

Intra-arterial Therapy for Ischemic Stroke

- Five prospective randomized controlled clinical trials have demonstrated the efficacy of intra-arterial therapy (I-AT) for patients with stroke secondary to large vessel occlusion (LVO)
- The presence of an LVO is typically established by non-invasive imaging (MRA, CT angiography) after non-contrast CT has ruled out hemorrhagic stroke and mass lesions
- The size of the established "core" infarct is quickly and accurately estimated by diffusion-weighted MRI (DWI)
- Close coordination between neuroradiologists, stroke neurologists, neuroendovascular specialists and Emergency Department physicians allows patients with an LVO, and a small core infarct (≤ 70 ml), to receive I-AT, when appropriate

Historically, prospective randomized controlled trials of intra-arterial therapies (I-AT) for stroke have been challenging to perform. These difficulties were compounded by lack of equipoise, rapidly evolving innovations in clot-retrieval devices and techniques as well as inadequate utilization of imaging for patient selection. Given these variations and resultant differences in study design, it is not surprising that some of these trials, including three large trials published in 2013, failed to show better outcomes for I-AT compared to medical therapies.

Closer examination reveals that these studies were fundamentally flawed. They took many years and by the time they were complete, the trials were not using contemporary devices or imaging protocols. For example, I-AT techniques treat strokes that are almost by definition secondary to large vessel occlusion (LVO); however, readily available, non-invasive vascular imaging to establish the presence of LVO was not required for participation in these trials. Additionally, almost no modern stent-retriever devices were used. Rather, these trials largely used the Merci Retriever device, which is much less effective and is now obsolete.

In 2014, the results of the Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands (MR CLEAN) study were announced. This study demonstrated that I-AT was superior to medical management with tPA alone: 32.6% of patients treated with I-AT achieved a positive stroke outcome as defined by the Rankin scale compared with 19.1% of those who received medical management. The adjusted common odds ratio was 1.67 (95% CI, 1.21 to 2.30). This study, which used more rigorous selection standards and employed more advanced stent-retrieval devices, clearly showed the benefits of I-AT in those patients with stroke caused by LVOs.

Mass General Acute Stroke Imaging Algorithm

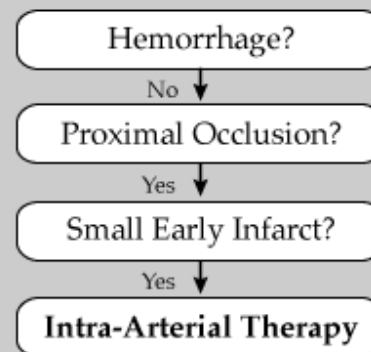


Figure 1. Mass General Acute Stroke Imaging Algorithm

The imaging algorithm answers three key pathophysiological questions: 1) is there a hemorrhage; 2) is there an occlusion that is treatable by I-AT; and 3) is early core infarct small enough that I-AT has a reasonable probability of helping the patient achieve a favorable outcome? Typically, a patient undergoes CT to assess for hemorrhage, immediately followed by CT angiography (CTA) to identify a treatable embolus. The most precise way to assess the size of the early infarct core is with diffusion MRI, an exam that takes less than two minutes. Less commonly, but nearly as effective, is to answer these questions with MRI-susceptibility imaging, MR angiography and diffusion MRI. CT and CTA alone are relied upon when a patient cannot undergo MRI, but the results are not as robust.

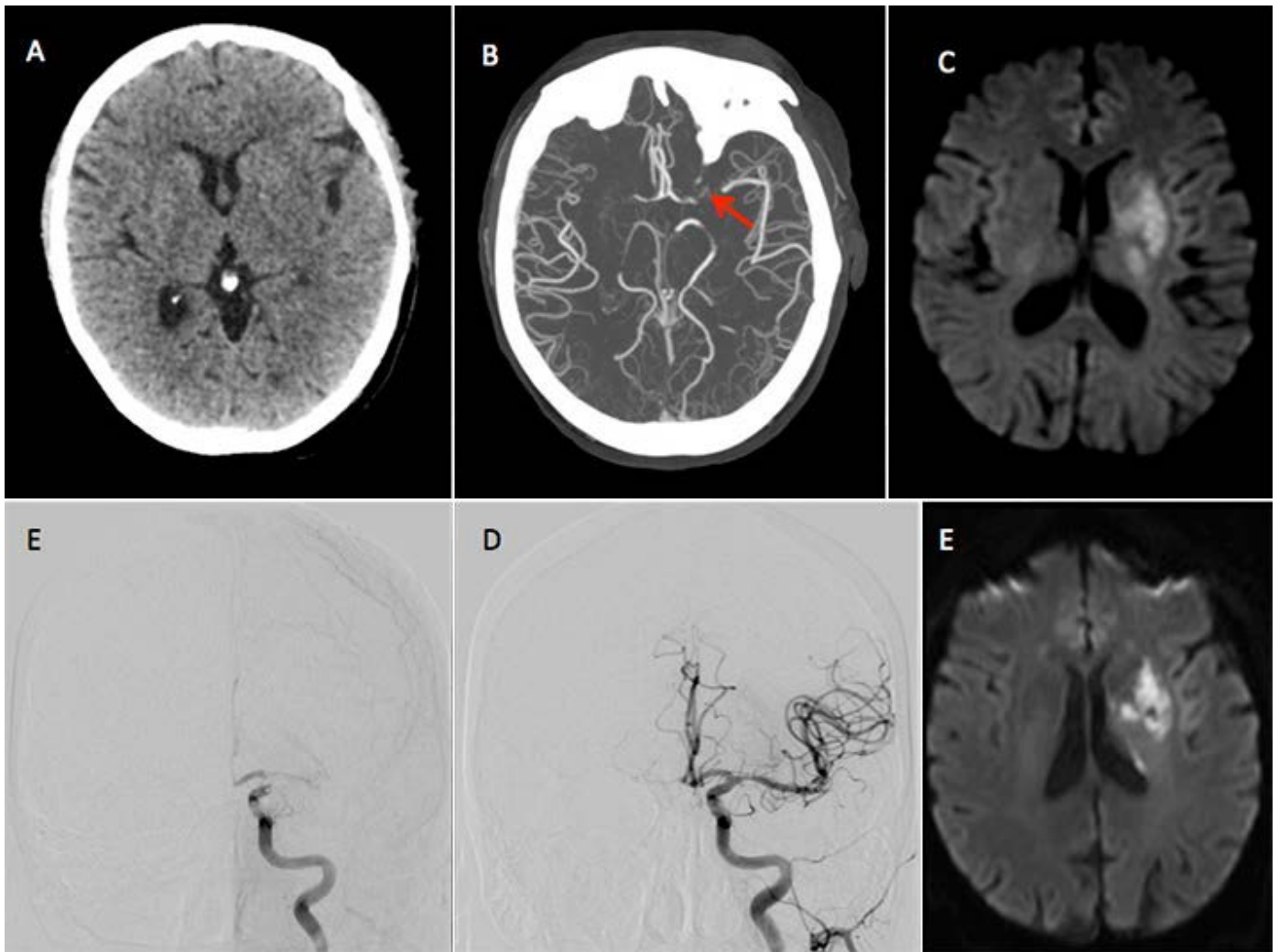


Figure 2. Illustrative images from an acute stroke case in which a previously healthy 79-year-old woman presented with a NIHSS of 22. Her last known well time was 5 hours previously. **(A)** Initial non-contrast CT was negative for hemorrhage. **(B)** CTA (axial maximal intensity projections) shows occlusion of the left middle carotid artery (MCA) (red arrow). **(C)** DWI, obtained immediately following the CT scan, shows a small established core infarct. Patient was deemed a good candidate for intervention. **(D)** Initial catheter angiographic image, anteroposterior view, shows opacified internal carotid artery (ICA), a filling defect at the terminus of the carotid artery, and faint opacification of the anterior cerebral artery (ACA) consistent with an ICA-T occlusion. **(E)** After mechanical thrombectomy, the ICA terminus, MCA, and ACA filled normally, indicating complete recanalization. **(F)** Follow-up MRI DWI at 24 hours shows no change in size of the core infarct following recanalization. The patient improved to NIHSS 4 and was NIHSS 2 at time of discharge on Day 3 post-op. She had no deficits at her three-month follow-up.

Soon after the results of MR CLEAN were announced, multiple ongoing randomized controlled trials were halted as their leadership evaluated their results to date. These trials, despite not having reached their anticipated enrollment, were all positive for the benefit of endovascular therapy. They include the Endovascular treatment for Small Core and Anterior circulation Proximal occlusion with Emphasis on minimizing CT to recanalization times (ESCAPE), the Extending the Time for Thrombolysis in Emergency Neurological Deficits–Intra-Arterial (EXTEND-IA), and Solitaire FR With the Intention For Thrombectomy as Primary Endovascular Treatment for Acute Ischemic Stroke (SWIFT PRIME). ESCAPE focused on process improvement, including improving time from arriving at hospital to treatment; EXTEND-IA treated patients with small infarcts; and SWIFT PRIME took a unique look at a specific retriever. These trials were published in *N Engl J Med* and demonstrated the same results, indicating an overwhelming benefit to mechanical thrombectomy (Level 1a) and thus introducing a revolution in the treatment of stroke from LVO.

Selecting Patients for Intra-Arterial Therapy

The I-AT clinical trials clearly demonstrate the importance of selecting patients who have LVOs. However, other factors are important to consider when selecting patients, including the extent of irreversibly damaged tissue or infarct core and the size of the ischemic penumbra, which is tissue that will progress to irreversible damage if blood

flow is not restored within a limited period of time. Both CT and MR imaging methods have been developed to assess these phenomena. Neuroradiologists at Massachusetts General Hospital have considered these methods and have developed an algorithm (Figure 1) based on the best evidence in the literature and on their clinical experience with the value these imaging methods bring to acute stroke patients.

The first step in the assessment of acute stroke is a non-contrast CT, which is outstanding for excluding intracranial hemorrhage and mass lesions. At Mass General, we typically then obtain a CT angiography (CTA), which allows for the rapid assessment of LVOs and should be performed whenever feasible. Important, peer-reviewed articles that were developed based on Mass General experience highlighted the value of using diffusion-weighted MRI (DWI) for detecting acute stroke. DWI represents the best method possible for determining the size of the infarct core, and it is rare for regions of DWI abnormalities to reverse. When they do, only a small part of the lesion is typically involved. Therefore, the DWI lesion (Figure 2) is considered representative of the infarct core, and a patient with a lesion <70 ml and an LVO is considered likely to benefit from I-AT.

In 2015, multiple positive randomized controlled trials were published that proved I-AT to be beneficial in patients with emergent LVO. In addition, a prospective cohort study, led by Leslie-Mazwi and Gonzalez, examined how I-AT-treated patients fared when selected with the aid of DWI. Forty patients were classified as likely to benefit and 32 patients as unlikely to benefit based on imaging that demonstrated an occlusion in the middle cerebral artery or the terminal carotid artery, core infarct volume as determined by DWI, and selected clinical criteria. Reperfusion was achieved in 70% of patients. In the likely-to-benefit group, 53% benefitted from I-AT as measured by modified Rankin Scores of 0-2 compared to 25% of those considered not likely to benefit. These results compared favorably with the various positive randomized controlled studies. Of note, a higher proportion of the screened patients were treated than in the previously published trials to obtain equivalent levels of benefit.

Work Flow

Delays to initiation of I-AT are likely to lead to worse outcomes for patients with LVOs. Public health initiatives have set a goal of initiating IV thrombolytic treatment within 60 minutes of a patient's arrival at the hospital. No such large-scale public health initiatives have proposed a similar goal for initiating I-AT, although some comprehensive stroke centers have set a goal of two hours from arrival to groin puncture. To achieve this, work flows must be highly efficient.

In a quality improvement project published by Mehta, delays in various phases from patient arrival time to groin puncture were examined. The longest delay was incurred after imaging was complete to the time when the procedure began. A new parallel processing protocol was put in place that alerted a neuroimaging fellow prior to imaging based only on a National Institutes of Health Score (NIHSS) of ≥ 8 and the time at which the patient was last seen well (≤ 8 hours). The fellow would then alert the rest of the multidisciplinary intervention team after confirmation of an LVO, with the goal of readying the suite and assembling the team in parallel with imaging. This process reduced the interval between completion of imaging and initiation of the procedure by approximately 30 minutes. Given the importance of time on outcome of stroke therapy, we have implemented these steps in our practice environment at Mass General and are continuing work on quality improvement initiatives to further reduce time to treatment.

Scheduling

I-AT for ischemic strokes caused by LVOs is performed at the main campus of Massachusetts General Hospital and is coordinated by teams from Stroke Neurology, Neuroendovascular and Diagnostic Neuroradiology, Neurocritical Care, and the Emergency Department.

Further Information

For further information on emergent large vessel occlusion leading to stroke, please contact [Joshua A. Hirsch, MD](#), Vice Chair, Interventional Radiology, Department of Radiology, Massachusetts General Hospital, at 617-726-1767.

We would like to thank Joshua A. Hirsch, MD, R. Gilberto Gonzalez, MD, PhD, and Thabele M. Leslie-Mazwi, MD for their advice and assistance in preparing this article.

References

Albuquerque FC, Fiorella D, Hirsch JA, *et al.* (2013). *Tribulations of stroke trials*. Journal of Neurointerv Surg 5:181-183.

Berkhemer, OA, Fransen, PSS, Beumer D, *et al.* (2015) *A Randomized Trial of Intraarterial Treatment for Acute Ischemic Stroke*. N Engl J Med 2015;372:11-20.

Fargen KM, Neal D, Fiorella DJ, Turk AS, *et al.* (2015) *A meta-analysis of prospective randomized controlled trials evaluating endovascular therapies for acute ischemic stroke*. J Neurointerv Surg. 7:84-9.

González RG, Copen WA, Schaefer PW, *et al.* (2013) *The Massachusetts General Hospital acute stroke imaging algorithm: an experience and evidence based approach*. J Neurointerv Surg. 5: Suppl 1:i7-12.

Leslie-Mazwi TM, Hirsch JA, Falcone GJ, *et al.* (2016) *Endovascular Stroke Treatment Outcomes After Patient Selection Based on Magnetic Resonance Imaging and Clinical Criteria*. JAMA Neurol. 73:43-9.

Mehta BP, Leslie-Mazwi TM, Chandra RV, *et al.* (2014) *Reducing door-to-puncture times for intra-arterial stroke therapy: a pilot quality improvement project*. J Am Heart Assoc. 3:e000963.

Mocco J, Fiorella D, Fargen KM, *et al.* (2015) *Endovascular therapy for acute ischemic stroke is indicated and evidence based: a position statement*. J Neurointerv Surg. 7:79-81.

©2016 MGH Department of Radiology

Janet Cochrane Miller, D. Phil., Author
Raul N. Uppot, M.D., Editor

