
Report From the 12th Thrombolysis, Thrombectomy, and Acute Stroke Therapy Conference

Pooja Khatri, MD, MSc; Werner Hacke, MD; Jens Fiehler, MD; Jeffrey L. Saver, MD; Hans-Christoph Diener, MD, PhD; Martin Bendszus, MD; Serge Bracard, MD; Joseph Broderick, MD; Bruce Campbell, MBBS, BMedSci, PhD; Alfonso Ciccone, MD; Antoni Davalos, MD, PhD; Stephen Davis, MD; Andrew M. Demchuk, MD; Diederik Dippel, MD; Geoffrey Donnan, MD; David Fiorella, MD, PhD; Mayank Goyal, MD; Michael D. Hill, MD, MSc; Edward C. Jauch, MD; Tudor G. Jovin, MD; Chelsea S. Kidwell, MD; Charles Majoie, MD, PhD; Sheila Cristina Ouriques Martins, MD; Peter Mitchell, MD; J Mocco, MD, MS; Keith Muir, MD; Raul G. Nogueira, MD; Wouter J. Schonewille, MD, PhD; Adnan H. Siddiqui, MD, PhD; Gotz Thomalla, MD; Thomas A. Tomitsch, MD; Aquilla S. Turk, DO; Philip M. White, MD; Osama O. Zaidat, MD; David S. Liebeskind, MD; Rachel Fulton, MD; Kenneth R. Lees, MD; on behalf of the VISTA-Endovascular Collaboration

(Stroke. 2015;46:1727-1734.)

급성혈관내치료에 대한 급성혈관내치료는 중요한 전기에 있다. 기구들을 비교한 최근의 무작위시험들을 통해 혈관내치료가 빠른 혈류 회복에 효과적이며 조기에 성공적으로 재개통되면 계속 폐색된 경우보다 기능적 예후가 좋다는 것을 알게 되었다.1,2 우리에게는 현재까지 나와 있는 급성혈관내치료가 환자의 예후를 호전시킨다는 무작위시험 결과가 없었다. 2013년 2월에 발표된 혈관내재관형성치료에 대한 세 개의 초기 무작위대조군시험—제2상 Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy (MR RESCUE), 제3상 Interventional Management of Stroke (IMS) III, Local Versus Systemic Thrombolysis for Acute Ischemic Stroke (SYNTHESIS) 시험—은 임상적 예후 개선에 실패하였다.3–5 이 세 개의 초기 임상시험의 실패를 설명하기 위해 여러 요인들이 있지만, 현재 가장 흔히 인정받는 것은 스테인트 리트리✈어(Stent Retriever)를 이용해 치료를 하였던 것으로 증명된 stent retriever 등 신세대 기구는 거의 사용하지 않았다.1,2 IMS III와 Prolyse in Acute Cerebral Thromboembolism (PROACT) II 사후분석 및 다른 연구결과들을 근거로 추론할 때 뇌졸중 중증도가 낮거나 중등도인 경우에는 혈관내치료의 효과가 없을 수 있다.3,6,7 이 연구들의 검증력은 두개내 혈관폐색이 없는 환자를 등록하여 희석되었고 IMS III의 사후분석은 초기 CT 혈관조영에서 폐색이 있는 뇌졸중 환자에서는 치료효과 있음을 시사하였다.8 재조합조직플라스미노겐활성제(recombinant tissue-type plasminogen activator, r-tPA)가 효과가 없는 두개내 속목동맥(internal carotid artery)에 대한 연구결과가 이미 보고되었으며, 이 점은 현재 أم시드의 치료를 주로 이용하는 경향이 있다.9,10 건강증진은 암시드의 치료를 주로 이용하는 경향이 있다.9,10
carotid artery, ICA)의 폐색이거나 8 mm 초과의 폐색 등 큰혈관폐색이 있는 경우 r-tPA 정맥주사를 보충하는 혈관내치료가치료효과를 보일 가능성이 더 크다. 혈관조영상 신속히 해결할 수 있는 혈관내치료로 시작한 결과를 이어간 내고 치료효과를 높일 수 있었다. 초기 영상에서 혈류 부담이 큰 경우(Alberta Stroke Program Early CT Score [ASPECTS], ≤4) 치료의 비효과와 입상상황의 재관류는 혈관내치료에서 개선된 결과를 보이기 위해 r-tPA 정맥주사를 보충하는 혈관내치료는 혈관내치료를 보여주기도 하였다. 혈관조영상 신속한 재관류는 혈관내치료군에서 개선된 결과를 이끌어내고 치료효과를 높일 수 있었다. 초기 영상에서 허혈 부담이 큰 환자들은 대상으로서 재관류를 증가시키고 치료효과를 높일 수 있는 환자들임이 있었다. 넓은 선정기준을 가졌던 이 세 임상시험에서 얻은 경험을 바탕으로 의료현장에서는 가장 유망한 환자군을 대상으로 proof-of-principle 실험을 계획하고 실현하는 방향으로 전환되었다.


이런 혈관내치료의 효과를 입증한 최초의 임상시험들이 진행 중인 무작위대조시험

2015년 5월 3일 기준으로 r-tPA 정맥주사 또는 보존적 치료를 한 경우와 혈관내치료를 한 경우를 비교한 무작위대조시험으로서 최근에 종료 또는 조기 종료되었거나 진행 중인 경우가 13개로 알려져 있다. 이 13개의 시험들은 원래는 7535명을 등록하기로 계획하였으나 실제로는 1707명으로 등록되었다. 13개의 시험 중에서낼 결론은 r-tPA 치료받은 환자들을 포함하였고 임금 계기는 r-tPA가 적합하지 않은 환자들을 포함하였다(Table 1). 네 개는 r-tPA 정맥주사를 치료받은 환자와 r-tPA에 부적합한 환자들 모두 포함하였다. r-tPA 치료를 받은 환자들을 포함하는 세 개의 시험 또한 다섯 개의 시험은 계속 환자 등록 중에 있다. 증상적 두개내폐색이 있다면 추가된 조건은 동일했으나 두개내폐색의 위치, 뇌졸중의 치료가 적합한지 판정되지 않았으며 두개내폐색의 위치를 판단하기 위해서는 운동중증도의 범위(기저 NIH 뇌졸중척도[National Institutes of Health Stroke Scale, NIHSS])가 등록일 시점에 제한되어, multimodal imaging 변수 등에 있어서 시험 전 포괄 기준은 다양한 것으로 보인다(Table 2).

최근에 종료한 무작위대조시험의 연구계획

최근에 나온 다섯 개의 시험—MR CLEAN, ESCAPE, EXTEND-IA, SWIFT-PRIME, THRACE—은 r-tPA 치료를 받은 환자들에서 혈관내치료의 효과가 있다고보고하였다(Table 3: MR CLEAN, ESCAPE, EXTEND-IA의 결과).

MR CLEAN 시험은 500명을 등록하였는데서 중후부의 자세를 하여 연구등록기준을 낮게 하였고 최근에 등록 여부는 임상적 판단에 따르도록 하였다. 구체적으로 보면 다양한 정도의 신증후군(뇌혈관혈전의 A2구역까지 포함)의 두개내동맥폐색을 등록하기도 하였고, 뇌졸중 중증도에 큰 제한을 두지 않았고 (NIHSS가 2점으로 낮은 경우도 포함), r-tPA 정맥주사의 적합
**Table 1. Randomized Controlled Trials Testing the Efficacy of Endovascular Therapy**

<table>
<thead>
<tr>
<th>Clinical Trial</th>
<th>Country</th>
<th>Total Planned Sample Size</th>
<th>First Patient In</th>
<th>No. of Enrolled IV r-tPA-Treated Subjects as of March 5, 2015</th>
<th>No. of Enrolled IV r-tPA-Ineligible Subjects as of March 5, 2015</th>
<th>Status as of March 5, 2015</th>
</tr>
</thead>
<tbody>
<tr>
<td>BASICS</td>
<td>EU</td>
<td>750</td>
<td>April/2011</td>
<td>47</td>
<td>N/A</td>
<td>Not Applicable</td>
</tr>
<tr>
<td>DAWN</td>
<td>US/EU</td>
<td>500</td>
<td>September/2014</td>
<td>150</td>
<td>N/A</td>
<td>Enrolling</td>
</tr>
<tr>
<td>ESCAPE</td>
<td>Canada/US/EU/South Korea</td>
<td>500</td>
<td>February/2013</td>
<td>238</td>
<td>78</td>
<td>Enrolling</td>
</tr>
<tr>
<td>EXTEND-IA</td>
<td>Australia/New Zealand</td>
<td>100</td>
<td>August/2012</td>
<td>70</td>
<td>N/A</td>
<td>Halted</td>
</tr>
<tr>
<td>MR CLEAN</td>
<td>Netherlands</td>
<td>500</td>
<td>December/2010</td>
<td>445</td>
<td>55</td>
<td>Completed</td>
</tr>
<tr>
<td>PISTE</td>
<td>United Kingdom/ Norway</td>
<td>450</td>
<td>April/2013</td>
<td>59</td>
<td>N/A</td>
<td>Enrolling</td>
</tr>
<tr>
<td>POSITIVE</td>
<td>US</td>
<td>750</td>
<td>September/2013</td>
<td>N/A</td>
<td>21</td>
<td>Halted for 8–12 h cohort; enrolling for 8–12 h cohort</td>
</tr>
<tr>
<td>RESILIENT</td>
<td>Brazil</td>
<td>690</td>
<td>N/A</td>
<td>0</td>
<td>0</td>
<td>Will start enrolling in March, 2015</td>
</tr>
<tr>
<td>REVASCAT</td>
<td>Spain</td>
<td>690</td>
<td>November/2012</td>
<td>150</td>
<td>56</td>
<td>Halted</td>
</tr>
<tr>
<td>SWIFT-PRIME</td>
<td>US/EU</td>
<td>833</td>
<td>January/2013</td>
<td>196</td>
<td>N/A</td>
<td>Halted</td>
</tr>
<tr>
<td>THERAPY</td>
<td>US/EU</td>
<td>692</td>
<td>March/2012</td>
<td>108</td>
<td>N/A</td>
<td>Halted</td>
</tr>
<tr>
<td>THRACE</td>
<td>France</td>
<td>480</td>
<td>June/2010</td>
<td>394</td>
<td>N/A</td>
<td>Halted</td>
</tr>
<tr>
<td>THRILL</td>
<td>Germany/Austria</td>
<td>600</td>
<td>May/2014</td>
<td>N/A</td>
<td>4</td>
<td>Halted</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>...</td>
<td>...</td>
<td>5685</td>
<td>1707</td>
<td>221</td>
</tr>
</tbody>
</table>

BASICS indicates Basilar Artery International Cooperation Study; DAWN, Trevo and Medical Management Versus Medical Management Alone in Wake Up and Late Presenting Strokes; ESCAPE, Endovascular Treatment for Small Core and Proximal Occlusion Ischemic Stroke; EU, European; EXTEND-IA, Extending the Time for Thrombolysis in Neurological Deficits-Intra-Arterial; IV r-tPA, intravenous recombinant tissue-type plasminogen activator; MR CLEAN, Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands; N/A, not applicable; PISTE, Pragmatic Ischemic Stroke Revascularization with Solitaire Device Versus Best Medical Therapy in Anterior Circulation Stroke Within 8 Hours; SWIFT-PRIME, Solitaire FR as Primary Treatment for Acute Ischemic Stroke; THERAPY, Assess the Penumbra System in Thrombectomy Evaluation; POSITIVE, Perfusion Imaging Selection of Ischemic Stroke Patients for Endovascular Therapy; RESILIENT, Endovascular Treatment With Solitaire FR vs Best Medical Therapy in Acute Ischemic Stroke; REVASCAT, Endovascular Revascularization With Solitaire Device Versus Best Medical Therapy in Anterior Circulation Stroke Within 8 Hours; SWIFT-PRIME, Solitaire FR as Primary Treatment for Acute Ischemic Stroke; THERAPY, Assess the Penumbra System in the Treatment of Acute Stroke; THRACE, Trial and Cost Effectiveness Evaluation of Intra-Arterial Thrombectomy in Acute Ischemic Stroke; THRILL, Comparison of Thrombectomy and Standard Care for Ischemic Stroke in Patients Ineligibility for Tissue Plasminogen Activator Treatment; and US, United States.
Table 2. Designs of Endovascular Randomized Controlled Trials Testing the Efficacy of Endovascular Therapy

<table>
<thead>
<tr>
<th>Trials</th>
<th>Device</th>
<th>Thrombus</th>
<th>Endovascular Start</th>
<th>NIHSS</th>
<th>Advanced Imaging Selection Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>BASICS</td>
<td>All available options</td>
<td>Basilar</td>
<td>≤8 h</td>
<td>NIHSS&gt;10</td>
<td>No</td>
</tr>
<tr>
<td>DAWN</td>
<td>TREVO</td>
<td>ICA/M1 equivalent</td>
<td>Randomized at 6–24 h</td>
<td>NIHSS&gt;5</td>
<td>Core, collaterals, or penumbra†</td>
</tr>
<tr>
<td>ESCAPE</td>
<td>Available choices since 2013</td>
<td>ICA/M1/M1 equivalent (≥ M2s)</td>
<td>≤12 h</td>
<td>NIHSS&gt;5</td>
<td>Core, collaterals, or penumbra†</td>
</tr>
<tr>
<td>EXTEND-IA</td>
<td>Solitaire</td>
<td>ICA/M1/M2</td>
<td>≤6 h</td>
<td>N/A</td>
<td>Core and penumbra‡</td>
</tr>
<tr>
<td>MR CLEAN</td>
<td>All CE marked devices</td>
<td>ICA/M1/M2/A1/A2</td>
<td>≤6 h</td>
<td>NIHSS&gt;2</td>
<td>No</td>
</tr>
<tr>
<td>PISTE</td>
<td>All CE marked since 2013</td>
<td>ICA/M1/M2</td>
<td>≤5.5 h</td>
<td>NIHSS&gt;8</td>
<td>No</td>
</tr>
<tr>
<td>POSITIVE</td>
<td>Penumbra, Solitaire, and TREVO</td>
<td>ICA/M1</td>
<td>≤12 h</td>
<td>NIHSS&gt;8</td>
<td>Core§</td>
</tr>
<tr>
<td>RESILIENT</td>
<td>Solitaire</td>
<td>ICA/M1</td>
<td>≤7.5 h</td>
<td>NIHSS&gt;10</td>
<td>Core‡</td>
</tr>
<tr>
<td>REVASCAT</td>
<td>Solitaire</td>
<td>ICA/M1</td>
<td>≤8 h</td>
<td>NIHSS&gt;6</td>
<td>Core#</td>
</tr>
<tr>
<td>SWIFT-PRIME</td>
<td>Solitaire</td>
<td>ICA/M1</td>
<td>≤5 h</td>
<td>NIHSS&gt;10, NIHSS&gt;30</td>
<td>Core&lt;Penumbra**</td>
</tr>
<tr>
<td>THERAPY</td>
<td>MERCI, Catch, Penumbra, Solitaire, Trevo, REVASCAT, Penumbra 3d Separator and ACE, Mindframe Capture and Flow, pREset</td>
<td>ICA/M1/basilar-distal</td>
<td>≤8 h</td>
<td>NIHSS&gt;20 and ≤25</td>
<td>No</td>
</tr>
<tr>
<td>THRACE</td>
<td>Solitaire or TREVO</td>
<td>ICA/M1</td>
<td>≤8 h</td>
<td>NIHSS&gt;7 and ≤26</td>
<td>Core††</td>
</tr>
</tbody>
</table>

ASPECTS indicates Alberta Stroke Program Early CT Score; BASICS, Basilar Artery International Cooperation Study; CE, Conformité Européenne (or European Conformity); CTP, computed tomographic perfusion; CTA-SI, CT angiography source images; DAWN, Trevo and Medical Management Versus Medical Management Alone in Wake Up and Late Presenting Strokes; ESCAPE, Endovascular Treatment for Small Core and Proximal Occlusion Ischemic Stroke; DWI, diffusion weighted imaging; EXTEND-IA, Extending the Time for Thrombolysis in Emergency Neurological Deficits-Intra-Arterial; ICA, internal carotid artery; IV r-PA, intravenous recombinant tissue-type plasminogen activator; MCA, middle cerebral artery; MR CLEAN, Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands; NIHSS, National Institutes of Health Stroke Scale; PISE, Pragmatic Ischemic Stroke Thrombectomy Evaluation; POSITIVE, Perfusion Imaging Selection of Ischemic Stroke Patients for Endovascular Therapy; rCBV, regional cerebral blood volume; RESILIENT, Endovascular Treatment With Solitaire FR vs Best Medical Therapy in Acute Ischemic Stroke; REVASCAT, Endovascular Revascularization With Solitaire Device Versus Best Medical Therapy in Anterior Circulation Stroke Within 8 Hours; SWIFT-PRIME, Solitaire FR as Primary Treatment for Acute Ischemic Stroke; THERAPY, Assess the Penumbra System in the Treatment of Acute Stroke; THRACE, Trial and Cost Effectiveness Evaluation of Intra-Arterial Thrombectomy in Acute Ischemic Stroke; and THRILL, Comparison of Thrombectomy and Standard Care for Ischemic Stroke in Patients Ineligibility for Tissue Plasminogen Activator Treatment.

*Less than 1/3 MCA territory involved. Clinical imaging mismatch defined as one of the following on Rapid Processing of Perfusion and Diffusion (RAPID) MR-DWI or CTP-rCBF maps: (1) 0–20 cc ischemic core and NIHSS ≥10 (and age, ≥80 y), (2) 0–30 cc ischemic core and NIHSS ≥10 (and age, <80 y), or (3) ≥30 cc to <50 cc ischemic core and NIHSS ≥20 (and age, <80 y).
†Baseline ASPECTS 6–10 on CT with confirmatory evidence of ASPECTS 6–10 on either CT angiography collateral or perfusion imaging.
‡CT perfusion demonstrating a penumbra (T flavorful >8 s) vs ischemic core (rCBF <30%) mismatch ratio >1.2, absolute mismatch >10 cc, and an ischemic core <70 cc.
§Absence of large (>1/3 of the middle cerebral artery) regions of clear hypodensity on the baseline CT scan or ASPECTS of <7. The presence of an associated large penumbra as defined by physiological imaging according to the standard of practice at the participating institution.
¶ASPECTS score of <7 on CT or CTA-SI or ≤6 on DWI magnetic resonance imaging.
#ASPECTS >6 on CT or CTA-SI or >5 on DWI magnetic resonance imaging.
**CT hypodensity or MR hyperintensity of >1/3 of the MCA or in other territories, ≤100 cc of tissue, baseline ASPECTS 6–10, and absence of imaging evidence that suggests, in the opinion of the investigator, the subject is not appropriate for mechanical thrombectomy intervention.
††Large infarct region (ex: >1/3 of the middle cerebral artery territory) and thin-slice reconstruction CT with thrombus ≥8 mm.

Note: M2 폐색이 있어서 뇌질환 발병 4.5시간 이내에 r-tPA 정맥주사시하고 발병 6시간 이내에 혈관내치료를 위한 동맥천자를 할 수 있으며 multimodal imaging 기준을 만족하는 경우에 자격이 되었다. 중요한 차이점은 환자를 선별할 때 Rapid Processing of Perfusion and Diffusion (RAPID) MR의 현장의 성공률을 관찰하는 주사로 1) 이상 1/3 MCA 영역의 존재, 2) 적어도 1/3 MCA 영역, 3) # ASPECTS 6–10, 4) NIHSS ≤10, 5) NIHSS ≥10, NIHSS ≥20 및 NIHSS ≥25의 환자에게 자격이 되었다. 불행히도 이 시험은 낮은 환자수로 봤지만 90일째의 기능적 결과를 보았다. 실험군의 추적 결과는 2016년 International Stroke Conference에서 발표될 예정이다.
자와 혈관내치료가 이득이 될 수 있는 영상 소견이 있는지 판단할 수 있도록 자격 조건을 확장하였다. 예비결과는 강력하게 긍정적인 것으로 2015 International Stroke Conference에서 발표하였고 최종결과의 발표는 미정이다.

마지막으로 제3상 THRACE 시험22에서 480명을 등록하기로 계획하였으나 Data Safety and Monitoring Board의 권고에 따라 412명만 등록하고 2015년 3월 3일에 종료하였다. 이 시험은 초기 385명의 임상적 결과가 중간 분석한 후 혈관내치료의 긍정적 지표 효과를 발표하였다. THRACE 시험의 자격 조건은 환자 가 ICA, M1 또는 원위부 바다동맥에 두개내폐색이 있고 NIHSS 가 10–25점이면서, 5시간 이내에 혈관내치료를 시작할 수 있는 경우이었다. 이전의 긍정적인 시험과 달리 영상선택조건이 없었고 다양한 혈관내치료 기구들을 허용하였다. 추가로 등록된 17명의 환자를 포함한 최종결과는 2015년 6월에 나중 것이다. THRACE 시험의 세부사항과 최종 결과는 2016 International Stroke Conference에서 발표할 것으로 기대하고 있다.

따라서 기념비적인 5개월의 기간 동안 네 개의 연속적인 무작위시험 모두가 선별된 급성혈관뇌증 환자에서 혈관내치료의 효능을 명확하게 보여주었고 다섯 번째 시험도 공표하였다. 종료한 네 개의 시험에서 등록한 환자들 중 대부분의 두개내폐색이 있었고 혈압증가가 적었으며 혈관조영사에서의 재판류가 높았으며 대부분 현대적인 가구로 혈관내치료를 했다. 이런 중요한 원칙이 외에도 각 연구지는 추가적인 조건을 요구했다. (1) MR CLEAN에서의 화색지대원칙, (2) ESCAPE에서의 유리한 접수한 양상, (3) EXTEND–IA에서의 유의한 반응성 조건, (4) SWIFT–PRIME에서의 반응영상성을 이용한 선별. 서로 다른 연구설계 때문에 입상의에게는 주어진 지침과 센터에서 혈관내치료에 적합한 환자를 선별하는 최적의 운영 방법을 결정하는 것이 과제로 남았다.

앞으로의 계획—통합 분석 계획

최근에 시험 결과들이 나오면서 임상현장은 혈관내치료가 임상적으로 이득이 있는지를 질문하는 단계에서 누가 혈관내치료로 효과를 보는가를 질문하는 단계로 발전했다. 나이가 비슷하거나 다른 집단 대비 이득의 비율(risk–benefit ratio)을 유지하면서 각 나라의 다양한 의료 체계에서 어떻게 이 시험들의 결과를 적용할 것인가를 포함해서 이런 시험 결과들의 일반화 가능성을 조사해야 한다. 통합 분석은 현장을 진일보시키는데 있어 중요한 역할을 할 것이다. 지금까지 결과를 보고한 시험들을 통합하는 것뿐만 아니라 조기에 종료된 추정적인 시험들로부터도 무언가를 배울 가능성이 있다. 이런 시험은 혈관내치료의 효과를 증명하기에는 임상군이 많을 수 있다. 계획대로 종료되었던 조기에 종료되었던 진행 중이든 어떤 시험도 독자적으로 환자 선별의 보다 세부적인 면에서 다음과도 확실한 지점을 주만한 검증력을 가질 수 있다. 이런 질문은 보통 대규모 시험을 진행하거나 환자 수준에서 여러 시험의 자료의 모아서 분석할 때 달변이 가능하다.

r–tPA 정맥주사로 치료한 환자를 포함하는 과거에 완료한 세 개의 시험(IMS III, SYNTHESIS, MR RESCUE)과 최근에 완료되었거나 진행 중인 13개의 혈관내치료시험(Table 1)의 연구진들은 임상적 분석으로 혈관내치료를 병행한 경우와 r–tPA 정맥주사만한 경우를 비교한 무작위시험을 후향적으로 환자 수준에서 통합 분석하기로 하였고 이를 Thrombectomy and tPA (TREAT) 분석이라고 명명하였다. VISTA–Endovascular consortium 내에서 TREAT 연구계획을 제안한 것이다. 종료된 각 시험의 연구진들은 TREAT/VISTA 공동연구를 시작하기 이전에 일자 결과 및 중요한 이차결과를 출간할 것이다.

TREAT의 일자결과 품은 치료받은 환자들 중 최소 85%를 포함하는 신세대 기구(직접적 흡인 카테터 또는 stent retriever)를 사용한 전향적 무작위시험에 등록한 환자가 될 것으로 민감도 분석(sensitivity analysis)은 구세대 기구를 사용한 시험들을 포함해서 시행한 것이다. 자체한 포함조건은 Table 4에 열거하였다. 2014년 3월 5일 기준으로 1700여명의 환자가 TREAT에 참가할 수 있는 환자를 갖추었으나, 관련된 결과에 대한 최종 서한을 작성하기 전에야 종료된 시험에 등록되었다.

<table>
<thead>
<tr>
<th>Table 3. Baseline Demographics and Results of the Recent Randomized Controlled Trials of Endovascular Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Trials</strong></td>
</tr>
<tr>
<td>MR CLEAN</td>
</tr>
<tr>
<td>ESCAPE</td>
</tr>
<tr>
<td>EXTEND–IA</td>
</tr>
</tbody>
</table>

ESCAPE indicates Endovascular Treatment for Small Core and Proximal Occlusion Ischemic Stroke; EXTEND–IA, Extending the Time for Thrombolysis in Emergency Neurological Deficits–Intra-Arterial; IV r-tPA, intravenous recombinant tissue-type plasminogen activator; mRS, modified Rankin Scale; mTICI, modified thrombolysis in cerebral infarction; NIHSS, National Institutes of Health Stroke Scale; and OR, odds ratio.

*Common OR for mRS was calculated with different statistical methods for each trial.
†The EXTEND–IA primary outcome measure was a combined end point of tissue reperfusion at 24 h and early neurological improvement at day 3 (ie, 8-point reduction in NIHSS score from baseline or death).
Table 4. Requirements for Datasets Included in the Thrombectomy and tPA (TREAT) Pooled Analysis

| Minimum data set of 20 subjects | Prospective and randomized data set of combined IV tPA with endovascular therapy versus IV tPA alone | IV tPA initiated within 3 or 4.5 h | Documented entry criteria | Documented consent after local IRB-approved procedure | Baseline NIHSS, age, sex, glucose, and side (right vs left) of brain ischemia recorded | Documented treatment times (IV r-TPA start, IA arterial access start time) | Blinded modified Rankin Score assessment at 90 days | Monitoring procedures in place to validate data | Registered with clinicaltrials.gov or comparable governmental Web site |

IA indicates intra-arterial; IRB, institutional review board; IV r-TPA, intravenous recombinant tissue-type plasminogen activator; and NIHSS, National Institutes of Health Stroke Scale.

Table 5. Primary and Secondary Clinical Outcomes for the Thrombectomy and tPA (TREAT) Pooled Analysis

<table>
<thead>
<tr>
<th>Primary outcome</th>
<th>mRS distribution at 90 days, adjusted*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Secondary outcomes</td>
<td>mRS distribution at 90 days, unadjusted</td>
</tr>
<tr>
<td></td>
<td>mRS 0–2 at 90 days, adjusted*</td>
</tr>
<tr>
<td></td>
<td>Symptomatic intracranial hemorrhage†</td>
</tr>
<tr>
<td></td>
<td>Mortality at 90 days</td>
</tr>
</tbody>
</table>

IV r-TPA indicates intravenous recombinant tissue-type plasminogen activator; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; and SITS-MOST, Safe Implementation of Thrombolysis in Stroke-Monitoring Study.

*Adjusted for age, baseline NIHSS, baseline glucose, time to IV r-TPA, and side of brain ischemia.
†SITS-MOST registry definition.

TREAT 분석은 주요 환자선별기준이 치료효과를 변경시키는 가에 대한 것이다. 구체적으로 우리는 두개내동맥백패색의 위치(두 개내ICA 대 M1 대 M2 대 A1/A2), 뇌졸중 증증도(기저 NIHSS), r-TPA 정부주사 시각 및 부작용방지가 지연된 시간, 초기 신경영상에서 초기의 혈혈성 변환, 나이 등의 변수가 치료효과에 영향을 주는지를 조사할 것이다. 이용가능한 자료가 있는 증례 중에서 우리는 초기 CT 혈관조영술 또는 MRA에 결손한 유무 및 관류영상과 혈관중증 사이에 병물질의 증가에 따라 치료효과 차이가 있는지 평가할 것이다. 각 시험에서 기록한 미리 정한 표준적인 영상 변수를 넘어서는 분석을 하기 위해서 Stroke Imaging Repository Consortium을 통해서 이 시험들에서 가지는지 않은 영상자료를 모으려고 노력 중이다. 또한 우리는 정신마취, 동축 두개외동맥백패색의 존재, 혈관내치료 시각까지 지연된 시간, 혈관조영재파관 등이 임상적 예후에 미치는 영향을 조사할 것이다. 계획한 임자 및 이자 임상결과는 Table 5에 나열한다.

저자들은 두 개 이상의 시험에서 사용할 수 있는 자료가 모아 빛 TREAT 연구를 시작할 것이다. 다중성(multiplicity)에 대한 하용 없이 메타분석을 반복적으로 시행할 경우 위양성의 소견이 나올 전반적인 위험이 메타분석을 시행하는 횟수에 비례하여 증가한다.24 미리 정한 각 질문들에 대한 해답을 얻기 위해 필요한 피험자 수를 아직 모르고, 각 시험이 종료될 때마다 증가하면서 누락될 것이므로 우리는 연속적 메타분석법(sequential meta-analysis technique)을 사용하여 여러 번 검증하는 문제를 달리 갖고 효율이나 무익을 증명할 수 있는 문헌을 넘어설 때에도 공식적으로 결과를 발표할 것이다. 연속적 메타분석법은 전통적인 누락메타분석법(cumulative meta-analysis technique)보다 더 강력한 방법인데 여러 번의 검증에 대해 point estimate와 interval estimate를 보장하기 때문이다. 또한 검증력을 저장화할 수 있고 효과가 없을 때 중단하는 것이 가능하고 효율은 증가한다.25 미리 정한 각 분석에 대해서 우리는 triangular testing procedure of Whitehead를 사용할 것이며 목표효과크기(effect size)는 mRS 순위변수에서 10% 호전이고 단측 P값은 0.005(양측 P값 0.01)이다. 자세한 통계분석계획은 분석을 시행하기 전에 발표할 것이다.

r-TPA 정부주사의 급성 환자를 대상으로 한 시험에 대한 통합 분석도 계획할 것이다. 피험자 중위가 너무 늦어서 가까운 미래에 이 분석을 하기 어렵다.

결론적으로 지금 다양한 환자선별 페라다임을 이용하였고 연속적이며 독립적인 무작위시험들로부터 기계적 혈전체결이 환자의 예후를 향상시킨다는 증거를 얻었다. 이 혈관내치료시험들과 추가적인 시험에 등록된 r-TPA 정부주사치료를 받은 1700여명의 피험자를 이용하여 대규모 국제 협력을 통해서 환자 수준의 통합 분석을 시작할 것이다. 이 분석은 일상의 진료 중에 혈관내 치료를 위한 최적의 환자를 선별하는 기준에 대한 이해를 증진시키며 급성 혈관내중증의 예후를 더 향상시키기 위한 미래의 임상시험을 계획하는데 도움을 줄 것으로 사료된다.

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References

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