Review

Acute Stroke Intervention
A Systematic Review

Shyam Prabhakaran, MD, MS; Ilana Ruff, MD; Richard A. Bernstein, MD, PhD

IMPORTANCE Acute ischemic stroke is a major cause of mortality and morbidity in the United States. We review the latest data and evidence supporting catheter-directed treatment for proximal artery occlusion as an adjunct to intravenous thrombolysis in patients with acute stroke.

OBJECTIVE To review the pathophysiology of acute brain ischemia and infarction and the evidence supporting various stroke reperfusion treatments.

EVIDENCE REVIEW Systematic literature search of MEDLINE databases published between January 1, 1990, and February 11, 2015, was performed to identify studies addressing the role of thrombolysis and mechanical thrombectomy in acute stroke management. Studies included randomized clinical trials, observational studies, guideline statements, and review articles. Sixty-eight articles (N = 108 082 patients) were selected for review.

FINDINGS Intravenous thrombolysis is the mainstay of acute ischemic stroke management for any patient with disabling deficits presenting within 4.5 hours from symptom onset. Randomized trials have demonstrated that more patients return to having good function (defined by being independent and having slight disability or less) when treated within 4.5 hours after symptom onset with intravenous recombinant tissue plasminogen activator (IV rtPA) therapy. Mechanical thrombectomy in select patients with acute ischemic stroke and proximal artery occlusions has demonstrated substantial rates of partial or complete arterial recanalization and improved outcomes compared with IV rtPA or best medical treatment alone in multiple randomized clinical trials. Regardless of mode of reperfusion, earlier reperfusion is associated with better clinical outcomes.

CONCLUSIONS AND RELEVANCE Intravenous rtPA remains the standard of care for patients with moderate to severe neurological deficits who present within 4.5 hours of symptom onset. Outcomes for some patients with acute ischemic stroke and moderate to severe neurological deficits due to proximal artery occlusion are improved with endovascular reperfusion therapy. Efforts to hasten reperfusion therapy, regardless of the mode, should be undertaken within organized stroke systems of care.

JAMA. 2015;313(14):1451-1462. doi:10.1001/jama.2015.3058

Supplemental content at jama.com

Author Affiliations: Department of Neurology, Northwestern University Feinberg School of Medicine, Chicago, Illinois.

Corresponding Author: Shyam Prabhakaran, MD, MS, Department of Neurology, Northwestern University, 710 N Lake Shore Dr, Ste 1422, Chicago, IL 60611 (shyam.prabhakaran@northwestern.edu).

Section Editor: Mary McGrae McDermott, MD, Senior Editor.

Stroke is a leading cause of disability in the United States and the fifth leading cause of death.[1] An acute ischemic stroke (AIS) occurs when an artery supplying the brain becomes occluded, leading to the death of brain tissue and focal neurological deficits. An estimated 700 000 ischemic strokes occur in the United States each year, costing more than $70 billion to society.[1] The toll exerted on individual patients and families by a devastating stroke is incalculable; most elderly patients fear a disabling stroke more than they fear death.[2] Thus, improving neurological outcome after an ischemic stroke is a major societal priority and has attracted intense attention of clinical and basic researchers, government funding agencies, and industry. Consistent with animal models of ischemia, the overarching goal of AIS therapy is relieving the arterial occlusion (recanalization) and restoring cerebral blood flow (reperfusion) as soon as possible to reduce tissue injury and improve outcomes.

There is general consensus based on strong evidence that in patients presenting within 4.5 hours of symptom onset, intravenous recombinant tissue plasminogen activator (IV rtPA) therapy is beneficial. However, many patients present with occlusion of a large proximal artery beyond 4.5 hours or have contraindications to systemic thrombolysis (ie, recent major surgery or active bleeding). For these reasons and because proximal artery occlusions are relatively resistant to intravenous thrombolysis, catheter-based or intra-arterial approaches to directly remove the clot and restore blood flow to the brain have been the focus of recent randomized clinical trials. We review acute stroke treatment with an emphasis on intra-

arterial treatments that have recently been shown to improve outcomes for the most severe of patients with AIS.

Search Methods and Results

Systematic literature search of MEDLINE databases published between January 1, 1990, and February 11, 2015, was performed to identify studies addressing the role of thrombolysis and mechanical thrombectomy in acute stroke management. We searched Medical Subject Headings (MeSH) terms in multiple combinations including *brain ischemia/drug therapy*, *stroke drug/therapy*, *tissue plasminogen activator*, *fibrinolytic agents*, *endovascular procedures*, *thrombectomy*, *time factors*, *emergency service*, *treatment outcome*, *multicenter study*, and *randomized controlled trial*. Studies reporting outcomes from acute thrombolysis and mechanical thrombectomy were included for review. The search was limited to human studies without language restrictions applied. This search was supplemented by reviewing additional references from included studies. Sixty-eight articles (N = 108 082 patients) were selected for review (eFigure in the Supplement).

Background

The central pathophysiological hypothesis underlying AIS therapy is that after a cerebral artery becomes occluded, there is some amount of hypoperfused brain tissue at risk for permanent infarction that could be salvaged by expeditious restoration of blood flow (**Box 1**). Preventing this tissue-at-risk, known as the ischemic penumbra, from progressing to irreversible infarction is the goal of acute reperfusion therapy (**Figure 1**). In contrast, the ischemic core defines brain tissue that has already experienced irreversible damage and, therefore, cannot be salvaged by reperfusion. The ischemic penumbra model predicts that earlier reperfusion leads to better outcomes in patients with AIS. Over the first few minutes to hours after an acute arterial occlusion, ischemic penumbral tissue progresses to an infarct core, and the potential benefit of restoring blood flow reduces over time. It is estimated that for every minute an artery is occluded during an ischemic stroke, 2 million neurons die, which over 10 hours is equivalent to the expected neuronal loss occurring with 26 years of normal aging.[3]

Although it is not controversial that an ischemic penumbra exists or that all penumbral tissue, by definition, in the absence of timely reperfusion, is destined for irreversible infarction, distinguishing true penumbra from core infarct has been challenging. Another major challenge is distinguishing true penumbra from regions of the brain that are hypoperfused but not at risk for infarction (benign oligemia).[4] Indeed, recent trials have produced mixed results when applying this concept of imaging-based selection for reperfusion therapies in part due to inaccurate determination of true penumbra and core infarct volumes.

Acute Reperfusion Therapy

Strategies to rapidly reperfuse brain tissue at risk of infarction include intravenous and intra-arterial administration of thrombolytic drugs and the use of various thrombectomy devices under angiographic and fluoroscopic guidance.[5-9]

Intravenous Thrombolysis

In the 1990s, the National Institute of Neurological Disorders and Stroke (NINDS) sponsored 2 randomized clinical trials[10] of IV rtPA vs placebo, which evaluated 624 patients presenting with ischemic stroke symptoms within 3 hours of symptom onset. Patients receiving IV rtPA compared with placebo had an absolute 16% increase in favorable outcome (modified Rankin Scale [mRS] 0-1) at 3 months (42.6% for IV rtPA vs 26.6% for placebo, $P < .01$; number needed to treat to benefit [NNTB], 6) (**Table 1**). Although there was an increased risk for symptomatic brain hemorrhage from IV rtPA (6.4% for IV rtPA vs 0.6% for placebo, $P < .001$), the benefits of this treatment outweighed this risk. Consequently, the US Food and Drug Administration (FDA) approved IV rtPA for treatment for patients with acute stroke who present within 3 hours of symptom onset. A subsequent European randomized clinical trial of 821 patients with moderate severity ischemic stroke symptoms who were younger than 80 years and presenting within 3 to 4.5 hours of symptom onset also showed the benefits of IV rtPA, but the effect size was lower (mRS 0-1: 52.4% for IV rtPA vs 45.2% for placebo, $P = .04$; NNTB, 14).[11]

Analyzed in this dichotomous manner for no or minimal disability, the results of the NINDS and European Cooperative Acute Stroke Study III (ECASS-3) trials are compelling; however, when analyzed for a shift toward improved outcomes across the full range of disability (ie, ordinal shift in the mRS), IV rtPA is even more strongly associated with benefit (NNTB: 3 in the 0-3-hour window; 7 in the 3-4.5-hour window).[12,13] These trials and further confirmatory

Box 1. Common Terminology in Acute Ischemic Stroke Management

Acute ischemic stroke (AIS): occlusion of the brain, retina, or spinal cord supplying artery that results in focal tissue infarction and corresponding sudden neurological deficits

Ischemic core: the area of irreversible severe ischemia with loss of oxygen and glucose supply and resultant depletion of energy stores, cellular necrosis, and cavitation

Ischemic penumbra: the area surrounding the ischemic core, characterized by moderate ischemia and cellular dysfunction but not cell death, which is potentially reversible with prompt reperfusion

Modified Rankin Scale (mRS): a scale used to measure disability after stroke with ordinal scores from 0 to 6 with 0 indicating no symptoms or disability; 1, symptoms but no disability; 2, slight disability but requires no assistance; 3, moderate disability, requiring some assistance with activities of daily living but able to walk independently; 4, moderately severe disability and unable to walk or care for bodily needs without assistance; 5, severe disability, bedridden, and requiring constant care; and 6, dead

National Institutes of Health Stroke Scale (NIHSS): a quantitative measure of neurological dysfunction or deficit after stroke across multiple domains including motor, sensory, visual, and language functions and ranging from 0 to 42 with a higher score indicating more severe neurological deficit

Coil retrievers: thrombectomy devices that engage from distally to proximally; wraps around the clot and is pulled back through the guide catheter to remove the occluding thrombus

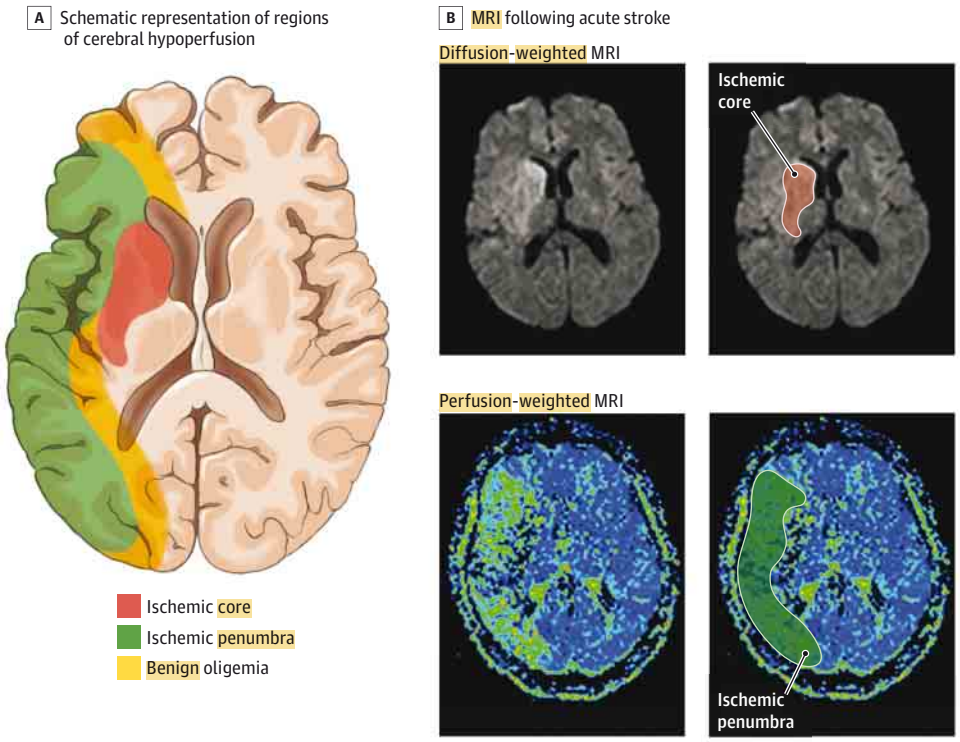
Aspiration devices: thrombectomy systems that use proximal suction to remove the occluding thrombus through the guide catheter

Stent retrievers: thrombectomy devices that allow for immediate restoration of blood flow by stent expansion at the site of occlusion followed by entrapment of the thrombus between the stent and the vessel wall and thrombus extraction when the stent is removed through the guide catheter

studies[14-16] have established IV rtPA as a standard therapy for patients with AIS within 3 hours from symptom onset. Although not approved by the FDA for use in the 3- to 4.5-hour window, IV rtPA is recommended for patients with moderately severe symptoms younger than 80 years and without contraindications in some guidelines for stroke management (**Box 2**).[17]

A meta-analysis of IV rtPA trials inclusive of 2775 patients confirmed the time dependency of thrombolytic therapy with the fol-

Figure 1. Regions of Cerebral Hypoperfusion Following Acute Ischemic Stroke



MRI indicates magnetic resonance imaging. A, Schematic representation of regions of hypoperfused brain tissue following acute occlusion of the middle cerebral artery. The ischemic core is an area of irreversible ischemia and cell death; ischemic penumbra, potentially salvageable tissue with prompt reperfusion; benign oligemia, decreased perfusion but no infarction risk regardless of treatment. The infarct core can enlarge into the penumbra if reperfusion is not successful. B, Top, Axial diffusion-weighted MRI (DWI) showing a hyperintensity consistent with irreversible ischemia (ischemic core) in the deep perforating territory of the right middle cerebral artery affecting the caudate, internal capsule, and lentiform nucleus. Bottom, Axial perfusion-weighted MRI (PWI) at the same level as the DWI showed a much larger area of hypoperfusion. Perfusion-weighted imaging uses contrast material to estimate cerebral blood flow. The color scale represents mean transit time of a contrast bolus; blue indicates normal transit time and shades of green, yellow, orange, and red indicate delay in transit time (ischemia). The region of the ischemic core as defined in the DWI shows areas of no contrast (black) in the PWI, indicative of irreversible injury. The area with abnormal transit time surrounding the core is considered the ischemic penumbra. These images are from a 49-year-old patient who presented with sudden onset of dysarthria and left hemiparesis. The MRI images were obtained following intravenous recombinant tissue plasminogen activator administered approximately 50 minutes after symptom onset to assess eligibility for mechanical thrombectomy.

Table 1. Summary of the NINDS and ECASS-3 Trials

	No. (%)		
	IV rtPA	Placebo	*P* Value
NINDS, 1995[10]			
No. enrolled	312	312	
Median baseline NIHSS score[a]	14	15	
Favorable 90-d outcome, mRS 0-1	133 (42.6)	83 (26.6)	<.01
Symptomatic intracranial hemorrhage[b]	20 (6.4)	2 (0.6)	<.01
ECASS-3, 2008[11]			
No. enrolled	418	403	
Median baseline NIHSS score[a]	9	10	
Favorable 90-d outcome, mRS 0-1	219 (52.4)	182 (45.2)	.04
Symptomatic intracranial hemorrhage[b]	33 (7.9)	14 (3.5)	<.01

Abbreviations: IV rtPA, intravenous recombinant tissue plasminogen activator; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale.

[a] The NIHSS is a quantitative measure of neurological dysfunction after stroke and ranges from 0 to 42 with a higher score indicating more severe neurological deficit.

[b] National Institute of Neurological Disorders and Stroke definition.

Box 2. Common Signs of Acute Stroke and Tests Used in Ischemic Stroke Diagnostic Evaluation

Examination Findings Suggestive of Acute Stroke

Aphasia

Hemiparesis

Hemisensory loss

Hemineglect

Visual field deficit

Gaze deviation and eye movement abnormalities

Dysarthria

Gait instability and incoordination

Diagnostic Tests to Establish Diagnosis and Cause of Acute Stroke

Magnetic resonance imaging or computed tomography of the brain to evaluate for ischemia and exclude hemorrhage

Computed tomography or magnetic resonance angiogram to evaluate for intracranial or extracranial stenosis or occlusion

Echocardiogram to evaluate for cardioembolic source (ie, thrombus)

Telemetry and extended outpatient cardiac monitoring to evaluate for arrhythmias (ie, atrial fibrillation)

Lipid panel to evaluate for hyperlipidemia

Hemoglobin A_{1c} to evaluate for diabetes mellitus

In select patients, consider inflammatory markers, hypercoagulable workup, ultrasound of the lower extremities, lumbar puncture, and blood cultures

lowing adjusted odds ratios (ORs) of good outcome by treatment time window: 2.55 (95% CI, 1.44-4.52) for 0 to 90 minutes, 1.64 (95% CI, 1.12-2.40) for 91 to 180 minutes, and 1.34 (95% CI, 1.06-1.68) for 181 to 270 minutes. There was no net benefit for patients receiving IV rtPA beyond 4.5 hours. It also confirmed a similar risk of symptomatic brain hemorrhage to that seen in the NINDS IV rtPA trial (5.2% for IV rtPA vs 1.0% for control; OR, 5.37 [95% CI, 3.2-9.0]).[18]

Outcomes are better in patients treated with IV rtPA than placebo treatment for all stroke subtypes and across the range of moderate to severe stroke severity.[10,19,20] However, after IV rtPA alone, only 10% to 15% of internal carotid artery occlusions and 25% to 50% of proximal middle cerebral artery occlusions recanalize and only 35% to 40% of patients achieve good outcomes (ie, functional independence).[21,22] These data suggest that proximal artery occlusions (ie, middle cerebral artery and internal carotid artery) may be relatively resistant to IV rtPA alone.[22-24] Because proximal artery occlusions account for one-third of AIS, typically result in more severe strokes, and are associated with poor outcomes without effective reperfusion,[23,25,26] efforts to improve recanalization rates beyond what is possible with IV rtPA alone, either with alternate or adjunctive methods, have been the focus of several large randomized clinical trials.

Intra-arterial Therapy

Although catheter-based treatment of large, proximal clots should improve outcomes, early trials using first-generation approaches failed to show clinical benefit despite successful recanalization rates (**Table 2**).

Chemical Thrombolysis

The Prolyse in Acute Cerebral Thromboembolism (PROACT) II trial[25] assessed the efficacy of intra-arterial recombinant prourokinase (r-proUK) with heparin (2000-U bolus and 500-U/h for 4 hours) compared with heparin alone for 180 patients presenting within 6 hours after symptom onset and with angiographically confirmed middle cerebral artery occlusions. No mechanical clot disruption was permitted in this trial, which makes the results difficult to interpret in the modern era. This study met the primary end point of functional independence (mRS 0-2) at 90 days (39.7% for r-proUK vs 25.4% for control; OR, 2.13 [95% CI, 1.02-4.42], $P = .04$; NNTB, 7). There was, however, a higher risk of symptomatic brain hemorrhage in the r-proUK group (10.2% for r-proUK vs 1.9% for control, $P = .06$). Because the benefits of r-proUK were marginal and offset partially by increased risk of harm, r-proUK was not approved by the FDA for intra-arterial thrombolysis in patients with AIS. Notably, a subsequent secondary analysis from an analogous Japanese study using urokinase in comparison with best medical care (control) later supported the findings of the PROACT II trial (mRS 0-1: 42.1% for urokinase vs 22.8% for control, $P = .045$; symptomatic brain hemorrhage: 8.8% for urokinase vs 1.8% for control, $P = .21$).[27]

Mechanical Thrombectomy

Endovascular treatment for AIS has continued to evolve with the introduction of catheter-based mechanical thrombectomy devices. The FDA has approved several mechanical thrombectomy devices to treat AIS based on technical efficacy and safety reported from large multicenter case registries. These devices can successfully recanalize proximal arterial occlusions with acceptable complication rates; in these studies, 7% to 19% of patients experienced device- and procedure-related complications such as device fracture, vessel perforation and hemorrhage, and nontarget artery embolization (**Figure 2**).[5-9]

Mechanical thrombectomy devices are introduced into the femoral artery via guide catheters and advanced to the affected artery using angiographic guidance. A microcatheter and guidewire are then inserted into the intracranial vessels beyond the guide catheter and thrombectomy is performed with proximal balloon occlusion to prevent distal embolization during the procedure. The approved devices have differing mechanisms of action: (1) a coil retriever device that engages and wraps around the clot and then is pulled back to the catheter to remove the thrombus; (2) an aspiration device that uses proximal suction to remove thrombus; and (3) stent retrievers that allow for immediate restoration of blood flow by stent expansion at the site of occlusion followed by entrapment of the thrombus between the stent and the vessel wall and thrombus extraction when the stent is removed (Figure 2).

Earlier Generation Devices

The coil retriever and aspiration devices were FDA-approved based on single-group studies showing improved revascularization for a variety of proximal artery occlusions compared with the historical control group from PROACT II.[5,8,9] However, clinical efficacy (ie, improving patient functional outcomes) was not proven because the devices were not compared directly with other treatments or to a placebo group.

Since then, two phase 3 randomized clinical trials evaluated the efficacy of earlier generation endovascular therapies (ie, coil retriever and aspiration devices and intra-arterial thrombolytics) in patients

Table 2. Summary of Device Studies and Randomized Clinical Trials of Endovascular Therapy in Acute Ischemic Stroke

	Device Studies Without a Control Group				RCTs of IA Thrombolysis With Control Group (IV rtPA Alone or No Treatment)			RCTs of Mechanical Thrombectomy vs Standard Medical Treatment Alone (IV rtPA When Noted)					
	MERCI, 2005[9]	Penumbra Pivotal Stroke Trial, 2009[5]	TREVO2, 2012[6]	SWIFT, 2012[7]	PROACT II, 1999[25,a]	MELT, 2007[27,a]	SYNTHESIS EXP, 2013[28,b]	IMS III, 2013[22]	MR RESCUE, 2013[29]	MR CLEAN, 2014[30]	ESCAPE, 2015[31]	EXTEND-IA, 2015[32]	SWIFT PRIME, 2015[33]
No. of centers (sites by country)	25 (US)	24 (20US)	27 (26US)	18 (17US)	54 (US and Canada)	57 (Japan)	24 (Italy)	58 (41US)	22 (21US)	16 (the Netherlands)	22 (11 Canada, 6 US, 3 Korea, 1 UK, and 1 Ireland)	14 (Australia and New Zealand)	39 (24 US and 15 Europe)
No. analyzed	141	125	Trevo, 88 Merci, 90	SOLITAIRE, 58 Merci, 55	IA, 121 control, 59[c]	IA, 57 control, 57[d]	IA ± EV, 181 IV rtPA, 181	EV + IVT, 434 IV rtPA, 222	EV ± IV rtPA, 64 control, 54[e]	EV ± IV rtPA, 233 control, 267[f]	EV ± IV rtPA, 165 control, 150[g]	EV + IV rtPA, 35 IV rtPA, 35	EV + IV rtPA, 98 IV rtPA, 97
Median baseline NIHSS score[h]	19	17	Trevo, 19 Merci, 18	SOLITAIRE, 18 Merci, 18	IA, 17 control, 17	IA, 14 control, 14	IA ± EV, 13 IV rtPA, 13	EV + IV rtPA, 17 IV rtPA, 16	EV ± IV rtPA, 17 control, 17	EV ± IV rtPA, 17 control, 18	EV ± IV rtPA, 16 control, 17	EV + IV rtPA, 17 IV rtPA, 13	EV + IV rtPA, 17 IV rtPA, 17
Time from onset to initiation of IA treatment, h[i]	4.3	4.3	Trevo, 4.1 Merci, 4.5	SOLITAIRE, 4.9 Merci, 5.3	IA, 4.7 control, 5.1	IA, 3.3 control, 3.4	NR	EV + IV rtPA, 3.5	EV ± IV rtPA, 6.4	EV ± IV rtPA, 4.3	EV ± IV rtPA, 3.1	EV + IV rtPA, 3.5	EV + IV rtPA, 3.1
Time from onset to reperfusion, h	NR	NR	NR	NR	IA, 5.3	NR	IA ± EV, 3.8	EV + IV rtPA, 5.4	NR	EV ± IV rtPA, 5.5	EV ± IV rtPA, 4.0	EV + IV rtPA, 4.1	EV + IV rtPA, 4.2
Final reperfusion grade (TICI grade 2 or 3), No. (%)[j]	68 (48.2)	102 (81.6)	Trevo, 76 (86.4) Merci, 54 (60.0)	SOLITAIRE, 37 (63.8) Merci, 16 (29.1)	IA, 71/108 (65.7) control, 9/50 (18.0)	IA, 42 (73.7) control, NR	NR	EV + IV rtPA, 243/324 (75.0)	EV ± IV rtPA, 28/64 (43.8)	EV ± IV rtPA, 156/196 (79.6)	EV ± IV rtPA, 147/156 (94.3)	EV + IV rtPA, 27/29 (93.1)	EV + IV rtPA, 78/83 (94.0)
P value			<.01	<.01	<.01								
Favorable 90-d outcome (mRS 0-2), No. (%)[k]	39 (27.7)	31 (24.8)	Trevo, 34/85 (40.0) Merci, 19/87 (21.8)	SOLITAIRE, 20/55 (36.4) Merci, 14/48 (29.2)	IA, 48 (39.7) control, 15 (25.4)	IA, 28 (49.1) control, 22 (38.6)	IA ± EV, 137 (75.7) IV rtPA, 152 (84.0)	EV + IVT, 177 (40.8) IV rtPA, 86 (38.7)	EV ± IV rtPA, 12 (18.8) control, 11 (20.4)	EV ± IV rtPA, 76 (32.6) control, 51 (19.1)	EV ± IV rtPA, 87 (53.0) control, 43 (29.3)	EV + IV rtPA, 25 (71.4) IV rtPA, 14 (40.0)	EV + IV rtPA, 59 (60.2) IV rtPA, 33 (35.3)
P value			.01	.53	.04	.35	.07	.70	>.99	<.01	<.01	<.01	<.01
Symptomatic intracranial hemorrhage, No. (%)	11 (7.8)	14 (11.2)	Trevo, 6 (6.8) Merci, 8 (8.9)	SOLITAIRE, 1 (1.7) Merci, 6 (10.9)	IA, 11/108 (10.2) control, 1/54 (1.9)	IA, 5 (8.8) control, 1 (1.8)	IA ± EV, 10 (5.5) IV rtPA, 10 (5.5)	EV + IV, 27 (6.2) IV rtPA, 13 (5.9)	EV ± IV rtPA, 3 (4.7) control, 2 (3.7)	EV ± IV rtPA, 18 (7.7) control, 17 (6.4)	EV ± IV rtPA, 6 (3.6) control, 4 (2.7)	EV + IV rtPA, 2 (5.7) IV rtPA, 0	EV + IV rtPA, 1 (1.0) IV rtPA, 4 (4.1)
P value			.78	.06	.06	.21	.99	.83	>.99	.55	.75	.31	.21

Abbreviations: EV, endovascular device; IA, intra-arterial thrombolytic drug; IV rtPA, intravenous recombinant tissue plasminogen activator; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; NR, not reported; RCT, randomized clinical trial; TICI, thrombolysis in cerebral infarction.

[a] Included middle cerebral artery occlusions only.

[b] Included less severe stroke patients and therefore higher proportions of patients achieved functional independence.

[c] Standard of care: intravenous heparin.

[d] Standard of care: best medical care.

[e] Standard of care: IV rtPA alone (30%) or no thrombolysis (70%).

[f] Standard of care: IV rtPA alone (91%) or no thrombolysis (9%).

[g] Standard of care: IV rtPA alone (78%) or no thrombolysis (22%).

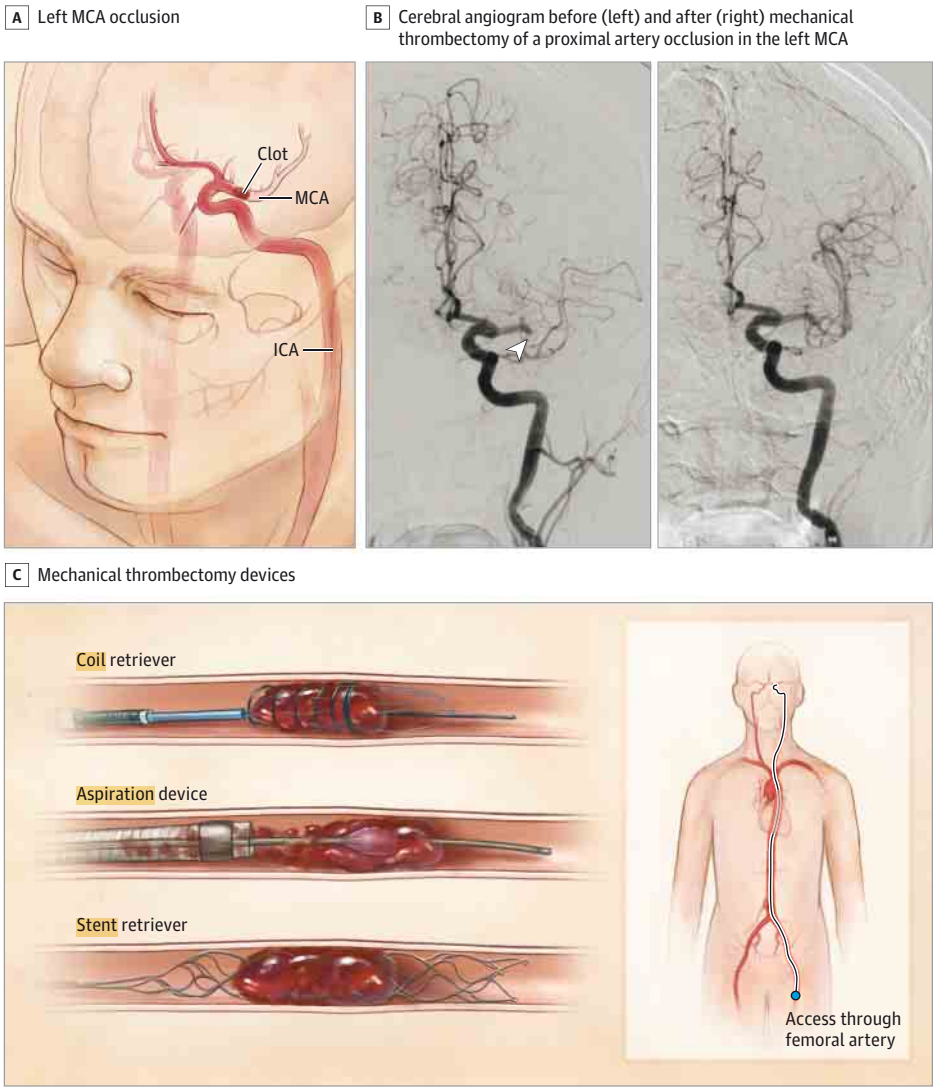
[h] The NIHSS is a quantitative measure of neurological dysfunction after stroke and ranges from 0 to 42 with a higher score indicating more severe neurological deficit.

[i] Time to groin puncture only reported for MERCI, Penumbra Pivotal Stroke Trial, TREVO2, and SWIFT trials; time to randomization only reported for MELT.

[j] The TICI score is used to describe reperfusion of the distal vessels after mechanical thrombectomy. It ranges from 0 to 3 with 3 representing complete reperfusion. We report percentage TICI 2 or 3, though later trials report 2b to 3 substantial reperfusion (>50%).

[k] The mRS is a scale used to measure disability after stroke; it ranges from 0 to 6 with 0 being alive with no disability and 6 being death.

Figure 2. Endovascular Treatment of Acute Ischemic Stroke



ICA indicates internal carotid artery, MCA, middle cerebral artery. A, Illustration of a proximal artery occlusion in the left MCA. B, Anterior-posterior fluoroscopic cerebral angiography showing interrupted blood flow distal to a left MCA occlusion and subsequent reperfusion following mechanical thrombectomy using a stent retriever device. The angiogram images are from a 40-year-old patient who presented with acute right hemiparesis and expressive aphasia. The patient received intravenous recombinant tissue plasminogen activator 1 hour and 15 minutes after symptom onset without clinical improvement. Mechanical thrombectomy following angiographic confirmation of the MCA occlusion was performed approximately 3 hours after symptom onset. C, Types of mechanical thrombectomy devices. Vascular access to the cerebral vasculature is generally via the femoral artery.

with AIS. The Interventional Management of Stroke (IMS) III trial compared standard-dose IV rtPA with a combination of low-dose IV rtPA and intra-arterial rtPA or mechanical thrombectomy (79% of the study patients received intra-arterial rtPA; 45% had clot removal with coil retriever and aspiration devices; and only in 1% were stent retrievers used).[22] Patients were enrolled after baseline neuroimaging excluded intracranial hemorrhage. No preprocedure vascular imaging selection was performed in 46.6% of patients, which led to the inclusion of 89 patients (21%) without proximal artery occlusion in the intra-arterial treatment group for intention-to-treat analysis. After enrolling 656 patients over 6 years, the trial was stopped for futility. There was no significant difference in long-term functional outcome between groups: (mRS 0-2 at 90 days between the groups: 40.8% for combined therapy vs 38.7% for IV rtPA; absolute difference, 1.5% [95% CI, −6.1% to 9.1%]) and no significant difference in mortality (19.1% for combined therapy vs 21.6% for IV rtPA, $P = .52$) or symptomatic brain hemorrhage (6.2% for combined therapy vs 5.9% for IV rtPA, $P = .83$).[22]

Based on a successful pilot trial comparing intra-arterial therapy with intravenous thrombolysis,[34] the Intra-arterial vs Systemic Thrombolysis for Acute Ischemic Stroke (SYNTHESIS EXP) study randomized patients with ischemic stroke into 2 groups of 181 patients each: 1 group received standard IV rtPA and the other received mechanical thrombectomy or intra-arterial therapy within 4.5 hours of symptom onset. Of the patients undergoing intra-arterial therapy, most were treated with rtPA infusion and microguidewire thrombus fragmentation (60%), 31% were treated with thrombectomy devices, and 13% were treated with stent retrievers. No benefit of endovascular therapy was observed in this trial as no difference in primary outcome, alive without disability at 90 days, was found (30.4% for endovascular vs 34.8% for IV rtPA, $P = .37$; OR, 0.82 [95% CI, 0.53-1.27]). No safety differences were noted between the 2 groups (symptomatic intracranial hemorrhage, 5.5% for endovascular vs 5.5% for IV rtPA, $P = .99$; mortality, 7.7% for endovascular vs 6.1% for IV rtPA, $P = .53$).[28]

Stent Retrievers

Two studies directly compared the newer stent retriever devices with the earlier coil retriever devices and observed improved recanalization, reduced mortality, and better functional outcomes with the stent retriever devices.[6,7] These studies established that stent retrievers are superior to coil retrievers. Though these trials included some patients who had received IV rtPA therapy initially in both treatment groups, there was no direct comparison with a control group that received IV rtPA alone or no acute reperfusion treatment at all.

Recently, 4 randomized clinical trials of stent retrievers against medical treatment have established the benefits of endovascular treatment in patients with proximal artery occlusions.[30-33] The Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke (MR CLEAN)[30] phase 3 randomized clinical trial provided the first evidence that mechanical thrombectomy within 6 hours of symptom onset improved 90-day clinical outcomes compared with standard medical treatment, in which 90.6% received IV rtPA within 4.5 hours. Acute stroke patients with confirmed proximal artery occlusions and treated at 1 of 16 stroke centers in Holland were randomized to standard medical management alone (n = 267) or standard medical management followed by intra-arterial (predominantly stent retriever) treatment (n = 233). Functional results were better for patients who underwent intra-arterial treatment (mRS 0-2: 32.6% for intra-arterial treatment vs 19.1% in IV rtPA; $P < .01$; NNTB, 8). Although there were no hemorrhagic safety concerns in MR CLEAN (symptomatic intracranial hemorrhage, 7.7% for intra-arterial treatment vs 6.4% for IV rtPA; 30-day mortality, 18.4% for intra-arterial treatment vs 18.9% for IV rtPA) , endovascular treatment increased the risk of new ischemic stroke within 90 days (5.6% for intra-arterial treatment vs 0.4% for IV rtPA, $P < .001$) presumably due to procedure-related embolization into other unaffected cerebral vasculature (noted in 8.6% of treated patients).

In the Endovascular Treatment for Small Core and Proximal Occlusion Ischemic Stroke (ESCAPE) trial,[31] 316 patients presenting within 12 hours from symptom onset at 22 global sites and in whom proximal artery occlusions were identified using computed tomography (CT) angiography were randomized to best medical therapy alone (78% IV rtPA in the control group) or with adjunctive intra-arterial treatment (of which 86% were stent retrievers). The trial was stopped early due to efficacy of endovascular therapy (mRS 0-2: 53.0% for intra-arterial treatment vs 29.3% for control, $P < .01$; NNTB, 4). Of note, improved workflow and enhanced patient selection using rapid-acquisition CT imaging was emphasized throughout with median time from symptom onset to reperfusion of 241 minutes such that only 15.5% of patients were treated beyond 6 hours.

A third recently published study, the Australian Extending the Time for Thrombolysis in Emergency Neurological Deficits—Intra-Arterial (EXTEND-IA) trial,[32] used CT perfusion imaging, analogous to the Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy (MR RESCUE) trial, to randomize patients with favorable mismatch patterns to IV rtPA alone vs IV rtPA plus stent retriever mechanical thrombectomy within 4.5 hours of symptom onset. Following MR CLEAN, this trial too was stopped early for technical efficacy in favor of endovascular treatment after enrolling just 35 patients in each group, and also found benefit on the lead secondary clinical efficacy outcome (mRS 0-2: 71.4% for IV rtPA plus stent retriever vs 40.0% for IV rtPA; $P < .01$; NNTB, 3).

A fourth trial, SOLITAIRE with Intention for Thrombectomy as Primary Endovascular Treatment (SWIFT PRIME),[33] also stopped early after enrolling 196 patients due to efficacy of endovascular treatment. This study found that in rtPA-treated patients able to undergo catheter intervention within 6 hours with anterior circulation occlusion, thrombectomy was superior to IV rtPA alone (mRS 0-2: 60.2% for intra-arterial treatment vs 35.5% for IV rtPA, $P < .01$; NNTB, 4).

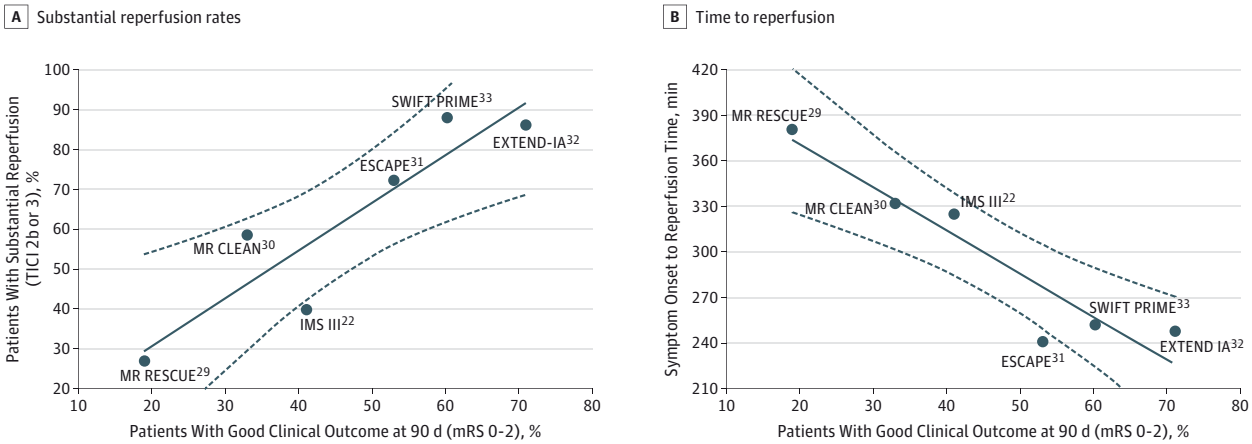
Imaging-Based Patient Selection

In parallel with advances in device technology, new neuroimaging techniques have been developed to evaluate the location of the arterial occlusion and the extent of the penumbra, collateral blood flow status, and core infarct areas and thereby to improve patient selection for endovascular therapy. In addition to, or instead of, clinical criteria, these tools have been adopted in recent trials to identify patients who will most benefit from acute reperfusion and exclude patients in whom reperfusion would be futile or dangerous.[35-37] However, although CT or magnetic resonance angiography can identify proximal artery occlusions with high accuracy, the ideal imaging modality (CT vs magnetic resonance perfusion) and the optimal marker for penumbra identification (ie, bolus transit times, blood flow, and volume measurements), and the potential for adverse consequences of acquiring such imaging (ie, contrast injury and time delays) remain controversial. Because the penumbra is an area of the brain with reversible ischemia, imaging techniques that provide high-quality information about the penumbra and its extent compared with the irreversibly infracted core should help guide stroke therapy.

The first of several perfusion imaging studies, the Diffusion and Perfusion Imaging Evaluation for Understanding Stroke Evolution Study-2 (DEFUSE-2),[38] was an uncontrolled, prospective cohort study of 99 patients with acute stroke. Patients with a favorable penumbral pattern (defined as penumbra to infarct core ratios >1.8) had better 90-day outcomes with successful reperfusion compared with no reperfusion (mRS 0-2: 56.5% for reperfusion vs 31.3% for no reperfusion, $P = .04$), whereas no benefit was seen in patients without a favorable penumbra pattern (mRS 0-2: 25.0% for reperfusion vs 22.2% for no reperfusion, $P > .99$). In contrast, the MR RESCUE study,[29] a phase 2b, open-label, randomized clinical trial with a blinded outcome of 118 patients with AIS found no benefit of mechanical thrombectomy in patients with favorable penumbral patterns (20.6% for mechanical thrombectomy vs 26.5% for medical management, $P = .78$). These 2 studies differed in that (1) DEFUSE-2 used only magnetic resonance imaging–based selection whereas MR RESCUE included CT perfusion in 20% of analyzed patients, introducing heterogeneity into the analysis of penumbra determination; (2) DEFUSE-2 defined the penumbra to core ratio as greater than 1.8 with a maximum core infarct volume of 70 mL whereas MR RESCUE used a smaller penumbra to core ratio of greater than 1.4 and larger maximum core infarct volume of 90 mL. These methodological differences may have led to greater rates of futile reperfusion in the MR RESCUE study compared with the DEFUSE-2 study. The recent EXTEND-IA trial[32] used a similar algorithm as the MR RESCUE investigators but at earlier time points (<4.5 hours) and was able to confirm the benefit of reperfusion therapy on improving clinical outcomes with similar effect sizes as seen in DEFUSE-2.

Varied approaches for patient selection have been adopted in the recent randomized clinical trials: (1) a pragmatic, simple ap-

Figure 3. Rate of Reperfusion and Time to Reperfusion Compared With Percentage of Good Outcomes in the 6 Trials Comparing Endovascular Treatment to Medical Treatment Alone



mRS indicates modified Rankin Scale; TICI, thrombolysis in cerebral infarction. The dotted lines indicate 95% CIs.

proach of identifying proximal artery occlusions by CT angiography and enrolling based on time window alone as done in MR CLEAN (<6 hours); (2) assessment of early infarct signs (ie, core infarct) using noncontrast head CT and time window as done in some patients in ESCAPE (<12 hours) and some patients in SWIFT PRIME (<6 hours); (3) additional CT angiography assessment of collateral blood supply as done in some patients in ESCAPE; and (4) penumbra imaging using CT or magnetic resonance perfusion imaging along with angiography to confirm the occluded artery within 4.5 hours as done in EXTEND-IA and some patients in SWIFT PRIME. Whether one approach is superior to another is not clear, but all 3 have now been shown in randomized clinical trials to select patients who benefit from adjunctive intra-arterial therapy. The number excluded on the basis of the enhanced selection process should be carefully examined. In the EXTEND-IA study, only 25% of otherwise eligible patients were excluded on the basis of the perfusion-imaging selection criteria. Overall, only 70 of 819 patients (8.5%) treated with IV rtPA and screened for the study were randomized, with absence of large artery occlusion being the most common reason for not qualifying for enrollment.

Further advances in the accurate and reliable measurement of brain ischemia are also needed. As stated in a recent review article regarding perfusion imaging selection, it may be prudent to "improve the science before changing clinical practice."[39] The lack of optimal consensus thresholds of blood flow and volume and validation of these on different scanner types and modalities still hamper its use in clinical practice. Accurate imaging parameters need to be standardized and each method tested against each other. It also remains unknown whether the time that elapses to acquire and analyze this advanced "penumbral" imaging (ie, up to 30 minutes) negates any efficacy advantage conferred by the additional pathophysiological information for optimal endovascular patient selection that the imaging study might provide. As a result, some investigators as in the ESCAPE and MR CLEAN trials have recommended using a simplified approach that assesses degree of early infarct changes on initial head CT and confirmatory CT angiography alone for endovascular triage.[40-42] Unless it is made quick, simple, and accurate, the primacy of time in AIS management may supplant penumbral imaging to a lesser role such as the evaluation of atypical presentations or in delayed treatment windows (ie, >6 hours or stroke upon awakening).

Endovascular Trial Comparisons

The Interventional Management of Stroke III (IMS III), SYNTHESIS EXP, and MR RESCUE trials tested various first-generation strategies for intra-arterial treatment of proximal artery occlusions. Three key factors differentiate the earlier trials from the most recent ones: (1) rates of substantial reperfusion; (2) time to reperfusion; (3) selection based on confirmed proximal arterial occlusion.

First, use of less effective, first-generation thrombectomy devices may have neutralized the potential benefit of endovascular therapy in the earlier trials. In fact, SYNTHESIS EXP used clot fragmentation with intra-arterial rtPA infusion in 60% of treated patients, a practice that is not common in the United States. In contrast, the MR CLEAN, ESCAPE, EXTEND-IA, and SWIFT PRIME trials predominantly used stent retrievers.[30-32] Rates of substantial reperfusion (ie, Thrombolysis In Cerebral Ischemia [TICI] grades 2b or 3) were lower in IMS III (40%) and MR RESCUE (27%) when compared with the stent retriever trials (58%-88%).

Second, time to reperfusion was lower in recent trials compared with earlier efforts. Although times to groin puncture were not significantly different (3.1-3.5 hours) from IMS III, times to reperfusion were lower in ESCAPE (4 hours), EXTEND-IA (4.1 hours), and SWIFT PRIME (4.2 hours) than in IMS III (5.4 hours). Therefore, another advantage of the stent retrievers may be their ability to reduce time from groin puncture to reperfusion. **Figure 3**A shows a scatterplot of substantial reperfusion rates (TICI 2b or 3) vs proportion with good outcomes (mRS 0-2 at 90 days) and Figure 3B shows onset to reperfusion times vs proportion with good outcomes in the 6 completed endovascular trials of mechanical thrombectomy.

Third, unlike IMS III and SYNTHESIS EXP, the MR CLEAN, ESCAPE, EXTEND-IA, and SWIFT PRIME trials required confirmation of proximal artery occlusion on baseline CT angiography for enrollment, leading to a more homogeneous cohort and one more likely

Box 3. Patient Information

JAMA has patient information available for stroke:

1. Torpy JM, Burke AE, Glass RM. Hemorrhagic stroke [JAMA Patient Page]. *JAMA*. 2010;303(22):2312.
2. Pluta RM, Lynm C, Golub RM. Stroke imaging [JAMA Patient Page]. *JAMA*. 2011;306(11):1277.
3. Jin J. Warning signs of a stroke. *JAMA*. 2014;311(16):1704.

to show benefit from endovascular therapy. Several also included more selective imaging-based approaches (see above) that may have reduced the likelihood of futile reperfusion.

Enhanced selection to enrich the trial population in favor of endovascular therapy is a potential criticism of 1 of the 4 trials. In the MR CLEAN trial, although there was an absolute benefit in favor of intra-arterial therapy, patients treated with standard management (90.6% of whom received IV rtPA) fared worse than that observed in prior studies (achieved mRS 0-2: 19.1% for the MR CLEAN trial vs 35%-40% in other studies with IV rtPA alone).[21,22] The prolonged time from IV rtPA to intra-arterial groin puncture (172 minutes) suggests that despite rapid onset to IV rtPA treatment times (median, 86 minutes), these patients may have been more resistant to IV rtPA, as evidenced by having persistent proximal arterial occlusion nearly 3 hours later, and selected on that basis. However, we cannot confirm this hypothesis because the numbers of total screened and excluded patients are not presented in the publication.

Another potential concern is that the halted trials are more prone to exaggerated effects due to reduced sample size.[43,44] Because the 3 most recent trials were terminated early following the publication of MR CLEAN after meeting prespecified stopping rules, one needs to consider their findings with caution with regard to treatment benefit magnitude. Indeed, the largest effect size was noted in the smallest, most selective trial, EXTEND-IA (n = 70; OR, 3.8 [95% CI, 1.4-10.0]), followed next by SWIFT PRIME (n = 196; OR, 2.7 [95% CI, 1.53-4.95]), and then ESCAPE (n = 316; OR, 1.8 [95% CI, 1.4-2.4]). However, this gradient also reflects the intensity of imaging selection in the 3 trials, so it may not be related to early cessation. Because these trials were replicated independently in separate health systems around the globe, it guards against the possibility that the direction of effect in favor of endovascular therapy was by chance alone.[45]

Future Directions

The use of intra-arterial therapy for stroke has remained low (1%-2% of all patients with AIS) and along with 5% to 7% of patients with AIS who are treated with IV rtPA, approximately 10% of patients are afforded reperfusion treatments in the United States.[15,46] Because successful stroke treatment requires rapid intervention, greater emphasis on improving prehospital systems and processes for rapid access and optimizing delivery of reperfusion therapies should be a public health priority. Insufficient community awareness of stroke signs and symptoms result in delayed use of emergency medical services and hospital arrival.[47,48] Educating the public about stroke signs and symptoms and the need for rapid treatment is important (**Box 3**). With the development of organized strokes systems of care, regional policies will also need to consider prehospital criteria for direct transport of stroke patients with high suspicion of proximal artery occlusion to comprehensive stroke centers, instead of primary or nonstroke centers.

Prehospital and hospital initiatives to avoid delays result in demonstrable reductions in stroke onset-to-treatment times.[49-52] Prior to these efforts, the majority of treated patients in the United States did not receive guideline-recommended[17] IV rtPA within 60 minutes of hospital arrival.[53] Implementation of prehospital and emergency department best practices in participating US hospitals in the American Stroke Association's Target: Stroke initiative reduced median door-to-needle times to less than 60 minutes.[54] Internationally, similar efforts have shown even better results with sustainable door-to-needle times averaging 20 to 30 minutes in Helsinki, Finland, and Melbourne, Australia.[50,51] Three key best practices lead to the major improvement: (1) prenotification by ambulances of emergency departments to enhance stroke team preparedness; (2) direct-to-CT imaging from the ambulance bypassing the emergency departments initially; and (3) premixing and delivering rtPA immediately after a CT scan excluded brain hemorrhage. In Berlin, an experiment using ambulances staffed by stroke experts and fitted with CT scanners advanced the concept of "ambulysis" (thrombolysis in the ambulance) prior to hospital arrival with 32% of patients receiving IV rtPA in the first 60 minutes of ischemia with ambulysis compared with 5% with standard hospital-based treatment ($P < .01$).[55,56] Earlier thrombolysis translates into reduced symptomatic intracranial hemorrhage and mortality and better functional outcomes following a stroke.[57]

Though time benchmarks have been recommended for intra-arterial therapy,[58,59] these have been less well-studied compared with IV rtPA process improvement. Several studies have observed that performance of additional imaging studies, use of combined endovascular and intravenous approaches, and interhospital transfer add significant delays to intra-arterial treatment and worsen outcomes.[47,60-63] Indeed, observational studies and the recently completed clinical trials have shown that the odds of good outcome following endovascular therapy decline rapidly with each 30- to 60-minute delay in time to treatment.[61-65] The successful ESCAPE, EXTEND-IA, and SWIFT PRIME trials emphasized workflow efficiency and speed with goals for first CT to groin puncture (picture to puncture) of less than 60 minutes, a practice reinforced by quality improvement initiatives and site performance monitoring visits.

Lastly, the costs associated with these interventions and the infrastructure that supports them need to be balanced against the actual patient benefits in terms of population health. Health systems will need to consider changes in current public education campaigns to emphasize early arrival and use of emergency medical services, prehospital triage and hospital bypass policies to divert patients to stroke centers capable of providing intra-arterial therapy, and streamlined protocols for imaging selection in the emergency department to effectively screen and treat eligible patients.

Evidence-Based Guidelines

Current American Heart Association and American Stroke Association guidelines[17] recommend that IV rtPA be administered to all eligible patients (**Table 3**) as quickly as possible (door-to-needle time should be less than 60 minutes) in the 0- to 3-hour window (Class I, level of evidence [LOE] A), in the 3- to 4.5-hour window (Class I,

Table 3. Eligibility Criteria for Intravenous and Endovascular Reperfusion Therapy in Acute Ischemic Stroke

	IV rtPA eligibility	Intra-arterial thrombolysis eligibility[a]	Mechanical thrombectomy eligibility[b]
Clinical diagnosis	Ischemic stroke causing moderate to severe disabling neurological deficit; NIHSS score <25 for 3- to 4.5-hr window	Major large artery ischemic stroke causing severe disabling neurological deficit; NIHSS score 4-30 except for isolate aphasia or hemianopia	Major large artery ischemic stroke causing severe disabling neurological deficit; NIHSS score 8-30[c]; CTA confirmation of MCA and/or ICA occlusion; small core by NCCT (ASPECTS >6); optional: mismatch by perfusion imaging; good collateral grade
Timing of administration	Known time of onset or last known well 4.5 h before IV rtPA administration	Planned intervention can be performed within 6 h of patient's last known well	Planned intervention can be performed within 8 h of patient's last known well
Age, y	>18 for 0- to 3-hr window; 18-80 for 3- to 4.5-hr window	18-85	18-85[d]
Eligibility for IV rtPA		Ineligible to receive IV rtPA	Ineligibility or failure to respond to IV rtPA
			Prestroke mRS >2; life expectancy >6 mo[e]
Exclusion Criteria			
Head CT findings	Evidence of hemorrhage or other large mass for 0- to 3-hr window; > one-third MCA territory infact for 3- to 4.5-hr window	Evidence of hemorrhage or other large mass or involvement of > one-third MCA territory	Evidence of hemorrhage or other large mass or involvement > one-third MCA territory (>100 mL volume)
History of nontraumatic intracranial hemorrhage	Yes	Yes	Yes
Symptoms suggestive of subarachnoid hemorrhage even with normal head CT	Yes	Yes	Yes
Blood pressure	>185/110 mm Hg or requiring aggressive measures to lower blood pressure to below these limits are needed	>180/100 mm Hg on 3 occasions at least 10 min apart or requiring IV medications	>185/110 mm Hg or requiring aggressive measures to lower blood pressure to below these limits are needed
Arteriovenous malformation, aneurysm, or intracranial neoplasm	Yes	Yes	Yes
Major surgery	Surgery with unacceptable bleeding risk within 14 d	Surgery, trauma with internal injuries, or lumbar puncture within 30 d	Surgery, trauma, or biopsy of parenchymal organ with unacceptable bleeding risk within 30 d
Major head trauma, intracranial/spinal surgery, or prior stroke (symptoms lasting >24 h) within 3 mo	Yes	Yes; history of stroke (symptoms lasting >24 h) within 6 weeks[f]	Yes
Hemorrhagic diathesis	Yes	Yes	Yes; coagulation factor deficiency
Vitamin K antagonist with INR>1.7 (current use of direct thrombin inhibitors or direct factor Xa inhibitors)	Yes for 0- to 3-hr window; any oral anticoagulant use within 24 h is a contraindication regardless of INR for 3- to 4.5-hr window	Yes	Vitamin K antagonist with INR >3
Heparin	Received within 48 h, resulting in abnormally elevated a PTT greater than the upper limit of normal	Heparin with PTT 1.5 over upper limit of normal	Heparin with PTT >2 × upper limit of normal
Platelets/μL	<100 000	<100 000	<30 000[f]
Evidence of major active internal bleeding	Yes	Yes	
Arterial puncture at noncompressible site in previous 7 d	Yes		
Blood glucose, mg/dL	<50; history of prior stroke and diabetes mellitus is an exclusion for 3- to 4.5-hr window	<50, >400	<50, >400
Seizure at the time of symptom onset	Yes	Yes	
Presumed septic embolus, or suspicion of bacterial endocarditis	Yes	Yes	Yes
Severe contrast allergy		Yes	Yes
Excessive tortuosity of the vessel precluding device delivery or >50% stenosis of vessel proximal to target lesion		Yes	Yes

Abbreviations: ASPECTS, Alberta Stroke Program Early Computed Tomography Score; CT, computed tomography; CTA, computed tomography angiography; NIHSS, National Institutes of Health Stroke Scale; ICA, internal carotid artery; INR, international normalized ratio; IV rtPA, intravenous recombinant tissue plasminogen activator; MCA, middle cerebral artery; mRS, modified Rankin Scale; NCCT, noncontrast computed tomography; PTT, partial thromboplastin time.

SI conversion factor: To convert blood glucose to mmol/L, multiply by 0.0555.

[a] Proposed intra-arterial thrombolysis criteria adapted from eligibility criteria for PROACT II study.

[b] Proposed mechanical embolectomy criteria based on SWIFT, MERCI, Penumbra Pivotal Stroke Trial, TREVO2, IMS III, MR CLEAN, ESCAPE, EXEND-IA, and SWIFT PRIME trials.

[c] Difference of NIHSS score ranges for eligibility across the trials: MERCI, higher than 8; TREVO2, 7 to 29; SWIFT, 8 to 30; IMS III, higher than 9 (changed to >8 later in trial); SWIFT PRIME, 8 to 29; MR CLEAN, higher than 2; EXTEND-IA and ESCAPE, no NIHSS criteria used (imaging criteria only).

[d] Difference of age ranges for eligibility across the trials: SWIFT, 22 to 85 years; TREVO2, 18 to 85 years; IMS III, 18 to 82 years; SWIFT PRIME, 18 to 80 years; MR CLEAN, ESCAPE, and EXTEND-IA, older than 18 years (no upper limit).

[e] Life expectancy: MERCI, more than 3 months; TREVO2: more than 6 months.

[f] MR CLEAN: less than 40 000 platelets/μL; severe head trauma less than 4 weeks with intended intra-arterial thrombolysis.

LOE B), and even if considering other adjunctive therapies (Class I, LOE A). Regardless of treatment mode, efforts should be made to reduce and avoid delays to reperfusion therapy as earlier treatment leads to better clinical outcomes (Class I, LOE A).

Current guidelines also recommend intra-arterial thrombolysis with rtPA in carefully selected (Table 3) patients with middle cerebral artery occlusion within 6 hours of symptom onset (Class I, LOE B) based on the Middle Cerebral Artery Embolism Local Fibrinolytic Intervention Trial (MELT) and the Prolyse in Acute Cerebral Thromboembolism II (PROACT II) trial. Although the guidelines published in 2013 recommend stent retrievers over earlier generation coil retrievers (Class I, LOE A), they provide much weaker recommendations for the clinical efficacy of mechanical thrombectomy (Class IIa, LOE B) as they do not include the MR CLEAN, ESCAPE, EXTEND-IA, and SWIFT PRIME trial results published in 2015.

Conclusions

Intravenous rtPA remains the standard of care for patients with moderate to severe neurological deficits who present within 4.5 hours of symptom onset. Outcomes for some patients with acute ischemic stroke and moderate to severe neurological deficits due to proximal artery occlusion are improved with endovascular reperfusion therapy. Efforts to hasten reperfusion therapy, regardless of the mode, should be undertaken within organized stroke systems of care.

Bottom-Line Clinical Messages

- Intravenous rtPA is the standard treatment for patients with acute stroke who are moderately or severely disabled presenting within 4.5 hours of symptom onset.
- Based on multiple randomized clinical trials, intra-arterial therapy using stent retrievers improves recanalization of proximal artery occlusions and clinical outcomes beyond that possible with IV rtPA or supportive care alone.
- Efforts should be made to hasten reperfusion therapy in organized systems of stroke care.
- Public education about the importance of stroke symptom recognition and use of emergency medical services remains paramount.

ARTICLE INFORMATION

Author Contributions: Drs Prabhakaran, Bernstein, and Ruff had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Drs Prabhakaran and Ruff contributed equally to this work as co-first authors.
Study concept and design: All authors.
Acquisition, analysis, or interpretation of data: Prabhakaran, Ruff.
Drafting of the manuscript: All authors.
Critical revision of the manuscript for important intellectual content: All authors.
Administrative, technical, or material support: Ruff, Bernstein.
Study supervision: Prabhakaran.

Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Prabhakaran reports receiving grant funding from the National Institutes of Health. No other disclosures were reported.

Submissions: We encourage authors to submit papers for consideration as a Review. Please contact Mary McGrae McDermott, MD, at mdm608@northwestern.edu.

REFERENCES

1. Mozaffarian D, Benjamin EJ, Go AS, et al. Heart disease and stroke statistics—2015 update. *Circulation*. 2015;131(4):e29-e322.
2. Solomon NA, Glick HA, Russo CJ, Lee J, Schulman KA. Patient preferences for stroke outcomes. *Stroke*. 1994;25(9):1721-1725.
3. Saver JL. Time is brain—quantified. *Stroke*. 2006;37(1):263-266.
4. Kidwell CS, Alger JR, Saver JL. Beyond mismatch. *Stroke*. 2003;34(11):2729-2735.
5. Penumbra Pivotal Stroke Trial Investigators. The penumbra pivotal stroke trial. *Stroke*. 2009;40(8):2761-2768.
6. Nogueira RG, Lutsep HL, Gupta R, et al. Trevo vs Merci retrievers for thrombectomy revascularisation of large vessel occlusions in acute ischaemic stroke (TREVO 2). *Lancet*. 2012;380(9849):1231-1240.
7. Saver JL, Jahan R, Levy EI, et al. Solitaire flow restoration device vs the Merci retriever in patients with acute ischaemic stroke (SWIFT). *Lancet*. 2012;380(9849):1241-1249.
8. Smith WS, Sung G, Saver J, et al. Mechanical thrombectomy for acute ischemic stroke. *Stroke*. 2008;39(4):1205-1212.
9. Smith WS, Sung G, Starkman S, et al. Safety and efficacy of mechanical embolectomy in acute ischemic stroke. *Stroke*. 2005;36(7):1432-1438.
10. Tissue plasminogen activator for acute ischemic stroke. *N Engl J Med*. 1995;333(24):1581-1587.
11. Hacke W, Kaste M, Bluhmki E, et al. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. *N Engl J Med*. 2008;359(13):1317-1329.
12. Saver JL. Number needed to treat estimates incorporating effects over the entire range of clinical outcomes. *Arch Neurol*. 2004;61(7):1066-1070.
13. Saver JL, Gornbein J, Grotta J, et al. Number needed to treat to benefit and to harm for intravenous tissue plasminogen activator therapy in the 3- to 4.5-hour window. *Stroke*. 2009;40(7):2433-2437.
14. Ahmed N, Wahlgren N, Grond M, et al. Implementation and outcome of thrombolysis with alteplase 3-4.5 h after an acute stroke. *Lancet Neurol*. 2010;9(9):866-874.
15. Schwamm LH, Ali SF, Reeves MJ, et al. Temporal trends in patient characteristics and treatment with intravenous thrombolysis among acute ischemic stroke patients at Get With The Guidelines-Stroke hospitals. *Circ Cardiovasc Qual Outcomes*. 2013;6(5):543-549.
16. Wahlgren N, Ahmed N, Dávalos A, et al. Thrombolysis with alteplase for acute ischaemic stroke in the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST). *Lancet*. 2007;369(9558):275-282.
17. Jauch EC, Saver JL, Adams HP Jr, et al. Guidelines for the early management of patients with acute ischemic stroke. *Stroke*. 2013;44(3):870-947.
18. Lees KR, Bluhmki E, von Kummer R, et al. Time to treatment with intravenous alteplase and outcome in stroke. *Lancet*. 2010;375(9727):1695-1703.
19. Ingall TJ, O'Fallon WM, Asplund K, et al. Findings from the reanalysis of the NINDS tissue plasminogen activator for acute ischemic stroke treatment trial. *Stroke*. 2004;35(10):2418-2424.
20. Generalized efficacy of t-PA for acute stroke. *Stroke*. 1997;28(11):2119-2125.
21. González RG, Furie KL, Goldmacher GV, et al. Good outcome rate of 35% in IV tPA–treated patients with computed tomography angiography–confirmed severe anterior circulation occlusive stroke. *Stroke*. 2013;44(11):3109-3113.
22. Broderick JP, Palesch YY, Demchuk AM, et al. Endovascular therapy after intravenous t-PA vs t-PA alone for stroke. *N Engl J Med*. 2013;368(10):893-903.
23. Jansen O, von Kummer R, Forsting M, Hacke W, Sartor K. Thrombolytic therapy in acute occlusion of the intracranial internal carotid artery bifurcation. *AJNR Am J Neuroradiol*. 1995;16(10):1977-1986.
24. Wolpert SM, Bruckmann H, Greenlee R, Wechsler L, Pessin MS, del Zoppo GJ. Neuroradiologic evaluation of patients with acute stroke treated with recombinant tissue plasminogen activator. *AJNR Am J Neuroradiol*. 1993;14(1):3-13.
25. Furlan A, Higashida R, Wechsler L, et al. Intra-arterial prourokinase for acute ischemic stroke. *JAMA*. 1999;282(21):2003-2011.

26. Alexandrov AV, Grotta JC. Arterial reocclusion in stroke patients treated with intravenous tissue plasminogen activator. *Neurology*. 2002;59(6):862-867.

27. Ogawa A, Mori E, Minematsu K, et al. Randomized trial of intra-arterial infusion of urokinase within 6 hours of middle cerebral artery stroke. *Stroke*. 2007;38(10):2633-2639.

28. Ciccone A, Valvassori L. Endovascular treatment for acute ischemic stroke. *N Engl J Med*. 2013;368(25):2433-2434.

29. Kidwell CS, Jahan R, Gornbein J, et al. A trial of imaging selection and endovascular treatment for ischemic stroke. *N Engl J Med*. 2013;368(10):914-923.

30. Berkhemer OA, Fransen PS, Beumer D, et al. A randomized trial of intra-arterial treatment for acute ischemic stroke. *N Engl J Med*. 2015;372(1):11-20.

31. Goyal M, Demchuk AM, Menon BK, et al. Randomized assessment of rapid endovascular treatment of ischemic stroke. *N Engl J Med*. 2015;372(11):1019-1030.

32. Campbell BC, Mitchell PJ, Kleinig TJ, et al. Endovascular therapy for ischemic stroke with perfusion-imaging selection. *N Engl J Med*. 2015;372(11):1009-1018.

33. Saver JL, Goyal M, Bonafe A, et al. *SOLITAIRE FR with the Intention for Thrombectomy as Primary Endovascular Treatment for Acute Ischemic Stroke*. Paper presented at: International Stroke Conference; February 2015; Nashville, TN.

34. Ciccone A, Valvassori L, Ponzio M, et al. Intra-arterial or intravenous thrombolysis for acute ischemic stroke? *J Neurointerv Surg*. 2010;2(1):74-79.

35. Furlan AJ, Eyding D, Albers GW, et al. Dose Escalation of Desmoteplase for Acute Ischemic Stroke (DEDAS). *Stroke*. 2006;37(5):1227-1231.

36. Hacke W, Albers G, Al-Rawi Y, et al. The Desmoteplase in Acute Ischemic Stroke Trial (DIAS). *Stroke*. 2005;36(1):66-73.

37. Albers GW, Thijs VN, Wechsler L, et al. Magnetic resonance imaging profiles predict clinical response to early reperfusion. *Ann Neurol*. 2006;60(5):508-517.

38. Lansberg MG, Straka M, Kemp S, et al. MRI profile and response to endovascular reperfusion after stroke (DEFUSE 2). *Lancet Neurol*. 2012;11(10):860-867.

39. Goyal M, Menon BK, Derdeyn CP. Perfusion imaging in acute ischemic stroke. *Radiology*. 2013;266(1):16-21.

40. Goyal M, Menon BK, Coutts SB, et al. Effect of baseline CT scan appearance and time to recanalization on clinical outcomes in endovascular thrombectomy of acute ischemic strokes. *Stroke*. 2011;42(1):93-97.

41. Yoo AJ, Zaidat OO, Chaudhry ZA, et al. Impact of pretreatment noncontrast CT Alberta Stroke Program Early CT Score on clinical outcome after intra-arterial stroke therapy. *Stroke*. 2014;45(3):746-751.

42. Barber PA, Demchuk AM, Zhang J, Buchan AM. Validity and reliability of a quantitative computed tomography score in predicting outcome of hyperacute stroke before thrombolytic therapy. *Lancet*. 2000;355(9216):1670-1674.

43. Montori VM, Devereaux PJ, Adhikari NK, et al. Randomized trials stopped early for benefit. *JAMA*. 2005;294(17):2203-2209.

44. Bassler D, Briel M, Montori VM, et al. Stopping randomized trials early for benefit and estimation of treatment effects. *JAMA*. 2010;303(12):1180-1187.

45. Ioannidis JP. Contradicted and initially stronger effects in highly cited clinical research. *JAMA*. 2005;294(2):218-228.

46. Menon BK, Saver JL, Goyal M, et al. Trends in endovascular therapy and clinical outcomes within the nationwide Get With The Guidelines-Stroke Registry. *Stroke*. 2015;46(4):989-995.

47. Asif KS, Lazzaro MA, Zaidat O. Identifying delays to mechanical thrombectomy for acute stroke. *J Neurointerv Surg*. 2014;6(7):505-510.

48. Faiz KW, Sundseth A, Thommessen B, Rønning OM. Prehospital delay in acute stroke and TIA. *Emerg Med J*. 2013;30(8):669-674.

49. Ford AL, Williams JA, Spencer M, et al. Reducing door-to-needle times using Toyota's lean manufacturing principles and value stream analysis. *Stroke*. 2012;43(12):3395-3398.

50. Meretoja A, Strbian D, Mustanoja S, Tatlisumak T, Lindsberg PJ, Kaste M. Reducing in-hospital delay to 20 minutes in stroke thrombolysis. *Neurology*. 2012;79(4):306-313.

51. Meretoja A, Weir L, Ugalde M, et al. Helsinki model cut stroke thrombolysis delays to 25 minutes in Melbourne in only 4 months. *Neurology*. 2013;81(12):1071-1076.

52. Ruff IM, Ali SF, Goldstein JN, et al. Improving door-to-needle times. *Stroke*. 2014;45(2):504-508.

53. Fonarow GC, Smith EE, Saver JL, et al. Timeliness of tissue-type plasminogen activator therapy in acute ischemic stroke: patient characteristics, hospital factors, and outcomes associated with door-to-needle times within 60 minutes. *Circulation*. 2011;123(7):750-758.

54. Fonarow GC, Zhao X, Smith EE, et al. Door-to-needle times for tissue plasminogen activator administration and clinical outcomes in acute ischemic stroke before and after a quality improvement initiative. *JAMA*. 2014;311(16):1632-1640.

55. Ebinger M, Winter B, Wendt M, et al. Effect of the use of ambulance-based thrombolysis on time to thrombolysis in acute ischemic stroke. *JAMA*. 2014;311(16):1622-1631.

56. Ebinger M, Kunz A, Wendt M, et al. Effects of golden hour thrombolysis. *JAMA*. 2015;72(1):25-30.

57. Saver JL, Fonarow GC, Smith EE, et al. Time to treatment with intravenous tissue plasminogen activator and outcome from acute ischemic stroke. *JAMA*. 2013;309(23):2480-2488.

58. Sacks D, Black CM, Cognard C, et al. Multisociety consensus quality improvement guidelines for intra-arterial, catheter-directed treatment of acute ischemic stroke, from the American Society of Neuroradiology, Canadian Interventional Radiology Association, Cardiovascular and Interventional Radiological Society of Europe, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, Society of NeuroInterventional Surgery, European Society of Minimally Invasive Neurological Therapy, and Society of Vascular and Interventional Neurology. *Catheter Cardiovasc Interv*. 2013;82(2):52-68.

59. Zaidat OO, Yoo AJ, Khatri P, et al. Recommendations on angiographic revascularization grading standards for acute ischemic stroke. *Stroke*. 2013;44(9):2650-2663.

60. Sun CH, Nogueira RG, Glenn BA, et al. "Picture to puncture." *Circulation*. 2013;127(10):1139-1148.

61. Sun CH, Ribo M, Goyal M, et al. Door-to-puncture: a practical metric for capturing and enhancing system processes associated with endovascular stroke care, preliminary results from the rapid reperfusion registry. *J Am Heart Assoc*. 2014;3(2):e000859.

62. Goyal M, Almekhlafi MA, Fan L, et al. Evaluation of interval times from onset to reperfusion in patients undergoing endovascular therapy in the Interventional Management of Stroke III trial. *Circulation*. 2014;130(3):265-272.

63. Menon BK, Almekhlafi MA, Pereira VM, et al. Optimal workflow and process-based performance measures for endovascular therapy in acute ischemic stroke: analysis of the SOLITAIRE FR thrombectomy for acute revascularization study. *Stroke*. 2014;45(7):2024-2029.

64. Khatri P, Yeatts SD, Mazighi M, et al. Time to angiographic reperfusion and clinical outcome after acute ischaemic stroke. *Lancet Neurol*. 2014;13(6):567-574.

65. Mazighi M, Chaudhry SA, Ribo M, et al. Impact of onset-to-reperfusion time on stroke mortality. *Circulation*. 2013;127(19):1980-1985.