Mechanical Thrombectomy Improves Functional Outcomes Independent of Pretreatment With Intravenous Thrombolysis

Georgios Tsivgoulis, MD; Aristeidis H. Katsanos, MD; Dimitris Mavridis, PhD; Georgios Magoufis, MD; Adam Arthur, MD, MPH; Andrei V. Alexandrov, MD

Background and Purpose—Endovascular intervention for emergent large-vessel occlusion (ELVO) has evolved rapidly during the past decade. The question of whether pretreatment with intravenous thrombolysis (IVT) has a significant impact on the functional outcome of patients with ELVO still remains unanswered.

Methods—We conducted a systematic review and meta-analysis of all available randomized controlled trials evaluating the efficacy of endovascular therapy (ET) for acute ischemic stroke. We performed a mixed-effects subgroup analysis of the reported odds ratios on the association of ET (versus standard therapy) with 3-month functional outcome, stratified by pretreatment with IVT.

Results—Six randomized controlled trials were included, comprising 1916 total patients (49.1% receiving ET with IVT pretreatment and 5.6% receiving ET without IVT pretreatment). In the subgroup analysis, ET was associated with a higher likelihood of better 3-month functional outcome in both the subgroup of patients with (odds ratio=1.83; 95% confidence interval, 1.37–2.44; P<0.001) and without (odds ratio=2.47; 95% confidence interval, 1.32–4.63; P=0.001) pretreatment with IVT. We documented no significant effect of ET pretreatment on the 3-month functional outcome of patients with ELVO undergoing ET, suggesting that ET is effective in all patients with ELVO. Heterogeneity was documented in the IVT pretreatment subgroup (F=68.3%; P for Cochran Q=0.014), but not in the subgroup that did not receive IVT pretreatment (F=0%, P for Cochran Q=0.927). The risk of bias was considered to be generally low in the qualitative assessment of the included trials.

Conclusions—Our observation provides evidence and further reassurance to stroke clinicians regarding the efficacy of ET in ELVO independent of pretreatment with IVT. (Stroke. 2016;47:1661-1664. DOI: 10.1161/STROKEAHA.116.013097.)

Key Words: randomized controlled trial ■ stroke ■ thrombectomy ■ thrombolytic therapy

Endovascular intervention for emergent large-vessel occlusion (ELVO) has evolved rapidly during the past decade leaving some trials obsolete and others incomplete because equipoise is no longer in place.1 The question of whether pretreatment with intravenous thrombolysis (IVT) has a significant impact on the functional outcome (FO) of patients with ELVO still remains unanswered.

In view of the former consideration, we performed a systematic review and meta-analysis of all available randomized controlled trials (RCTs) evaluating the efficacy of endovascular thrombectomy (ET) compared with standard therapy (ST) for acute ischemic stroke patients with ELVO.

Methods

Using data from available RCTs, we performed a mixed-effects subgroup analysis of the reported common odds ratios (ORs) on the association of ET (versus ST) with 3-month FO, stratified by pretreatment with IVT. In studies not reporting common ORs but providing data on modified Rankin Scale stratification, we calculated the common ORs with the use of ordinal logistic regression analysis. In each eligible study, we used the Cochrane risk of bias assessment tool.2 Data abstraction and bias identification within studies were independently performed by 2 authors (G.T. and A.H.K.), and all emerging conflicts were resolved with consensus.

In the subgroup analysis, we used a random-effects model to combine studies within each subgroup, and then a fixed-effects model to combine subgroups and yield the overall effect. The study-to-study variance (τ²) was assumed to be the same for all subgroups.3 Heterogeneity between studies was assessed with the Cochran Q and F statistics, as per the Cochrane Handbook.4 All statistical analyses were conducted using the Comprehensive Meta-analysis version 2 software,5 whereas graphs for the qualitative analysis were generated using the Review Manager (RevMan) version 5.3 software (The Nordic
Results
Six RCTs, comprising 1916 total patients (49.1% receiving ET with IVT pretreatment and 5.6% receiving ET without IVT pretreatment), were included in both qualitative and quantitative synthesis (Table I in the online-only Data Supplement). The complete search algorithm and the flow chart of the literature search (Figure I in the online-only Data Supplement) are both available in the online-only Data Supplement. Two studies were excluded because (1) the distribution of modified Rankin Scale scores between the 2 groups was not available, and (2) they reported differences in large-vessel occlusion status, and there is a possibility of enrolled patients without ELVO (Table II in the online-only Data Supplement). In the qualitative assessment of included trials, which is presented in detail in the online-only Data Supplement, the risk of bias was considered to be generally low (Figures II and III in the online-only Data Supplement).

In the subgroup analysis of all included studies, ET was associated with a higher likelihood of favorable 3-month FO both in the subgroup of patients without (OR=2.47; 95% confidence interval [CI], 1.32–4.63; \( P=0.005 \)) and with (OR=1.83; 95% CI, 1.37–2.44; \( P=0.001 \)) pretreatment with IVT. No significant effect of IVT pretreatment on the 3-month FO of patients with ELVO undergoing ET was found (\( P=0.397 \)), suggesting thus a clear benefit in both subgroups. Heterogeneity was documented in the IVT pretreatment subgroup (\( I^2=68.3\% \), \( P \) for Cochran \( Q=0.014 \)), but not in the subgroup that did not receive IVT pretreatment (\( I^2=0\% \), \( P \) for Cochran \( Q=0.927 \); Figure 1). In an additional sensitivity analysis, after excluding the 3 studies that pretreated all patients with IVT (and thus reported no corresponding group treated solely with ET), the difference between the 2 subgroups remained nonsignificant (OR=2.48; 95% CI, 1.43–4.30 without IVT pretreatment versus OR=1.85; 95% CI, 1.44–2.36 with IVT pretreatment; \( P \) for subgroup difference: 0.338; Figure 2). No evidence of heterogeneity was detected in both the subgroup with IVT pretreatment (\( I^2=26.1\% \), \( P \) for Cochran \( Q=0.258 \)) and in the subgroup without IVT pretreatment (\( I^2=0\% \), \( P \) for Cochran \( Q=0.927 \)).

Discussion
Our findings suggest that IVT pretreatment has no significant effect on the 3-month FO of patients with ELVO undergoing ET. We have an increased confidence on the credibility of the

<table>
<thead>
<tr>
<th>Group by Statistics for each study</th>
<th>Odds ratio 95% CI</th>
<th>Study name</th>
<th>Subgroup within study</th>
<th>Subgroup within study</th>
<th>Odds ratio 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>ET+IVT ET+IVT</td>
<td>2.471 4.636 2.817</td>
<td>ET+IVT</td>
<td>ET+IVT</td>
<td>ET+IVT</td>
<td>2.471 4.636 2.817</td>
</tr>
<tr>
<td>Overall</td>
<td>1.930 4.509 4.908</td>
<td>Overall</td>
<td>Overall</td>
<td>Overall</td>
<td>1.930 4.509 4.908</td>
</tr>
</tbody>
</table>

Figure 1. Pooled subgroup analysis of all included studies reporting patients receiving endovascular treatment and patients receiving best medical care, according to the previous administration of intravenous thrombolysis (IVT). CI indicates confidence interval; ESCAPE, Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion With Emphasis on Minimizing CT to Recanalization Times; ET, endovascular therapy; EXTEND-IA, Extending the Time for Thrombolysis in Emergency Neurologic Deficits–Intra-Artial; IMS III, Interventional Management of Stroke III Trial; MR CLEAN, Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands; 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; ST, standard therapy; and SWIFT PRIME, Solitaire With the Intention for Thrombectomy as Primary Endovascular Treatment for Acute Ischemic Stroke.
results from our subgroup analysis because our hypothesis was prespecified and supported by the both individual RCT data\textsuperscript{5,8,9} and by clinical experience. Moreover, as evident from Figure 2, the lack of differences among subgroups not only remains consistent between subgroups and across included studies\textsuperscript{11,12} but subgroup estimates are also significantly overlapping making thus a potential difference highly unlikely. In addition, we should underline that each subgroup refers to a comparison between ET and ST; hence, patient data randomized to the standard are entered twice and artificially inflate the sample size and the precision of the estimates. That increases the validity of the research finding that ET+IVT does not differ with ET-IVT in terms of its effectiveness with ST.

However, it should be noted that even though the studies have been properly randomized, patients within ET were not randomized to receive either IVT+ET or IVT−ET. Hence, data included in this meta-analysis should be regarded as observational study data, with a considerable risk for confounding bias as we do not know whether patients receiving IVT differ from those who did not receive. Results from subgroup analyses should be interpreted with caution, and a significant association is not necessarily a true one.

This is a limitation that holds for another recent meta-analysis on the topic that combined data from several trials on the association of ET were associated with 3-month FO, and contradicts our findings.\textsuperscript{13} As substantial heterogeneity (P=75.4\%) was detected in their overall analysis the authors performed multiple sensitivity analyses to account for this heterogeneity.

In one of these analyses that was performed using data from all included trials,\textsuperscript{13} they documented that in the subgroup of patients pretreated with IVT, ET was associated with a higher likelihood of functional independence compared with ST (OR=2.07; 95\% CI, 1.46–2.92; P<0.001). In contrast, ET was not found to be associated with better FO in the subgroup of patients who were not pretreated with IVT (OR=0.86; 95\% CI, 0.45–1.62; P=0.63), underscoring that this interaction as statistically significant (P=0.018).\textsuperscript{13} This finding drew our attention, as no such interaction was detected in the individual trials that included acute ischemic stroke patients with and without pretreatment with IVT,\textsuperscript{5,8,9} and this has been attributed possibly to the limited sample sizes and thus the inadequate statistical power to detect this interaction.\textsuperscript{5} The Local Versus Systemic Thrombolysis for Acute Ischemic Stroke (SYNTHESIS) trial did not actually ensure that enrolled patients were having ELVO, and was the only RCT in which patients enrolled within the 4.5-hour window were denied IVT if they were randomized to the endovascular group. Because of the aforementioned methodological shortcomings and the large number of patients included in the SYNTHESIS trial, we are skeptical about the results of the subgroup analysis performed by Badhiwala et al.\textsuperscript{13} We consider the inclusion of SYNTHESIS trial inappropriate, as the patient populations considered are fundamentally different, an unfortunately common occurrence in the neurointerventional literature.\textsuperscript{14}
It is thus clear that patient selection (verifying ELVO) and effective intervention are key maneuvers, and misinterpretation of these facts can result in real harm to patients with stroke. Subgroup analyses can generate misleading recommendations if presented as definitive conclusions. We consider both the present and the previous meta-analysis on the topic underpowered, given both the small number of studies included in each subgroup and the wide confidence intervals. Power calculations are difficult, partly because we do not have access to arm-level data and because results from the 2 subgroups are not independent. Assuming a ratio of 5:1 between +IVT/−IVT groups, we would need $\approx 10000$ patients randomized to ET+IVT and 2000 randomized to ET−IVT to detect an OR of 1.2. That would entail an additional 9000 patients randomized to ET+IVT and 1800 randomized to ET−IVT plus a similar number randomized to ST. This is a conservative estimate given that the results from the 2 subgroups are not independent, but it clearly portrays the aforementioned notion of underpowered analyses.

Given that there is a clear benefit of ET when compared with ST and in view of the findings of the present meta-analysis, we consider that the efficacy of ET extends to all patients with ELVO independent of pretreatment with system thrombolysis.

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Disclosures
Dr Arthur has served as a consultant for Medtronic, Microvention, Penumbra, Sequent, Siemens and Stryker, Inc. The other authors report no conflicts.

References
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http://stroke.ahajournals.org/content/suppl/2016/04/19/STROKEAHA.116.013097.DC1

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SUPPLEMENTAL MATERIAL

Complete search algorithm used in MEDLINE search

Qualitative assessment of included studies

Characteristics of included studies are presented in Supplemental Table I. Selection bias was considered generally low, as in all trials the initial randomization of included participants to ET or ST was performed adequately. However, it should be noted that in two trials the method of endovascular treatment was left to the discretion of the local interventionist, while in another trial the neurointerventionists used not a sole, but every available thrombectomy device to achieve reperfusion. Even though there is a theoretical risk of introducing unmeasured biases both within subgroup and across subgroups in these trials, we considered that the aforementioned approaches were dictated by technical issues and thus were unlikely to introduce systematic biases. Even though all 6 RCTs had open-label treatment with blinded end-point evaluation (PROBE design), we considered that the outcome measure was likely not influenced by the lack of double blinding. Industry financial support was reported in 4 of the 6 trials and mainly public funding in the remaining two. Although it is stated that the study funders had no involvement in the study design or execution, we could not disregard the presence of a clear conflict of interest, and thus the risk of bias was considered as "unclear" in these studies (Supplemental Figures II&III).
Supplemental Table I. Characteristics of trials included in the meta-analysis that reported common odds ratios of the association between endovascular reperfusion therapies (ET) and three-month functional outcome stratified by pretreatment with intravenous thrombolysis (IVT).

<table>
<thead>
<tr>
<th>Study name</th>
<th>Total Patients</th>
<th>IVT (n, %)</th>
<th>ET (n, %)/ ST(n, %)</th>
<th>cOR Adjusted for</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESCAPE</td>
<td>315</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>No: 77 (24.5%)</td>
<td>45 (58.4%)/ 32 (41.6%)</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Yes: 238 (75.5%)</td>
<td>120 (50.4%)/ 118 (49.6%)</td>
<td>-</td>
</tr>
<tr>
<td>EXTEND-IA</td>
<td>70</td>
<td>Yes: 70 (100%)</td>
<td>35 (50%)/ 35 (50%)</td>
<td>-</td>
</tr>
<tr>
<td>IMS III</td>
<td>629</td>
<td>Yes: 629 (100%)</td>
<td>415 (66%)/ 214 (34%)</td>
<td>-</td>
</tr>
<tr>
<td>MR CLEAN</td>
<td>500</td>
<td>No: 55 (11%)</td>
<td>30 (54.5%)/ 25 (45.5%)</td>
<td>age, NIHSS_adm, SOR time, pre-stroke status, AF, DM, TICA occlusion</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Yes: 445 (89%)</td>
<td>203 (45.6%)/ 242 (54.4%)</td>
<td></td>
</tr>
<tr>
<td>REVASCAT</td>
<td>206</td>
<td>No: 56 (27.2%)</td>
<td>33 (58.9%)/ 23 (41.1%)</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Yes: 150 (72.8%)</td>
<td>70 (46.7%)/ 80 (53.3%)</td>
<td></td>
</tr>
<tr>
<td>SWIFT PRIME</td>
<td>196</td>
<td>Yes: 196 (100%)</td>
<td>98 (50%)/ 98(50%)</td>
<td>-</td>
</tr>
</tbody>
</table>
ST: standard therapy, cOR: common odds ratio, NIHSS<sub>adm</sub>: NIHSS on admission, SOR time from stroke onset to randomization, AF: atrial fibrillation, DM: diabetes mellitus, TICA: terminal internal carotid artery

**Supplemental Table II.** Excluded studies from the meta-analysis with reasons for exclusion

<table>
<thead>
<tr>
<th>Study name</th>
<th>Reason for exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>MR RESCUE&lt;sup&gt;7&lt;/sup&gt;</td>
<td>distribution of mRS scores between the two groups not available</td>
</tr>
<tr>
<td>SYNTHESIS&lt;sup&gt;8&lt;/sup&gt;</td>
<td>differences in large vessel occlusion status/ the possibility of enrolled patients without ELVO, patients randomized to endovascular treatment were precluded from intravenous thrombolysis</td>
</tr>
</tbody>
</table>

mRS: modified Rankin Scale, ELVO: emergent large vessel occlusion
Supplemental References


Supplemental Figure I. Flow chart presenting the selection of eligible studies

Records identified through MEDLINE database searching (n = 54)

Records identified through SCOPUS database searching (n = 48)

Records after duplicates removed (n = 100)

Records screened (n = 100)

Full-text articles assessed for eligibility (n = 8)

Full-text articles excluded, distribution of mRS scores between the two groups not available (n=1)

differences in large vessel occlusion status/ possibility of enrolled patients without ELVO (n=1)

Studies included in qualitative synthesis (n = 6)

Studies included in quantitative synthesis (meta-analysis) (n = 6)

ELVO: emergent large vessel occlusion
**Supplemental Figure II.** Risk of bias summary that reviews authors' judgments about each risk of bias item for each included study.

**Supplemental Figure III.** Risk of bias graph that reviews authors' judgments about each risk of bias item presented as percentages across all included studies.