

**MRCLEAN** Trial: The **M**ulticenter **R**andomized **C**linical trial of **E**ndovascular treatment for **A**cute ischemic stroke in the **N**etherlands



Berkhemer OA, et al. "A randomized trial of intraarterial treatment for acute ischemic stroke". *The New England Journal of Medicine*. 2015. 372(1):11-20

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**Clinical question:**

In patients with large proximal anterior circulation strokes, does intra-arterial intervention (thrombectomy) in addition to usual care offer improved neurological outcomes?

**Background:**

Proximal anterior circulation ischemic strokes in the ICA, M1, M2, A1, and A2 account for approximately one-third of all ischemic strokes. Prior to MR Clean only conventional IV tPA had been standardized as treatment for this patient population, however recanalization rates were as low as 20% and approx. 5% in ICA occlusions. Intra-arterial intervention was around however efficacy was anecdotal at best. Trials such as IMS III, SYNTHESIS Expansion, and MR RESCUE suggested a potential for benefit for thrombectomy but was not substantial for the introduction of thrombectomy as a standard treatment for stroke. The authors of MR CLEAN hypothesized that newly available neuroimaging technology and improved thrombectomy tools like the MERCI device and new stent retrievers would improve outcomes.

**Methods:** Multi-center, open label randomized controlled trial. 500 subjects (233:intra-arterial therapy in addition to usual care vs 267: Usual care. Setting: 16 centers in the Netherlands. Enrollment (2010-2014). Follow-up at 90 days. Primary outcome: Modified Rankin Scale at 90 days. Funding: Dutch Heart Foundation with grants from AngioCare Covidien, Medac/Lamepro, and Penumbra.

*Inclusion criteria:* Age >18, Acute ischemic stroke due to occlusions of distal ICA, MCA at M1/M2, ACA at A1/A2 (as seen on CTA, MRA, digital subtraction angiography, or TCD), NIH stroke scale  $\geq 2$ , Possibility of treatment within 6 hours of symptom onset

*Exclusion criteria:* History of ICH, or ICH seen on CT or MRI, History of severe head injury or contusion in previous 4 weeks, BP >185/110 mmHg, Blood glucose <2.7 or >22.2 mmol/L, Platelets <90, APTT>50 sec, or INR>1.7, IV alteplase dose exceeding .9mg/kg or 90mg max, IV alteplase administration despite contraindication for thrombolytics, infarction within distribution of the relevant occluded artery in previous 6 weeks.

**Results:**

After randomization, about 82% of patients in the intra-arterial intervention arm received mechanical thrombectomy with retrievable stents. These patients went on to have significantly improved 90-day outcomes vs the usual care arm. Median Modified Rankin Scale of 3 vs 4, respectively with an odds ratio: 1.67 and confidence interval of 1.21 to 2.30. There was no significant difference between the rates of symptomatic ICH or mortality between the two arms, but the intra-arterial intervention arm had a higher rate of ischemic stroke in another territory compared to usual care (5.6% vs .4%, P = <.001)

**Conclusions:**

MR CLEAN was the first and largest of five multicenter open-label randomized controlled trials which demonstrated that early intra-arterial interventions with second generation thrombectomy devices dramatically improved neurological outcomes after ischemic stroke involving a large anterior artery occlusion compared to standard IV tPA alone without a significant increase in rates of symptomatic ICH or 90-day mortality.

The announcement of this at the World Stroke Conference in 2014 led to early termination of other similar trials. The impact on the stroke community was reflected in the 2015 AHA/ASA focused update of the 2013 Guidelines for Early Management of Patients with Acute Ischemic Stroke which now included endovascular therapy with a stent retriever if the patient presented with symptom onset within 6 hours and meeting all inclusion criteria.

**Additional study of interest:**

A recent trial published in the NEJM in May 2020 entitled Endovascular Thrombectomy with or Without Intravenous Alteplase in Acute Stroke explored the possibility of foregoing treatment with IV alteplase and pursuing direct treatment with thrombectomy. The authors concluded that thrombectomy alone was noninferior with regard to functional outcome. However, criticism of this study has not led to the termination of ongoing clinical trials covering this same topic.