Critical Review Form
Therapy

ESCAPE Trial Investigators. Randomized assessment of rapid endovascular treatment of ischemic stroke. N Engl J Med. 2015 Mar 12;372(11):1019-30.

Objectives: **"to test whether patients with acute ischemic stroke, who were selected on the basis of results of computed tomography (CT) and CT angiography (CTA), would benefit from rapid endovascular treatment involving contemporary endovascular techniques." (p. 1020)**

Methods: **This prospective, multicenter, randomized controlled attempted to enroll consecutive adult patients with a "disabling ischemic stroke." Potential study sites were selected for participation after evaluation for "fast treatment times and efficient work-flow" (p. 1020) by the principal investigator. Patients were randomized to receive either endovascular treatment plus standard "guideline-based" care (intervention group) or standard care alone (control group). Patients were randomized using an Internet-based randomization minimization procedure to achieve balance with regards to age, sex, baseline National Institutes of Health Stroke Scale (NIHSS) score, site of occlusion, baseline Alberta Stroke Program Early Computed Tomography Score (ASPECTS), and status with regards to alteplase treatment. Eligibility requirements included:**

1. **Adults (with no upper age limit).**
2. **A Barthel Index score of ≥ 90 prior to the stroke indicating an independent functional status.**
3. **Enrollment within 12 hours of symptom onset.**
4. **A small infarct core on CT, defined as an ASPECTS of 6 to 10.**
5. **An occluded proximal artery in the anterior circulation with moderate-to-good collateral flow.**

Patients in the intervention group underwent a cerebral angiogram and reperfusion using "available thrombectomy devices." Subjects in both groups received alteplase if symptom onset was < 4.5 hours and they qualified under local practice guidelines.

The primary outcome was the score on the modified Rankin scale at 90 days after randomization, and was assessed by trained personnel blinded to group allocation. Secondary outcomes included early recanalization and reperfusion, intracranial hemorrhage, angiographic complications, neurologic disability at 90 days, and death.

The trial was stopped early due to a perceived benefit observed during an unplanned interim analysis. A total of 316 subjects were enrolled at 22 centers in Canada (n = 11), the US (n = 6), South Korea (n = 3), Ireland (n = 1), and the UK (n = 1). There

were 165 subjects in the intervention group and 150 in the control group; one subject was excluded due to improper consent procedures. Among patients in the intervention group, 151 (91.5%) underwent endovascular treatment and 120 (72.7%) received alteplase; retrievable stents were used in 130 of 151 (86.1%) patients in the intervention group who underwent endovascular treatment. The median time from symptom onset to reperfusion was 241 minutes (interquartile range 176 to 359). In the control group, 118 (78.7%) subjects received alteplase.

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. "Randomization was performed with the use of a real-time, dynamic, Internet-based, randomized minimization procedure (minimal sufficient balance method) to achieve distribution balance with regard to age, sex, baseline National Institutes of Health Stroke Scale (NIHSS) score…site of arterial occlusion, baseline Alberta Stroke Program Early Computed Tomography Score (ASPECTS), and status with respect to intravenous alteplase treatment." (p.1020)
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. One participant in the control group crossed over to receive endovascular treatment. In the intervention group, 14 participants did not receive any interventional therapy. In spite of this crossover, patients were analyzed in the groups to which they were randomized rather than the treatment actually received (intention to treat).
4.	Were patients in the treatment and control groups similar with respect to known prognostic factors?	Yes. The two groups were similar with respect to age, gender, baseline NIHSS score, blood pressure, ASPECTS on CT, location of occlusion, and the percent who received alteplase. Patients in the intervention group received alteplase somewhat earlier than the control group (median 110 vs. 125 minutes) and had lower rates of pre-existing hypertension (63.6% vs. 72.0%).
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?	No. "The primary outcome — the score on the modified Rankin scale at 90 days after randomization — was assessed by trained personnel who were unaware of the treatment-group assignments." (p. 1021) "Interpretation of the imaging was performed at an external core laboratory by personnel who were unaware of the treatment-group assignments (when they interpreted the CT images), clinical data, and outcomes." (p. 1021)
4.	Was follow-up complete?	Yes. Follow-up was quite excellent, as only four participants (1.3%) were lost to follow-up, one in the intervention group and 3 in the control group.
II.	**What are the results (answer the questions posed below)?**	
1.	How large was the treatment effect?	• For the primary outcome (an improvement of 1 point on the modified Rankin scale), the common odds ratio was 2.6 (95% CI 1.7-3.8) favoring the intervention. • The median 90-day modified Rankin score was 2 in the intervention group and 4 in the control group ($p < 0.001$). • The proportion of patients with a modified Rankin score of 0 to 2 at 90 days was 53.0% in the intervention group and 29.3% in the control group (relative risk [RR] 1.8, 95% CI 1.4-2.4). • Mortality at 90 days was 10.4% in the intervention and 19.0% in the control group (RR 0.5, 95% CI 0.3-1.0). • A symptomatic intracranial hemorrhage occurred in 3.6% in the intervention group and 2.7 in the control group (RR 1.4, 95% CI 0.4-4.7). • The proportion of patients with a Barthel Index of 95-100 at 90 days was 57.7% in the intervention group

		and 33.6% in the control group (RR 1.7, 95% CI 1.3–2.2). • The proportion of patients with a NIHSS of 0 to 2 at 90 days was 51.6% in the intervention group and 23.1% in the control group (RR 2.2, 95% CI 1.6–3.2). • The median score on the EuroQoL Group 5-dimmension Self-Report Questionaire, in which a higher number indicates better quality of life, was 80 in the intervention group and 65 in the control group. •
2.	How precise was the estimate of the treatment effect?	See above. The results achieved statistical significance for almost all of the outcomes provided.
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. These were patients suffering acute stroke at multiple centers worldwide, being treated at centers capable of performing neuro-interventional procedures in a timely fashion. Assuming agreement between stakeholders here at our institution, we should be capable of performing these interventions in a similar timely fashion.
2.	Were all clinically important outcomes considered?	Yes. The authors considered both long-term functional outcomes such as the modified Rankin scale and Barthel index, as well as measure of quality of life.
3.	Are the likely treatment benefits worth the potential harm and costs?	Yes. The article certainly suggests a significant improvement in functional status with the use of interventional procedures in select patients with acute stroke, small core size, and good collateral circulation. While patients in the intervention group received alteplase in a more timely fashion than those in the control group, there still appears to be a significant benefit that would not be entirely explained by this difference. The study was unfortunately stopped early for perceived benefit during an unplanned interim analysis, which raises some concerns regarding the study's validity.

Limitations:

1. **The study was stopped early for perceived benefit during an unplanned interim analysis with only 316 subjects enrolled. This increases the risk of a type I error.**

2. **Patients in the intervention group received alteplase somewhat earlier than the control group (median 110 vs. 125 minutes) and had lower rates of pre-existing hypertension (63.6% vs. 72.0%).**

3. **A majority of participants were enrolled at selected endovascular centers that are capable of implementing efficient workflow and imaging processes. This level of efficiency and expertise is not currently widespread, which limits the immediate generalizability of our results (external validity).**

4. **This was an open-label study with no blinding of either patients or clinicians.**

Bottom Line:

This multicenter randomized controlled trial demonstrated a significant improvement in 90-day modified Rankin scale score with the use of neuro-interventional procedures in select patients with acute stroke, small core size, and good collateral circulation. Care should be taken when applying these results to ensure that correct patient selection is utilized.