Commentary on:
Mechanical Thrombectomy for Distal Occlusions: Efficacy, Functional and Safety Outcomes: Insight from the STAR Collaboration **by Anadani et al. World Neurosurg 2021**
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Distal Cerebral Vessel Occlusions and Mechanical Thrombectomy: Straightforward Questions, Generating Evidence, and Gearing Toward Submillimetric Vessels

***Victor Volovici*[1] *and Pieter Jan van Doormaal*[2]**

It sounds more straightforward than resecting an inflamed appendix or a low-grade glioma: removing a thrombus soon after it clogs up a vessel in the brain restores blood flow and leads to recovered neurologic function. Nevertheless, it took decades of innovation in endovascular technology, multiple trials (3 failed), and improvements in trial methodology and logistics to deliver the high-quality evidence necessary to support this logical statement.[1]

Still, there is a large variability when it comes to acute ischemic strokes (AIS): cause, clinical presentation, time of onset, vascular anatomy, and clot location. The question arises whether the currently available evidence can be extrapolated at the patient level for any patient presenting with an AIS.

Most of what we coin "high-quality evidence" nowadays stems from trials such as the Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands (MR CLEAN).[1] These trials include, preponderantly, patients with large-vessel occlusions (LVOs) in the anterior circulation. LVOs in which mechanical thrombectomy (MT) is considered "proven" effective are the carotid artery bifurcation, M1 and proximal M2. The cerebral arterial tree, however, is far more intricate. A total of 34 arterial branches supplying blood to highly heterogeneous neuroanatomic regions can be defined.[2] Every one of these branches can be primarily occluded by a small clot or secondarily by emboli during MT for an LVO. These occlusions are termed *distal medium vessel occlusions* (DMVOs). Whether the big randomized trials showing the clinical benefit of MT in LVO can be extrapolated to DMVOs is subject to debate. Compared with LVOs, DMVOs present more often with relatively mild symptoms. Intravenous thrombolysis (IVT) is more effective,[2] and MT is more challenging to perform. So far, only weak evidence exists of the effectiveness of distal thrombectomies, consisting mainly of underpowered retrospective series.[3-6]

Anadani et al[7] recently presented **WORLD NEUROSURGERY** with multicenter data from the Stroke Thrombectomy and Aneurysm Registry (STAR) and included all adult patients treated with MT with modern devices at 15 comprehensive stroke centers in the United States between January 2015 and December 2018. A total of 4719 patients from the STAR with vessel occlusions were included in the study, among which 189 had DMVOs and MT. In direct comparisons, subject to confounding by indication, DMVOs had a higher rate of good outcome but a lower rate of successful reperfusion. After adjustment for confounders, however, the differences were no longer significant.[7] The techniques used for MT comprised the entire spectrum of endovascular possibilities: direct aspiration, stent retrievers, combinations, and intraarterial delivery of tissue plasminogen activator. The overall rate of complications was low (7 patients, 4%).

A flood of new research questions appeared after publication of the first large MT trials.[1] Some of these questions have already

Key words
- Distal occlusion
- Hemorrhage
- Stroke
- Thrombectomy

Abbreviations and Acronyms
AIS: Acute ischemic strokes
DMVO: Distal medium vessel occlusions
IVT: Intravenous thrombolysis
LVO: Large-vessel occlusion
MT: Mechanical thrombectomy
STAR: Stroke Thrombectomy and Aneurysm Registry

From the Departments of [1]*Neurosurgery and* [2]*Radiology, Division of Neuro-interventional Radiology, Erasmus MC, Rotterdam, The Netherlands*

To whom correspondence should be addressed: Victor Volovici, M.D., Ph.D. [E-mail: v.volovici@erasmusmc.nl]

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been answered, such as the additional value of MT in the setting of unwitnessed AIS and AIS presenting beyond 6 hours with favorable computed tomography–perfusion characteristics (DAWN and DEFUSE-3).[8,9] Others are still open for debate, such as which MT technique or device is superior, the role of MT in patients with unfavorable imaging characteristics, and the additional value of certain drugs. Yet other trials raise more questions than they deliver answers. The BASICS (Basilar Artery International Cooperation Study) trial[10] could not show benefit of MT in posterior circulation stroke. Within this backdrop of ongoing arduous research, MT for DMVOs seems to be the next frontier.

DMVOs account for 30%–40% of AIS, either spontaneous or iatrogenic.[2] While half of these respond to IVT, the other half might still end up with severe disability if not treated. MT for distal occlusions is technically more challenging, as the vessels become smaller, more tortuous, and more fragile. Nevertheless, new technologies are emerging and endovascular devices are becoming smaller and less traumatic. Prior research into LVOs has shown the power large-scale collaborations or registries may muster. When faced with a straightforward research question, but also with a heterogeneous patient population and disease, pragmatic trials and large-scale collaborations are the answer. The STAR collaboration has shown that, despite being done in the "early years" of MT (right after the publication of the MT trials), thrombectomy for distal occlusion is feasible and can be performed safely. The 189 patients were well selected—>75% had successful reperfusion, and the complication rate was low, comparable with MT in LVOs.

The time seems ripe to tackle the issue of evidence for distal occlusions. Multicenter collaborations are already set up. The research questions are mounting: Which patients do not achieve reperfusion by IVT alone? Who will benefit from MT? Is there a role for local tissue plasminogen activator? and How can MT be optimally performed in distal occlusions? More side avenues are being opened: Why did the BASICS trial fail to show effect? Is there a role for microsurgical thrombectomy in the treatment of AIS?[11]

Evidence is often extrapolated to substantiate inflated claims.[12] Trials are sometimes used to justify interventions in patient populations that are unrepresented in the original trial sample or to justify interventions that appear similar to those used in the trial but are de facto quite different. The efficacy of distal MT is, so far, not backed by high-quality evidence. The question is, again, simple: Can the swift removal of a blood clot in a small blood vessel to restore circulation to a small part of the brain be effective in alleviating symptoms, given that it is effective for big clots in large vessels? The answer could be straightforward. Hopefully the investigators learn from past endeavors and use their international collaborative efforts to deliver high-quality evidence in order to answer these questions.

REFERENCES

1. Berkhemer OA, Fransen PS, Beumer D, et al. A randomized trial of intraarterial treatment for acute ischemic stroke. *N Engl J Med*. 2015;372:11-20.
2. Saver JL, Chapot R, Agid R, et al. Thrombectomy for distal, medium vessel occlusions: a consensus statement on present knowledge and promising directions. *Stroke*. 2020;51:2872-2884.
3. Bernsen MLE, Goldhoorn RB, Lingsma HF, et al. Importance of occlusion site for thrombectomy technique in stroke: comparison between aspiration and stent retriever. *Stroke*. 2021;52:80-90.
4. Grossberg JA, Rebello LC, Haussen DC, et al. Beyond large vessel occlusion strokes: distal occlusion thrombectomy. *Stroke*. 2018;49:1662-1668.
5. Sweid A, Head J, Tjoumakaris S, et al. Mechanical thrombectomy in distal vessels: revascularization rates, complications, and functional outcome. *World Neurosurg*. 2019;130:e1098-e1104.
6. Vargas J, Spiotta AM, Fargen K, Turner RD, Chaudry I, Turk A. Experience with A Direct Aspiration First Pass Technique (ADAPT) for thrombectomy in distal cerebral artery occlusions causing acute ischemic stroke. *World Neurosurg*. 2017;99:31-36.
7. Anadani M, Alawieh A, Chalhoub R, et al. Mechanical thrombectomy for distal occlusions: efficacy, functional and safety outcomes: insight from the STAR Collaboration [e-pub ahead of print]. *World Neurosurg*. https://doi.org/10.1016/j.wneu.2021.04.136, accessed July 14, 2021.
8. Albers GW, Marks MP, Kemp S, et al. Thrombectomy for stroke at 6 to 16 hours with selection by perfusion imaging. *N Engl J Med*. 2018;378:708-718.
9. Nogueira RG, Jadhav AP, Haussen DC, et al. Thrombectomy 6 to 24 hours after stroke with a mismatch between deficit and infarct. *N Engl J Med*. 2018;378:11-21.
10. Langezaal LCM, van der Hoeven E, Mont'Alverne FJA, et al. Endovascular therapy for stroke due to basilar-artery occlusion. *N Engl J Med*. 2021;384:1910-1920.
11. Thongphetsavong Gautam A, Seh H, Jain A, et al. Open microvascular thrombectomy for acute intracranial large vessel occlusion: microsurgery in the endovascular thrombectomy era. *World Neurosurg*. 2021;145:e278-e290.
12. Volovici V, Steyerberg EW. Lost in translation between evidence and recommendations: expert opinion is needed to define "level I". *World Neurosurg*. 2021;150:39-41.

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