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What is the Role for Intra-Arterial Therapy in Acute Stroke Intervention?

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Abstract

Intravenous recombinant tissue plasminogen activator continues to be first-line therapy for patients with acute ischemic stroke presenting within the appropriate time window, but one potential limitation is the low rate of recanalization in the setting of large artery occlusions. Intra-arterial (IA) treatment is effective for emergency revascularization of proximal intracranial arterial occlusions, but proof of benefit has been lacking until recently. Our goal is to outline the history of endovascular therapy and review both IA thrombolysis and mechanical interventions. In addition, we will discuss the impact of important trials such as the Third Interventional Management of Stroke (IMS3) trial, and the more recent trials Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands (MR CLEAN), Endovascular Treatment for Small Core and Proximal Occlusion Ischemic Stroke (ESCAPE), Extending the Time for Thrombolysis in Emergency Neurological Deficits—Intra-Arterial (EXTEND-IA), and Solitaire With the Intention for Thrombectomy as Primary Endovascular Treatment (SWIFT PRIME) on acute stroke management and the implications for the practicing neurohospitalist.

Keywords

cerebrovascular disorders, carotid artery thrombosis, stroke, neurohospitalist, clinical specialty, cerebrovascular disease

Introduction

Stroke continues to be a leading cause of death and disability in the United States, with the worst prognosis usually expected in patients with stroke having large artery occlusions.[1-5] With the approval of recombinant tissue plasminogen activator (rt-PA) for acute ischemic stroke after publication of the results of the National Institute of Neurological Disorders and Stroke (NINDS) rt-PA trial in 1995, acute stroke care changed forever.[6] The US Food and Drug Administration (FDA) approved rt-PA for treatment of acute ischemic stroke within 3 hours of symptom onset in 1996, and since then the American Stroke Association (ASA) has extended the intravenous (IV) rt-PA treatment window to 4.5 hours in select patients based on the results of the European Cooperative Acute Stroke Study III.[7,8] Current acute stroke interventions aim to recanalize occluded arteries, thus restoring cerebral blood flow to areas of ischemia and improving clinical and functional outcomes.[9]

Although IV rt-PA is the first-line therapy for patients with acute ischemic stroke presenting within the appropriate time window and continues to be the best studied of the therapies, one limitation is the low rate of recanalization in the setting of large artery occlusions.[2,9,10] Depending on the study, as well as the location of the occluded artery, it is estimated that recanalization rates with IV rt-PA in acute ischemic stroke range from 4% to 68%, with a meta-analysis finding an overall recanalization rate of 46%.[2,11-14]

There have been attempts through the years to improve recanalization rates using novel thrombolytic agents such as tenecteplase (TNK), as it is more resistant to plasminogen activator inhibitor, has greater fibrin specificity, and has a longer half-life.[9] Although there have been randomized clinical trials of IV rt-PA versus IV TNK, definitive phase 3 trials comparing the 2 are lacking.[15,16]

A novel approach to recanalization during rt-PA administration, first reported in 1999[17] and then a larger series published in 2000,[18] described the use of 2-MHz ultrasound (with commercially available transcranial Doppler [TCD] devices) to facilitate "enhanced" thrombolysis. An initial, small randomized trial demonstrated that TCD

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''augments t-PA-induced arterial recanalization'' with a trend toward better stroke outcomes.[19] A phase III multicenter randomized trial is currently recruiting and should answer the question as to the role of ''therapeutic ultrasound'' in acute cerebral ischemia.[20]

Additionally, others have explored using combinations such as thrombolytics and antiplatelet agents to treat acute stroke, such as in the Combined Approach to Lysis Utilizing Eptifibatide and rt-PA in Acute Ischemic Stroke—Enhanced Regimen (CLEAR-ER) trial.[21] The CLEAR-ER trial studied the combined regimen of IV rt-PA and eptifibatide and demonstrated that the glycoprotein IIb/IIIa inhibitor may be safely used in combination with a lower dose of 0.6 mg/kg rt-PA, paving the way for a phase 3 trial to determine efficacy of this regimen. However, adjunctive antiplatelet use in the setting of thrombolysis must be considered against the results of the Antiplatelet Therapy in Combination with rt-PA Thrombolysis in Ischemic Stroke (ARTIS) trial,[22] a randomized controlled trial of 300 mg of IV aspirin within 90 minutes of standard rt-PA administration, which demonstrated increased symptomatic intracranial hemorrhage (sICH) and no change in 3-month outcome when compared to rt-PA alone and delayed antiplatelet.

A recent Cochrane review in 2013 concluded that IV rt-PA at 0.9 mg/kg continues to represent best practice in many countries and that other drugs, doses, or routes of administration should only be considered in the setting of randomized controlled trials.[23]

Alternative strategies to treat acute ischemic stroke have substantially increased over the past decade and have been used in both clinical practice and research, including multimodal intra-arterial (IA) thrombolysis (both chemical and mechanical) as well as bridging strategies that combine IV and IA thrombolysis. Current endovascular approaches not only include pharmacologic thrombolysis but also include clot manipulation with guidewire and/or catheter, mechanical, and aspiration thrombectomy as well as stent retriever technology.[24,25] Endovascular therapy has been used to treat patients with occlusions of large intracranial arteries, given the perceived advantage of this modality leading to more frequent and rapid recanalization of occlusions when compared to IV rt-PA.[24,26] A disadvantage of endovascular therapy is the delay in initiation of treatment due to the time required to mobilize an interventional team, as well as the need to transfer patients to centers with the required expertise.[26-28] Furthermore, risk of complications such as reperfusion injury, liberation of thrombus for distal embolization, and vessel injury is higher than complications with IV rt-PA.

Recent American Heart Association/ASA guidelines recommend that those patients eligible for IV rt-PA receive it even if IA options are being considered.[10] Additionally, the guidelines state that IA fibrinolysis is beneficial in acute stroke patients with major stroke caused by an occlusion of the middle cerebral artery within 6 hours of symptom onset, even if they are not otherwise candidates for IV rt-PA (class I; level of evidence B). Currently, rt-PA does not have FDA approval for IA use, and the optimal rt-PA dose is not well established, but the guidelines suggest IA fibrinolysis or mechanical thrombectomy is reasonable in those patients who have contraindications to the use of IV rt-PA or as rescue therapy in patients with large artery occlusion who have not responded to IV fibrinolysis.[10] As with IV rt-PA, reduced time from symptom onset to reperfusion with IA therapies is correlated with better clinical outcomes, thus the importance of minimizing delays to treatment.

We will briefly outline the history of endovascular therapy, reviewing both local IA thrombolysis and mechanical interventions. Additionally, we will discuss the impact of the Third Interventional Management of Stroke (IMS III) trial, as well as recently published trials including Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands (MR CLEAN), Endovascular Treatment for Small Core and Proximal Occlusion Ischemic Stroke (ESCAPE), Extending the Time for Thrombolysis in Emergency Neurological Deficits—Intra-Arterial (EXTEND-IA), and Solitaire With the Intention for Thrombectomy as Primary Endovascular Treatment (SWIFT PRIME) on acute stroke management.

Endovascular Treatment of Acute Ischemic Stroke

History of Local IA Thrombolysis

The first significant trial of IA thrombolytic therapy to show benefit was the Prourokinase (Prolyse) in Acute Cerebral Thromboembolism (PROACT) study, which was a multicenter, randomized, double-blinded, placebo-controlled trial of a plasminogen activator delivered intra-arterially.[29] In this phase II trial, recombinant prourokinase (r-proUK) at a dose of 6 mg was delivered intra-arterially at the thrombus face within 6 hours of symptom onset, and compared to placebo with regards to recanalization of M1 and M2 middle cerebral artery (MCA) occlusion. A total of 40 patients were treated in the study before premature termination after less than 1 year of recruitment. The baseline National Institutes of Health Stroke Scale (NIHSS) score was 17 in the treatment group and 19 in the placebo group. Prourokinase resulted in a significant increase in recanalization of MCA occlusions as well as an increase in hemorrhagic transformation. The heparin infusion used for the purpose of maintaining sheath patency was thought to have contributed to the hemorrhage.[25,29] This study paved the way for a phase III trial, PROACT II, which followed shortly thereafter.[30]

PROACT II was a multicenter open-label, unblinded, randomized controlled clinical outcome trial testing the efficacy and safety of IA r-proUK in patients with acute MCA occlusion presenting within 6 hours of stroke onset.[30] A total of 180 patients were randomized to receive 9 mg of IA r-proUK plus heparin or heparin only. The primary clinical outcome was based on the number of patients with minimal or no neurologic disability at 90 days, as measured by a modified

Rankin Scale (mRS) score of 2 or less. This trial showed significant positive results with regard to the primary end point, with 40% of r-proUK patients and 25% of control patients having a modified Rankin score of 2 or less ($P = .04$). Recanalization rates were greater in the IA r-proUK group compared to the controls (66% vs 18%; $P < .001$) as were the rates of sICH within 24 hours of treatment (10% vs 2%; $P = .06$). Despite this higher rate of ICH at 24 hours, IA r-proUK was still associated with improvement in clinical outcome at 90 days, and thus this trial provided support for this endovascular technique. No further studies on r-proUK have been completed, and it is not currently available for clinical use.[25] There have been other trials since PROACT II with trends in favor of IA fibrinolysis, but these studies have been inadequately powered to show statistically significant outcomes and/or were terminated early.[31] To date PROACT II remains the only randomized controlled trial of IA thrombolysis demonstrating statistically significant clinical benefit.

History of Mechanical Interventional Approaches

Mechanical thrombectomy devices for acute ischemic stroke intervention were first developed in the 1990s, along with the evolution of directed delivery of plasminogen activators.[31] These devices were designed to navigate cerebral arteries, in order to capture and retrieve thrombi through the use of microcatheters and guidewires, thus reestablishing cerebral blood flow. Mechanical interventions were thought to offer several theoretical advantages over pharmacological treatment, including rapid achievement of recanalization, lower risk of hemorrhage, longer treatment time window, revascularization of large artery occlusions, and application to refractory proximal thrombi such as carotid "T" occlusions.[25,31] Modern thrombectomy devices work through entrapment and retrieval (eg, Merci Retriever; Stryker Neurovascular), aspiration (eg, Penumbra System), and the newest generation of devices through stenting and retrieval combined (eg, Solitaire and Trevo).[25] The clinical trials that have evaluated mechanical thrombectomy devices for acute ischemic stroke have predominantly been single-arm studies aiming to show safety of recanalization for the purpose of device regulatory approval.

The Merci Retriever (Stryker Neurovascular, Fremont, CA) was the first mechanical device approved by the FDA in 2004 to retrieve thrombi from cerebral arteries in patients presenting within 8 hours of stroke onset.[32] The first-generation device was a corkscrew-shaped device that was devised to cross the site of occlusion and pull the occlusive thrombus into an extracranial guide catheter under active suction. At the time of its approval, there were no data available to suggest its superiority over IV rt-PA in the recanalization of intracranial large arteries or in clinical outcomes. In fact, in the Multi MERCI trial, the mortality rate at 90 days was 34% compared to a 90-day mortality rate of 17% seen in the NINDS trial.[6,32] Although this trial did show higher rates of recanalization compared to the first-generation devices, the differences were not statistically significant.

Subsequently, the Penumbra Pivotal Stroke Trial looked at the safety and effectiveness of the Penumbra system in the revascularization of large intracranial arteries in patients having an acute ischemic stroke presenting within 8 hours of symptom onset.[33] The Penumbra device (Penumbra, Inc, Alameda, CA) does not traverse the occluded artery but instead acts on the proximal face of the occlusion, with an aspiration device used to debulk and extract the clot used in combination with a separator wire to fragment larger fragments lodged in the aspiration catheter. This trial had an all-cause 90-day mortality of 32.8%, which was similar to the Multi MERCI trial, with 25% of the patients achieving an mRS of ≤ 2. The study investigators concluded that the Penumbra system was safe and effective for revascularization.

In an attempt to achieve rapid recanalization using an endovascular approach, detachable intracranial stent technology was used to achieve a temporary endovascular bypass by temporarily deploying a stent but never detaching the stent.[34,35] Instead, the stent is gently retracted into the guide catheter along with the imbedded clot. This method is best combined with temporary flow arrest using an inflatable balloon on the tip of the guide catheter in the cervical internal carotid artery in order to prevent the clot from embolizing to a nontarget territory, as it is pulled from the site of occlusion into the extracranial guide catheter. Examples of these devices are TREVO (Stryker Neurovascular, Fremont, CA) and SOLITAIRE (Covidien/ev3, Plymouth, MN). Since the FDA has recently required comparison of new devices to their approved predecessors in order to achieve support, both the Trevo and the Solitaire stent retrievers were compared to the Merci Retriever in 2 separate noninferiority randomized controlled trials with the results published in 2012. The Trevo 2 trial compared the safety and efficacy of the Trevo retriever with the Merci retriever in 178 patients with large cerebral artery occlusions presenting within 8 hours of acute stroke onset and ineligible for IV rt-PA or failing to respond to it.[36] The Trevo stent retriever demonstrated significantly higher rates of recanalization when compared to the Merci device (86% vs 60%; $P < .0001$) with no difference in safety end points. The SWIFT trial compared the safety and efficacy of the Solitaire stent retriever to the Merci retriever, with the same inclusion criteria as the Trevo 2 trial.[37] Similarly, the SWIFT trial demonstrated superiority of the Solitaire stent retriever over the Merci device with higher rates of recanalization in the Solitaire group (61% vs 24%; $P < .0001$) as well as lower rates of 90-day mortality. No studies thus far have established the superiority or equivalence of any of the devices to current acute medical treatment with IV rt-PA.

The Third Interventional Management of Stroke Trial

The rationale for combining IV rt-PA with endovascular therapy came from the higher recanalization rates as well as treatment delays associated with endovascular treatment as

illustrated in a pilot study by Lewandowski et al, Emergency Management of Stroke (EMS) Bridging Trial.[38] The IMS III began enrollment in 2006 and compared combined IV rt-PA and endovascular therapy to IV rt-PA alone, with all eligible patients receiving IV rt-PA within 3 hours of symptom onset.[26] This international, phase 3, randomized controlled trial was designed to randomize 900 patients with acute stroke to combination therapy or IV rt-PA alone, in a 2:1 ratio. Inclusion criteria included patients 18 to 82 years of age, an NIHSS score of $\geq$10 or an NIHSS of 8 to 9 with computed tomographic (CT) angiographic evidence of a proximal artery occlusion (M1, internal carotid, or basilar), and administration of rt-PA within 3 hours of symptom onset. Patients randomly assigned to endovascular therapy underwent angiography as soon as possible and received endovascular intervention when appropriate, with the approach chosen by the study site neurointerventionalist. The angiography had to begin within 5 hours of stroke onset and be completed within 7 hours of onset. Endovascular treatment options used in the study included IA rt-PA with or without EKOS (EKOS Corporation), Merci, Penumbra, or Solitaire devices. As they received regulatory approval, the newer more effective mechanical thrombectomy devices were allowed in the study. However, stent retrievers were rarely used, with only 2 patients treated with the Trevo device and 12 patients with the Solitaire device. This point exemplifies the difficult task of conducting a trial in the face of rapidly evolving technology. Unfortunately, the most commonly used devices in the trial were outdated before the trial was complete. The primary outcome measure for the study was a mRS score of 2 or less.

In 2012, the IMS III trial was stopped early by the Data and Safety Monitoring board because of futility, after the randomization of 656 participants.[9,26] A total of 434 patients were randomized into the combined therapy group, with 334 patients actually undergoing endovascular intervention, and 222 patients randomized into the IV rt-PA alone group. The baseline characteristics of the 2 groups were similar with the exception of the number of patients with a history of coronary artery disease, with a larger proportion in the IV rt-PA alone group (32.4% vs 23.5%; $P = .01$). Of the 334 patients receiving endovascular therapy, the majority were treated with IA rt-PA alone or in combination with mechanical thrombectomy. There was no significant difference between the endovascular therapy group and the IV rt-PA group in overall functional independence as measured by an mRS of 0 to 2 at 90 days, (40.8% vs 38.7%, respectively). Study investigators hypothesized that the efficacy of endovascular therapy would be greatest in those patients with an NIHSS score of $\geq$20, given the higher chance of a major artery occlusion and a large volume of brain at risk of infarction, but this was not the case. The IMS III trial showed similar safety outcomes in both groups with no significant difference in mortality at 7 or 90 days, the rate of symptomatic intracerebral hemorrhage (sICH), or in the rate of parenchymal hematoma. However, the rate of asymptomatic hemorrhage was higher in the combination therapy group (27.4% vs 18.9%; $P = .01$).[26]

At baseline, before randomization, 47% of the participants had CT angiography or magnetic resonance (MR) angiography.[9] Of these participants, 147 were in the endovascular therapy group, and the rate of complete or partial recanalization at 24 hours was 81% for an internal carotid artery occlusion, 86% for an M1 occlusion, and 88% for an M2 occlusion. In the IV rt-PA alone group, 69 participants had imaging at baseline and at 24 hours, with recanalization rates of 35% for an internal carotid occlusion, 68% for an M1 occlusion, and 77% for an M2 occlusion.[26] Importantly, in IMS III, the recanalization rates for the MCA in the IV rt-PA group were higher than previously attained.[9,11] However, time to endovascular therapy was significantly longer than what was achieved in previous studies, with a mean time of 249 minutes, which was 32 minutes longer than in the IMSI trial.[21,39] This was considered a significant factor to contemplate when reconciling the fact that M1 recanalization rates 2 to 3 hours status post-IV rt-PA treatment as seen with TCD ultrasound and MR angiography were greater in the endovascular treatment group when compared to IV rt-PA only (81% vs 40%). In spite of this greater reperfusion rate of approximately 40% in the endovascular therapy group compared to the IV rt-PA only group, there was still no significant clinical benefit to combined therapy. It would seem that revascularization time remains essential to improved outcome whether IA or IV therapies are employed.

Recent Clinical Trials

Until recently, a crucial question left unanswered by clinical trials was whether or not endovascular treatment alone or in combination with IV thrombolysis can result in superior outcomes when compared to IV thrombolysis alone. The newly published results of the MR CLEAN trial as well as ESCAPE, EXTEND-IA, and SWIFT PRIME have shed some light on this subject and will likely result in a dramatic change in acute stroke management.[40-46]

Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands

MR CLEAN is a Dutch, phase 3, multicenter randomized controlled trial with open-label treatment and blinded end point evaluation enrolling 500 patients between December 2010 and March 2014 from 16 centers in the Netherlands.[40] This trial compared IA treatment (IA thrombolysis, mechanical intervention, or both) plus usual care (which could include IV alteplase) to usual care (control group) in patients with acute ischemic stroke and a proximal intracranial arterial occlusion of the anterior circulation confirmed on vessel imaging. Patients included in the study were 18 years of age or older with no upper age limit; had an occlusion of the distal intracranial carotid artery, MCA (M1 or M2), or anterior

cerebral artery (A1 or A2) confirmed by CTA, MRA, or digital-subtraction angiography (DSA); and an NIHSS of 2 or higher, with patients having additional extracranial internal carotid artery occlusion or dissection included at the discretion of the treating physician. All IA treatment had to be initiated within 6 hours of stroke onset. The primary outcome measured was the mRS score at 90 days. Secondary outcomes included the NIHSS score at 24 hours and at 5 to 7 days or discharge, activities of daily living as measured by the Barthel index, and health-related quality of life measured by the EuroQol Group 5-Dimension Self-Report Questionnaire (EQ-5D) at 90 days.[47,48] Safety outcomes included progression of ischemic stroke, new ischemic stroke into a different vascular territory, hemorrhagic complications, and death.

Five hundred study participants were included in the final analysis with a mean age of 65 years (range 23-96), 58.4% being men, and 89.0% treated with IV alteplase before randomization. A total of 233 (46.6%) patients were assigned to the intervention group, while 267 (53.4%) patients were assigned to the control group, with risk factors for poor outcome as well as vascular risk factors evenly distributed between the 2 groups. The median time from stroke onset to start of IV alteplase was 85 minutes in the intervention group and 87 minutes in the control group, with the median time from start of IV alteplase to randomization 204 and 196 minutes, respectively. Intra-arterial treatment (with or without mechanical thrombectomy) was provided to 84.1% of patients in the intervention group, with retrievable stents used in 81.5%. The median time from stroke onset to groin puncture in the intervention group were 260 minutes. All data on primary outcome measures were complete, with an adjusted common odds ratio (OR) of 1.67 (95% confidence interval [CI], 1.21-2.30). There was an absolute difference of 13.5 percentage points (95% CI, 5.9-21.2) in the rate of functional independence (mRS 0-2) in favor of intervention (32.6% vs 19.1%) with an adjusted OR of 2.16 (95% CI, 1.39-3.38). All secondary outcomes also favored intervention, with the NIHSS score after 5 to 7 days being on average 2.9 points lower in the intervention group (95% CI, 1.5-4.3) and absence of residual occlusion at the target site being more common in the intervention group compared to the control group on CTA at 24 hours (75.4% vs 32.9%). Although data on infarct volume were available for only 298 of the 500 enrolled patients, these data also favored the intervention group with the between-group difference in volume of 19 mL (95% CI, 3-34). There was no significant difference in mortality or the occurrence of sICH. However, 5.6% of patients in the intervention group had clinical signs of a new ischemic stroke in a different vascular territory within 90 days compared to 0.4% in the control group.

The results of the MR CLEAN trial demonstrate that IA treatment administered within 6 hours of stroke onset to patients with acute ischemic stroke caused by a proximal intracranial occlusion of the anterior circulation in the context of systemic rt-PA is both safe and effective. Investigators showed that this intervention led to a clinically significant increase in functional status and independence at 90 days without increasing mortality.

Endovascular Treatment for Small Core and Proximal Occlusion Ischemic Stroke

ESCAPE is a Canadian, phase 3, randomized controlled trial with open-label treatment and blinded end point evaluation which began enrollment in January 2013.[41,42] The primary objective of this study was to show that prompt endovascular intervention in patients with acute ischemic stroke and proximal intracranial artery occlusion results in improved outcomes when compared to usual care. This trial compared IA treatment (IA thrombolysis, mechanical intervention, or both) plus usual care (which included IV rt-PA within 4.5 hours) to usual care (control group) in patients with acute ischemic stroke and a proximal intracranial arterial occlusion of the anterior circulation confirmed on vessel imaging. Patients eligible for the study were 18 years of age or older, with a disabling stroke defined as a baseline NIHSS >5, had a prestroke-modified Barthel Index >90, and had a confirmed symptomatic intracranial occlusion based on CTA, at 1 or more of the following locations: carotid T/L, M1 MCA, or M1-MCA equivalent (2 or more M2-MCAs). Additionally, eligible participants had to have symptom onset within 12 hours prior to randomization and endovascular treatment (groin puncture) within 60 minutes of baseline noncontrast CT. Participants had a small infarct core on baseline noncontrast CT, defined as an Alberta Stroke Program Early Computed Tomography Score (ASPECTS) of 6 to 10. The primary outcome measure was the shift in mRS score at 90 days, defined by a proportional odds model. Secondary outcomes included the proportion of patients achieving an NIHSS score of 0 to 2, the proportion of patients who achieved a mRS of 0 to 2, and the proportion of patients who achieved a Barthel Index >90.

The ESCAPE trial was halted early due to efficacy after enrollment of 316 of the anticipated 500 study participants, 238 of who received IV rt-PA (120 in the intervention group and 118 in the control group). The median time from stroke onset to first reperfusion was 241 minutes in the intervention group, with retrievable stents used in 86.1% of the participants. The primary end point favored intervention with a common OR (odds of improvement of 1 point on the mRS) of 2.6 (95% CI, 1.7-3.8), a median 90-day mRS score of 2 in the intervention group compared to 4 in the control group ($P < .001$), and a higher rate of functional independence (90-day mRS score 0-2) in the intervention group, 53.0% versus 29.3%. Additionally, the mortality rate at 90 days was lower in the intervention group compared to control group (10.4% vs 19.0%, $P = .04$), and there was no significant difference in the occurrence of sICH between the 2 groups. All secondary outcomes also favored intervention with a higher rate of patients in the intervention group having a Barthel Index of 95 to 100 at 90 days (57.7% vs 33.6%), an NIHSS score of 0 to 2 at 90 days (51.6% vs 23.1%), and higher

90-day scores on the EQ-5D, indicating better quality of life. Although this trial allowed enrollment of patients up to 12 hours after symptom onset, only 15.5% of participants underwent randomization 6 or more hours after symptom onset, and thus the study was not adequately powered to assess endovascular therapy among patients presenting in the 6 to 12 hour window.

The ESCAPE trial confirms the benefit of rapid endovascular therapy in improving functional outcomes and reducing mortality in patients with acute ischemic stroke with proximal vessel occlusion and small infarct core. Like MR CLEAN, there were clear benefits and low rates of complications with endovascular intervention, with both trials predominantly using retrievable stents. ESCAPE achieved shorter interval times than prior trials, with a median time from baseline CT head to first reperfusion of 84 minutes. This rapid treatment time was achieved due to parallel decision making, with patients in the intervention group undergoing groin puncture while the alteplase was still being infused and in some cases achieving reperfusion before the alteplase infusion was even complete.

Extending the Time for Thrombolysis in Emergency Neurological Deficits—Intra-Arterial

EXTEND-IA is a multicenter, randomized controlled trial with open-label treatment and blinded end point evaluation, which planned on enrolling 100 patients with ischemic stroke receiving IV rt-PA within 4.5 hours of stroke onset in Australia and New Zealand.[43] This trial compared IV rt-PA plus endovascular thrombectomy with Solitaire Flow Restoration (FR) stent retriever to IV rt-PA alone in patients with an anterior circulation acute stroke and proximal intracranial arterial occlusion with evidence of salvageable brain tissue on CT perfusion imaging. Patients included in the study were of all ages with no age restrictions, were eligible to receive IV rt-PA within 4.5 hours, had an occlusion of the internal carotid artery or MCA (M1 or M2) on CT angiography, had evidence of salvageable brain on CT perfusion with an ischemic core of less than 70 mL, and had undergone endovascular therapy (groin puncture) within 6 hours of stroke onset. Although there were no restrictions on the clinical severity of the stroke, with all NIHSS scores included, participants had to have functional independence at baseline with an mRS score of less than 2. The co-primary outcomes measured were early neurologic improvement and reperfusion at 24 hours. Early neurologic improvement was defined as a reduction of 8 or more points on NIHSS or a score of 0 or 1 at 3 days and reperfusion as the percentage reduction in the perfusion-lesion volume between baseline imaging and imaging at 24 hours. Secondary outcomes included the mRS at 90 days, death from any cause, and sICH.

The EXTEND-IA trial was also stopped early in October 2014 due to efficacy, after randomization of 70 patients (35 in each group). The median time from stroke onset to endovascular intervention (groin puncture) was 210 minutes. Both primary outcomes favored the endovascular therapy group with increased reperfusion at 24 hours ($P < .001$) and a probability of reperfusion that was greater than 90% without sICH when compared to the IV rt-PA only group (89% vs 34%; $P < .001$). Endovascular therapy resulted in greater early neurological recovery at 3 days when compared to the control group (80% vs 37%, $P = .002$) and improved functional outcome at 90 days, with a greater number of patients in the endovascular group achieving functional independence as measured by an mRS score of 0 to 2 (71% vs 40%; $P = .01$). There was no significant difference in mortality or the occurrence of sICH between the 2 groups. Six percent of patients in the endovascular group had embolization into a different vascular territory, but this did not result in clinical symptoms.

EXTEND-IA confirms the results of both MR CLEAN and ESCAPE and emphasizes the benefit of early mechanical thrombectomy with a Solitaire ER stent retriever after the administration of IV rt-PA in achieving more complete reperfusion and greater functional recovery when compared to the use of alteplase alone. A unique feature of the EXTEND-IA trial was the use of CT perfusion imaging in all patients, with the goal of selecting patients with the greatest potential to benefit from rapid endovascular intervention and exclude patients with large ischemic cores, who are at greater risk of sICH and malignant edema and have a lower chance of good outcomes.

Solitaire With the Intention for Thrombectomy as Primary Endovascular Treatment for Acute Ischemic Stroke Trial

SWIFT PRIME is a multicenter, 2-arm, randomized controlled trial with open-label treatment and blinded end point evaluation which began enrollment in November 2012.[44-46] The purpose of the study was to demonstrate that patients with an anterior circulation acute ischemic stroke and proximal arterial occlusion treated with IV rt-PA and endovascular intervention (Solitaire FR) have less disability 3 months poststroke. This trial compared IV rt-PA plus endovascular thrombectomy with Solitaire FR to IV rt-PA alone. Eligible patients were between the ages of 18 and 80, with an acute anterior circulation ischemic stroke and proximal intracranial arterial occlusion (intracranial ICA, carotid terminus, and M1 segment of the MCA) confirmed on CTA or MRA, had a baseline NIHSS $\geq$8 and <30, had a prestroke mRS of $\leq$1, and received IV rt-PA within 4.5 hours of stroke onset. Additionally, study participants had to be treated with endovascular therapy within 6 hours of stroke onset and have groin puncture within 90 minutes of CTA or MRA. The primary outcome was the degree of disability at 90 days poststroke as measured by the mRS. Secondary outcomes include mortality at 90 days, functional independence (mRS $\leq$ 2) at 90 days, the change in NIHSS at 27 hours postrandomization, infarct volume at 27 hours postrandomization, reperfusion at 27 hours

postrandomization, and arterial revascularization measured by thrombolysis in cerebral ischemia (TICI) 2b or 3following the intervention. Safety outcomes evaluated in the study were all serious adverse events and sICH at 27 hours post-randomization.

SWIFT PRIME was halted in January 2015 due to efficacy of endovascular treatment after enrollment of 196 of the anticipated 833 study participants. The study results have not yet been published (www.clinicaltrials.gov), but preliminary results were recently presented at the International Stroke Conference by Saver et al[46] and were consistent with positive results seen in recent trials. There was a similar pattern of downshift in disability and favorable 90-day outcomes in the endovascular intervention group with 60.2% having an mRS $\leq$2 compared to 35.5% in the IV rt-PA only group, $P = .0002$. There were also excellent reperfusion rates as well as significant improvement in NIHSS at 72 hours, with minimal complications and no difference in sICH between groups. Thus, SWIFT PRIME confirmed that endovascular intervention with SOLITAIRE stent retrievers was not only safe and technically successful but also significantly reduced disability at 90 days.

Implications for the Neurohospitalist

The results of MR CLEAN, ESCAPE, EXTEND-IA, and SWIFT PRIME stand in clear contrast to other randomized controlled trials that have come before, such as the IMSIII trial, as MR CLEAN investigators first showed the benefit of endovascular intervention in acute ischemic stroke, whereas trials before had failed to do so. Important differences certainly exist between most recent trials and earlier trials (eg, IMSIII) including improved rates of reperfusion, swifter times to reperfusion, and more appropriate patient selection based on confirmed proximal artery occlusion. Unlike the IMSIII trial where CTA use was still limited and the presence of a proximal arterial occlusion was uncertain in 47% of the study population, MR CLEAN, ESCAPE, EXTEND-IA, and SWIFT PRIME investigators required a radiologically proven intracranial occlusion for study enrollment. It is unlikely that IA treatment alters the natural course of an acute ischemic stroke without the presence of a proximal artery occlusion. As mentioned previously, in the IMSIII trial, stent retrievers were rarely used, while in recent trials, they were used in 82% to 100% of patients in the intervention group. These newer devices have been shown to be superior in both revascularization and clinical outcomes when compared to the first-generation Merci devices used in IMSIII.[36,37] In the IMSIII trial, rates of considerable reperfusion (defined as TICI grades 2b or 3) were lower (40%) compared to recent stent retriever trials (58%-88%).[40-46,49] Additionally, the speed at which reperfusion was achieved in most of the recent trials was faster than IMSIII (ESCAPE 4 hours, EXTEND-IA 4.1 hours, SWIFT PRIME 4.2 hours, and IMSIII 5.4 hours),[49] possibly suggesting that stent retrievers may reduce time from groin puncture to reperfusion. Overall, there was an absolute benefit in favor of endovascular therapy in MR CLEAN, but there were relatively few patients in the control group that had an mRS of 0 to 2 at 90 days. It should be highlighted that this trial had very broad inclusion criteria including octogenarians and nonagenarians (similar to ESCAPE and EXTEND-IA), as well as patients with extracranial internal carotid artery occlusions and/or dissections, and patients with contraindications to IV alteplase. This resulted in a study population of less healthy individuals with poorer prognosis at baseline. One could infer that this makes the results of MR CLEAN more generalizable. It is important to mention that despite the positive results of recent endovascular trials, there is the potential to have embolization into a new vascular territory during the procedure itself (EXTEND-IA 6% and MR CLEAN 9%) most likely due to clot fragmentation on retraction. This complication can be reduced with judicious use of temporary flow arrest with a balloon guide catheter. Finally, we must consider the fact that 3 of the 4 positive trials were halted early after MR CLEAN was published, resulting in greatly reduced sample sizes and raising concern regarding the magnitude of the treatment benefit. The largest effect size was in fact seen in the smallest trial, EXTEND-IA (n = 70; OR, 3.8 [95% CI, 1.4-10.0]), but this trial also had the most rigorous imaging selection of all, which may explain the magnitude of the results. It is unlikely that the direction of this effect in favor or endovascular intervention can be explained by chance alone, since all 4 trials were reproduced almost simultaneously in different parts of the world within diverse health systems.[49,50]

These data and their implications are of great practical importance to the practicing neurohospitalist. Considering the majority of hospital neurology practice is cerebrovascular[51] and the potentially devastating nature of an acute ischemic stroke due to a large artery occlusion,[52] expert navigation of acute stroke evaluation and management is paramount for the provision of excellent emergent neurologic care and best outcomes in otherwise bad situations.

Where do we stand? It is the authors' practice and recommendation to follow AHA/ASA guideline-based evaluation and management of acute ischemic stroke, including provision of rt-PA to those eligible by established criteria without delay, irrespective of localization of a large artery occlusion. Multiparametric imaging (eg, CT or MR perfusion) may assist in identifying patients with "brain to save" (eg, a "penumbra").[53] However, optimization of patient selection for stroke therapy using available perfusion and diffusion imaging technology is still a work in progress. After the thrombolysis decision is made, patients with a large artery occlusion—particularly those in proximal anterior or posterior circulation—who were previously very functional and now greatly disabled should be considered for and counseled on the benefits, risks, and alternatives of endovascular reperfusion therapies early after the provision of rt-PA. Transcranial Doppler monitoring can be employed to "monitor rt-PA" and evaluate vessel patency in real time, assisting in the triage of patients doing poorly with persistent

Table 1. Summary of Endovascular Trials.

Trial	Study Design	Study Population	Main Results
PROACT 2[30]	PROBE, IA r-proUK + heparin vs heparin only	AIS <6 hours from onset, age 18-85, angiographically proven MCA occlusion, no hemorrhage or major early infarction signs; n = 180	40% of r-proUK vs 25% control had mRS ≤ 2 at 90 days ($P = .04$), mortality 27% r-proUK vs 25% control, MCA recanalization 66% r-proUK vs 18% control ($P < .001$), sICH at 24 hours 10% r-proUK vs 2% control ($P = .06$)
MR RESCUE[56]	PROBE, IA mechanical thrombectomy (Merci Retriever or Penumbra System) vs standard care	AIS <8 hours from onset, age 18-85, NIHSS 6-29, large artery anterior circulation, including "tPA failure" if persistent target occlusion identified; n = 118	Mean 90-day mRS did not differ embolectomy vs standard care (3.9 vs 3.9, $P = .99$). No interaction between pretreatment imaging ("penumbra") and outcome between groups ($P = .14$)
IMS[39]	Multicenter open-label, single-arm pilot of feasibility, and safety of combined IV and IA tPA as compared to NINDS patient data	AIS <3 hours from onset age 18-80, NIHSS ≥ 10, reduced-dose tPA in all patients (0.6 mg/kg, max 60 mg) and IA tPA 22 mg infusion if clot identified in any intracranial large artery; n = 80	Three-month mortality 16% in IMS-treated patients vs 24% and 21% in placebo and tPA NINDS patients (nonsignificant). sICH was 6.3% in IMS-treated patients, similar to NINDS tPA (6.6%). As compared to NINDS placebo, IMS-treated patients 90-day mRS 0-1 (OR 2.26, 95% CI 1.15-4.47) and mRS 0-2 (OR 2.18, 95% CI 1.20-3.99). As compared to NINDS tPA, IMS-treated patients 90-day mRS 0-1 (OR 1.00, 95% CI 0.51-1.96) and mRS 0-2 (OR 1.28, 95% CI 0.70-2.33)
IMS II[57]	Multicenter open-label, single-arm pilot of feasibility, and safety of combined IV and IA tPA as compared to NINDS patient data; only difference from IMS was the use of an ultrasound-emitting microcatheter	AIS <3 hours from onset age 18-80, NIHSS ≥ 10, reduced-dose tPA in all patients (0.6 mg/kg, max 60 mg) and IA tPA 22 mg infusion if clot identified in any intracranial large artery; n = 80	Three-month mortality 16% in IMS-treated patients vs 24% and 21% in placebo and tPA NINDS patients (nonsignificant). sICH was not statistically significantly different in IMS-treated patients (9.9%) compared to NINDS tPA (6.6%). As compared to NINDS placebo, IMS-treated patients 90-day mRS 0-1 (OR 2.78, 95% CI 1.46-5.31) and mRS 0-2 (OR 2.82, 95% CI 1.54-5.16). As compared to NINDS tPA, IMS-treated patients 90-day mRS 0-1 (OR 1.36, 95% CI 0.72-2.56) and mRS 0-2 (OR 1.74, 95% CI 0.95-3.19)
IMS III[26]	Phase III, international, multicenter, randomized, open-label, and blinded outcome combined IV and IA tPA (including ultrasound-emitting microcatheter) as compared to standard tPA (2:1)	AIS <3 hours from onset age 18-82, NIHSS ≥ 10 (NIHSS ≥ 8 with CTA evidence of large artery clot), IV + IA tPA per IMS/IMS II vs standard dose tPA; n = 656	Ninety-day mRS not different treatment (40.8%) vs control (38.7%), 95% CI (-6.1-9.7). 90-Day mortality was similar between treatment and control groups (19.1% vs 21.6%, $P = .52$). sICH within 30 hours of tPA was similar between treatment and control groups (6.2% vs 5.9%, $P = .83$)
SYNTHESIS[55]	"Pragmatic" multicenter, open-label blinded end point of primary IA therapy (tPA, mechanical, or both) vs IV tPA	AIS <4.5 hours from onset age 18-80; n = 362	Three-month mRS 0-1 no difference between IA (30.4%) vs IV tPA (34.8%), OR 0.71 95% CI (0.44-1.14). Onset to start of treatment 3.75 hours for IA vs 2.75 hours for IV tPA ($P < .001$)
MR CLEAN[40]	"Pragmatic" PROBE, IA intervention (thrombolysis and/or mechanical extraction) plus usual care (including IV tPA) vs usual care alone.	AIS <6 hours from onset, age 18+, Dutch population, angiographically proven anterior circulation occlusion, NIHSS ≥ 2; n = 500	Ninety-day mRS 0-2 in 32.6% of intervention vs 19.1% of usual care patients (95% CI 5.9-21.2). No significant differences in mortality or sICH between groups. 89% of patients received IV tPA and retrievable stents were used in 81.5% of patients assigned to intervention
EXTEND-IA[43]	Investigator-initiated PROBE, IA intervention + IV tPA vs IV tPA alone (1:1)	AIS within 4.5 hours (for IV tPA) of onset, IA initiated within 6 hours of onset and completed within 8 hours of onset, age ≥ 18, ICA or M1/M2 MCA occlusion, and penumbra imaging pattern; n = 70	Three-day early recovery (80% vs 37%) and mRS 0-2 (71% vs 40%, $P = .01$) favored interventional group, no significant differences in rates of death or sICH

(continued)

Table 1. (continued)

Trial	Study Design	Study Population	Main Results
SWIFT PRIME[44-46]	Global multicenter PROBE, IA intervention (Solitaire) + IV tPA vs IV tPA alone (1:1)	AIS within 4.5 hours of onset, IA initiated within 6 hours of onset, intracranial ICA or M1 MCA occlusion, age 18-80, premorbid mRS ≤ 1, NIHSS 8-29; n = 196	Ninety-day mRS 0-2 in 60.2% intervention + tPA vs 35.5% in tPA alone ($P = .0002$), sICH 1% intervention vs 3.1% tPA alone, death at 90 days 9.2% intervention vs 12.4% tPA alone ($P = .50$)
ESCAPE[41,42]	Multicenter PROBE, 1:1 endovascular treatment + guideline-based care vs guideline-based care alone	AIS within 12 hours of onset, age ≥ 18, premorbid BI ≥ 90, intracranial ICA or M1 MCA occlusion, ASPECTS 6-10; n = 316	Ninety-day mRS 0-2 53% intervention vs 29.3% control ($P < .001$), mortality 10.4% intervention vs 19% control ($P = .04$), sICH 3.6% intervention vs 2.7% control ($P = .75$). Median time from study CT to first reperfusion = 84 min in intervention group.

Abbreviations: PROBE, prospective, randomized, open-label, blind end point; IA, intra-arterial; r-proUK, recombinant pro-urokinase; AIS, acute ischemic stroke; MCA, middle cerebral artery; mRS, modified Rankin Scale; sICH, symptomatic intracranial hemorrhage; CI, confidence interval; MR RESCUE, Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy; NIHSS, National Institutes of Health Stroke Scale; IV tPA, intravenous tissue plasminogen activator; ICA, internal carotid artery; M1, first segment of MCA; M2, second segment of MCA; BI, Barthel Index; SYNTHESIS Expansion, a Randomized Controlled Trial on Intra-arterial Versus Intravenous Thrombolysis in Acute Ischemic Stroke; MR CLEAN, Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands; ESCAPE, Endovascular Treatment for Small Core and Proximal Occlusion Ischemic Stroke; EXTEND-IA, Extending the Time for Thrombolysis in Emergency Neurological Deficits—Intra-Arterial; SWIFT PRIME, Solitaire With the Intention for Thrombectomy as Primary Endovascular Treatment; NINDS, National Institute of Neurological Disorders and Stroke; CT, computed tomographic; PROACT, Prourokinase in Acute Cerebral Thromboembolism; IMS III, Third Interventional Management of Stroke; OR, odds ratio; ASPECTS, Alberta Stroke Program Early Computed Tomography Score.

large artery occlusion to endovascular reperfusion, but this approach has not been rigorously studied.[18,54] However, there should be no delay in getting the patient with stroke having a large vessel occlusion to the angiography suite, with a goal of less than 60 minutes from first CT to groin puncture, as emphasized in ESCAPE, EXTEND-IA, and SWIFT PRIME. If a patient is initially cared for at a facility without the latest endovascular reperfusion capabilities, they should be transferred to the nearest stroke center with such expertise and that process can begin as soon as a large artery occlusion is diagnosed (Table 1).

Conclusion

Evidence from clinical trials thus far suggests that faster times to reperfusion lead to better clinical outcomes, and IV rt-PA remains the standard of care for patients with acute stroke presenting within 4.5 hours of stroke onset and experiencing significant neurologic deficits. Results from recent randomized controlled trials (MR CLEAN, ESCAPE, EXTEND-IA, and SWIFT PRIME) confirm that endovascular intervention using stent retrievers in patients with acute stroke and proximal intracranial artery occlusions improves recanalization and functional outcomes beyond what is possible with IV rt-PA alone.

Declaration of Conflicting Interests

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