Acute ischemic stroke (AIS) is the leading cause of disability worldwide and among the leading causes of mortality. Although intravenous tissue plasminogen activator (IV-rtPA) was approved nearly 2 decades ago for treatment of AIS, only a minority of patients receive it due to a narrow time window for administration and several contraindications to its use. Endovascular approaches to recanalization in AIS developed in the 1980s, and recently, 5 major randomized trials showed an overwhelming superior benefit of combining endovascular mechanical thrombectomy with IV-rtPA over IV-rtPA alone. In this paper, we discuss the evolution of catheter-based treatment from first-generation thrombectomy devices to the game-changing stent retrievers, results from recent trials, and the evolving stroke systems of care to provide timely access to acute stroke intervention to patients in the United States. (J Am Coll Cardiol 2016;67:2631–44) © 2016 by the American College of Cardiology Foundation.

Acute ischemic stroke (AIS) occurs when there is a sudden occlusion of the arterial blood supply to part of the brain, and is most commonly manifested by focal neurological deficits. More than 750,000 stroke cases occur every year in the United States, making it the fifth leading cause of death and the leading cause of disability. Strokes cost more than $70 billion annually, and have a devastating effect on the quality of life of a significant proportion of patients and their caregivers (1).

The mechanisms of ischemic stroke can be divided into embolic (artery to artery or cardioembolic), lipohyalinotic occlusion of small arteries, or in situ thrombosis over an atherostenotic plaque (atherothrombosis). Thrombolysis to recanalize the occlusion and reperfuse the brain, through either pharmacological or mechanical means, is the mainstay of treatment options for patients with AIS. Until recently, intravenous recombinant tissue plasminogen activator (IV-rtPA) was the only approved therapy for patients with AIS presenting within 0 to 4.5 h (2). Although approval of IV-rtPA was a landmark step toward treatment of AIS, more than 50% of patients receiving IV-rtPA were still either severely disabled or dead (3,4). The absolute reduction in chance of poor outcome in patients treated with IV-rtPA within 3 h is 10%, which amounts to a number needed to treat (NNT) of 10. In a 3- to 4.5-h time window, the effect is reduced further, to 7% (NNT of 14) (5,6). Delays in achieving reperfusion, inadequately complete recanalization, and hemorrhagic transformation were some of the limitations of intravenous thrombolysis. To overcome these limitations, minimally invasive endovascular approaches were developed over the last 2 decades. After initial disappointing results from trials using the first generation of mechanical thrombectomy devices, in 2015, endovascular mechanical thrombectomy with a retrievable stent (commonly called a stent retriever), along with IV-rtPA was established as the new standard of care for AIS due to large vessel occlusion (LVO) (7). In this paper, we shall review the evolution of endovascular catheter-based
treatment of stroke, the reasoning behind the overwhelming success of recent endovascular clinical trials in AIS, and their effect on acute stroke care.

**EVOLUTION OF AIS TREATMENT**

**INTRAVENOUS THROMBOLYSIS.** IV-rtPA treatment was shown to benefit patients with AIS in the 1995 NINDS (National Institute of Neurological Disorders and Stroke) study. IV-rtPA was a major milestone in stroke treatment, as the first disease-modifying therapy for AIS (3). On the basis of the NINDS study results, in 1996, the Food and Drug Administration (FDA) approved the use of IV-rtPA for patients with AIS presenting within 3 h of symptom onset. Subsequently, in 2008, ECASS (European Cooperative Acute Stroke Study) III showed benefit of IV-rtPA over placebo among those treated within 3 to 4.5 h of symptom onset (6,8). These studies established IV-rtPA as a standard therapy for patients with AIS within 4.5 h of symptom onset. Although the FDA did not modify the original indication for use of IV-rtPA beyond 3 h, recent stroke guidelines from the American Heart Association (AHA) recommended using it up to 4.5 h from onset of symptoms in eligible patients (2). Despite this recommendation, the use of IV-rtPA is estimated to occur in <3% of patients presenting with AIS (9). The narrow therapeutic time window of 4.5 h is the most common reason that patients do not receive IV-rtPA, along with a few others (Table 1). Also IV-rtPA has major therapeutic limitations, including unresponsiveness of large thrombi to enzymatic digestion, resulting in a low recanalization rate (13% to 50%) in LVO stroke and a low rate of benefit in the patients having the most disabling strokes (10,11). To overcome these major limitations of IV-rtPA, endovascular approaches have been developed over the last 2 decades using catheters that are delivered intra-arterially to the site of the intracranial clot to recanalize the occluded vessel.

**INTRA-ARTERIAL THROMBOLYSIS.** PROACT (Prolyse in Acute Cerebral Thromboembolism Trial) was the first prospective randomized controlled trial (RCT) to investigate the safety and efficacy of intra-arterial recombinant prourokinase (IA-proUK) and heparin compared with intra-arterial heparin alone, applied within 6 h of stroke symptom onset in patients with middle cerebral artery occlusion (12). This phase II study, which randomized 46 patients, showed a significantly higher recanalization rate with IA-proUK along with a nonsignificant, but higher symptomatic hemorrhage rate. PROACT II, a phase III study of 180 patients, soon followed and showed the clear superiority of IA-proUK in achieving the primary outcome of no or slight disability, defined as a modified Rankin Scale (mRS) of 0 to 2 at 90 days, functionally independent outcome (FIO) in 60% versus 18% (p < 0.001) of patients, as well as a greater recanalization rate of 40% versus 25% (p < 0.04) compared with intra-arterial (IA) heparin alone. The improved clinical outcome occurred despite a higher symptomatic hemorrhage rate of 10% in the treatment arm compared with 2% in control subjects. Despite the success of PROACT II, the FDA did not approve IA-proUK, and soon afterward, this pharmacological agent was no longer commercially available (13). The AHA 2005 and 2013 guidelines recommended IA thrombolysis in carefully selected patients with middle cerebral artery (MCA) occlusions within 6 h who were not candidates for IV-rtPA (Class I, Level of Evidence: B), but it was not enough to make it a standard of care (14,15).

**MECHANICAL THROMBECTOMY**

The era of mechanical thrombectomy (MT) began with development of the “mechanical embolus removal in cerebral ischemia” (MERCI) device. The device is made of a corkscrew-shaped nitinol wire that is deployed into the thrombus in the occluded intracranial artery. Both the device and corkscrew are removed as one unit to recanalize the artery acutely. This device was tested for safety and early efficacy in the MERCI trial, a single-arm, multicenter trial of thrombectomy in patients with LVO treated within
8 h of symptom onset. Successful recanalization was defined as achieving Thrombolysis In Myocardial Infarction (TIMI) grade 2 or 3 flow in the target artery. The device achieved a recanalization rate of 46%, against a recanalization rate of 18% (p < 0.001) seen in historical control subjects in PROACT. A good neurological outcome was achieved in 27.7% of patients, a relatively low rate compared with the 60% rate seen in the PROACT II trial. This led to FDA approval of the MERCI device in August 2004, the first mechanical thrombectomy device approved for treatment of occluded intracranial arteries. The Multi MERCI trial ensued with the second-generation device and expanded on the MERCI trial results, demonstrating a recanalization rate of 57% with MT only and 69% if used in conjunction with IA-rtPA. The rate of FIO was 36%, a slight improvement over the MERCI trial result. The rate of symptomatic intracranial hemorrhage (sICH) was 7.8% in MERCI and 9.8% in Multi MERCI subjects, respectively (16,17). A pooled analysis of both studies concluded that final recanalization status represents the strongest predictor of independent clinical outcome at 90 days in patients undergoing thrombectomy (18).

Another mechanical thrombectomy device for stroke that works by thromboaspiration in occluded intracranial vessels was also developed. The Penumbra stroke trial was a single-arm, multicenter, phase II study. The trial enrolled 125 patients with National Institutes of Health Stroke Scale (NIHSS) scores of 8 or more, presenting within 8 h of symptom onset and with angiographic occlusion (TIMI 0 to 1) of a treatable LVO. The study demonstrated successful recanalization (TIMI grade 2 or 3) in 81.6% of target vessels. This led to FDA approval of the Penumbra Stroke system in January 2008. Again, the rate of FIO was low (25%) in this study, and the rate of sICH was 11.2% (19).

The MERCI and Penumbra devices were breakthroughs in the field of mechanical thrombectomy, with recanalization rates higher than those seen in the PROACT trials for IA thrombolysis and with acceptable safety. However, the clinical results of these trials demonstrated relatively low rates of good neurological outcomes.

**RANDOMIZED TRIALS WITH FIRST-GENERATION DEVICES**

To demonstrate functional benefit of MT/IA-rtPA plus standard medical management over standard medical management alone, several RCTs were conducted, including the MR RESCUE (Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy), the IMS (Interventional Management of Stroke) III, and the SYNTHESIS EXP (Intra-arterial vs. Systemic Thrombolysis for Acute Ischemic Stroke) trials. The IMS III trial was an international RCT comparing standard-dose IV-rtPA with a combination of low-dose IV- and IA-rtPA or mechanical thrombectomy (20). Patients presenting with AIS within 3 h were randomized to receive either a full dose of IV-rtPA or to stop IV-rtPA after 40 min and proceed to endovascular treatment. No pre-procedure vascular imaging was required before enrolling patients for the study, which led to 89 (21%) patients enrolled in the endovascular arm without LVO. The first-generation MERCI device was the only FDA-approved device at the time of the study, and it was used in the majority of patients. Although the Solitaire stent retriever became available at a later phase of the study, it was used in a minority of patients. In 2012, the study was stopped due to futility after enrolling 656 patients over 6 years and showing no significant difference in long-term functional outcome between groups: FIO at 90 days was 40.8% for mechanical thrombectomy with IV-rtPA versus 38.7% for IV-rtPA alone; absolute difference, 1.5% (95% confidence interval [CI]: 6.1% to 9.1%) (20).

Similar neutral results were seen in the SYNTHESIS EXP trial, conducted in Europe. SYNTHESIS EXP randomized patients into IV-rtPA or endovascular arms (MT with or without IA thrombolyis) (21). Vascular imaging was not mandatory to randomize patients in the endovascular arm, similar to IMS III. Second-generation devices were used in only 13% of patients undergoing endovascular treatment. No functional benefit of endovascular therapy was observed in this trial (30.4% for endovascular therapy vs. 34.8% for IV-rtPA therapy; p = 0.37) (20,21).

The MR RESCUE trial was an RCT of first-generation device MT in the anterior circulation in patients randomized by magnetic resonance imaging (MRI) perfusion imaging, in addition to randomization of embolectomy versus medical therapy (22). Among 118 patients enrolled with moderately severe stroke up to 5.5 h from onset, there were no significant differences between the MT and medical therapy groups (FIO at 90 days, 18.75% vs. 20%), regardless of recanalization status. There was also no significant benefit with MT seen in either of the subgroups with penumbral versus nonpenumbral patterns. Similar to IMS-III and SYNTHESIS EXP, sICH rates were low, at 4% and 3% in the endovascular and medical therapy arms, respectively.

Thus, the 3 trials using mainly first-generation MT devices and done within acute stroke systems of care between 2004 and 2012 did not show functional
benefit in treatment of moderate to severe AIS. All of the trials discussed in the preceding text were published in 2013 and raised serious concerns about the efficacy of acute endovascular reperfusion in LVO. However, there were 2 reasons to continue with new studies of MT: 1) in 2012, 2 phase 2b studies of 2 second-generation devices, thrombus retrievers with a stent design, called stent retrievers, showed significant superiority over first-generation devices in achieving recanalization as well as improved functional outcomes (23,24); and 2) a post hoc analysis from IMS-3 showed significant functional benefit in the subgroup of patients with proven LVO when computed tomography angiography (CTA) was performed prior to endovascular therapy compared with IV-rtPA alone (25).

MAJOR PROGRESS WITH STENT RETRIEVERS

MECHANISM OF THE STENT RETRIEVERS. Stent retrievers were formerly designed for purpose of stent-assisted coiling and for retracting errant coils dislodged during endovascular procedures (26). Soon, it was realized that these devices are also very effective in capturing naturally occurring thrombus and could have a major effect on early vessel recanalization. The most recent generation of these devices is a novel form of clot retrievers, commonly known as stent retrievers. These are self-expanding stents that are delivered across the thrombus with the help of a microcatheter. Their design, with multiple crisscrossing struts, ensures capture of the thrombus within the stent wall, followed by withdrawal of the then-unfolded stent into the guide catheter under constant aspiration. After the clot is removed from the vessel, flow in the vessel is immediately restored (Figure 1A).

STENT RETRIEVER PHASE 2 TRIALS. The SWIFT (Solitaire Flow Restoration Device Versus the Merci Retriever in Patients With Acute Ischemic Stroke) and TREVO 2 (Trevo Versus Merci Retrievers for Thrombectomy Revascularization of LVO in Acute Ischemic Stroke) phase 2 studies showed stent retrievers (Figure 1B and C) to have better reperfusion and good neurological outcomes at 90 days compared with the first-generation Merci Retrieval System (23,24). The SWIFT study enrolled eligible patients to undergo MT either by stent retriever (n = 58) or MERCI device (n = 55). The primary outcome of a TIMI score of 2 or 3 was greater among the Solitaire group compared with the MERCI group (61% vs. 24%; p < 0.0001). Good FIO was also seen more frequently in the Solitaire group than in the MERCI group (58% vs. 33%; p < 0.0001). Similar results were found in the TREVO trial, which enrolled patients to undergo MT, either by Trevo device (stent retriever) or by MERCI device. The primary outcome was defined as a TICI (Thrombolysis in Cerebral Infarction) score (explained later in the section “Comparison of Past and Present Trials: Key Factors That Made the Difference”) of ≥2, and was seen in 76 (86%) patients in the Trevo group compared with 54 (60%) in the Merci group (p < 0.0001). Compared with the Merci group, more patients in the Trevo group had good long-term FIO (40% vs. 22%; p < 0.013). Incidence of the primary safety endpoint (sICH or other complications) did not differ between groups (23,24).

STENT RETRIEVER PHASE 3 TRIALS. In late 2014 and early 2015, the results of 5 RCTs were published in quick succession, all showing clear superiority of MT done with second-generation devices in combination with IV-rtPA (a minority of patients received only MT) compared with IV-rtPA alone. Figure 2 demonstrates complete restoration of blood flow after MT using a stent retriever in a young patient with MCA occlusion.

MR CLEAN (Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands) randomized acute stroke patients
presenting within 6 h of stroke onset to standard medical management alone (n = 267) or standard medical management followed by MT (n = 233) (27). Noninvasive vascular imaging before enrolling a patient into MT was mandatory, and as long as there was clear vessel occlusion, a wide range of NIHSS (0 to 42, where higher numbers indicate severe neurological deficit) was allowed. Patients with AIS who were older than 18 years of age and with anterior circulation LVO confirmed on noninvasive vascular imaging were eligible to be enrolled in the trial. Contrary to first- and second-generation trials, which did not include patients over 80 years of age, MR CLEAN had no cutoff on the upper age limit. The authors did report the rate of FIO in relation to the Alberta Stroke Program Early CT score (ASPECTS); however, ASPECTS was not used for randomization of patients. To avoid selection bias, insurers in the Netherlands did not reimburse the procedure outside of the study, a truly remarkable step not seen in previous endovascular trials. Stent retrievers were used in 190 of the 233 patients (81.5%) assigned to IA treatment. Although the reperfusion rates (TICI 2b or 3) were lower than expected (only 59%), good FIO was superior among those treated with the combination of MT and standard medical management (32.6% vs. 19.1%; odds ratio: 1.67 [95% CI: 1.21 to 2.30]). There were no significant differences in mortality or occurrence of sICH (27).

In light of the MR CLEAN results, the ESCAPE (Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion With Emphasis on

![FIGURE 2](image-url)

(A) Digital subtraction angiograms (DSAs) showing no opacification of the right middle cerebral artery (MCA) due to clot in the M1 segment of the artery in the anterior posterior (AP) plane. (B) Unsubtracted AP image showing stent retriever placement in the occluded portion of the artery through the microcatheter. (C and D) DSA showing complete opacification of the right MCA artery in AP and lateral planes after removal of the clot. (Thrombolysis in Cerebral Infarction score 3).
Minimizing CT to Recanalization Times) trial was stopped early for the first interim analysis. The ESCAPE trial had several unique protocol features. It encouraged the use of CTA (preferably multiphase CTA for better estimation of collateral blood supply) and discouraged use of MRI. ESCAPE focused on improving workflow in enrolling hospitals and set ambitious goals of door-to-puncture times <60 min and door-to-recanalization times <90 min. The first interim analysis, with 315 patients enrolled, showed a rate of FIO in 53% of the MT patients versus 29% with standard therapy (p < 0.001). Good reperfusion (TICI 2b or 3) was achieved in 72% of patients. Intervention was associated with reduction in mortality of 10% (MT) versus 19% in the control group, and rates of sICH were similar in both groups (3.6% MT vs. 2.7% control) (28).

SWIFT PRIME (Solitaire with the Intention for Thrombectomy as Primary Endovascular Treatment) was the next trial stopped by the data safety monitoring board after interim analysis (29). The trial enrolled 196 patients between 2012 and 2014. This study randomized patients who were between 18 and 80 years of age, had NIHSS scores between 8 and 30, and had pre-stroke mRS <1 into intervention and control groups. Noninvasive vascular imaging to identify LVO was mandatory before randomization. Enrolling centers were encouraged to use RAPID, an operator-independent image post-processing system software for target-mismatch penumbral profile (Figure 3); however, it was not mandatory for patient randomization. A desirable rate of reperfusion (TICI 2b or 3) was achieved in 73 of 83 (88%) patients. The rate of FIO at 90 days was higher in the MT group than in the control group (60% vs. 35%; p < 0.001). The efficacy of MT was better than in the MR CLEAN trial (60% vs. 32%) and comparable to the ESCAPE trial (60% vs. 53%). There were no significant between-group differences in 90-day mortality (9% vs. 12%; p = 0.50) or sICH (0% vs. 3%; p = 0.12) (29).

EXTEND-IA (Extending the Time for Thrombolysis in Emergency Neurological Deficits–Intra-Arterial) was an Australian trial that required mandatory computed tomography (CT) perfusion imaging with post-processing by standardized software (RAPID) to randomize patients with a favorable penumbral mismatch pattern to IV-rtPA alone versus IV-rtPA plus MT (30). This trial had some unique inclusion criteria. For example, there were no restrictions on age or clinical severity, as assessed by the NIHSS score; however, like SWIFT PRIME, it required IV-rtPA to be given to patients within 4.5 h and MT to be started within 6 h of symptom onset. Similar to all the new trials, noninvasive vascular imaging to identify LVO in the anterior circulation was mandatory. A pre-treatment mRS score of 0 to 2 was required to be eligible for randomization. The trial was stopped after enrolling 35 patients in each group. It showed vastly superior functional outcomes in the MT plus IV-rtPA arm of 70% versus 40% in the control group (p = 0.001). No significant difference was noted in the rates of sICH or mortality between the 2 groups (30). Figure 4 demonstrates the result from meta-analysis of all trials of endovascular therapy versus standard therapy for the outcome of proportional treatment benefit (31).

REVASCAT (Randomized Trial of Revascularization with Solitaire FR Device versus Best Medical Therapy in the Treatment of Acute Stroke Due to Anterior Circulation LVO Presenting within Eight Hours of Symptom Onset) was conducted primarily in Spain and enrolled patients within 8 h after symptom onset (32). REVASCAT randomly assigned 206 patients in a 1:1 ratio to receive either medical therapy (including IV-rtPA when eligible) and MT treatment with the Solitaire stent retriever or medical therapy alone. Eligible patients were between 18 and 80 years of age, had an occlusion in the anterior circulation confirmed by noninvasive vascular imaging, had an NIHSS >6, and had a pre-treatment mRS score ≤1. The main exclusion criteria were ASPECTS <7 on CT scan or <6 on diffusion-weighted imaging on MRI. After enrolling 160 patients, study inclusion criteria were modified to restrict age to <85 years and ASPECTS to ≥8 on CT scan. The primary outcome of functional independence at 3 months was more frequent in the intervention group (43.7% vs. 28.2%; odds ratio: 2.1; 95% CI: 1.1 to 4.0). The rates of sICH were similar (1.9%) in both groups, and rates of mortality were 18.4% and 15.5%, respectively (p = 0.06) (32). Table summarizes the results of these most recent RCTs.

**COMPARISON OF FIRST GENERATION AND CURRENT ENDOVASCULAR TRIALS: KEY FACTORS THAT MADE THE DIFFERENCE**

**CT NEUROIMAGING IN PATIENT SELECTION.** A non-contrast brain CT scan is often the initial imaging performed to exclude patients presenting with intracranial hemorrhages. In addition to detecting hemorrhage, CT scans can be useful to detect early ischemic changes. ASPECTS is a 10-point scoring system that reliably predicts the extent of early ischemic changes from CT scans (33). Multiple studies have shown that patients with pre-treatment ASPECTS of 7 or more have better outcomes (34,35). Earlier RCTs using first-generation devices did not adequately assess the extent of early ischemic...
changes on the initial CT scan for selectively enrolling the patient into the trial. Post hoc analysis of the IMS III trial showed that the probability of achieving recanalization and good functional outcomes was higher in subjects with higher ASPECTS of 8 to 10 compared with those with ASPECTS of 0 to 7 (36). Contemporary trials, such as ESCAPE, SWIFT PRIME, and REVASCAT (Except MR CLEAN and EXTEND-IA), used ASPECT scores ≤6 as strict exclusion criteria for randomizing and enrolling patients, which essentially led to better outcomes.

MT is targeted for patients with LVO. One of the biggest criticisms of first-generation trials, such as IMS-III and SYNTHESIS-EXP, was enrollment and randomization of acute stroke patients on the clinically assessed NIHSS score rather than confirmed LVO on noninvasive vascular imaging (20,21). Recent RCTs have mandated confirmation of LVO on CT angiography or MR angiography prior to randomization. This change in design in patient selection was in line with the post hoc findings in IMS-3 of a trend toward functional benefit in patients with confirmed LVO (36,37). This change was likely one of the critical factors in showing clear benefit of MT in patients with AIS.

**FASTER AND IMPROVED RECANALIZATION.** It has been well documented that faster treatment from stroke onset to IV-rtPA is associated with better clinical outcomes (38-40). In a post hoc analysis of
FIGURE 4 Forest Plot Assessment of Pre-Defined Subgroups From the 4 Recent Major Endovascular Trials

<table>
<thead>
<tr>
<th>Control/Intervention</th>
<th>Odds Ratio (95% CI)</th>
<th>Interaction P-value</th>
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</thead>
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<tr>
<td>Age</td>
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<tr>
<td>&lt;70y</td>
<td>2.45 (1.68, 3.56)</td>
<td>0.39</td>
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<tr>
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<tr>
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<tr>
<td>Female</td>
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<td>0.91</td>
</tr>
<tr>
<td>Male</td>
<td>2.80 (1.91, 4.11)</td>
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<tr>
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<tr>
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<tr>
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<tr>
<td>Site of Vessel Occlusion</td>
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<tr>
<td>ICA</td>
<td>5.23 (2.60, 10.53)</td>
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<tr>
<td>M1 MCA</td>
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</tr>
<tr>
<td>M2 MCA</td>
<td>1.77 (0.55, 5.65)</td>
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<tr>
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<tr>
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<td>2.76 (2.05, 3.72)</td>
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<tr>
<td>&gt;5h</td>
<td>2.00 (1.04, 3.84)</td>
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</table>

Treatment effect in pre-defined subgroups from the 4 recent endovascular trials (SWIFT PRIME [Solitaire with the Intention for Thrombectomy as Primary Endovascular Treatment], ESCAPE [Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion With Emphasis on Minimizing CT to Recanalization Times], EXTEND-IA [Extending the Time for Thrombolysis in Emergency Neurological Deficits—Intra-Arterial], REVASCAT [Randomized Trial of Revascularization with Solitaire FR Device versus Best Medical Therapy in the Treatment of Acute Stroke Due to Anterior Circulation LVO Presenting within Eight Hours of Symptom Onset]), adjusted for age, sex, baseline stroke severity, site of occlusion, intravenous alteplase treatment, carotid occlusion, Alberta Stroke Program CT Score, and time from onset to randomization. Reprinted with permission from Campbell et al. (31). ASPECTS = Alberta Stroke Program Early CT Score; CI = confidence interval; ICA = internal carotid artery; MCA = middle cerebral artery; NIHSS = National Institute of Health Stroke Scale.

The pooled IMS pilot trials, the relative probability of a good outcome declined by 12% to 15% for every 30-min delay in recanalization (41,42). Moreover, post hoc analysis of the STAR (Solitaire FR Thrombectomy for Acute Revascularization) trial showed that faster recanalization results in better outcomes (43). The mean time from symptom onset to IA in the MR-RESCUE study was 381 min. In SYNTHESIS EXP and IMS III, the median times from symptom onset to start of endovascular treatment were 225 and 240 min, respectively, indicating significant time delays. Learning from the time delays in previous trials, the recent endovascular trials all emphasized the importance of faster door-to-recanalization times. Of all recent trials, ESCAPE stands out for its rapid workflow design. The ESCAPE trial achieved remarkably short door-to-puncture times of <60 min, which eventually led to better outcomes (FIO of 52% patients in the intervention arm vs. 29% in the IV-rtPA arm). In comparison, MR CLEAN reported a time of 114 min to randomize patients after receiving IV-rtPA, resulting in a lower FIO of 32% among patients in the intervention arm. A comparison of NNTs between the 5 trials and the IMS-III trial is shown in Table 3.

Another significant difference in the recent trials was the tremendously improved rate of substantial recanalization, primarily through the use of stent retriever devices. Angiographic recanalization is measured by the TICI scale, which ranges from 0 (no perfusion) to 2a (<50% reperfusion of target vessel), 2b (>50% reperfusion of target vessel), and 3 (full perfusion of target vessel), which is a modification of a previously simplified version of the TICI 0 or 1, 2, 3, scoring system (adapted from the cardiology TIMI scoring system) (44). The rates of substantial recanalization (TICI 2b or above) of individual vessels noted in IMS III were 38% for an occlusion in the internal carotid artery, 44% for an occlusion in M1, and 44% for an occlusion in M2. A further analysis of IMS III reported the proportion of patients with mRS scores 0 to 2 at 90 days was: 12.7% with TICI 0; 27.6% with TICI 1; 34.3% with TICI 2a; 47.9% with TICI 2b; and 71.4% with TICI 3; these scores clearly indicate the role of recanalization in improving outcomes (42). MR RESCUE reported substantial recanalization in only 27% of subjects, whereas the rate of recanalization was not reported by SYNTHESIS-EXP. In comparison, the rates of substantial recanalization noted in recent studies were: MR CLEAN 58%, ESCAPE 72%, SWIFT PRIME 88%, EXTEND IA 94%, and REVASCAT 66%, showing remarkable improvement over previous studies. Figure 5 shows comparison among workflow times, rates of substantial reperfusion, and co-relation to NNT in recent trials.

ROLE OF PERFUSION-WEIGHTED IMAGING. The ischemic penumbra is an area of the brain with reversible ischemia, whereas the core represents...
irreversible brain damage. Modern imaging techniques have been explored to provide high-quality information about the penumbra and its extent compared with the irreversibly infarcted core in selecting patients who could receive maximal benefit with MT. DEFUSE-2 (Diffusion and Perfusion Imaging Evaluation for Understanding Stroke Evolution Study-2) was the first of many trials to evaluate the role of perfusion imaging in selecting patients for MT. Patients with target tissue mismatch (penumbra/core mismatch >1.8 and core volumes <70 ml) had better 90-day outcomes with successful recanalization compared with no recanalization (mRS 0 to 2: 56.5% for recanalization vs. 31.3% for no recanalization compared with no recanalization (mRS 0 to 2; 56.5% for recanalization vs. 31.3% for no recanalization; p = 0.04), whereas no benefit was seen in patients without a target mismatch penumbral pattern (45). The MR RESCUE trial randomized patients according to favorable penumbral pattern (substantial salvageable tissue and small infarct core) or a nonpenumbral pattern (large core, or small or absent penumbra). MR RESCUE found no benefit of MT in patients with favorable penumbral patterns (FIO of 20.6% for MT vs. 26.5% for medical management; p = 0.78) (22).

The SWIFT PRIME trial also encouraged and showed benefit for the use of RAPID software for identifying patients with a favorable penumbral pattern (same as DEFUSE-2). The EXTEND-IA trial also used a perfusion-imaging algorithm, similar to MR RESCUE, and was able to confirm the benefit of recanalization on improving clinical outcomes. Shorter symptom onset to recanalization times (<4.5 h in EXTEND-IA vs. 5.5 h in MR RESCUE), exclusion of patients with ASPECTS <6, and use of modern thrombectomy devices are some possible explanations for the better results seen with the EXTEND-IA study.

### TABLE 2: Comparison of Recent Trials on the Basis of Initial NIHSS, Patients Receiving IV-rtPA, ASPECTS, Functional Outcome (mRS Score at 90 Days), and Revascularization Measured by TICI Score 2b or 3

<table>
<thead>
<tr>
<th>Trial (Ref. #)</th>
<th>NIHSS</th>
<th>Patients Receiving IV-rtPA (%)</th>
<th>ASPECTS (%)</th>
<th>TICI Score (2b/3)</th>
<th>mRS (0-2) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CG</td>
<td>IA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MR CLEAN (27)</td>
<td>12</td>
<td>17</td>
<td>90</td>
<td>9</td>
<td>59</td>
</tr>
<tr>
<td>ESCAPE (28)</td>
<td>17</td>
<td>16</td>
<td>78</td>
<td>9</td>
<td>71</td>
</tr>
<tr>
<td>SWIFT-PRIME</td>
<td>13</td>
<td>17</td>
<td>100</td>
<td>9</td>
<td>88</td>
</tr>
<tr>
<td>EXTEND-IA</td>
<td>12</td>
<td>17</td>
<td>100</td>
<td>NR</td>
<td>86</td>
</tr>
<tr>
<td>REVASCAT</td>
<td>12</td>
<td>17</td>
<td>77</td>
<td>7</td>
<td>66</td>
</tr>
</tbody>
</table>

ASPECTS = Alberta Stroke Program Early CT score; CG = control group; ESCAPE = Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion With Emphasis on Minimizing CT to Recanalization Times; EXTEND-IA = Extending the Time for Thrombolysis in Emergency Neurological Deficits–Intra-Arterial; IA = intervention arm; MR CLEAN = Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands; mRS = modified Rankin Score; NIHSS = National Institutes of Health Stroke Scale; REVASCAT = Randomized Trial of Revascularization with Solitaire FR Device versus Best Medical Therapy in the Treatment of Acute Stroke Due to Anterior Circulation LVO Presenting within Eight Hours of Symptom Onset; SWIFT PRIME = Solitaire with the Intention for Thrombectomy as Primary Endovascular Treatment; TICI = Thrombolysis in Cerebral Infarction; other abbreviations as in Table 1.

### CARDIOLOGY AND ACUTE ENDOVASCULAR STROKE TRIALS: HISTORY REPEATS ITSELF OR LESSON LEARNED?

The evolution of endovascular stroke therapy appears to closely parallel the evolution of acute coronary treatment. The major breakthrough in treatment of acute ST-segment elevation myocardial infarction started with the use of fibrinolytic drugs. Subsequently, percutaneous balloon angioplasty, bare-metal stents, and then drug-eluting stents along with advanced fibrinolytic agents were developed. Studies have also shown that fibrinolytic drugs achieve recanalization in only 50% to 55% of cases, whereas with primary percutaneous intervention it was possible to achieve rates of close to 90% (46-48). Remarkably similar trends are seen in the evolution of endovascular stroke therapy, starting with the approval of IV-rtPA in 1996, and now, after numerous failed trials, we finally have strong evidence to support...
(A) Relationship between onset to intra-arterial therapy/reperfusion and NNT in patients undergoing EVT among second- and third-generation endovascular trials. The NNT to have good outcome decreases with rapid treatment times. (B) Relationship between good reperfusion (TICI 2b) score and NNT among second- and third-generation trials. IA = intra-arterial; IMS = Interventional Management of Stroke; MR CLEAN = Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands; MR RESCUE = Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy; NNT = number needed to treat; TICI = Thrombolysis In Cerebral Infarction; other abbreviations as in Figure 4.

**TABLE 4** Summary of Updated (June 2015) AHA Guidelines for Patients Undergoing MT

<table>
<thead>
<tr>
<th>Indication</th>
<th>Recommendation</th>
<th>Level of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eligible patients should receive IV-rtPA, even if IAT is considered.</td>
<td>Class I A</td>
<td></td>
</tr>
<tr>
<td>Patient presenting within 0–6 h of symptom onset, mRS 0–1, age &gt;18 years, NIHSS &gt;6, ASPECTS &gt;6, with proven occlusion of internal carotid artery or proximal middle cerebral artery (M1), should receive IAT with stent retriever.</td>
<td>Class I A</td>
<td></td>
</tr>
<tr>
<td>Aim of the revascularization procedure should be to receive a TICI 2b/3 score as early as possible.</td>
<td>Class I B</td>
<td></td>
</tr>
<tr>
<td>In selected patients with anterior circulation stroke who have contraindication to IV-rtPA, it is reasonable to perform IAT with stent retrievers. IAT with stent retrievers may be useful for certain patients with occlusion of M2, M3, (distal MCA), anterior cerebral artery, or vertebral artery, if treatment can be initiated within 6 h.</td>
<td>Class II C</td>
<td></td>
</tr>
<tr>
<td>Observing patients after IV-rtPA to assess for clinical response before pursuing IAT is not required to achieve beneficial outcomes and is not recommended.</td>
<td>Class III B</td>
<td></td>
</tr>
<tr>
<td>Emergent imaging of brain, preferably CT scan, should be obtained before beginning any specific treatment for AIS.</td>
<td>Class I A</td>
<td></td>
</tr>
<tr>
<td>If IAT is considered, then nonvascular imaging (CTA or MRA) should be performed to confirm vascular obstruction; however, IV-rtPA administration should not be delayed.</td>
<td>Class I A</td>
<td></td>
</tr>
<tr>
<td>Benefit of additional imaging beyond CT, CTA, or MRA, such as perfusion imaging with CT or MRI, is unknown.</td>
<td>Class IIb C</td>
<td></td>
</tr>
<tr>
<td>Patient should be transferred to the nearest certified primary stroke or comprehensive stroke center.</td>
<td>Class I A</td>
<td></td>
</tr>
<tr>
<td>A regional system of stroke care, including health care facilities to provide initial emergent treatment, a primary stroke center, and comprehensive centers capable of performing IAT, should be developed.</td>
<td>Class I A</td>
<td></td>
</tr>
</tbody>
</table>

Data from Powers et al. (7).

AHA = American Heart Association; CTA = computed tomography angiography; IAT = intra-arterial thrombolysis; MRA = magnetic resonance angiography; MRI = magnetic resonance imaging; other abbreviations as in Tables 1 to 3.
the superiority of endovascular therapy compared with fibrinolytic therapy alone. Moreover, the field of acute coronary intervention has evolved tremendously. In addition to the development of new drugs and percutaneous coronary intervention techniques, it was soon acknowledged that faster door-to-perfusion times led to better outcomes, leading to initiatives such as door-to-balloon time (49). A study reviewed the effect of these initiatives and noted that door-to-balloon times have decreased nationally from a median of 96 min in 2005 to 64 min in 2010 (50). The impressive results in shortening the time to myocardial reperfusion for acute MI obtained through such initiatives provided the inspiration for launching projects like Target Stroke. Target Stroke is a national initiative organized by the AHA/American Stroke Association in partnership with other organizations, and aims to assist hospitals in increasing the proportion of IV-rtPA-treated patients in whom guideline-recommended door-to-needle times are achieved. The initial goal is to achieve a door-to-needle time of no more than 60 min for at least 50% of patients with AIS (51). More recently, the new Target Stroke goal has been revised to achieve a door-to-needle time of 45 min. We now have the evidence needed to support MT; however, the implementation of endovascular stroke practice has yet to achieve the level of refinement seen in the treatment of acute coronary syndrome.

**LIMITATIONS OF CURRENT ENDOVASCULAR TRIALS**

The 5 recent randomized trials prove the consistent benefit of endovascular therapy plus IV-rtPA over standard medical management alone; however, the recent trials are not without limitations. For example the EXTEND-IA screen to enrollment ratio was 100:1 (70 patients were enrolled after screening 7,000 patients), and ESCAPE recruited only 1.44 patients/month/center. Hence, the primary message, which reverberates across all trials, is that limited numbers of patients will benefit from intervention, and clinicians must be selective when choosing patients for endovascular therapy. Moreover, centers participating in the trials were high-volume centers with very experienced neurointerventionalists. These centers also had streamlined workflow protocols for rapid triage of the stroke patients (ESCAPE and SWIFT PRIME, in particular), hasty transfer of patients from the primary center to tertiary centers, along with incredibly fast door-to-treatment times. This, however, needs to be translated into all centers across the country, which may have less volume and less experienced house staff than the centers chosen for the studies. Additionally, these trials differed in the effect size of intervention, from 13% to 31%. As a result, there has been some speculation that the 4 of 5 trials that were stopped early (except MR CLEAN, the only completed study) may have overestimated the treatment effect. An additional prospective
registry should be able to answer this question effectively.

CURRENT RECOMMENDATIONS AND FUTURE DIRECTIONS

Due to consistent findings across multiple endovascular trials, in the recent (June 2015) revision of guidelines from the AHA/American Stroke Association, Class I recommendations were made (Level of Evidence: A) for the use of MT along with IV-rtPA treatment for AIS for eligible patients. The guidelines endorsed the use of IV-rtPA in combination with MT in patients with AIS of <6 h duration who had LVO confirmed with vascular imaging, were >18 years of age, had NIHSS score >6, and had ASPECTS >6. The evidence for MT is less clear for patients presenting >6 h after symptom onset. The evidence for MT is also not clear for patients with posterior circulation strokes, as the majority of present and past trials have excluded these patients. Evidence of the benefit of MT in posterior circulation stroke is from prospective and retrospective patient cohorts, rather than RCTs.

In the future, trials focusing on posterior circulation stroke are needed to establish effective windows and techniques for this group of patients. The guidelines also recommend use of stent retrievers as the first-line device; however, other devices may be useful in certain situations. Other recommendations include faster door-to-recanalization time, the angiographic goal of TICI 2b/3 for better clinical outcomes, and development of comprehensive stroke centers capable of performing MT. Table 4 summarizes the current updated guidelines for MT (7).

These trials certainly are landmark studies, and undoubtedly have advanced a new era in the field of acute stroke intervention. However, we still have long way to go. Use of MT for AIS has remained low in the United States, ranging from 0.6% to 2% of all patients with AIS (52,53). A recently published study reported that only 1.6% of patients with ischemic stroke received MT, including 1.1% of patients receiving MT alone and 0.5% receiving both MT and IV-rtPA. By comparison, 8.0% of patients with ischemic stroke in these hospitals received IV-rtPA alone, without endovascular therapy (53). Delay in arrival to the hospital is the most common reason seen in exclusion of patients with AIS for intravenous thrombolysis, along with other contraindications mentioned earlier (Table 1). In contrast, exclusion criteria for MT are less stringent, and patients are generally considered good candidates for MT as long as they present within 6 h from symptom onset, have LVO on noninvasive imaging, have an NIHSS score >5, and ASPECTS >6. Unfortunately, there are still too many patients with acute stroke who do not recognize the warning signs of stroke, call 911, and arrive quickly enough to be eligible for these therapies. Ongoing education of the general population about early recognition of stroke signs and symptoms and the need for rapid treatment is of paramount importance. In addition, greater emphasis on improving pre-hospital systems, rapid transport of patients from primary stroke centers to comprehensive centers, or bypass of primary stroke centers when there is a suspicion of a LVO should be priorities. There are still areas in which further research is needed to evaluate the expanded indications for MT, including the role of MT in wake-up stroke; the use of MT in selected patients treated beyond 6 h, particularly with image selection criteria; and the use of adjunctive pharmacological therapies, such as hypothermia and neuroprotection.

ACCESS TO ACUTE STROKE INTERVENTION FOR LVOs IN THE UNITED STATES

There are not yet any focused epidemiological studies of LVO ischemic stroke qualifying for mechanical thrombectomy. However, in 2012, Zaidat et al. (54) estimated that 4% to 14% of the total of 675,000 ischemic strokes in the United States could have LVO, yielding a range of 27,000 to 97,000 patients annually for whom mechanical thrombectomy would be indicated. Their estimate was derived by averaging the numbers of LVOs from previous studies of stroke subtypes in the population, endovascular stroke clinical trial recruitment numbers, and local and regional registries. Of note, in their analysis, if only the proportion of LVO from population and epidemiology studies were used for this estimate, LVOs would be approximately 9% to 27% of the total, yielding numbers as high as 60,750 to 182,250 total LVO patients per year in the United States.

Access to acute stroke intervention for LVO patients in the United States has been evolving in the last decade. A study estimated, using 2011 data, that 56% of the U.S. population had access within 60 min by ground to endovascular stroke treatment-capable hospitals (55). Comprehensive stroke centers (CSCs) are certified stroke centers that have the resources and meet criteria for achieving good outcomes with endovascular treatment of stroke (56). Recent modeling data, with an assumption of addition of 20 optimally located CSCs per state, estimate that 63% of the U.S. population would have 60-min ground access and 83% would have 60-min ground/air access to a CSC (57). Thus, AHA guidelines
recommend the current tiered system of acute stroke care with acute stroke-ready hospitals, primary stroke centers, and CSCs to ensure starting IV-rtPA with the least possible delay after symptom onset, and rapid transfer to CSCs for mechanical thrombectomy for LVO patients (7). In terms of the available workforce for MT, using the mean estimate of the number of LVO cases provided previously, and 1,000 fellowship-trained neurointerventionalists, there would be a wide range from 27 to 97 MT cases/year per practitioner (54). Thus, it is clear that workforce demand-supply for MT is in a rapid state of evolution and more data are needed for accurate determinations.

CONCLUSIONS

Recent endovascular acute stroke trials have compellingly demonstrated the superiority of combined treatment with MT (with stent retriever) and IV-rtPA over medical therapy alone for patients with LVO who present within 6 h. This is a revolutionary advance in our ability to combat the massive disability that results from stroke. The Central Illustration outlines the overall approach to implementing this new standard of care in clinical practice. The challenge now is to increase access to MT for acute stroke patients in the shortest time possible by building up the stroke systems of care in the United States and worldwide.

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**KEY WORDS** Large vessel occlusion, mechanical thrombectomy, stent retrievers, stroke systems