Endovascular therapy in acute ischemic stroke: where we are, the challenges we face and what the future holds


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Stroke is the third leading cause of death and a leading cause of severe long-term disability worldwide. It costs the world’s economy billions of dollars each year in physician services, hospital costs, lost wages and decreased productivity. Rapid advances in medical technology have resulted in an explosion of treatment strategies in the management of acute ischemic stroke. Each clinical scenario presents unique challenges related to risks and benefits of therapy. In this article, we review the evolution of endovascular therapy in acute ischemic stroke, discuss the latest advances, challenges and controversies in the field and speculate on the future of this therapy.

Keywords: acute ischemic stroke • endovascular therapy • intra-arterial thrombolysis • recanalization • patient selection

“Every great advance in science has issued from a new audacity of imagination.” – John Dewey

Endovascular management of acute ischemic stroke is a story of many parts, with the initial chapters filled with tales of struggles and failures. The imagination, fortitude and perseverance of the early pioneers helped lay the foundation for this field. The present success of this field and the difference it makes in the management of patients with acute ischemic stroke, owes much of its success to these early pioneers as well as to the rapid technological advancements made in drugs and devices. The focus of endovascular therapy in acute ischemic stroke, at present, is centered not so much on whether the technique is useful in opening occluded arteries, but rather on how best to improve clinical outcomes by increasing the efficacy and safety of the procedure and identifying which patients would benefit the most. Therefore, in this article, we focus not on evidence suggesting efficacy of the procedure in achieving target vessel recanalization, but on appropriate patient selection using clinical and imaging paradigms, newer advances in devices and techniques and controversies and challenges facing the field, and we speculate on how the field will develop in the future. We will however, begin with a brief history of the evolution of endovascular therapy for acute ischemic stroke.


Although reports of successful intra-arterial (IA) thrombolysis date back to the late 1950s when Sussman and Fitch described the recanalization of an acutely occluded internal carotid artery with IA injection of plasmin [1], the first case series on endovascular therapy for acute ischemic stroke was published in 1983 when Zeumer et al. first reported on five patients with vertebro-basilar occlusions treated with local IA fibrinolysis [2]. Following this pioneering work, a large number of case series were published.

A Phase II randomized trial of recombinant prourokinase by direct arterial delivery in acute middle cerebral artery (MCA) stroke (PROACT I) was the first placebo-controlled randomized trial of endovascular therapy in acute ischemic strokes [3]. The trial demonstrated the safety of recombinant prourokinase in a uniform population of stroke patients presenting within 6 h of symptom onset with MCA M1 or M2 occlusions, and led to the much larger PROACT II study, which compared
recombinant prourokinase plus intravenous heparin (treatment arm) with intravenous heparin alone (control) in patients with angiographically confirmed MCA M1 occlusion [4]. The primary outcome was the ability to live independently at 3 months as judged by a modified Rankin scale (mRS) score of 0–2. Although the study did show a statistically significant difference in the primary outcome measure in favor of treatment (40 vs 25%; \( p = 0.04 \)), it did not lead to regulatory approval.

The Mechanical Embolus Removal in Cerebral Ischemia (MERCI) retriever (Figure 1) was the first mechanical device for thrombus removal in the setting of acute ischemic stroke. Its initial design was a tapered wire with helical loops of decreasing diameter, approximating the diameter (from 2.8 to 1.1 mm at its distal end) of intracranial arteries. A Phase I study evaluating safety and efficacy of this first-generation device demonstrated successful recanalization in 12 patients (43%) with device alone and with additional IA tissue plasminogen activator (tPA) in 18 out of 28 patients (64%). At 1 month, nine out of 18 revascularized patients and zero out of ten nonrevascularized patients had achieved significant recovery [5]. The therapeutic landscape changed dramatically with the publication of these results in 2004 [5], as it did following the results of the MERCI trial in 2005, which compared 141 patients treated with the device with the control arm of PROACT II [6]. Although clinical outcome (mRS ≤2 at 90 days of 27.7%) was only marginally better than the control arm of PROACT II, recanalization rates (48 vs 18%) were higher. Data from these studies lead to regulatory approval of this device (Concentric Medical, CA, USA) for removal of thrombi in the setting of acute ischemic stroke. The MultiMERCI trials followed, evaluating newer generation (L series) devices in a multicenter, prospective, single-arm trial of patients with large vessel occlusions treated within 8 h of symptom onset. The study included patients treated with intravenous tPA. A recanalization rate of 57.3% with device alone and 69.5% with adjunctive IA tPA with good clinical outcome (mRS 0–2) of 36% compared favorably with the treatment arm of PROACT II recanalization rate of 66% and good clinical outcome (mRS 0–2) of 40% [7]. Controversy regarding regulatory approval of the device in the absence of a randomized trial persisted [8].

This early period also saw some other techniques evolve. Clot angioplasty was based on using balloon angioplasty to mechanically disrupt intravascular thrombus. Ueda et al. described their initial experience with this technique with very good technical results [9]. Lum et al., in a small retrospective series, also report excellent technical results [10]. However, the technique was limited by risks of vessel wall rupture due to overinflation of the balloon and distal embolization, despite efforts to reduce these potential risks by technical modifications [11]. Intracranial and coronary stents not approved for use in acute strokes were also used to attempt stent-assisted angioplasty of intravascular thrombus [12–14].

With the publication of the National Institute of Neurological Disorders and Stroke (NINDS) trials in 1995 and the subsequent regulatory approval for the use of intravenous tPA within 3 h of stroke symptom onset, the era of acute stroke treatment had begun [15]. Results of the Safe Implementation of Thrombolysis in Stroke Monitoring Study (SITS-MOST) registry on intravenous tPA use in clinical practice demonstrated efficacy that was similar to that reported in the NINDS trials, thus establishing intravenous tPA as the standard of care in acute ischemic stroke management within 3 h of stroke symptom onset [16,17]. With the publication of the ECASS-III trial results and pooled data from the large intravenous tPA trials, intravenous thrombolysis up to 4.5 h from stroke symptom onset is now accepted as the standard of care in many stroke centers across the globe [18–20]. Endovascular therapy had to take into account the evolution of intravenous thrombolysis in acute ischemic stroke management.

Combination intravenous IA treatment was a concept that provided standard of care (intravenous tPA) to acute ischemic stroke patients presenting within an approved time window, offsetting the disadvantages of endovascular therapy – namely delayed initiation of therapy and potential inability to access the target vessel with the ability to provide higher recanalization rates when compared with intravenous thrombolysis. The Emergent Management of Stroke (EMS) trial, published in 1999, first used this concept and compared combined intravenous plus IA treatment with IA therapy alone [21]. Although not statistically significant, the

Figure 1. Clot retrieved from the basilar artery using the Mechanical Embolus Removal in Cerebral Ischemia (MERCI) retriever.
Provided courtesy of Concentric Medical, Inc. (CA, USA).
study showed higher recanalization in the combined intravenous plus IA arm versus the IA alone arm (55 vs 10%). The design of this study, comparing combination therapy with IA alone, became increasingly untenable as intravenous tPA became the standard of care. The Interventional Management of Stroke (IMS-1) trial used a safety and futility design, comparing historical control subjects from the NINDS rt-PA stroke study. In IMS-1, a total of 80 patients with the NIH Stroke Scale (NIHSS) ≥10 were treated with intravenous rt-PA (0.6 mg/kg) within 3 h of symptom onset. At angiography, 62 patients received additional IA rt-PA to a maximum dose of 22 mg after documentation of an IA occlusion [22]. IMS-1 subjects had a significantly better clinical outcome at 3 months than NINDS placebo-treated subjects for all outcome measures (odds ratio [OR]: ≥2). The 3-month mortality in Intervventional Management Study (IMS) subjects (16%) was numerically lower, but not statistically different to the mortality rate seen in placebo-(24%) and tPA-treated subjects (21%) in the NINDS trial [22]. The IMS-II trial, published in 2007, used a similar study design with the addition of an investigational EkoSonic® Endovascular System (EKOS) IA ultrasound system that uses low-energy ultrasound waves to facilitate and potentially accelerate thrombolysis to the combined intravenous plus IA arm. Subjects enrolled in this trial had significantly better clinical outcome at 3 months than NINDS placebo-treated subjects for all end points (OR: ≥2.7) [23].

With increasing evidence that early recanalization remains the most critical process for impacting clinical outcome by restoring blood flow to salvageable brain tissue [24–26], and that early recanalization in the first 2 h with intravenous tPA is less than 25% [27,28] and barely half by 24 h [29] with the magnitude of benefit directly related to the speed that recanalization is achieved [30], higher recanalization rates in the major IA studies reported earlier with regulatory approval of mechanical devices has resulted in increasing use of endovascular techniques in the management of patients with acute ischemic strokes. This shift in practice has not been accompanied by evidence suggesting better clinical outcomes with endovascular treatment. Randomized trials of endovascular therapy focusing on clinical outcomes, along with efforts to understand who would benefit most from treatment and how to improve safety and efficacy of the technique further, are challenges for the future.

From 2008 to 2011: new devices, better & faster recanalization

Endovascular treatment in acute ischemic stroke is aimed at opening up the occluded artery by fragmenting and retrieving the thrombus. Newer mechanical devices aim to improve on these dual goals when compared with older generation devices, in addition to creating a temporary bypass for blood flow while accomplishing the first two goals.

The Penumbra system (Figure 2) is a new-generation mechanical device designed to remove thrombus in large intracranial vessels by thrombus debulking and aspiration followed by direct thrombus extraction if clots remain. Continuous aspiration and debulking of thrombus is achieved by advancing and withdrawing a ‘separator’ through the Penumbra reperfusion catheter into the proximal end of the clot, and maintaining aspiration through the reperfusion catheter at 20 inches/Hg vacuum via an aspiration pump. In the Penumbra Pivotal Stroke Study (PPST), Thrombolysis In Myocardial Infarction (TIMI) 2/3 recanalization rate of 82% was observed with good clinical outcome (mRS ≤2 at 3 months) of 25% and all-cause mortality of 33% [31]. The clinical outcome (mRS ≤2 at 90 days) was, however, similar to the rates in the control arm of PROACT II [4]. Similar high recanalization rates are reported in other series using this device [32,33]. Using this device either alone or as a rescue therapy, we have reported TIMI grade 2/3 reperfusion in 67% of patients, with 48% of patients achieving mRS ≤2 on follow-up. We achieved an acceptable rate of serious parenchymal hematoma, no complications of arterial puncture and no serious intracranial vascular complications. All-cause mortality rate at 90 days in our series was 19% [34]. These case series suggested that the Penumbra system was able to achieve consistently high recanalization rates when compared with previous generation devices without in any way compromising on procedural safety and complication rates.

Self-expanding retrievable stents are the newest class of mechanical devices used in endovascular management of acute ischemic strokes. They produce instantaneous occluded artery recanalization and ischemic territory reperfusion by forcing the thrombus against the artery wall when deployed. By achieving an endovascular bypass with first deployment, albeit temporarily, and thereby restoring blood flow to the ischemic brain, these retrievable stents also help in resetting the ischemic ‘clock,’ unlike other mechanical embolectomy devices. The ability to retrieve a significant proportion of thrombi using this technique potentially improves final reperfusion rates (Figure 3). They can be captured
and redeployed again if the vessel recolludes. In situations that warrant permanent deployment, they can be so deployed. In our study of 14 subjects in whom the retrievable stent was deployed as part of endovascular management of acute ischemic strokes with arterial occlusions, a recanalization (TIMI 2–3) rate of 85.7% and good clinical outcome (mRS 0–2) at 3 months or discharge of 57.1%, was achieved. Parenchymal hemorrhage was noted in 7.1% with all-cause mortality of 14.3%. No significant periprocedural complications were documented [35]. Consistently high recanalization rates ranging from 75 to 100% have been reported with the use of these stents in other series [36–40]. These recanalization rates compare favorably with, or are better than, those reported with other devices.

The Penumbra system, and in particular retrievable stents, have also managed to achieve faster recanalization when compared with older devices. Although direct device comparisons with respect to interval times have never been reported, we have noted a median puncture to recanalization time of 80 min with the penumbra device [34]. Retrievable stents achieve instantaneous recanalization, albeit temporarily in some cases, with initial deployment. Median puncture to recanalization time in our series was 84 min with a median time interval from first stent deployment to recanalization of 17.5 min (range: 1–60 min).

**Controversies & challenges**

**Poor clinical outcome in spite of successful recanalization**

Although endovascular techniques have shown increasingly high recanalization rates not seen with intravenous thrombolysis with newer generation devices and techniques, this increase in recanalization rate has not been matched by a corresponding increase in the rate of good clinical outcomes. In the MultiMERCI trial, an arterial recanalization rate of 69.5% but good clinical outcome of only 36% with a mortality rate of 34% was noted [7]. The PPST demonstrated an 81.6% recanalization rate with only 25% positive clinical outcome [31]. Numerous reasons have been put forward to explain the discrepancy between high recanalization rates and poor clinical outcomes [41,42].

Prognostic factors at baseline have often been used to conjecture why a large proportion of treated patients do not benefit from treatment [43]. Age, baseline stroke severity and admission serum glucose level are well known prognostic factors that influence clinical outcomes with IA therapy. In an analysis of data from six studies of acute ischemic stroke treated with mechanical and/or pharmacologic endovascular treatment studying ‘futile recanalization,’ defined by absence of clinical benefit from recanalization, Hussein et al. identify age ≥70 years (OR: 4.4; 95% CI: 1.9–10.5; p = 0.0008), initial NIHSS score 10–19 (OR: 3.8; 95% CI: 1.7–8.4; p = 0.001) and initial NIHSS score 20 (OR: 64.4; 95% CI: 28.8–144; p < 0.0001) as predictors of futile recanalization [44]. In a post hoc analysis of the PROACT II trial, age ≥68 years (OR: 0.23; 95% CI: 0.11–0.48; p < 0.0001), NIHSS 11–20 (OR: 0.36; 95% CI: 0.13–1.00; p = 0.0005), NIHSS >20 (OR: 0.085; 95% CI: 0.022–0.33; p = 0.0005) and computer tomography hypodensity >5.25 ml (OR: 0.47; 95% CI: 0.23–0.96; p = 0.038) were predictors of poor clinical outcome [45]. In another study, age (OR: 1.028; p = 0.049), NIHSS (OR: 1.084; p = 0.013) and admission glucose (OR: 1.011; p = 0.031) are identified as predictors of poor clinical outcome in spite of recanalization with IA therapy. Using these data, the same group devised the Houston Intra-Arterial Therapy (IAT) score: 1 point for age >75 years; one point for NIHSS score >18, and one point for glucose >150 mg/dl (range: 0–3 mg/dl). The percentage of poor outcome by Houston IAT score was: score of 0, 44; 1, 67; 2, 97; and 3, 100%. Recanalization rates were similar across the scores (p = 0.4). The score was validated in an external cohort and showed comparable results [46].

The extent of ischemic changes on imaging at baseline is also an important prognostic factor determining clinical outcomes in patients undergoing endovascular therapy for acute ischemic stroke. In a post hoc analysis of the PROACT-II scans re-evaluated for early ischemic changes using A Study of Patients’ Experiences of Treatments (ASPECTS), the benefit of IA thrombolysis progressively increased from ASPECTS 8 through to 10 (risk ratio [RR]: 3.2; 95% CI: 1.2–9.1) for ASPECTS >7 (RR: 7.5; 95% CI: 1.1–51.4) for ASPECTS >8; and infinite for ASPECTS >9. By contrast, on average, patients with a baseline ASPECTS value ≤7 did not benefit from IA thrombolysis (RR: 1.2; 95% CI: 0.5–2.7) [47]. A post hoc analysis of the PPST [31] showed that good clinical outcome (mRS 0–2) was significantly greater in the ASPECTS >7 group when compared with the ≤7 group (relative ratio: 3.3; 95% CI: 1.6–6.8) [31]. No patient with an ASPECTS score ≤4 had good clinical outcome [48].

Eloquence of brain tissue (the real estate factor) with early ischemic changes on imaging plays a significant role in determining whether recanalization results in good clinical outcome. In an interesting proof-of-concept study, Phan et al. demonstrate that stroke outcome correlates well with infarct location. Infarction of the striatum and the right corona radiata covaried with moderate-to-severe disability (Rankin scale >2). The right middle frontal gyrus and left superior temporal gyrus and angular gyrus also contributed to estimating the likelihood of moderate-to-severe disability (Figure 4), thus raising the possibility that poor clinical outcome is not just a function of extent of early ischemic changes, but also determined by infarct location [49].

Willisian and leptomeningeal collaterals are responsible for preserving blood flow distal to the site of occlusion in patients with acute ischemic strokes. Growing clinical evidence has clearly noted that good leptomeningeal collateral status is associated with smaller final infarct volumes and better clinical outcomes in patients with acute ischemic strokes [50,51]. We have shown that patients with excellent leptomeningeal collateral status at baseline do best with endovascular therapy [52]. They may also potentially increase recanalization rates with endovascular therapy, thereby improving clinical outcomes [53].

Progression to irreversible infarction in the penumbra is a time-dependent phenomena and early treatment aimed at recanalization affects this process. Final infarct size is reduced and functional outcomes are better if this is achieved rapidly [54]. In an analysis of a subset of cases with angiographic MCA (M1
and M2) or distal internal carotid artery occlusions on baseline angiogram from the IMS Phase I and II trials, Khatri et al. demonstrated that as time to successful angiographic reperfusion (OR: 0.982; 95% CI: 0.969–0.996) and age (OR: 0.945; 95% CI: 0.899–0.993) increased, the probability of good clinical outcome significantly decreased in the final multivariable model [55]. An analysis of data from the PPST showed that in patients with a baseline noncontrast CT (N CCT) ASPECTS ≥7, 62.5% of patients with onset to recanalization time ≤300 min had good clinical outcome when compared with 45.5% patients with either onset to recanalization time >300 min or nonrecanalizers [31]. In the ASPECTS ≤7 group, the corresponding figures were 33.3% with onset to recanalization time ≥300 min versus 7.9% in the >300 min or nonrecanalizer group (Figure 5). After adjusting for baseline stroke severity, there was evidence of an ASPECTS by onset-to-recanalization time interaction (p = 0.066) in the multivariable model. The direction of interaction was such that among patients with ASPECTS ≤7, the relative effect of onset-to-recanalization time (≤300 min or >300 min) in predicting outcome was significant. The best outcomes are achieved among patients with favorable scans and fast recanalization times thus, answering why the PPST showed a good clinical outcome rate of only 25% despite a recanalization rate of 81.6% [48].

**Is vascular imaging using computed tomography angiogram or magnetic resonance angiogram needed prior to endovascular therapy in acute ischemic stroke?**

There is growing evidence to show that recanalization rates in patients with proximal occlusions are significantly lower with intravenous tPA when compared with endovascular therapy [27,28]. Among 388 patients in the computed tomography angiogram (CTA) database at our center with proximal occlusions, 127 patients underwent further imaging to assess recanalization, of which only 27 (21.25%) patients had acute recanalization. By occlusion subtype, the rates of recanalization were: distal internal carotid artery (4.4%); M1-MCA (32.3%); M2-MCA (30.8%); and basilar artery (4%) [56]. In these studies, recanalization itself was a powerful independent predictor of good clinical outcome. The low rates of recanalization with intravenous tPA in proximal occlusions, vascular imaging using CTA or magnetic resonance angiogram could potentially be useful in triaging patients for appropriate therapy. CTA can be used to assess the extent of thrombus in the arterial tree using a clot burden score (CBS). With increasing CBS values (i.e., less thrombus burden), patients are significantly more likely to have an independent functional outcome and less likely to die. In addition, final infarct sizes were smaller and hemorrhagic transformation rates lower [57]. Higher clot burden scores (smaller clot) were associated with higher recanalization rates in a recent study by Tan et al. [58]. When triaging patients for endovascular therapy, opponents of this approach point out the fact that vascular imaging may delay treatment [59]. In a recent study, Sallotolo et al. showed that the use of multimodal imaging, including vascular imaging and perfusion CT, did not delay initiation of intravenous tPA [60].

Our experience has been that time spent on additional vascular imaging at baseline (4–5 min) has not delayed treatment, and has helped in triaging patients for endovascular therapy.

**A multimodal approach: different thrombi, different techniques?**

Thrombus formation is a heterogeneous process and the fibrin/platelet/red blood cell architecture is altered by various disease states, environmental and genetic factors [61]. Thrombus characteristics may play a significant role in determining lysability to thrombolytic agents and endovascular techniques [62,63]. MRI has been used to study thrombus composition using Gradient Echo Pulse (GRE) and susceptibility-weighted imaging (SWI) sequences. GRE MRI detects deoxyhemoglobin in trapped red blood cells and therefore may give some indication of whether the thrombus is composed of red blood cells and fibrin (red clot) or platelets (white clot) [64]. ‘GRE susceptibility vessel sign’ has been correlated to
cardioembolic strokes and increased lysability with intravenous tPA [65,66]. It is therefore plausible that GRE or SWI sequences may be used to determine whether an intravascular thrombus is susceptible to chemical thrombolysis using IA tPA or whether it would need fragmentation and extraction using mechanical devices. Preprocedural assessment of thrombus lysability may also help in determining whether to use mechanical devices that extract thrombus predominantly (e.g., MERCI retriever), devices that either fragment and aspirate thrombus (Penumbra system), attempt recanalization by angioplasty/stenting (stent retrievers) or use local ultrasound pulses (EKOS infusion catheter).

The site of the thrombus within the arterial tree also determines the choice of endovascular technique. Present generation device profiles are tailored to the target artery with each device available in different sizes. Small pial arteries can, however, only be accessed by microcatheters and chemical thrombolysis with IA tPA. Increasingly, neurointerventional practice is now based on achieving recanalization using multiple devices and techniques tailored to the needs of a specific situation.

Is endovascular therapy safe in octogenarians presenting with acute ischemic strokes?

Although there is increasing evidence that intravenous thrombolysis with intravenous tPA has a beneficial treatment effect even in octogenarians [67,68], with no significant increase in the risk of symptomatic intracerebral hemorrhage (ICH) [69], use of endovascular techniques in octogenarians presenting with acute ischemic strokes is often clouded by the fear of periprocedural complications including hemorrhage. In a pooled analysis of data from four prospective studies, age ≥80 years was associated with a lower likelihood of a favorable outcome (OR: 0.40; 95% CI: 0.13–1.2; p = 0.11) and recanalization (OR: 0.36; 95% CI: 0.12–1.1; p = 0.07) and with higher mortality rate (OR: 3.17; 95% CI: 1.05–9.55; p = 0.04) [70]. Kim et al., in analysis of a retrospective registry, demonstrated that endovascular therapy in the elderly can be accomplished with recanalization rates and hemorrhage rates equal to that in younger patients. They do, however, report lower rates of excellent functional outcome (mRS 1, 26 vs 40%; p = 0.02) and survival (57 vs 80%; p = 0.01) among octogenarians [71]. These results suggest that endovascular therapy may be associated with increased risk in octogenarians; however, treatment effect may still be shown if patients are selected appropriately for therapy. A randomized trial similar to the IST-3 is needed if this question is to be answered [72].

Role of anesthesia & blood pressure management during endovascular interventions for acute ischemic stroke

In addition to baseline prognostic factors mentioned earlier and treatment effects, including reperfusion, periprocedural factors such as type of anesthesia, oxygen saturation and blood pressure, may play a role in determining postprocedural clinical outcomes. Possible benefits of general anesthesia include patient immobility, thus increasing operator comfort, better and tightly controlled hemodynamics, better airway control in patients with severe stroke symptoms, and cerebral protection.

However, in a retrospective of the IMS-SII trial, Nichols et al. demonstrated that only mild or no sedation (OR: 5.7; 95% CI: 1.8–17.8; p < 0.01) and male gender (OR: 4.2; 95% CI: 1.5–12.3; p < 0.01) were independently associated with good clinical outcome, and heavy sedation or pharmacological paralysis (OR: 5.0; 95% CI: 1.3–18.7; p = 0.02) was the only independent predictor of death [73]. In a case series of 126 consecutive patients with acute stroke owing to MCA M1 segment occlusions treated with endovascular therapy, Jumaa et al. show that local anesthesia (nonintubated state) was significantly associated with lower in-hospital mortality (OR: 0.32; p = 0.011), good clinical outcome (OR: 3.06; p = 0.042), and lower final infarct volume (OR: 0.25; p = 0.004) when compared with general anesthesia [74]. In a large retrospectively studied cohort of 960 patients with anterior circulation strokes undergoing IA therapy, Abou-Chebl et al. demonstrated that the use of general anesthesia was associated with poor neurologic outcome at 90 days (OR: 2.33; 95% CI: 1.63–3.44; p < 0.0001) and higher mortality (OR: 1.68; 95% CI: 1.23–2.30; p < 0.0001) compared with conscious sedation [75].
These results pose a difficult challenge to stroke physicians and neurointerventionists, and raise the question of whether general anesthesia independently increases the likelihood of poor outcome in individual patients unable to tolerate the interventional procedure under local anesthesia, or whether patients undergoing general anesthesia are a cohort with poor baseline prognostic factors such as increased stroke severity, decreased level of consciousness, airway compromise and multiple medical comorbidities. Detailed analysis of these multiple covariates associated with general anesthesia are lacking in previous studies [74,75]. In a retrospective analysis of patients at our center undergoing IA therapy, the proportion of patients with good outcomes were 15 and 66% in the general anesthesia group and local anesthesia group, respectively (p < 0.001). Periprocedural systolic blood pressure and general anesthesia were collinear variables (r = -0.7; p < 0.001). In patients managed with general anesthesia, the average lowest recorded systolic blood pressure (104 ± 17 mmHg) was lower than that observed in patients managed with local anesthesia (134 ± 32 mmHg; p ≤ 0.001). Logistic regression analysis suggested that independent periprocedural predictors for good neurological outcome were local anesthesia or systolic blood pressure ≥140 mmHg, low NIHSS score and low blood glucose levels [Davis et al., Pers. Comm.]. Induction of anesthesia is probably associated with a reduction in blood pressure, which may potentially decrease blood flow to the ischemic penumbra due to impaired autoregulation. Our analysis suggests that this may well be a reason for poorer clinical outcomes with IA therapy under general anesthesia in patients with acute ischemic strokes, although the fact that these patients are more ill than patients undergoing IA therapy under local anesthesia/conscious sedation suggests that in patients undergoing IA therapy, poor baseline prognostic factors produce ‘confounding by indication,’ and therefore affect interpretation of these observational studies [43]. There is very little evidence pertaining to the role of periprocedural blood pressure augmentation in patients with acute ischemic stroke undergoing IA, and a large randomized trial would be needed to answer this question.

**Combined intravenous & IA therapy, primary IA therapy or intravenous tPA in acute ischemic strokes presenting early?**

Combined intravenous/IA therapy is based on the concept of combining the advantages of intravenous thrombolysis (speed of initiation, ease of use and widespread availability) with those of an IA approach (titrated dosing, mechanical aids to recanalization and possible superior and earlier recanalization) while resources for IA therapy are mobilized. The rate of recanalization (thrombolysis in cerebral infarction (TICI) grades 2 and 3) at the end of the procedure with combined intravenous/IA therapy in IMS-II was 73% when compared with 56% in similar subjects enrolled in IMS-I [23]. Favorable clinical outcome (mRS of 0–2 at 90 days) was noted in 46% with combined intravenous/IA therapy. The 3-month mortality in IMS-II subjects was 16% with a symptomatic ICH rate of 9.9%. In the RECANALISE study, a prospective registry, patients treated with the intravenous/IA approach achieved 87% recanalization rate with early neurological improvement (NIHSS score of 0 or 1 or an improvement of 4 points or more at 24 h) in 60%, and favorable clinical outcome (mRS of 0–2 at 90 days) in 57% of patients. The mortality rate at 90 days was 17% in this group with symptomatic intracranial hemorrhage in 9% [76]. In the IA-alone arm of PROACT II, a recanalization (TIMI 2 or 3) rate of 66% with role of recombinant prourokinase (r-proUK) noted. Favorable clinical outcome (mRS of 0–2 at 90 days) occurred in 40% of patients with a symptomatic intracranial hemorrhage rate of 10% [4]. A comparison of these historical cohorts suggests that the combined intravenous/IA approach achieves equal or better recanalization rates, and better clinical outcomes when compared with the IA-alone approach. Although there is no randomized controlled study to compare the safety and efficacy of these treatment modalities, we feel that the argument for an IA-alone approach is predominantly economic and has to be seen in the context of reducing additional costs of intravenous tPA in a comprehensive stroke center where neurointerventionists are available on call round the clock. Therefore, in our opinion, comparison of a combined IV/IA approach with a primary IA approach may be a moot point, and we favor the combined approach.

The Local Versus Systemic Thrombolysis for Acute Ischemic Stroke (SYNTHESIS) pilot trial compared IA alone versus intravenous tPA in patients presenting within 3 h where the clinician was uncertain about the balance of risks and benefits between IA and intravenous tPA. A total of 54 patients (25 IA-alone arm) were enrolled. Almost twice as many patients on IAT as those on IV tPA survived without residual disability (12 out of 25 vs 8 out of 29; OR: 3.2; 95% CI: 0.9–11.4; p = 0.067). Symptomatic ICH occurred in two out of 25 patients on IAT and in four out of 29 on IVT (OR: 0.5; 95% CI: 0.1–3.3; p = 0.675). Mortality at day 7 was five out of 25 (IAT) compared with four out of 29 (IVT; OR: 1.6; 95% CI: 0.4–6.7; p = 0.718) thus suggesting that IA alone may be better than intravenous tPA within 3 h of stroke onset [77]. The larger SYNTHESIS expansion trial is currently ongoing.

Although evidence from IMS-I and -II [22,23] and the Comparison of Intravenous Alteplase with a Combined Intravenous-Endovascular Approach in Patients with Stroke and Confirmed Arterial Occlusion (RECANALISE) study [76] suggest that a combined IV/IA approach is better than intravenous tPA alone in achieving better recanalization rates and clinical outcomes, the IMS III study is a large NIH-funded randomized study that seeks an answer to this question [78].

**Flow augmentation: friend or foe?**

Induced hypertension has been used as a way of augmenting blood flow to the ischemic brain, potentially through leptomeningeal collaterals. Although there are some animal studies showing augmentation of cerebral blood flow with induced hypertension in stroke models with MCA occlusions [79,80], evidence of benefit is equivocal. An additional possibility of harm due to hemorrhage and edema could also potentially balance possible
benefits due to reperfusion [81]. Clinical studies in the acute phase of ischemic strokes are limited. Rordorf et al., in a small study of 13 patients presenting within 12 h of stroke symptom onset, induced a blood pressure increase of 20% or a target systolic blood pressure of 160 mmHg with intravenous phenylephrine and looked for a 2 point change in NIHSS with treatment [82]. A beneficial neurological response was noted in seven out of 13 (54%) patients with no adverse effects. Although the study may suggest feasibility and safety of this technique in the acute phase, all patients included in the study were outside the time window for intravenous thrombolysis. At present, there is no evidence available supporting the use of induced hypertension for flow augmentation before an endovascular procedure in acute ischemic stroke.

Partial aortic occlusion, by diverting splanchnic blood flow to the upper body, may theoretically increase cerebral blood flow. In a porcine model, Hammer et al. studied the effect of partial aortic occlusion on cerebral perfusion and cardiac performance using the intra-aortic NeuroFlotm (CoAxia, Inc., MN, USA) catheter deployed in the abdominal aorta with a target desired pressure drop of 10–15 mmHg across the suprarenal and infrarenal balloons. In the six pigs that were studied, there was no relevant change in cardiac output, and cerebral blood flow increased significantly with inflation of the suprarenal balloon and remained elevated 90 min after deflation [83]. Although there is some anecdotal evidence for showing DWI lesion reversal with partial aortic occlusion in acute ischemic stroke [84], large randomized studies have yet to show efficacy in improving clinical or imaging outcomes [85] although subgroup analyses of the recently published SENTIS study with the intra-aortic NeuroFlo catheter shows some promising results.

External counterpulsation (ECP) is a noninvasive technique in which pressure cuffs on the extremities are inflated synchronously and in sequences. As a result, the blood vessels in the legs are gently compressed and the blood is forced back to the heart. This technique could potentially augment cerebral perfusion [86]. In a small Phase IIa study, using bilateral 2 MHz pulsed wave transcranial Doppler (TCD) probes mounted on head frames, Alexandrov et al. demonstrated that ECP induces marked changes in cerebral arterial waveforms and augmented peak diastolic and mean MCA flow velocities on TCD in five healthy subjects [87]. Han et al. compared the use of this technique in a randomized crossover proof of concept study design with patients randomized to either early (ECP weeks 1–7 and no ECP weeks 8–14) or late group (no ECP weeks 1–7 and ECP weeks 8–14). At week 7, there was a significant change in NIHSS (early 3.5 vs late 1.9; p = 0.042). ECP was associated with a favorable change in NIHSS of 2.1 versus 1.3 for non-ECP (p = 0.061) after adjusting for treatment differences. At week 14, a favorable functional outcome was found in 100% of early group patients compared with 76% in the late group (p = 0.022) [88]. Although the results of these studies are promising, the role of this technique in a true acute scenario, or as a bridging therapy before endovascular procedure, has not yet been evaluated [89].

**Expert commentary**

**Patient selection**

Endovascular intervention in acute ischemic stroke is a resource-intensive procedure that requires significant manpower and economic investments. At a time when medical practice is increasingly limited by scarce resources, physicians and neurointerventionists must carefully tailor treatment strategies in order to achieve optimal clinical outcomes. This involves identifying patients who would benefit most from endovascular therapy using clinical criteria and imaging tools. In earlier sections, we have discussed in detail variables that determine clinical and imaging outcomes in patients undergoing endovascular therapy. In this section, we aim to summarize these variables in a manner that could be used easily in neurointerventional practice.

**Clinical criteria**

- **Age**: the benefits of endovascular therapy decrease with age, with some evidence from cohort studies showing that octogenarians do not benefit from therapy and may have an increased risk of periprocedural complications [70,71]. Age, however, should not be chosen as an a priori exclusion criteria if other clinical and imaging criteria suggests good prognosis and treatment effect;

- **Baseline mRS**: premorbid functional status is a major determinant of final clinical outcome. It is therefore imperative that a careful history be elicited from family or caregivers regarding premorbid functional status including cognitive status and mobility. Neurointervention should only be considered if, in the treating physician’s opinion, there is a reasonable chance of achieving good functional status post-procedure;

- **Baseline NIHSS**: this scale is used to assess stroke severity in the acute phase. A greater NIHSS score correlates with the presence of a large artery occlusion and with the presence of significant salvageable tissue in the absence of extensive early ischemic changes on baseline imaging. Although there is some evidence to suggest that a greater NIHSS score may suggest futile recanalization [44], an imaging (CT/MR DWI) NIHSS mismatch remains a tool of practical utility for patient selection [90]. Similarly, patients with a low NIHSS score may not be ideal candidates for neurointervention when the possibility of good prognosis even without intervention is balanced with periprocedural risks;

- **Time to recanalization**: there is a growing body of evidence to suggest that faster recanalization results in better clinical outcomes [54]. Delayed treatment in itself may be detrimental, as suggested by animal data demonstrating that late reperfusion results in higher rates of hemorrhagic conversion [91]. Available evidence supports the use of endovascular therapy in acute ischemic stroke to 8 h from stroke symptom onset. There is, at present, no evidence for treatment beyond 8 h or in patients with unknown time of symptom onset. Imaging selection may be used as a surrogate for time from symptom onset and is discussed later.
Endovascular therapy in acute ischemic stroke

Review

Imaging criteria

- Small core/occlusion paradigm: there is evidence to suggest that patients with smaller core as measured on either NCCT or MRI benefit most with endovascular therapy [47,48,92]. Patients with small core as assessed by NCCT ASPECTS or DWI MRI and the presence of an occlusion on baseline CT or MR angiography would, in our opinion, show most treatment effect with endovascular therapy. The addition of noninvasive neurovascular imaging helps in patient selection and does not result in any significant prolongation of interval times;
- Perfusion imaging-based mismatch (DWI/PWI on MR or perfusion CT): though a diffusion/perfusion mismatch on MRI or a similar perfusion CT-based mismatch paradigm has been used to select appropriate patients for recanalization, there is, at present, no evidence to conclude that patients with acute stroke selected for thrombolysis based on a perfusion-imaging based-mismatch paradigm will have better outcomes than patients selected using a simple CT/CTA-based paradigm (small core/occlusion);
- Managing work flow: management of acute ischemic stroke is a team effort, with each interval time – from stroke onset to arrival in ER, to CT, to needle, to angio suite and to recanalization – being determined by multiple factors. A focus on reducing each interval time and optimizing work flow is essential in reducing time to recanalization, thereby achieving good clinical outcomes. Efforts should be made to tailor therapy and devices towards the primary goal of any endovascular therapy: fast, effective and safe recanalization.

Five-year view

Endovascular therapy in acute ischemic stroke is a rapidly evolving field with many new devices and techniques at the disposal of the neurointerventionist. This has been possible due to an exponential growth in technology. With the latest devices and with intravenous tPA on board, neurointerventionists are now able to achieve very high recanalization rates. The ‘law of accelerating returns’ [101] although more applicable in the computing world, suggests the possibility of a ‘technological singularity’ in the near future. In neurointerventional terms, this could mean that in the next few years, mechanical devices along with adjunct therapy would be capable of recanalizing almost any thrombus with minimal periprocedural complications. In our opinion, we are in a unique time, as the next 5 years will see us move significantly closer to this technological singularity.

There is a growing body of evidence that suggests that combined intravenous plus IA therapy is better than intravenous tPA alone in the management of acute ischemic stroke. The IMS-III trial could provide an answer to this question and potentially change the way stroke is treated at present [78]. More comprehensive stroke centers with round the clock availability of trained neurointerventionists along with excellent telestroke capabilities encouraging a drip and ship policy could well be the future of acute ischemic stroke management.

Results of trials such as the MR and Recanalization of Stroke Clots by Embolectomy (MR RESCUE) trial [102] and the DWI/PWI and CTP Assessment in the Triage of Wake-Up and Late Presenting Strokes Undergoing Neurointervention (DAWN) trial [103] will help us to understand whether multimodal imaging selection paradigms can be used to better select patients for endovascular therapy.

Neuroprotection and flow augmentation potentially extend the time window available for recanalization by reducing infarct growth. Results of trials using these adjunctive techniques in the very acute phase such as the Field Administration of Stroke Therapy – Magnesium (Fast Mag) Phase III clinical trial [104] and other trials focusing on using these techniques as a bridge towards endovascular therapy could potentially suggest new ways to achieve better clinical outcomes with endovascular therapy.

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Key issues

- Endovascular therapy in acute ischemic stroke is a rapidly evolving field with new devices and technology resulting in faster, more effective and safer recanalization.
- Patient selection using well-recognized clinical and imaging criteria is essential in achieving better clinical outcomes.
- A focus on reducing interval times from stroke onset to recanalization and improving procedural efficacy and work flow is essential in improving outcomes with this therapy.
- The importance of tailoring devices and techniques to each individual patient cannot be overstated.
- Adjunctive therapy such as neuroprotection and flow augmentation along with intravenous tPA, may be the future of endovascular therapy in patients with acute ischemic stroke.
- Randomized trials that test new imaging and treatment strategies will result in evidence-based management of patients in the future.
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Endovascular therapy in acute ischemic stroke

Review


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Menon & Goyal

Review

Websites


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103 DAWN Trial [DWI/PWI and CTP Assessment in the Triage of Wake-up and late presenting strokes undergoing neurointervention www.strokecenter.org/trials/TrialDetail.aspx?tid=960

104 Fast Mag (The Field Administration of Stroke Therapy – Magnesium) Phase III clinical trial http://clinicaltrials.gov/ct2/show/NCT00059332