Critical Review Form
Therapy

Interventional Management of Stroke (IMS) III Investigators.
Endovascular therapy after intravenous t-PA versus t-PA alone for stroke.
N Engl J Med. 2013 Mar 7;368(10):893-903.

Objectives: **"to test the approach of intravenous t-PA followed by protocol-approved endovascular treatment, as compared with standard intravenous [IV] t-PA" (p. 894) in the management of acute stroke.**

Methods: **This international, multicenter, open-label randomized controlled trial was conducted between August 25, 2006, and April 17, 2012 at 58 centers in the United States (41 sites), Canada (7 sites), Australia (4 sites), and Europe (6 sites). Patients receiving IV t-PA within 3 hours of acute stroke were eligible for inclusion if they had a National Institutes of Health Stroke Scale (NIHSS) score ≥10. Following the enrollment of the first 284 participants, patients with a score of 8 or 9 with CT angiographic (CTA) evidence of a major arterial occlusion - including the first segment of the middle cerebral artery, internal carotid artery, or basilar artery - were also eligible.**

Patients were randomized in a 2:1 fashion to either IV t-PA plus endovascular-therapy (treatment group) - which consisted of either thrombectomy or endovascular delivery of t-PA - or to IV t-PA alone (control group). Patients in the treatment group with no angiographic evidence of a treatable occlusion had no additional intervention performed. The angiographic procedure had to begin within 5 hours - and completed within 7 hours - of symptom onset. Patients enrolled in the treatment group prior to June 2011 received two-thirds of the standard dose of IV t-PA; following June 2011, all patients received the full dose of IV t-PA.

The primary outcome was a modified Rankin scale score of 2 or less at 90 days. Study investigators not involved in treatment and who were blinded to group allocation assessed the Rankin scale for all patients. All patients underwent CT initially and at 24 hours, as well as CTA at 24 hours to assess vascular patency. The Thrombolysis in Cerebral Infarction (TICI) score was used to evaluate for recanalization of the primary occlusive lesion and reperfusion of the distal vasculature on completion of the angiographic procedure.

The authors initially planned to enroll 900 patients based on their power analysis. The trial was stopped early for futility - according to a prespecified rule - after a total of 656 patients were randomized: 434 to endovascular therapy and 222 to IV t-PA alone. Of the patients in the endovascular therapy group, 334 underwent intra-arterial therapy (77%), with 266 receiving intra-arterial t-PA (61.3%).

Guide		Comments
I.	**Are the results valid?**	
A.	**Did experimental and control groups begin the study with a similar prognosis (answer the questions posed below)?**	
1.	Were patients randomized?	Yes. "Participants were randomly assigned in a 2:1 ratio to endovascular therapy or intravenous t-PA alone with the use of an Internet-based, computerized algorithm of minimization and the biased-coin method, which accounted for two factors: clinical center and baseline NIHSS strata (scores of 8 to 19 vs. ≥20)." (p. 896)
2.	Was randomization concealed (blinded)?	Yes. The internet-based randomization procedure would not allow subversion of the randomization technique. (allocation concealment)
3.	Were patients analyzed in the groups to which they were randomized?	Yes. Out of 434 patients in the endovascular treatment group, 334 (77%) underwent intra-arterial treatment. There were 3 patients in the control group who underwent an endovascular procedure. Patients were analyzed according to the group to which they were randomized, rather than the intervention received (intention to treat).
4.	Were patients in the treatment and control groups similar with respect to known prognostic factors?	Yes. Patients were similar with respect to age, gender, race, initial NIHSS, ASPECTS, presumed location of stroke, and history of atrial fibrillation, diabetes, CHF, and hyperlipidemia. The incidence of coronary artery disease was higher in the control group than in the endovascular therapy group (32.4% vs. 23.5%, p = 0.01).
B.	**Did experimental and control groups retain a similar prognosis after the study started (answer the questions posed below)?**	
1.	Were patients aware of group allocation?	Yes. This was an open-label study with no sham interventional studies performed. It seems unlikely that performance bias on the part of the patients would affect the outcomes.

2.	Were clinicians aware of group allocation?	Yes. This was an open-label study with no sham interventional studies performed. It seems unlikely that performance bias on the part of the clinicians would affect the outcomes.
3.	Were outcome assessors aware of group allocation?	Yes, for the primary outcome. "All modified Rankin scale assessments at 90 days were to be performed by study investigators who were not involved in the treatment of the patient and who were unaware of the treatment assignment." (p.896) The authors do not mention if CT angiography results were based on read by radiologists blinded to treatment group or intervention received.
4.	Was follow-up complete?	No. For the 13 participants the primary outcome was not assessed. For 14 participants the primary outcome was assessed outside the specified 30-day window. A 24-hour CT scan was not obtained in 32 patients.
II.	**What are the results (answer the questions posed below)?**	
1.	How large was the treatment effect?	• For the primary outcome, modified Rankin scale score of two or less at 90 days, there was no significant difference between the treatment and control groups (40.8% and 38.7%, respectively; adjusted risk difference [ARD] 1.5%, 95% CI -6.1% to 9.1%). Subgroup analysis • For patients with NIHSS score ≥20 there was no significant difference in the primary outcome (ARD 6.8% favoring the treatment group, 95% CI -4.4% to 18.1%). • For patients with NIHSS score 8-19 there was no significant difference in the primary outcome (ARD -1.0% favoring the control group, 95% CI -10.8% to 8.8%). The primary outcome appeared to occur more frequently in patients with greater reperfusion (based on TICI score). A modified Rankin score of two or less at 90 days was seen in 12.7% of patients with a score of zero, 27.6% of patients with a score of one, 34.3% of patients with a score of 2a, 47.9% of patients with a score of 2b, and 71.4% of patients with a score of 3 ($p < 0.001$).
2.	How precise was the estimate of the treatment effect?	See above.

III.	**How can I apply the results to patient care (answer the questions posed below)?**	
1.	Were the study patients similar to my patient?	Yes. While this was an international multicenter trial, the majority of the study sites were in the United States. These were large academic medical centers capable of performing neuro-interventional procedures, similar to our institution. Patients with acute stroke were enrolled. However, all patients receiving IV t-PA were enrolled, rather than including only goes with radiographic evidence major arterial occlusion. Changing the inclusion criteria in subsequent studies may therefore have a significant effect on the results
2.	Were all clinically important outcomes considered?	No. The primary outcome was a significant one as it reflects patient's functional status 90 days after treatment. The use of ordinal analysis, rather than a dichotomous evaluation of the modified Rankin score, has grown in popularity, but would likely not affected the results of this study. Additionally the authors did not evaluate cost, length of stay, or patient satisfaction.
3.	Are the likely treatment benefits worth the potential harm and costs?	No. The use of endovascular therapy in all patients with stroke receiving IV t-PA does not appear to improve functional status at 90 days. This was true for subsets of patients with both moderate and severe stroke based on NIHSS score. When evaluating CT angiography results at 24 hours, greater reperfusion was associated with an improvement in the primary outcome, suggesting that patients more amenable to reperfusion may benefit from the intervention. Improve patient selection in subsequent studies based on this finding may result in a different outcome.

Limitations:

1. **This was an industry-sponsored trial, subject to associated biases.**
2. **This was an open-label study with no blinding of either patients or clinicians.**
3. **The study was stopped early for futility, raising the possibility of a Type II error.**
4. **Use of NIHSS rather than CT angiography to determine the presence of a major arterial occlusion may have resulted in the inclusion of patients with lesions not amenable to reperfusion.**

5. **Multiple protocol changes were instituted following the initiation of patient enrollment, including changes in inclusion criteria to include patients with NIHSS 8-9 with CTA evidence of major occlusion, change in IV t-PA dosage from 2/3 standard dose to full dose**

6. **Patients in the endovascular treatment group received a lower mean dose of IV t-PA compared to patients in the control group (60.3 vs. 72.5 mg).**

<u>Bottom Line:</u>

In this international multicenter study enrolling all patients with acute stroke eligible to receive IV t-PA, the use of endovascular therapy did not appear to have a significant effect on the modified Rankin score at 90 days. The authors defined that greater reperfusion was associated with improvement in the primary outcome, suggesting that improved patient selection aimed at enrolling those patients with lesions more amenable to reperfusion may result in a different study outcome.