

# **AANS/CNS Response to CTAF Thrombectomy Brief**

## **Consideration of the IMS III, MR RESCUE and SYNTHESIS Thrombectomy Trials**

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## **Introduction**

Recent publication of the Interventional Management of Stroke (IMS III), Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy (MR RESCUE), and SYNTHESIS trial results prompted skepticism in the lay press about the clinical value of mechanical thrombectomy for the treatment of ischemic stroke. As a professional society representing the subspecialists responsible for the surgical and catheter-based treatment of ischemic stroke, the Joint Cerebrovascular Section of the American Association of Neurological Surgeons (AANS) and Congress of Neurological Surgeons (CNS) endeavors to provide guidance on clinical trial results that may influence medical practice or impact the availability of these treatment options to patients.

The following manuscript examines the results of the IMS III, MR RESCUE, and SYNTHESIS trials in a broader clinical context. First, to what extent did the conduct of these trials comport with modern thrombectomy practice? Second, what lessons emerge from the data in these trials to inform or support elements of that practice?

Deconstruction of these two fundamental questions requires a characterization of modern endovascular practice along the following dimensions: (1) Patient selection, (2) Technical performance and adequacy of Intra-Arterial Therapy, and (3) Systems-Based Processes in the Comprehensive Stroke Center era. By these standards, the reviewed trials failed to reflect modern thrombectomy practice and render the conclusions of the lay press premature. (Figure 1)

Taken together, these trials further provide compelling support for preserving the best elements of endovascular practice. Review of the data will demonstrate (1) the absence of competing therapeutic alternatives for non-iv TPA eligible patients, (2) the importance of pre-procedural arterial imaging to identify and distinguish strokes due to Large-Vessel Occlusions (LVO), (3) the statistically significant clinical advantage of endovascular therapy in patients with confirmed LVO by pre-procedural imaging, (4) the criticality of process efficiency to minimize delays in care as emphasized by the Joint Commission (TJC), and (5) dramatic improvements in the technical performance and safety profile of modern endovascular devices.

Ultimately, our strongest professional commitment remains to the advancement of medical science through transparent scientific inquiry. We herald the conclusion of IMS III, SYNTHESIS and MR RESCUE as steps in that process, and bear the responsibility to our patients to ensure this progress does not become a basis for the denial of endovascular treatment access to stroke patients beyond the narrow cohorts studied in these trials.

## **Trial Summaries**

### *IMS III*

The Interventional Management of Stroke (IMS III) Trial was a randomized, open-label multi-center study to compare a combined intravenous (IV) and intra-arterial (IA) treatment approach to restoring blood flow to the brain to the current standard FDA approved treatment approach of giving IV rt-PA alteplase, Activase®/Actilyse® alone. Both approaches required treatment initiation within three hours of stroke onset. A projected 900 subjects with moderate to severe ischemic stroke were to be enrolled at 50+ centers in the United States, Canada, Australia and Europe. The study began in August 2006 and was halted prematurely on April 9, 2012. Importantly, the Data Safety and Monitoring Board emphasized safety concerns between the two arms were not the basis for trial suspension.

After randomization of 656 participants, the endovascular group and IV tPA cohorts experienced similar rates of functional independence (mRS 0-2) (40.8% versus 38.7%) and mortality (19.1% and 21.6%, P=0.52) at 3-month follow-up. Sub-group analysis based on NIHSS severity (NIHSS 8-19 and NIHSS > 20) showed greater therapeutic benefit for endovascular therapy, but did not achieve statistical significance. Rates of symptomatic intracerebral hemorrhage were additionally comparable (6.2% and 5.9%, P=0.83). The following analysis will explore the IMS III data and particularly address the endovascular population of interest; patients with confirmed large vessel occlusion (LVO). Additionally, changes in the technical performance and success of thrombectomy will be explored.

## *MR RESCUE*

The Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy (MR RESCUE) Trial was a multi-center, randomized trial comparing standard medical care to embolectomy in patients presenting within 8 hours with a large-vessel anterior circulation stroke. All patients received pre-procedural parenchymal imaging by CT or MRI to assess penumbral profile; randomization protocols allocated an equivalent number of favorable and unfavorable penumbral profiles to each group. Patients treated with iv-TPA were only enrolled if arterial imaging demonstrated persistence of a large-vessel occlusion.

Of 118 enrolled patients, Rankin scores did not differ between embolectomy and standard medical care (3.9 vs. 3.9,  $P = 0.99$ ). Embolectomy was not superior to standard medical care in patients with either a favorable penumbral pattern (mean score, 3.9 vs. 3.4;  $P = 0.23$ ) or a nonpenumbral pattern (mean score, 4.0 vs. 4.4,  $P=0.32$ ).

Importantly, patients with reperfusion or revascularization did demonstrate mean improvements in 3-month mRS (3.2 [2.6-3.8] versus 4.1 [3.7-4.5],  $P=0.04$ ) and median absolute infarct growth (9.0 versus 72.5 mL,  $P<0.001$ ). Moreover, MR RESCUE only included first generation Merci and Penumbra endovascular technologies. Partial or complete reperfusion was defined by Thrombolysis in Cerebral Infarction (TICI) Scale 2a-3 results; modern stentriever trials define adequate recanalization as a TICI 2b or 3 result. The disparity between TICI 2a and

2b results in terms of both clinical and technical adequacy will be borne out by later statistical analysis.

### *SYNTHESIS*

The Intra-Arterial versus Systemic Thrombolysis for Acute Ischemic Stroke (SYNTHESIS) Trial was a multi-center Italian trial that randomized 362 patients presenting with an acute ischemic stroke to iv tPA within 4.5 hours of onset versus intra-arterial therapy within 6 hours of onset. No pre-procedural imaging was obtained to confirm LVO nor was a lower bound to NIHSS for study inclusion present. It cannot therefore be established that the SYNTHESIS study population reflects the LVO stroke population targeted in the United States.

Moreover, only 165 of the 181 patients randomized to intra-arterial therapy (IAT) received an endovascular procedure. Due to endovascular treatment differences between the study centers and the United States, 109 patients received IAT with pharmacologic agents and wire manipulation; only 56 patients received mechanical thrombectomy procedures in the IAT arm. The efficacy of these alternative IAT was not reported in terms of post-procedural TICI and time to reperfusion. The SYNTHESIS Trial failed to demonstrate a 3-month clinical benefit by mRS for this unconventional endovascular therapy. However, despite withholding Class I indicated IV tPA, and delivering IA tPA in patients without occlusion, endovascular therapy had no increase in death or symptomatic ICH. SYNTHESIS thereby affirms the safety of endovascular therapy.

## Patient Selection

- I. **Large-vessel occlusions (LVO) remain a distinct subset of ischemic stroke patients responsible for disproportionate economic costs, morbidity and mortality. Beyond the natural history of LVO detailed below, the poor predictive value of NIHSS in the absence of arterial imaging deprives endovascular methods a therapeutic target; a full 20% of endovascular patients in IMS III lacked a large-vessel occlusion. SYNTHESIS provided no LVO incidence though only a subset (56/165) of IAT subjects underwent mechanical thrombectomy.**

Ischemic stroke trials over the past decade have emphasized the existence of LVO patients as a distinct clinical entity. Aside from the practical matter of providing a target for IAT, LVO patients suffer higher odds of disability, death and increased economic costs. Appendix A pages 18-22 offer the literature supporting these proven LVO elements, and details the cost-effectiveness of mechanical thrombectomy in the LVO subset.

Moreover, experience with Dose Escalation of Desmoteplase for Acute Ischemic Stroke trial (DEDAS) inadvertently exposed the poor concordance of presenting NIHSS and LVO. Though the mean NIHSS in the DEDAS trial was 9, only 30% of DEDAS patients harbored a confirmed LVO. The DEDAS Trial failed to show a benefit of desmoteplase from 3-9 hours guided by MR perfusion. In the placebo arm, only 46% were mRS > 2 and only 6% died. LVO patient natural history, by contrast, carries a 50% mortality rate in the anterior circulation and 70-80% mortality rate in the posterior circulation; functional dependence with an mRS > 2 consistently remains at approximately 10%.

At ISC 2013, Janardhan and colleagues presented natural history data for patients with an NIHSS > 10 and a confirmed LVO. In their prospective, multicenter study, the investigators presented stroke cohort eligible patients who did not receive mechanical thrombectomy and received standard medical care. At 90 days, 80% of patients had a poor outcome (mRS 3-6); 24 of 59 (40.7%) died, six (10%) patients suffered intracerebral hemorrhage, and only 10% enjoyed a TICI 2a-3 spontaneous recanalization. Thus, in the target population of acute ischemic stroke from confirmed large vessel occlusion (LVO), these data affirm the terrible natural history associated with this devastating disease. (27)

By failing to confirm LVO, the IMS III protocol diminished the opportunity of IAT to always treat a target and suffered from the poor concordance of an initial NIHSS and ultimate LVO that plagued the DEDAS trial. Therefore, the IMS III trial cannot fully capture the potential benefit of IAT to LVO patients. (Appendix A, pages 22-23). Of the 656 subjects enrolled in IMS III, 47% obtained pre-procedural CTA or MRA (Figure 2). Of the 423 subjects who obtained angiographic imaging, 80 harbored no LVO and 89 ultimately received no IAT (Figures 3 and 4). Moreover, the endovascular therapeutic effect size for patients with NIHSS > 20 approached significance and was far greater than in the NIHSS 8-19 cohort; these high NIHSS patients more likely harbored an LVO (Figure 5). These findings comport with the significant clinical benefit of endovascular therapy in patients who harbored a known LVO in IMS III (Figure 6).



**II. IMS III trial design pre-specified an analysis of clinical benefit in patients who presented with an LVO by pre-procedural imaging. Van Elteren analysis of 3-month mRS distribution demonstrated superiority of endovascular therapy to iv-tPA alone in patients who harbored a baseline LVO (P=0.01) (Figure 6).**

Van Elteren analysis detects the statistical significance of a global shift in outcome distribution. Given mRS scores range from 0-6, this statistical method provides a more accurate assessment of therapeutic effect than dichotomized collapse of the mRS outcome measure into 0-2 and 3-6 categories. For these reasons, the IMS III investigators applied van Elteren methodology in asserting the absence of therapeutic benefit to endovascular therapy in the complete IMS III cohort.

However, pre-specified subset analysis in the 271 patients who harbored an LVO by baseline CTA supersedes these results; it represents the only study population with confirmed presence of the target disease (LVO) for mechanical thrombectomy. These patients more aptly reflect the target population for modern endovascular therapy. Figure 6 details the improved 3-month clinical outcomes by mRS enjoyed by patients in the endovascular cohort (P=0.01). Thus, in patients with confirmed LVO, endovascular therapy improves 3-month clinical outcomes beyond iv-tPA alone.

**III. IMS III, in comparing iv-tPA against iv-tPA + IAT in patients presenting within 3 hours of symptom onset, applies to roughly 5-10% of ischemic stroke patients who are TPA eligible. For the 26% of patients who present with an unknown onset or “wake-up strokes” and the large percentage that present within 8 hours of symptom**

**onset, mechanical thrombectomy remains the only available treatment. Moreover, stroke patients with any contraindication to iv-TPA rely on IAT for LVO as the therapy of last resort. SYNTHESIS and MR RESCUE similarly capture a minority of stroke patients in their study populations.**

As a stroke community, we cannot extrapolate the treatment situation of 5-10% of patients eligible for iv-TPA to the 750,000 stroke patients in the U.S. every year. Extracranial arterial dissection patients offer an additional patient subset where mechanical revascularization strategies remain the unique treatment option. Endovascular therapy now serves as a primary treatment option for many of these non-IMS III patients. The Joint Commission (TJC) recognized the value of endovascular therapy at these centers of excellence in the development of Comprehensive Stroke Center designations. The process measures emphasized by TJC find empiric support in the recent IAT stroke trials and will be the subject of a later section.

**IV. Imaging advancements and stroke profiles developed since the inception of IMS III have dramatically refined patient selection for IAT. IMS III results do not reflect these advancements nor the nuance of vascular territory, involved parenchymal tissue, and collateral circulation so central to stroke patient assessment. Though MR RESCUE attempted to incorporate these modalities into its trial design, inadequate reperfusion achieved with first generation devices (detailed in next section) failed to capitalize on this benefit. However, those MR RESCUE patients with favorable penumbral profile who achieved reperfusion in either arm, enjoyed significantly reduced infarct progression (9 mL versus 72.5 mL  $p<0.001$ ). Imaging triage therefore would have been beneficial had higher reperfusion rates been achieved; limitations in MR RESCUE IAT technologies frustrated the realization of this benefit.**

Imaging advancements in CT and MR modalities refine distinction of penumbra and completed infarct, thus allowing triage of IAT candidates based on end organ damage. These efforts were not captured in the IMS III protocol. Ironically, though IMS III represents the very small percentage of patients eligible for iv-TPA, these same patients may not be the appropriate candidates for IAT. In the absence of proven LVO or the presence of a meaningful penumbra, IMS III diluted the salutary benefits of image-guided triage for IAT detailed above.

## **Technical Performance of Endovascular Therapy: The Modern Standards of Safety and Reperfusion**

### *Safety of Endovascular Therapy in the Setting of iv tPA*

- I. **IMS III trial design initially included full dose iv-TPA against (2/3) iv-TPA + IAT. Prior dose escalation studies of iv-TPA alone demonstrated the decreased efficacy of a two-thirds dose. Moreover, death and symptomatic intracerebral hemorrhage rates were comparable among the two study groups and demonstrates the safety of endovascular therapy in the setting of tPA (Figure 7).**

Thus, the marginal benefit of IAT would need to overcome the disadvantage of reduced systemic dosing. Though IMS III investigators ultimately changed the protocol to reflect the current treatment standard of full-dose iv-TPA in eligible patients + IAT, this initial protocol skews the results against IAT. Importantly, this initial design reflects the past consideration of iv-TPA and mechanical thrombectomy as dueling modalities as opposed to the complementary tools they are viewed today. The safety data presented in Figure 7 cements this result.

- II. **SYNTHESIS likewise demonstrated no significant difference in death or intracerebral hemorrhage between IV and IA treatment groups (Figure 8). The safety profile of endovascular therapy endured the withholding of Class I iv-tPA, the mean administration of 40 mg IA tPA in the endovascular arm that dwarfs prior IAT studies, and the absence of a confirmed LVO target. SYNTHESIS affirms the absence of safety concerns with endovascular therapy.**

### *Adequacy and Rate of Reperfusion Compared to Modern Endovascular Standard*

- III. **IMS III demonstrated the strong concordance between adequacy of reperfusion and 3-month clinical outcome. Figure 9 demonstrates that patients who obtained TICI 2b or 3 results were statistically more likely to be functionally independent (mRS 0-2) at 3 months.**
- IV. **Modern Stentriever technologies (Solitaire FR and TREVO) achieve**

**TICI 2b and 3 revascularization at much higher rates and with improved safety profiles compared to first generation technologies. Class IB evidence supports their superiority to Merci.**

The SWIFT Trial compared the MERCI retriever to the Solitaire FR and was stopped prematurely due to the substantial safety advantage of Solitaire FR over the Merci arm. Across 113 randomized patients, the SWIFT study demonstrated a statistically significant difference in mortality, core lab evaluated recanalization (TIMI II/III) and good neurological outcome (mRS 2 or more, or 10 point improvement in NIHSS). Similarly, TREVO EU involved 60 patients with confirmed LVO and a mean NIHSS of 18; the TREVO Stentriever device achieved a 78.3% recanalization (TICI 2b or better) and 55% of patients enjoyed 90-day functional independence (mRS < 2). The Merci device was the predominant IAT adjunct in IMS III. Thus, IMS III cannot fully account for the substantial, data proven improvements in mechanical thrombectomy safety and technical efficacy.

**V. IMS III, MR RESCUE and SYNTHESIS all fell short of modern device performance and the potential of tandem device use common in modern endovascular therapy. In IMS III, only four patients received Solitaire FR. In SYNTHESIS, only 56 of 165 endovascular therapy patients received mechanical thrombectomy. In MR RESCUE, the preponderance of endovascular treatment was Merci; these endovascular treatment arms therefore do NOT reflect modern thrombectomy practice.**

Though the IMS III trialists should be commended for their flexibility in IAT devices included in the trial, the study time horizon confounds IAT results due to heterogeneous device performance. Only four patients were treated with

Solitaire FR. Moreover, the IMS III protocol was rigid in the employment of only one device type per case. This design does not reflect the tailored use of tandem devices that characterizes many expert interventionalist practices.

Since 2006, tremendous progress has been made in first generation thrombectomy devices. Moreover, device selection now varies based on the etiology of the occlusion and the vessel involved. Endovascular revascularization may require multiple strategies in large vessel occlusions with a substantial clot burden. The IMS III protocol prohibited tandem use of distal retrieval and proximal aspiration techniques. Artificial restriction to one device per case restricted operators who now commonly employ multiple strategies in a given case. Indeed, these technically demanding occlusions are often the clinical situations where IAT may demonstrate the most benefit.

Restriction to one device and the preponderance of MERCI device use in the early stages of IMS III stunts the IAT arm with first generation technology. Dramatic advancements in materials science and device applications, ranging from refinement of the Penumbra system to the Solitaire FR evaluated by the SWIFT trial, realized substantial clinically proven progress in technical efficacy. Despite the heroic efforts of IMS III investigators to include these advancements in the later phases of the trial, seven years of results cannot be easily overcome by more recent progress.

**VI. Angiographic reperfusion rates reflected these limitations in study device technology. SYNTHESIS failed to report adequacy of reperfusion rates. Figure 10 details the low TICI 2b-3 reperfusion**

**rates in IMS III compared to the SWIFT and TREVO standard. Similarly, the MR RESCUE endovascular versus standard medical therapy arms that presented with favorable penumbral profiles had near identical rates of complete and partial revascularization. Thus, endovascular therapy in MR RESCUE failed to achieve its technical objective due to first generation device limitations and therefore could not possibly demonstrate therapeutic benefit.**

Figures 10 and 11 demonstrate the TICI 2b and 3 revascularization rates in IMS III by location are roughly half that achieved with modern endovascular methods. Moreover, MR RESCUE embolectomy patients achieved reperfusion rates comparable to standard medical care, implying low revascularization rates even by a permissive TICI 2a-3 standard (Figures 12 and 13). Seven-day reperfusion rates bear out the technical inadequacy of endovascular therapy in MR RESCUE in contradistinction to modern endovascular devices and methods.

## **Systems and Process Issues in the Era of Comprehensive Stroke Center Designation**

- I. Relative to IMS I and II, the IMS III trial suffered from a dramatic delay between the initiation of iv tPA and endovascular therapy (Figure 14). At over two hours, this lag impedes the ability of reperfusion to realize clinical benefit.**

It is well established the benefits of reperfusion attenuate with time. The substantial lag diminishes the ability of endovascular treatment to provide therapeutic benefit. These delays offer two lessons from a systems perspective: (1) the importance of limiting the lag between iv and endovascular therapy to 1 hour as emphasized in TJC Comprehensive Stroke Center designation, and (2) the disadvantage of decentralization of Primary Stroke Centers that may drive transport times and increase this therapeutic gap.

- II. Moreover, the average time of groin access to initiation of IA treatment in IMS III was 44 minutes (Figure 15). Improved guide and distal access catheter technologies render that time very slow by modern endovascular standards. Additionally, operator experience or the absence of arterial imaging to plan macrovascular access may have compounded this delay.**

Stentriever technologies do not represent the only areas of endovascular advancement since the advent of IMS III and MR RESCUE trials. Dramatic improvements in catheter technologies and the availability of pre-procedural aortic arch imaging have shortened the period from arterial access to initiation of thrombectomy. While this interval was 44 minutes in the trials, reported values at high volume centers are routinely half that time.



**III. Pre-procedural arterial imaging in IMS III translated into a 20-minute advantage in the initiation of IA Therapy (Figure 16). Far from slowing therapy with additional imaging, the practice likely enhanced timely diagnosis and device planning. Pre-procedural CTA is further the common practice of high-volume comprehensive centers. The time advantage reflects the efficiency and importance of hospital processes that facilitate rapid care.**

IMS III provides essential empirical data to support the use of pre-procedural imaging. Aside from the statistically significant clinical benefit of endovascular therapy in patients with confirmed LVO, centers employing pre-procedural imaging were 20 minutes faster to IAT. This advantage likely reflects the urgency of a known diagnosis, the streamlined processes of an experienced comprehensive center, and the procedural information that accelerates the macrovascular portion of the procedure.

## Conclusion

IMS III, SYNTHESIS and MR RESCUE collectively provided the technical reperfusion threshold required to realize a clinical benefit. TIC1 2b and 3 reperfusion results uniformly corresponded with strong clinical outcomes at 3 months. Class Ib evidence supports high rates of TIC1 2b and 3 with modern stentriever technologies (i.e. 77% with Trevo) not addressed in these trials. MR RESCUE in particular was hampered by revascularization rates with device technology that failed to exceed the control group; first generation devices in this trial therefore represented a dramatic technical failure. Endovascular therapy in the SYNTHESIS trial dramatically deviated from U.S. endovascular standards; only 56 of 165 IAT patients received mechanical thrombectomy and adequacy of reperfusion or technical success was not even reported.

Despite the limitations of employed endovascular technology, IMS III subset analysis demonstrated a clinical benefit to endovascular therapy in patients known to harbor an LVO ( $P=0.01$ ). Thus, mechanical thrombectomy was beneficial as an adjunct to tPA in the target population of interest. The salutary benefit overcame long lag times to therapy and inferior technical performance of first generation devices compared to modern endovascular standards.

The long patient accrual times of IMS III and MR RESCUE speak to the narrow subset of stroke patients who are ultimately iv tPA eligible and therefore qualified for these studies. The success of endovascular therapy in the setting of confirmed LVO is therefore particularly important to the large majority of stroke patients who are not iv tPA eligible and therefore lack access to any competing therapy. The presented data from the PROACT and Multi-Merci experience speaks to the terrible natural history of confirmed LVO without intervention.

Finally, the IMS III experience brings into sharp relief the importance of pre-procedural arterial imaging to identify the subset of patients who benefit from endovascular therapy and inform macrovascular access planning. Far from slowing the treatment process, these patients received care faster than those lacking imaging. Given pre-procedural imaging is more commonly obtained at high volume, experienced endovascular centers, these gains speak to the advantages of centralization and process efficiencies central to TJC Comprehensive Stroke Center efforts. The lag between iv and IAT in IMS III further speaks to a revisiting of diluting care between PSC's and suffering longer lags in care due to transport.

Overall, despite limitations in design, endovascular technologies, and suboptimal study populations, these reviewed trials provide essential data in the continued refinement of endovascular therapy for large vessel ischemic stroke.

## **Appendix A: Excerpted AANS/CNS, SNIS, and SCAI brief to AHRQ on Mechanical Thrombectomy**

### *Deconstructing the Clinical Problem: Large-Vessel Occlusions and Wake-Up Strokes*

Large vessel occlusions (LVO), namely the vertebral, basilar, carotid terminus, anterior and middle cerebral arteries, represent an all-to-common and particularly severe form of acute ischemic stroke. These lesions represent the primary therapeutic target for mechanical thrombectomy technologies. IV-tPA, by way of comparison, performs poorly in the treatment of these lesions, with revascularization rates ranging from 10% in ICA occlusions to less than 30% in MCA occlusions (4). The LVO clinical distinction is critical given the concentration of morbidity and cost associated with these strokes. Furthermore, the differential performance of iv-TPA and mechanical thrombectomy in this gravely ill subset of patients carries important policy implications.

In an assessment of 72 consecutive acute ischemic stroke patients in 2006, 56% of patients enjoyed a good functional outcome at 6 months (mRS <2). Twenty-eight patients (38.9%) presented with an LVO. Admission NIHSS and LVO (OR 4.48, 95% CI 1.19-16.9) independently predicted poor neurologic outcome. Indeed, LVO carried the predictive value of an 8 point increase in baseline NIHSS. Smith et al. initial work began to establish LVO as a common and significant predictor of poor outcome in ischemic stroke (5).

Smith et al. followed this work with the Screening Technology and Outcome Project in Stroke Study, and prospectively evaluated 735 patients presenting within 24 hours of ictus. Of these patients, 578 were adjudicated as strokes with the balance excluded as Transient Ischemic Attacks (TIAs). LVO accounted for 267

(46%) of strokes and 13 (13%) of TIAs. LVO further predicted 6-month mortality (OR, 4.5; 95% CI, 2.7-7.3;  $P < 0.001$ ) and negatively correlated with 6-month functional outcome (mRS  $< 2$ ) (OR; 0.33; 95% CI, 0.24 to 0.45;  $P < 0.001$ ). Multivariate analysis identified baseline NIHSS and the presence of basilar or carotid terminus occlusions as independent predictors of poor neurologic outcome. Thus, in an unselected group of acute stroke patients presenting to two academic medical centers, Smith et al. demonstrated nearly half of strokes were due to LVO; these patients suffered substantially poorer functional outcomes and higher mortality risk. (6)

Mechanical thrombectomy therefore targets an LVO subset that incurs the greatest cost and suffers the worst prognosis among ischemic stroke patients-at-large. Posterior circulation LVO, with mortality rates of 70% or 80% without therapeutic recanalization, (7,8) offer the most extreme example of this case-mix principle. Control and subset data in PROACT, IMS, MERCI and Multi-MERCI trials (**Figures 17-19**) suggest the natural history of anterior circulation LVO without revascularization carries a near 50% mortality and only 10% functional outcome (mRS  $< 2$ ) at 3 months. The public health potential of endovascular strategies that target LVO, once widely adopted, will be tremendous.

The AHRQ Technical Brief, in presenting iv-TPA as the most viable alternative to mechanical thrombectomy, reviews the system challenges of timely patient presentation and the widespread ineligibility of stroke patients for iv-TPA. Even with ECASS expansion of the therapeutic window to 4.5 hours, (9,10) the number-needed-to-treat (NNT) rises without a dramatic expansion of eligible

patients, implying diminishing returns with expanded IV therapy. Given this health system environment, the common occurrence of wake up strokes (WUS) merits special mention in any comprehensive consideration of stroke epidemiology.

WUS refer to the clinical scenario in which the patient awakes symptomatic, and the onset of the ictus is indeterminate. Wake up strokes represent 16-28% of all ischemic strokes. (11,12) Though Bareto et al. suggests potential benefit in the treatment of these patients, (13) this significant proportion of stroke patients remain beyond the reach of iv-TPA or IA thrombolysis by American Heart Association guidelines. Our review of endovascular state-of-the-art will explore the tandem use of CT perfusion and mechanical thrombectomy to treat select WUS patients.

Indeed, thirty patients with onset greater than 8 hours and mean NIHSS of 13 underwent mechanical revascularization. Sixty-seven percent enjoyed TIMI 2 or 3 recanalization; symptomatic intracranial hemorrhage rate was 10%. Three-month mortality for these patients was 33.3% and 20% improved to a good functional outcome (mRS < 2) (14). Endovascular therapy therefore offers promise for a significant percentage of ischemic stroke patients currently without any therapeutic alternatives. These gains are beyond the extension of the therapeutic time window to 8 hours already offered by mechanical thrombectomy.

Taken together, the clinical scenarios of large-vessel occlusions and wake-up-strokes represent a substantial share of the cost, morbidity, and mortality of all ischemic stroke. Later sections emphasize the unique and clear advantages of mechanical thrombectomy for these patients. By casting the epidemiologic

challenge of stroke in clinical terms, we reinforce the absence of meaningful alternatives and the promise of endovascular strategies in reducing the monolith introduced by the AHRQ Technical Brief.

*Stroke Human Impact: Utility Theory and Cost-Effectiveness Analysis*

The AHRQ Technical Brief appropriately introduces utility theory studies of at-risk patients that view “the consequences of experiencing and ischemic stroke as being worse than death.” (Lines 375-376; Page 1) Significant decreases in health-related quality of life in the year following an ischemic stroke (Line 374; Page 1) bear out this negative perception. Moreover, the common functional dependence of stroke patients carries significant caregiver burden with implicit, uncaptured negative cost and utility effects beyond the patient (Line 378; Page 1). These findings reinforce the importance of any therapeutic intervention that may diminish these negative externalities.

Patil et al. developed a Markov model to assess the cost-effectiveness of mechanical thrombectomy in acute ischemic stroke. Clinical percentages for Markov states were taken from MERCI, Penumbra, and PROACT and NINDS trials for mechanical revascularization and medical therapy controls. The dependent utility state (mRS > 3) was valued at 0.4 QALY. Despite widely ranging sensitivity analyses in cost, recanalization rates, and conservative cost estimates for continued inpatient care, mechanical thrombectomy yielded a cost-effectiveness ratio of \$12,120, well below the \$50,000 per QALY threshold considered in the literature for other medical interventions. (15) Thus, mechanical thrombectomy for acute ischemic stroke, the bias of uncaptured prevention of negative utility and foregone costs

notwithstanding, dwarfs the cost-effectiveness of widely adopted medical interventions in other clinical arenas.

## **Positive Externalities of Endovascular Stroke Care**

### *Human and Physical Infrastructure*

In the years since the approval of mechanical thrombectomy, substantial infrastructure developed to support this meaningful advance in stroke therapy. From a human capital standpoint, specialists in multiple clinical arenas began to ardently pursue endovascular training. Specialty societies devoted to the catheter-based treatment of stroke grew from these advances. Physicians recognized the promise in these methods, and convergence to the field across specialties speaks to the massive public health need for mechanical thrombectomy in acute ischemic stroke. This document represents the consensus across those specialties.

Capital infrastructure also evolved in response to the efficacy of mechanical thrombectomy. In Western New York, comprehensive stroke centers with full endovascular and support capabilities accompanied the development and designation of NY State DOH “Designated Stroke Centers” capable of IV tPA therapy. Furthermore, spoke-hub relationships involving telemedicine networks emerged to allow timely stroke patient presentation. Aside from the efficiency gained from these positive system developments, the anecdotal use of iv-TPA increased with endovascular support. Large academic medical centers, including the Cleveland Clinic, are beginning to emulate this model of stroke care.

Overall, mechanical thrombectomy for acute ischemic stroke improves outcomes and reduces long-term dependence. Physician experts, Departments of

Health, and hospital systems recognize the tremendous promise and established effectiveness of mechanical thrombectomy in the most severe and unforgiving strokes. The AHRQ Technical Brief fails to acknowledge the important shifts in health systems delivery prompted by these endovascular advances. Given the tremendous epidemiologic and economic burden of ischemic stroke, any complete treatment of the subject merits acknowledgement of an active and robust response in the medical community.

Congress named the 1990's the "Decade of the Brain". Endovascular stroke care reimbursement provides the critical impetus for bringing that promise to fruition. Device technology advances will continue in an iterative fashion, informed by initial successes and failures in small single and multicenter published series. Following this explosion of materials science growth, randomized multidisciplinary trials will make scientific sense. As things now stand, the devastating trajectory of stroke epidemiology, the critical mass of device technology advancements, and the dramatic gains in health care infrastructure demand robust and sustained support for endovascular mechanical thrombectomy efforts.



## Bibliography

1. Mocco J, Hanel RA, Sharma J, et al. Use of a vascular reconstruction device to salvage acute ischemic occlusions refractory to traditional endovascular recanalization methods. *J Neurosurg* 2010;112:557-62.
2. Levy EI, Siddiqui AH, Crumlish A, et al. First Food and Drug Administration-approved prospective trial of primary intracranial stenting for acute stroke: SARIS (stent-assisted recanalization in acute ischemic stroke). *Stroke* 2009;40:3552-6.
3. Broderick JP. William M. Feinberg Lecture: stroke therapy in the year 2025: burden, breakthroughs, and barriers to progress. *Stroke* 2004;35:205-211.
4. Wolpert SM, Bruckmann H, Greenlee R, Wechsler L, Pessin MS, del Zoppo GJ. Neuroradiologic evaluation of patients with acute stroke treated with recombinant tissue plasminogen activator. The rt-PA Acute Stroke Study Group. *AJNR Am J Neuroradiol* 1993;14:3-13.
5. Smith WS, Tsao JW, Billings ME, et al. Prognostic significance of angiographically confirmed large vessel intracranial occlusion in patients presenting with acute brain ischemia. *Neurocrit Care* 2006;4:14-7.
6. Smith WS, Lev MH, English JD, et al. Significance of large vessel intracranial occlusion causing acute ischemic stroke and TIA. *Stroke* 2009;40:3834-40.
7. Zeumer H, Freitag HJ, Grzyska U, Neunzig HP. Local intraarterial fibrinolysis in acute vertebrobasilar occlusion. Technical developments and recent results. *Neuroradiology* 1989;31:336-340.
8. Archer CR, Horenstein S. Basilar artery occlusion: clinical and radiological correlation. *Stroke* 1977;8:383-390.
9. Hacke W, Kaste M, Bluhmki E, et al. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. *N Engl J Med* 2008;359:1317-29.
10. del Zoppo GJ, Saver JL, Jauch EC, Adams HP, Jr. Expansion of the time window for treatment of acute ischemic stroke with intravenous tissue plasminogen activator. A Science Advisory From the American Heart Association/American Stroke Association (doi 10.1161/STROKEAHA.109.192535). *Stroke* 2009; epub May 28.
11. Fink JN, Kumar S, Horkan C, et al. The stroke patient who woke up: clinical and radiological features, including diffusion and perfusion MRI. *Stroke* 2002;33:988-993.
12. Serena J, Davalos A, Segura T, Mostacero E, Castillo J. Stroke on awakening: looking for a more rational management. *Cerebrovasc Dis* 2003;16:128-133.
13. Barreto AD, Martin-Schild S, Halleivi H, et al. Thrombolytic therapy for patients who wake-up with stroke. *Stroke* 2009;40:827-832.
14. Natarajan SK, Snyder KV, Siddiqui AH, Ionita CC, Hopkins LN, Levy EI. Safety and effectiveness of endovascular therapy after 8 hours of acute ischemic stroke onset and wake-up strokes. *Stroke* 2009;40:3269-74.
15. Patil CG, Long EF, Lansberg MG. Cost-effectiveness analysis of mechanical thrombectomy in acute ischemic stroke. *J Neurosurg* 2009;110:508-13.

16. Haley EC, Jr., Levy DE, Brott TG, et al. Urgent therapy for stroke. Part II. Pilot study of tissue plasminogen activator administered 91-180 minutes from onset. *Stroke* 1992;23:641-5.
17. Brott TG, Haley EC, Jr., Levy DE, et al. Urgent therapy for stroke. Part I. Pilot study of tissue plasminogen activator administered within 90 minutes. *Stroke* 1992;23:632-40.
18. Tissue plasminogen activator for acute ischemic stroke. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. *N Engl J Med* 1995;333:1581-7.
19. Qureshi AI, Siddiqui AM, Kim SH, et al. Reocclusion of recanalized arteries during intra-arterial thrombolysis for acute ischemic stroke. *AJNR Am J Neuroradiol* 2004;25:322-328.
20. Rha JH, Saver JL. The impact of recanalization on ischemic stroke outcome: a meta-analysis. *Stroke* 2007;38:967-973.
21. Ginsberg MD. Current status of neuroprotection for cerebral ischemia: synaptic overview. *Stroke* 2009;40:S111-4.
22. Albers GW, Thijs VN, Wechsler L, Kemp S, Schlaug G, Skalabrin E, Bammer R, Kakuda W, Lansberg MG, Shuaib A, Coplin W, Hamilton S, Moseley M, Marks MP. Magnetic resonance imaging profiles predict clinical response to early reperfusion: The diffusion and perfusion imaging evaluation for understanding stroke evolution (defuse) study. *Ann Neurol*. 2006;60:508-517
23. Davis SM, Donnan GA, Parsons MW, Levi C, Butcher KS, Peeters A, Barber PA, Bladin C, De Silva DA, Byrnes G, Chalk JB, Fink JN, Kimber TE, Schultz D, Hand PJ, Frayne J, Hankey G, Muir K, Gerraty R, Tress BM, Desmond PM. Effects of alteplase beyond 3 h after stroke in the echoplanar imaging thrombolytic evaluation trial (epithet): A placebo-controlled randomised trial. *Lancet Neurol*. 2008;7:299-309
24. Hacke W, Albers G, Al-Rawi Y, Bogousslavsky J, Davalos A, Eliasziw M, Fischer M, Furlan A, Kaste M, Lees KR, Soehngen M, Warach S. The desmoteplase in acute ischemic stroke trial (dias): A phase ii mri-based 9-hour window acute stroke thrombolysis trial with intravenous desmoteplase. *Stroke*. 2005;36:66-73
25. Furlan AJ, Eyding D, Albers GW, Al-Rawi Y, Lees KR, Rowley HA, Sachara C, Soehngen M, Warach S, Hacke W. Dose escalation of desmoteplase for acute ischemic stroke (dedas): Evidence of safety and efficacy 3 to 9 hours after stroke onset. *Stroke*. 2006;37:1227-1231
26. Hacke W, Furlan AJ, Al-Rawi Y, Davalos A, Fiebach JB, Gruber F, Kaste M, Lipka LJ, Pedraza S, Ringleb PA, Rowley HA, Schneider D, Schwamm LH, Leal JS, Soehngen M, Teal PA, Wilhelm-Ogunbiyi K, Wintermark M, Warach S. Intravenous desmoteplase in patients with acute ischaemic stroke selected by mri perfusion-diffusion weighted imaging or perfusion ct (dias-2): A prospective, randomised, double-blind, placebo-controlled study. *Lancet Neurol*. 2009;8:141-150
27. Vallabh Janardhan, Gianatasio, S. Chen, P . . . Siu Po Sit for the Penumbra FIRST Trial Investigators, " Preliminary Results from the FIRST Trial: Natural History of Acute Stroke from Large Vessel Occlusion" Honolulu, HI (ISC 2013)

