

12-6-2019

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Recommended Citation

Shukla,S, Baigorri,B, Fourzali,R, Serulle,Y, Evolution of Acute Ischemic Stroke Treatment as Supported by Clinical Trials. Presented at: Radiological Society of North America 2019 Scientific Assembly and Annual Meeting, December 1 - December 6, 2019, Chicago IL.

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Evolution of Acute Ischemic Stroke Treatment as Supported by Clinical Trials

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STROKE

- Stroke kills about **140,000** Americans each year—that's **1 out of every 20 deaths**
- Someone in the United States has a stroke every **40 seconds**. Every **4 minutes**, someone dies of stroke
- Every year, more than **795,000 people** in the United States have a stroke. About 610,000 of these are first or new strokes
- About 185,00 strokes—**nearly 1 of 4**—are in people who have had a previous stroke
- About **87%** of all strokes are ischemic strokes in which blood flow to the brain is blocked
- Stroke costs the United States an estimated **\$34 billion** each year. This total includes the cost of health care services, medicines to treat stroke, and missed days of work
- Stroke is a leading cause of serious long-term disability. Stroke reduces mobility in more than half of stroke survivors age 65 and over

Evolution of Acute Ischemic Stroke (AIS) treatment

INTRAVENOUS THROMBOLYSIS

1995 - NINDS (National Institute of Neurological Disorders and Stroke) Study

AIS patients benefitted from IV-rtPA treatment, a significant milestone in stroke treatment, a first disease-modifying therapy for AIS.¹



1996 - FDA approved the use of IV-rtPA for patients with acute ischemic stroke within 3 hours of symptom onset



2008 - ECASS (European Cooperative Acute Stroke Study) III

ECASS showed benefit of IV-rtPA over placebo among those treated within 3 to 4.5 h of symptom onset.^{2,3}

Evolution of Acute Ischemic Stroke (AIS) treatment

INTRAARTERIAL THROMBOLYSIS

1998 - PROACT (Prolyse in Acute Cerebral Thromboembolism)

The PROACT was the first randomized control trial (RCT) that enrolled 46 patients with middle cerebral artery occlusion and investigated the safety and efficacy of intra-arterial recombinant prourokinase and heparin compared with intra-arterial heparin alone, applied within 6 h of stroke symptom onset in patients with. It showed higher recanalization with intra-arterial recombinant prourokinase.⁴



1999 - PROACT II (Prolyse in Acute Cerebral Thromboembolism II)

The PROACT II trial, a multi-center RCT, conducted between 1996 – 1998, enrolled 180 patients with AIS of less than 6-hour duration from occlusion of the MCA, without hemorrhage. It demonstrated the superiority of intra-arterial recombinant prourokinase in achieving the primary outcome of no or slight disability, defined as a modified Rankin Scale (mRS) of 0 to 2 at 90 days, in 40% versus 25% ($p = 0.04$) of patients. It also showed a higher recanalization rate of 66% versus 18% ($p < 0.001$) compared with intra-arterial (IA) heparin alone. The mortality rates were 27% in the control group and 25% in the intra-arterial recombinant prourokinase group. The treatment arm demonstrated an increased rate of intracranial hemorrhage within 24 hours at 10%, compared to 2% in the control group. The drug did not get FDA approval.⁵

Evolution of Acute Ischemic Stroke (AIS) treatment

MECHANICAL THROMBECTOMY

MERCI TRIAL (Mechanical Embolus Removal in Cerebral Ischemia Trial)

*The MERCI trial, a single-arm, prospective, nonrandomized multicenter trial of thrombectomy in patients with large vessel occlusion treated within 8 hours of stroke symptoms, achieved a **recanalization rate of 46%** compared to the historical control of 18%. Higher rates of improved neurological outcome (mRS 0-2) at 90 days in patients with successful recanalization (46%) versus unsuccessful recanalization (10%). The MERCI device is made of a corkscrew-shaped nitinol wire that is deployed into the thrombus in the occluded intracranial artery, with the device and corkscrew removed as a single unit to recanalize the vessel.⁶*



FDA approval of the first mechanical thrombectomy device in 2004



MULTI MERCI TRIAL

The multi merci trial, a single-arm, prospective nonrandomized, international clinical trial enrolled 164 patients, using a newer (L5 retriever) device achieved a recanalization rate of 57% with MT only and 69.5% if used in conjunction with IV-rtPA. The rate of FIO was 36%, a slight improvement over the MERCI trial result. The rate of symptomatic intracranial hemorrhage (sICH) was 7.8% in MERCI and 9.8% in Multi MERCI subjects, respectively.⁷

A pooled analysis of both studies concluded that the final recanalization status was the strongest predictor of independent clinical outcomes at 90 days in patients undergoing thrombectomy.^{8,24.}

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MECHANICAL THROMBECTOMY

PENUMBRA TRIAL

*The Penumbra pivotal stroke trial, a multicenter, prospective, single-arm, study enrolled 125 patients with National Institutes of Health Stroke Scale (NIHSS) scores of 8 or more, presenting within 8 h of symptom onset and with angiographic occlusion (TIMI 0 to 1) of a treatable LVO. The study demonstrated successful recanalization (TIMI grade 2 or 3) in 81.6% of target vessels. **The rate of FIO was low (25%) with mortality of 32.8% at 90 days and, the rate of sICH was 11.2%.⁹***



FDA approval of Penumbra Stroke System in January 2008

MERCI and PENUMBRA trials demonstrated higher recanalization rates. These trials were major breakthroughs in the field of mechanical thrombectomy. However, the clinical/neurological outcomes were still relatively low.²⁴

Evolution of Acute Ischemic Stroke (AIS) treatment

MECHANICAL THROMBECTOMY

Multiple Randomized Trials with First Generation Devices (2004 -2012)

IMS (Interventional Management of Stroke) III

The IMS III trial, was an international RCT, enrolling 656 patients, comparing standard-dose IV-rtPA with a combination of low dose IV- and IA-rtPA or mechanical thrombectomy. No pre-procedure vascular imaging was required. It led to 89 (21%) patients enrolled in the endovascular arm without LVO. The majority of the patients underwent mechanical thrombectomy with a first-generation MERCI device, while solitaire stent was used in a minority of the patients in the later stages. The study was stopped in 2012 due to futility after no significant difference in long-term functional outcome was discerned between groups: FIO at 90 days was 40.8% for mechanical thrombectomy with IV-rtPA versus 38.7% for IV-rtPA alone; the mortality rates at 90 days were also similar between the endovascular-therapy and intravenous t-PA groups (19.1% and 21.6%, respectively).^{10,24}

Evolution of Acute Ischemic Stroke (AIS) treatment

MECHANICAL THROMBECTOMY

Multiple Randomized Trials with First Generation Devices (2004 -2012)

MR RESCUE (Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy)

The MR RESCUE trial, an RCT that enrolled 118 patients within 8 hours of LVO, anterior-circulation strokes, comparing clinical outcomes in MT (using Merci Retriever or Penumbra System) vs. standard care. Pre-procedure CT and MRI perfusion imaging were performed for stratified randomization based upon favorable vs. non-favorable penumbral pattern. No significant differences between the MT and medical therapy groups (FIO at 90 days, 18.75% vs. 20%) was demonstrated. Revascularization was obtained in 67% of embolectomy patients, with 21% 90-day mortality, and 4% sICH.^{11,24}

SYNTHESIS EXP (Intra-arterial vs. systemic thrombolysis for acute ischemic stroke trials)

The SYNTHESIS EXP trial, an RCT with 362 patients with AIS within 4.5 hours after onset, compared survival free of disability (mRS score between 0-1 at 90 days) between the endovascular therapy group (IA-rtPA+/-MT) and IV-tPA. No functional benefit of endovascular therapy (30.4%) over IV-rtPA therapy (34.8%).^{12,24}

Uncertain future of Intra-Arterial Stroke Therapy in 2013

However, there were 2 main reasons amongst other to continue with new studies of MT:

- 1) In 2012, a subset analysis of the phase 2 studies demonstrated significant superiority in achieving recanalization and improved functional outcomes in patients in whom the new stent retrievers were used, compared to the previously used 1st generation devices.²⁴.
- 1) An analysis from IMS-3 data showed significant functional benefit in the subgroup of patients with proven LVO when computed tomography angiography (CTA) was performed prior to endovascular therapy compared with IV-rtPA alone.²⁴.

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MECHANICAL THROMBECTOMY

SWIFT TRIAL

The SWIFT (Solitaire Flow Restoration Device Versus the Merci Retriever in Patients With Acute Ischemic Stroke) trial was a multicenter RCT that compared the Thrombolysis In Myocardial Ischemia (TIMI) scale 2 or 3 flow in all treatable vessels without symptomatic intracranial hemorrhage, after up to three passes of the assigned device in patients with acute ischaemic stroke with moderate to severe neurological deficits and were treatable by thrombectomy within 8 h of stroke symptom onset. Fifty-eight (58) patients underwent MT with the self-expanding stent retriever (Solitaire) and 55 patients with the Merci stent.¹³

The primary efficacy outcome was achieved more often in the Solitaire group than it was in the Merci group (61% vs. 24%). More patients had a good 3-month neurological outcome with Solitaire than with Merci (58% vs. 33%). 90-day mortality was lower in the Solitaire group than it was in the Merci group (17 vs. 38).¹³

TREVO 2 TRIAL

***TREVO 2** (Trepo Versus Merci Retrievers for Thrombectomy Revascularization of LVO in Acute Ischemic Stroke) phase 2 studies also demonstrated stent retrievers to have better reperfusion and good neurological outcomes at 90 days compared with the first-generation Merci Retrieval System.¹⁴*

Evolution of Acute Ischemic Stroke (AIS) treatment

MECHANICAL THROMBECTOMY

STENT RETRIEVAL PHASE 3 TRIALS

5 RCTs were published in 2014-2015, which demonstrated the superiority of MT done with second-generation devices with IV-rtPA compared to IV-rtPA alone.

MR CLEAN

ESCAPE

SWIFT PRIME

EXTEND -1A

REVASCAT

In these trials, patients with acute ischaemic stroke caused by occlusion of the proximal anterior artery circulation were randomly assigned to receive either endovascular thrombectomy within 12 h of symptom onset or standard care (control), with a primary outcome of reduced disability on the modified Rankin Scale (mRS) at 90 days.

Key differences in these trials vs. first generation trials:

- 1. CT neuroimaging in patient selection - Patients with pretreatment ASPECTS ≥ 7 have better outcomes.*
- 2. Faster and improved recanalization - MR RESCUE reported substantial recanalization in only 27% of subjects, whereas the rate of recanalization was not reported by SYNTHESIS-EXP. In comparison, the rates of substantial recanalization noted in the aforementioned studies were: MR CLEAN 58%, ESCAPE 72%, SWIFT PRIME 88%, EXTEND IA 94%, and REVASCAT 66%, showing remarkable improvement over previous studies.^{15,16,17,18,19,24.}*

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MECHANICAL THROMBECTOMY

HERMES COLLABORATION

HERMES collaboration pooled patient-level data from the previously mentioned five trials (MR CLEAN, ESCAPE, REVASCAT, SWIFT PRIME, and EXTEND IA) done between December 2010, and December 2014. In these trials, patients with acute ischemic stroke caused by occlusion of the proximal anterior artery circulation were randomly assigned to receive either endovascular thrombectomy within 12 h of symptom onset or standard care (control), with a primary outcome of reduced disability on the modified Rankin Scale (mRS) at 90 days.²⁰

*Analysis of the individual data for 1287 patients (634 assigned to endovascular thrombectomy, 653 assigned to control) demonstrated significantly reduced disability at 90 days in endovascular thrombectomy compared with control (adjusted cOR 2.49, 95% CI 1.76–3.53; $p < 0.0001$) for all sub-groups of patients. **The number needed to treat with endovascular thrombectomy to reduce disability by at least one level on mRS for one patient was 2.6.** Mortality at 90 days and risk of parenchymal hematoma and symptomatic intracranial hemorrhage did not differ between populations. Endovascular thrombectomy is of benefit to most patients with acute ischaemic stroke caused by occlusion of the proximal anterior circulation, irrespective of patient characteristics or geographical location.²⁰*

Evolution of Acute Ischemic Stroke (AIS) treatment

MECHANICAL THROMBECTOMY

DEFUSE 3 TRIAL

*The DEFUSE 3 trial was a multicenter trial that enrolled 182 patients that were randomized (92 to the endovascular-therapy group and 90 to the medical-therapy group) and had proximal middle cerebral artery or intracranial internal carotid artery occlusion and a region of tissue that was ischemic but not infarcted up to **6-16 hours** after a patient was last known to be well. The primary outcome was the ordinal score on the modified Rankin scale (range, 0 to 6, with higher scores indicating greater disability) at day 90.²¹*

The DEFUSE 3 trial showed that endovascular therapy (thrombectomy plus standard medical therapy) provided better functional outcomes than standard therapy alone. It was associated with a favorable shift in the distribution of functional outcomes on the modified Rankin scale at 90 days (odds ratio, 2.77; $P < 0.001$) and a higher percentage of patients who were functionally independent, defined as a score on the modified Rankin scale of 0 to 2 (45% vs. 17%, $P < 0.001$). The 90-day mortality rate was 14% in the endovascular-therapy group and 26% in the medical-therapy group ($P = 0.05$), and there was no significant between-group difference in the frequency of symptomatic intracranial hemorrhage (7% and 4%, respectively; $P = 0.75$) or of serious adverse events (43% and 53%, respectively; $P = 0.18$).²¹

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MECHANICAL THROMBECTOMY

DAWN TRIAL

*The Dawn trial was a multicenter randomized controlled trial that enrolled 206 patients (107 to the endovascular-therapy group and 90 to control group) who had occlusion of the intracranial internal carotid artery or the proximal middle cerebral artery up to **6-24 hours** after a patient was last known to be well. The coprimary end points were the mean score for disability on the utility-weighted modified Rankin scale (which ranges from 0 [death] to 10 [no symptoms or disability]) and the rate of functional independence (a score of 0, 1, or 2 on the modified Rankin scale, which ranges from 0 to 6, with higher scores indicating more severe disability) at 90 days.²²*

The DAWN trial showed that the endovascular therapy group demonstrated better outcomes for disability and functional independence at 90 days. The mean score on the utility-weighted modified Rankin scale at 90 days was 5.5 in the thrombectomy group as compared with 3.4 in the control group and the rate of functional independence at 90 days was 49% in the thrombectomy group as compared with 13% in the control group. The rate of symptomatic intracranial hemorrhage did not differ significantly between the two groups (6% in the thrombectomy group and 3% in the control group, $P = 0.50$), nor did 90-day mortality (19% and 18%, respectively; $P = 1.00$).²²

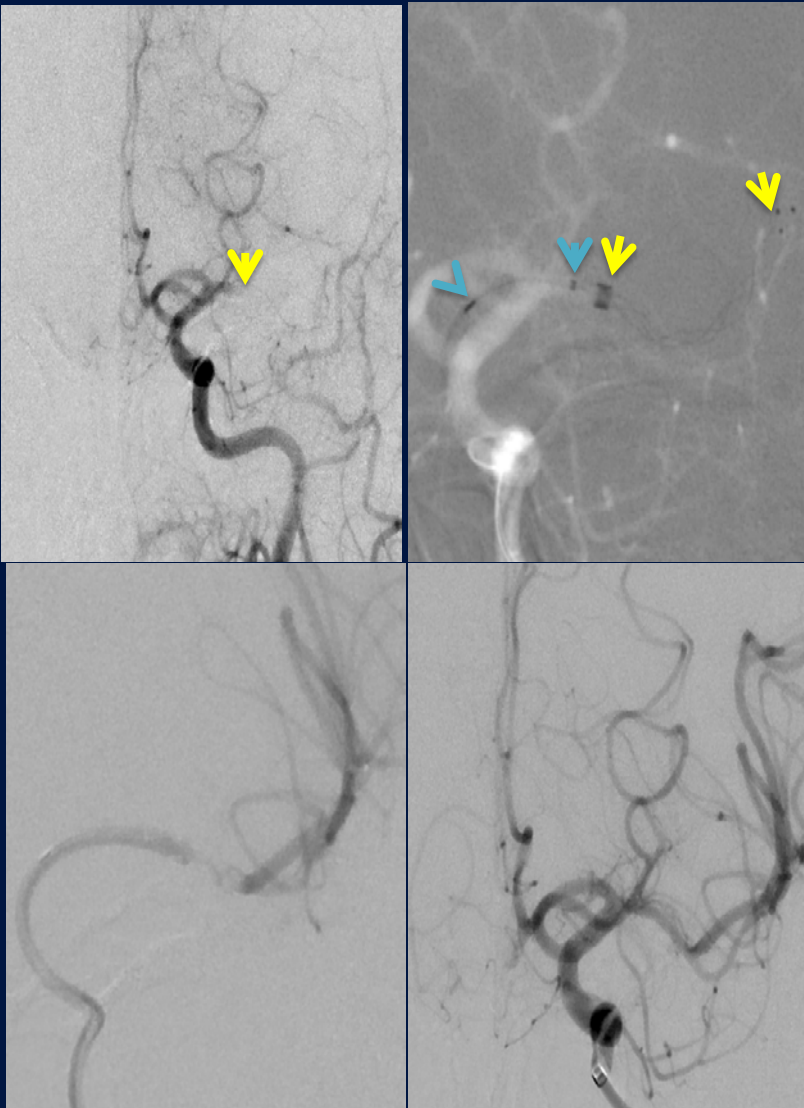


Figure 5: (a) Diagnostic angiogram showing M1 occlusion (yellow arrow) (b) Aspiration catheter (cyan arrowhead), microcatheter (cyan arrow), and stent retriever (yellow arrows) traversing through the M1 clot and engaging it. (c) Stent retriever in partially recanalized vessel (d) Post stent retriever removal showing recanalized vessel with improved blood flow



Figure 6: Angiography images showing (a) Right M1 occlusion (Yellow arrow) and (b) Post endovascular treatment of Right M1 occlusion using Solumbra technique showing good revascularization



Figure 7: Graphics of (a) stent retriever and (b) stent suction devices

MECHANICAL THROMBECTOMY

SUMMARY

- National Institute of Neurological Disorders and Stroke Study in 1995 established IV-rtPA treatment as the first disease-modifying therapy for acute ischemic stroke, establishing a significant milestone in stroke treatment. FDA approved the use of IV-rtPA for up to 3 hours of symptom onset. ECASS extended that window to 4.5 hours.
- MERCI AND PENUMBRA trials were the breakthrough studies establishing mechanical thrombectomy as a treatment modality with a higher recanalization rate; however, neurological outcomes were not shown to be significantly improved.
- Multiple RCT from 2004-2012 (IMS 3, MR RESCUE, SYNTHESIS EXP) used first-generation mechanical thrombectomy devices and failed to demonstrate significant improvement in the functional outcomes.
- SWIFT AND TREVO 2 trials demonstrated improved reperfusion and good neurological outcomes at 90 days with the stent retrievers vs. the 1st generation MERCI device.
- Multiple trials (MR CLEAN, ESCAPE, SWIFT PRIME, EXTEND -1A, REVASCAT) published since 2015 have demonstrated the superiority of mechanical thrombectomy in combination with standard care compared to standard care alone. Faster and improved recanalization from newer endovascular devices, together with the optimized patient selection, were crucial factors leading to positive outcomes compared to prior trials.
- DAWN (2018) has further extended the treatment time frame up to 24 hours.

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