Critical Review Form
Therapy

A randomized trial of intraarterial treatment for acute ischemic stroke. N Engl J Med. 2015 Jan 1;372(1):11-20.

Objectives: **To determine "whether intraarterial treatment plus usual care would be more effective than usual care alone in patients with a proximal arterial occlusion in the anterior cerebral circulation that could be treated intraarterially within six hours after symptom onset." (p. 12)**

Methods: **This multi-center, randomized, open label trial was conducted at 16 centers in the Netherlands between December 2010 and March 2012. Patients aged 18 years or older - with no upper age limit - with acute ischemic stroke and proximal arterial occlusion of the anterior cerebral circulation, confirmed on imaging, were randomized to either intra-arterial treatment plus usual care or usual care alone. Eligibility requirements included the ability to initiate intra-arterial treatment within six hours of stroke onset; occlusion of the distal intracranial carotid artery, middle cerebral artery, or anterior cerebral artery on either CT angiography (CTA) magnetic resonance angiography (MRA) or digital subtraction angiography (DSA); and a National Institutes of Health Stroke Scale (NIHSS) score of two or higher.**

Primary outcome was the score on the modified Rankin scale at 90 days, determined by telephone interview by an experienced trial investigator who was blinded to group allocation. Secondary outcomes included the NIHSS score 24 hours and 5 to 7 days, score on the Barthel Index, and quality of life as measured by the EuroQol Group 5-Dimension Self-Report Questionnaire had 90 days. Additional outcomes included arterial regionalization rates measured with CTA or MRA at 24 hours, and final infarct volume on CT 5 to 7 days. Two neuroradiologists who were blinded to group allocation evaluated all imaging studies.

Prespecified subgroup analyses were performed by NIHSS score (2 to 15, 16 to 19, or ≥ 20), age (≥80 years or < 80 years), occlusion of the internal carotid artery terminus (yes or no), time from stroke onset to randomization (≤ 120 minutes or 120 minutes, and Alberta Stroke Program Early Computed Tomography Score (ASPECTS) (0 to 4, 5 to 7, or 8 to 10).

A total of 502 patients underwent randomization, two of whom withdrew consent. The mean age of the 500 patients in the final analysis was 65 years and 58.4% were men. There were 233 patients (46.6%) assigned to the intervention group and 267 patients (53.4%) assigned to the control group.

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. "The randomization procedure was Web-based, with the use of permuted blocks. We stratified randomization according to medical center, use of intravenous alteplase (yes or no), planned treatment method (mechanical or other), and stroke severity (NIHSS score of ≤14 or >14)." (p. 13)
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. An intention to treat analysis was performed. One patient in the control group received intra-arterial treatment, and intra-arterial treatment was never initiated in 17 patients (7.3%) assigned to the intervention group. Actual intra-arterial therapy was only performed in 196 of the 233 patients in the intervention group (84.1%). All patients were analyzed according to the group to which they were randomized rather than the treatment they received.
4.	Were patients in the treatment and control groups similar with respect to known prognostic factors?	Yes. Patients were similar respect to age, gender, baseline NIHSS score, prior history of stroke, pre-stroke modified Rankin scale score, initial blood pressure, treatment with IV alteplase, time from stroke onset to initiation of IV alteplase, ASPECTS, location of arterial occlusion, and time from stroke onset to randomization.
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	No. "A single experienced trial investigator, who was

	of group allocation?	unaware of the treatment-group assignments, conducted the follow-up interviews at 90 days by telephone with the patient, proxy, or health care provider. This interview provided reports for the assessment of the modified Rankin score by reviewers who remained unaware of the treatment-group assignments." (p. 13) "All neuroimaging studies were evaluated by two neuroradiologists who were unaware of the treatment-group assignments." (p. 13)
4.	Was follow-up complete?	Yes. Two patients out of 502 initially enroll withdrew consent after randomization. Complete outcome data was available for the remaining 500 subjects.
II.	**What are the results (answer the questions posed below)?**	
1.	How large was the treatment effect?	• There was a shift in the distribution of modified Rankin scores in favor of the intervention group (adjusted odds ratio [AOR] 1.67, 95% CI 1.21 to 2.30). • The intervention group had a higher proportion of patients with a modified Rankin score of two or less (21.2% versus 13.5%; AOR 2.16, 95%CI 1.39 to 3.38). • The mean NIHSS after 5 to 7 days was lower in the intervention group compared to the control group (mean difference -2.9, 95% CI -1.5 to -4.3). • For the 394 patients with CTA results at 24 hours, an absence of residual occlusion was more common in the intervention group (75.4%) compared to the control group (32.9%). Data on infarct volume were available for 298 patients, and were lower in the intervention group (mean difference 19 mL, 95% CI 3 to 34). • Good reperfusion, defined as a TICI score of 2b or 3), was achieved in 115 of 196 patients (58.7%) in the intervention group.
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?	Likely yes. Although the study was conducted in the Netherlands, only patients with acute stroke were enrolled. While these patients may have had fewer medical comorbidities, it is likely that the results of the study do apply to patients in the US. Our institution is capable of performing CTA and MRA, as well as neuro-interventional procedures.
2.	Were all clinically important outcomes considered?	Yes. The authors to consider the most clinically important outcomes including the modified Rankin score, an assessment of functional status, and the NIHSS, and assessment of persistent stroke symptoms. The authors did not consider cost, length of stay, or patient satisfaction.
3.	Are the likely treatment benefits worth the potential harm and costs?	Yes. Given the significant improvement in functional status based on the modified Rankin score, it would seem that the use of neuro-interventional procedures in select patients with acute ischemic stroke and proximal arterial occlusion of the anterior cerebral circulation, confirmed on imaging, is beneficial.

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 conducted in the Netherlands, and as such patients likely had fewer medical comorbidities than those in the US: e.g. only ~14% of patients in the study had diabetes (external validity).**
4. **The primary outcome was a shift in the distribution of the modified Rankin scale. Some have argued that the use of such an ordinal analysis may be overly sensitive and detect clinically insignificant changes in outcome.**

Bottom Line:

This multi-center, randomized controlled trial conducted in the Netherlands enrolled patients with acute stroke, occlusion of a major artery confirmed by imaging, and an NIHSS score of 2 or more. The trial demonstrated a favorable improvement in the shift in the distribution of modified Rankin scores in favor intra-arterial treatment compared to usual care (AOR 1.67, 95% CI 1.21 to 2.30). Careful attention to the strict inclusion criteria will need to be employed when applying the results of the study.