# Reperfusion Therapy in the Acute Management of Ischemic Stroke

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**KEYWORDS**

- Acute ischemic stroke • Stroke system of care
- Intravenous recombinant tissue plasminogen activator (IV-tPA) • Mechanical thrombectomy
- Thrombolysis in cerebral infarction (TICI score) • American Heart Association
- American Stroke Association

**KEY POINTS**

- Reperfusion, or restoration of blood flow, is an effective means of reducing disability in the setting of acute stroke.
- Rapid evaluation of stroke begins with community education to recognize signs and symptoms of stroke, an organized system of care by the emergency medical services (EMS) and the emergency department (ED), timely evaluation by the stroke team, and critical care capability.
- Stroke is the fourth leading cause of death after ischemic heart disease, lung cancer, and chronic lower respiratory disease and a leading cause of disability and societal cost in the United States.

## INTRODUCTION

An estimated 6.8 million Americans greater than or equal to 20 years of age have had a stroke, and there are approximately 795,000 new or recurrent cases per year with an annual direct and indirect cost of $36.5 billion in 2010.[1,2] Stroke is the fourth leading cause of death after ischemic heart disease, lung cancer, and chronic lower respiratory disease[3] and a leading cause of disability and societal cost in the United States.[3]

This review provides an overview of the acute evaluation and treatment of ischemic stroke, focusing on the role of reperfusion therapy. The discussion is framed around the most recent American Heart Association/American Stroke Association guidelines.[4] Rapid evaluation of stroke begins with community education to recognize signs and symptoms of stroke, an organized system of care by the EMS and the ED, timely evaluation by the stroke team, and critical care capability. Intravenous (IV) thrombolysis with a recombinant tissue plasminogen activator (IV-tPA) within the first 3 hours of stroke symptom onset is the only therapy approved by the US Food and Drug Administration (FDA) for acute ischemic stroke.[5] Recanalization rates for IV-tPA are limited, however, in large-vessel occlusions, which led to the exploration of endovascular therapy.[6] Landmark trials in IV-tPA, endovascular perfusion therapy, and acute medical treatments, including

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blood pressure (BP) management, aspirin, statin, and anticoagulation, have shaped current understanding of acute stroke care.

## EVALUATION OF ACUTE REPERFUSION THERAPY

Rapid recognition of stroke is critical for stroke outcome. The National Institutes of Neurological Disorders and Stroke (NINDS) has established target timeframes in the evaluation of stroke suspects, dubbed "stroke chain of survival" (**Table 1**). A fairly standardized algorithm for evaluating and treating acute ischemic stroke. The first step is to recognize traditional stroke symptoms, including acute facial paresis, arm drift, or abnormal speech, for instance. Analogous to atypical angina, many patients, in particular women, may present with nontraditional stroke symptoms, such as generalized weakness, fatigue, and cognitive changes that can make rapid diagnosis challenging.[7,8] There are major campaigns aimed at the public to improve stroke system recognition, including the face, arm, speech, and time (FAST) educational program. Emergency dispatch operators and paramedics are also trained in stroke recognition using tools, such as the Los Angeles Prehospital Stroke Screen. Routing of patients with suspected stroke to specialized centers bypassing the nearest hospital is increasing throughout the United States.

After arrival in the ED, door-to-noncontrast CT head initiation ought to be done in less than or equal to 25 minutes, and door-to-CT head interpretation in less than or equal to 45 minutes. CT head is useful in differentiating ischemic stroke from hemorrhage stroke, because the treatment pathways of these 2 entities is different. MRI head with diffusion-weighted images is helpful in distinguishing true stroke from stroke mimics, although a vast majority of centers in the US use CT only in the ED. Common stroke mimics include seizure, migraine, hypertensive encephalopathy, space-occupying lesions, toxic/septic/metabolic conditions, or psychogenic.[9] Key blood work to obtain includes complete blood cell count, international normalized ratio/partial thromboplastin time, blood glucose, creatinine, toxicology screen, and troponin. Clinical assessment (history, general examination, and neurologic examination) remains the cornerstone of the evaluation. Stroke scales, such as the National Institutes of Health Stroke Scale (NIHSS), provide important information about the severity of stroke and prognostic information and influence decisions about the acute treatment.

**Table 1**
**Emergency department–based care: stroke chain of survival**

| Action | Time |
|---|---|
| Door-to-physician | ≤10 min |
| Door-to-stroke team | ≤15 min |
| Door-to-CT scan initiation | ≤25 min |
| Door-to-CT scan interpretation | ≤45 min |
| Door-to-drug (≥80% compliance) | ≤60 min |
| Door-to-stroke unit admission | ≤3 h |

*From* Jauch EC, Saver JL, Adams HP, et al. Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2013;44:870–947; with permission.

## INTRAVENOUS THROMBOLYSIS (INTRAVENOUS THROMBOLYSIS WITH A RECOMBINANT TISSUE PLASMINOGEN ACTIVATOR)

In 1996, the FDA approved the use of IV-tPA for the treatment of acute ischemic stroke within 3 hours of symptom onset, based on the results of the NINDS tPA stroke trial.[5] The trial showed that patients treated with tPA were 30% more likely to have minimal or no functional disability at 3 months (defined as a modified Rankin Scale score [mRS] of 0 or 1)].[4] Later, the European Cooperative Acute Stroke Study III further demonstrated global favorable outcomes when IV-tPA was administered 3 to 4.5 hours after symptom onset (52% vs 45%; OR 1.28; 95% CI, 1.0–1.6), although the effect was less pronounced than in those who received IV-tPA from 0 to 3 hours in the NINDS study (odds ratio [OR] 1.9; 95% CI, 1.2–2.9).[10] Approximately 4.5 patients need to be treated within 1.5 hours, 9 from 1.5 to 3 hours, and 14.1 from 3 to 4.5 hours to have 1 additional patient with no disability at 90 days.[11] The primary complication of treating patients with IV-tPA for acute ischemic stroke is brain hemorrhage. In a pooled analysis, large intracranial hemorrhage (ICH) occurred in 5.2% of patients in the IV-tPA group versus 1.0% of controls (OR 5.37; 95% CI, 3.22–8.95).[11]

Similar to recanalization of occluded coronary vessels, recanalization of intracranial vessels is clearly associated with improved clinical outcome. Zangerle and colleagues[12] reported that 58.3% of patients with recanalization had favorable 90-day mRS scores compared with 5.6% of patients without recanalization ($P$<.001). In a meta-analysis, Rha and Saver[6] showed that recanalization significantly improved 90-day clinical

outcome (OR 4.43; 95% CI, 3.32–5.91) and mortality (OR 0.24; 95% CI, 0.7–17.4). Clinical efficacy of IV-tPA and its ability to achieve successful recanalization, however, are limited in patients presenting with acute stroke due to large-vessel occlusion, in particular proximally located clots. Sillanpää and colleagues[13] found that greater than 80% of stroke patients treated with IV-tPA with a more distally located clot had good neurologic outcome at 3 months. Proximal middle cerebral artery (MCA) occlusion was associated with only a 22% chance of good outcome, and none of the patients with occlusion located in the most distal segment of the internal carotid artery (ICA) experienced good recovery.[13]

## ENDOVASCULAR INTERVENTIONS

Endovascular procedures are often performed in individuals who have received IV-tPA but who have severe strokes with large vessel occlusion and high clot burden. These individuals are thought to respond poorly to IV-tPA, and most ongoing clinical trials with the newer devices are aimed at demonstrating a benefit of a combined IV and intra-arterial (IA) approach versus IV alone.[14] The second group in whom endovascular therapy is potentially beneficial is those ineligible for IV-tPA (eg, time of onset beyond 3–4.5 hours, coagulopathy, recent major surgery within 14 days, or on anticoagulation). Although clinical trials have focused on intervention within a 6-hour window for thrombolytic- and an 8-hour window for device-based therapy, there are situations in which procedures can be performed outside of these time windows, such as in the setting of basilar artery occlusion.

### *Revascularization Grading Systems*

Thrombolysis in Myocardial Infarction (TIMI) and Thrombolysis in Cerebral Infarction (TICI) are 2 of the most commonly used angiographic scores for revascularization/reperfusion in neurointervention for acute ischemic stroke.[15] The TIMI grading system was originally developed to assess the degree of cardiac reperfusion during interventions for acute myocardial infarction. Its prognostic value categorizes a patient's risk of death and ischemic events and provides a basis for therapeutic decision making; it was subsequently applied to neurointerventions.[16] The TICI grading system is a modification of the TIMI scale developed specifically for the intracranial circulation.[17] Grades in both systems range from 0 (no recanalization/reperfusion) to 3 (complete recanalization/reperfusion), but TICI allows a more detailed description of partial recanalization and a greater reperfusion range: none to minimal limited to the parent artery (TICI grade 0 or 1), partial reperfusion beyond the occlusion site (TICI grade 2a), near-complete or greater than 50% reperfusion beyond the occlusion site (TICI grade 2b), or complete (TICI grade 3). **Fig. 1** provides examples of cerebral angiographic runs that correspond to different degrees of the TICI scale.

### *Intra-arterial Fibrinolysis*

As with IV fibrinolysis therapy, reduced time from symptom onset to reperfusion with IA therapies is highly correlated with better clinical outcomes. The Prolyse in Acute Cerebral Thromboembolism (PROACT) II trial evaluated IA thrombolysis with recombinant prourokinase (r-proUK) in patients with NIHSS score greater than or equal to 4 and

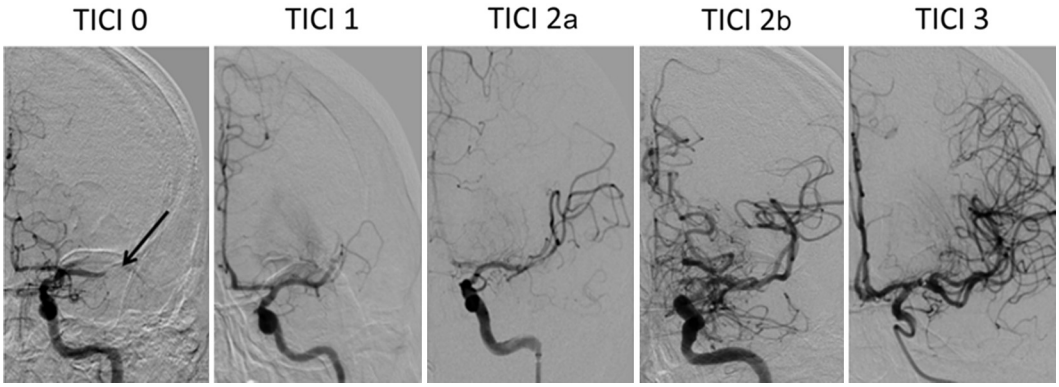


**Fig. 1.** Examples of the TICI score in a case of proximal MCA occlusion. From left to right: TICI 0 shows no recanalization/reperfusion of the primary occluded vessel (*arrow*). TICI 1 shows partial reperfusion beyond the initial occlusion but no filling of distal MCA branches. TICI 2a and TICI 2b correspond to partial (<50%) and near-complete (>50% but less than full) reperfusion beyond the occlusion site, respectively. TICI 3 indicates complete reperfusion of the entire MCA territory. (*From* Mokin M, Khalessi A, Mocco J, et al. Endovascular treatment of acute ischemic stroke: the end or just the beginning? Neurosurg Focus 2014;36:E5; with permission.)

suspected of having MCA occlusion.[18] Among the 180 randomized patients, 40% of the 121 patients treated with IA thrombolysis (IV r-proUK + IV heparin) and 25% of the 59 control (IV heparin) patients had an mRS score of 0 to 2 at 90 days ($P$ = .04). MCA recanalization was achieved in 66% of the r-proUK arm and in 18% of the control group ($P$ = .001). Symptomatic ICH occurred in 10% of patients treated with r-proUK and in 2% of the control group ($P$ = .06).[18] Mortality rates were similar between the 2 groups.

### *Mechanical Thrombectomy*

The number of options for endovascular treatment of ischemic stroke has increased substantially over the past decade to include IA fibrinolysis, mechanical clot retrieval, mechanical aspiration, and acute angioplasty and stenting. There are currently 4 devices cleared by the FDA for recanalization of arterial occlusion in patients with ischemic stroke. Fig. 2A shows the Mechanical Embolus Removal in Cerebral Ischemia (MERCI) clot retrieval system (Stryker Neurovascular, Fremont, California). Fig. 2C shows the mechanical clot aspiration with the Penumbra system (Penumbra Inc, Alameda, California). Fig. 2B, D shows the stent retrieval systems, Solitaire (ev3 Neurovascular, Irvine, California) and Trevo (Stryker Neurovascular).

Table 2 summarizes the key randomized controlled trials done on endovascular therapy for acute ischemic stroke. Two randomized trials—Solitaire With the Intention for Thrombectomy (SWIFT) and Trevo versus MERCI retrievers for thrombectomy revascularization of large vessel occlusions in acute ischemic stroke (TREVO2)—that compared the MERCI clot-retriever to Solitaire or Trevo stent retrievers in patients treated within 8 hours of symptom onset demonstrated higher revascularization rates of greater than 80%.[19,20] In the SWIFT trial, a remarkable 58% of patients achieved good neurologic outcome at 3 months, compared with only 33% of patients in the MERCI group.[19] At the same time, mortality rates were lower in the Solitaire group than in the MERCI group (17% vs 38%, respectively). Solitaire FR and Trevo were both approved by FDA for treatment of stroke due to large-vessel occlusion. The relative effectiveness of the Penumbra system versus stent retrievers is not yet characterized.

### *Angioplasty/Stenting Versus Intravenous Thrombolysis with Recombinant Tissue Plasminogen Activator Trials*

Three randomized controlled trials, Interventional Management of Stroke (IMS) III, Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy (MR RESCUE), and SYNTHESIS-Expansion,[21–23] aimed to compare the efficacy of endovascular treatment to IV-tPA. The design and key outcomes of the trials are summarized in Table 2.

The IMS III trial randomized eligible patients who had received IV alteplase within 3 hours after symptom onset to receive additional endovascular treatment or no additional treatment, in a 2:1 ratio.[21] The primary outcome measure was an mRS score of less than or equal to 2 at 90 days (see Table 2). The proportion of participants with the desired primary outcome at 90 days was not statistically significant among patients treated with endovascular treatment and those treated with IV-tPA (40.8% vs 38.7%; $P$ .25). The proportion of patients with symptomatic ICH within

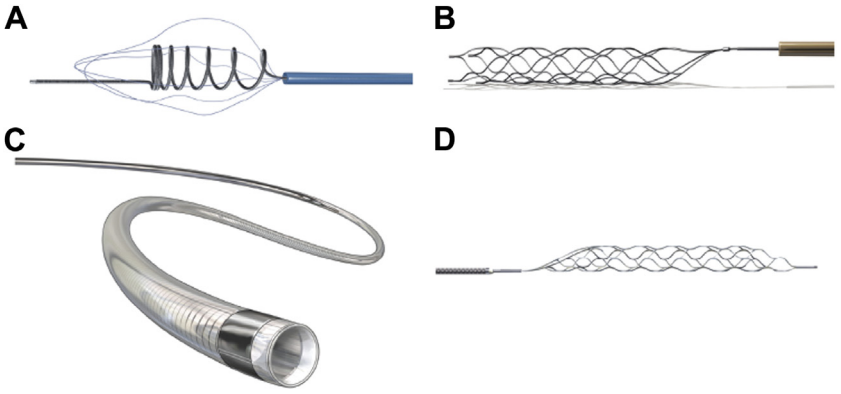


**Fig. 2.** Devices approved by the FDA for acute stroke clot removal: (*A*) MERCI retriever, (*B*) Solitaire stent retriever, (*C*) Penumbra aspiration system, and (*D*) TREVO2 stent retriever (ev3 Neurovascular, Irvine, California). (*From* Khatri P. Evaluation and management of acute ischemic stroke. Continuum (Minneap Minn) 2014;20:283–95; with permission.)

30 hours after initiation of IV-tPA was similar between the 2 groups (6.2% vs 5.9%; $P = .8$).[21]

In the MR RESCUE trial, patients were randomized to mechanical embolectomy (MERCI retriever or Penumbra system) with optional IA thrombolysis or IV-tPA.[22] Patients were further stratified by the presence of a favorable penumbral pattern (substantial salvageable tissue and small infarct core) or not, prior to randomization on pretreatment CT or MRI of the brain. The mean scores on the mRS at 3 months did not differ between embolectomy and standard care (3.9 vs 3.9; $P = .99$). Symptomatic ICH was seen in 3 of 64 and in 2 of 54 patients randomized to embolectomy or standard care, respectively. Patients with penumbral pattern had smaller infarct volumes and lower mRS at 90 days regardless of the treatment modality.[22]

The SYNTHESIS-Expansion trial randomized 362 patients to endovascular treatment, which was predominantly IA thrombolysis and the option of mechanical thrombectomy or IV-tPA The primary outcome was defined by an mRS of 0 or 1 at 3 months.[23] The primary outcome was seen in 30.4% of the patients treated with endovascular treatment and in 34.8% of those treated with IV alteplase at 3 months.[23] The adjusted odds of primary outcome were not statistically significant (OR 0.71; 95% CI, 0.44–1.14; $P = .16$). Symptomatic ICH within 7 days occurred in 6% of patients from each group.[23]

Overall, the 3 trials did not demonstrate superiority of endovascular treatment and the safety parameters were comparable. However, it is possible that endovascualr treatment may benefit selected subgroups such as in those with severe deficits (NIHSS>20), in patients with large proximal arterial occlusion. In addition, the effectiveness of newer retriever devices have not been thoroughly studied.[24,25]

### *Coronary Versus Cerebral Artery Reperfusion Therapy*

Endovascular reperfusion therapies for myocardial infarction and ischemic stroke have evolved in similar patterns: first was IV fibrinolysis, followed by IA fibrinolysis, and then mechanical thrombectomy. Patel and Saver[26] performed a systematic, comparative analysis of recanalization/reperfusion outcomes of these 2 distinctive circulatory beds: 37 trials of coronary reperfusion that enrolled 10,908 patients from 1983 to 2009 and 10 trials of cerebral reperfusion that enrolled 1064 patients from 1992 to 2009 were compared.[26] In both circulatory beds, endovascular treatments were more efficacious at achieving reperfusion than peripherally administered fibrinolytics. In the coronary bed, rates of achieved reperfusion began at high levels in the 1980s and improved modestly over the subsequent 3 decades. In the cerebral bed, reperfusion rates began at modest levels in the early 1990s and increased more slowly (**Fig. 3**).[26] With an anchor added for spontaneous reperfusion rates in the reperfusion therapy era, analysis of complete reperfusion rates showed a rapid rise to plateau of 80% to 90% for coronary reperfusion versus a slow rise to plateau of 20% to 25% for cerebral reperfusion (see **Fig. 3**).[26]

## STANDARD MEDICAL THERAPY

Postreperfusion therapy care is essential because approximately 25% of patients may have neurologic worsening during the first 24 to 48 hours after stroke and it is difficult to predict which patients will deteriorate.[27] A dedicated stroke unit with nursing expertise is pivotal in the management of acute stroke patients. Key components of medical therapy for acute stroke beyond IV-tPA include BP modulation, antiplatelet and neuroprotective agents (statins), cardiac monitoring, respiratory support, normothermia, and normoglycemia.[4,27]

### *Blood Pressure*

Elevated BP is common during the acute phase of ischemic stroke, but, owing to a lack of data, BP goal in this setting is controversial and is based on expert opinion. Due to the concern regarding reducing perfusion to an already ischemic brain, “permissive hypertension” is recommended to a goal of less than 220/120 mm Hg among those who did not receive tPA or less than 185/110 mm Hg over the first 24 hours. In cases where systemic hypotension has produced neurologic sequelae, vasopressors may be used to improve cerebral blood flow.[4] Several recent trials have found that lowering BP in the acute setting may be associated with worse clinical outcomes.

First, one analysis found that low-normal systolic BP (SBP) was associated with a higher risk of early recurrence by 2 weeks and poor functional outcome at 6 months compared with high-normal SBP.[28] Second, results of a randomized trial in patients with acute stroke and raised BP levels (SBP $\geq$140 mm Hg) suggested a trend toward greater risk of poor functional outcome at 180 days after BP-lowering treatment was initiated within 30 hours of the index stroke.[29] Third, the recent China Antihypertensive Trial in Acute Ischemic Stroke showed that immediate BP reduction by 10% to 25% within 24 hours of acute ischemic stroke, or achievement of BP less than 140/90 mm Hg within 7 days of acute ischemic stroke,

**Table 2**
**Characteristics of the included randomized controlled trials on endovascular therapy for acute ischemic stroke**

| Author | Intervention vs Control | No. of Patients (% Male) | Age (y) Mean ± SD or Median (Range) | Inclusion Criteria | mRS Score ≤2 at 90 d | Recanalization (TICI) | Key Conclusion |
|---|---|---|---|---|---|---|---|
| PROACT II, 1999 | I = IA r-proUK + IV heparin | 121 (58%) | 64 ± 14 | New focal neurologic signs in the MCA distribution allowing initiation of treatment within 6 h of the onset of symptoms, NIHSS ≥4 | 40%, *P* = .04 | Grade 2a–3 66%, *P*<.001 | Improved good neurologic outcome (mRS score), recanalization with IA thrombolysis |
| | C = IV heparin | 59 (61%) | 64 ± 14 | | 25% | Grade 2a–3 18% | |
| SWIFT, 2012 | I = Solitaire FR stent retriever | 58 (48%) | 67 ± 12 | NIHSS 8–29 and stroke onset ≤8 h with anterior/ posterior large-vessel occlusion | 58%, *P* = .017 | Grade 2a–3 61%, *P*<.0001 | Improved good neurologic outcome (mRS score 0–2 or NIHSS improvement by ≥10 points), recanalization, and lower mortality with Solitaire |
| | C = MERCI clot retriever | 55 (51%) | 67 ± 11 | | 33% | Grade 2a–3 24% | |
| TREVO2, 2012 | I = Trevo stent retriever | 88 (45%) | 70 (61–77) | NIHSS 8–29 and stroke onset ≤8 h with anterior/ posterior large-vessel occlusion | 40%, *P* = .013 | Grade 2a–3 86%, *P*<.0001 | Improved good neurologic outcome (mRS score 0–2) and recanalization with Trevo; similar mortality rates |
| | C = MERCI clot retriever | 90 (40%) | 71 (58–79) | | 22% | Grade 2a–3 60% | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| IMS III, 2013 | I = IV tPA + IV heparin ± MT | 434 (50%) | 69 (23–89) | NIHSS ≥10 without CTA/MRA or NIHSS ≥8 in patients with CTA/MRA showing large vessel occlusion | 40.8%, $P = .25$ | Grade 2b–3: ICA (38%), M1 (41%), single M2 (44%), multiple M2 (23%) | No difference in good neurologic outcome (mRS score 0–2), symptomatic ICH, or mortality |
| | C = IV tPA | 222 (55%) | 68 (23–84) | | 38.7% | NA | |
| MR RESCUE, 2013 (Penumbra) | I = IA/IV tPA ± MT | 34 (50%) | 66 ± 13 | Stroke onset ≤8 h, NIHSS 6–29, anterior circulation large-vessel occlusion on MRA/CTA, infarct core on perfusion imaging ≤90 ml and pneumbral mismatch ≤70% | 21%[a], $P = .14$ | Grade 2a–3 at day 7 = 67% | No difference in good neurologic outcome (mRS score 0–2) among all 4 groups; smaller final infarct volume in good penumbral pattern groups |
| | C = IV tPA | 34 (44%) | 66 ± 17 | | 26%[a] | Grade 2a–3 at day 7 = 93% | |
| SYNTHESIS-Expansion, 2013 | I = IA tPA ± IV heparin ± MT | 181 (59%) | 66 ± 11 | No defined NIHSS threshold; lack of confirmation of large-vessel occlusion before intervention | 30.4%[b], $P = .16$ | NA | No difference in good neurologic outcome (mRS score 0–2), symptomatic ICH, or mortality |
| | C = IV tPA | 181 (57%) | 67 ± 11 | | 34.8%[b] | NA | |

*Abbreviations:* CTA, computer tomography angiography; I, intervention; IA, intraarterial; ICH, intracranial hemorrhage; IV, intravenous; MRA, magnetic resonance angiography; mRS, modified Rankin Score; MT, mechanical thrombectomy; NA, not applicable; NIHSS, NIH stroke scale; r-proUK, recombinant prourokinase; tPA, tissue plasminogen activator; TICI, thrombolysis in cerebral infarction.

[a] Improved in mRS score level in 90 days.

[b] mRS score 0 or 1.

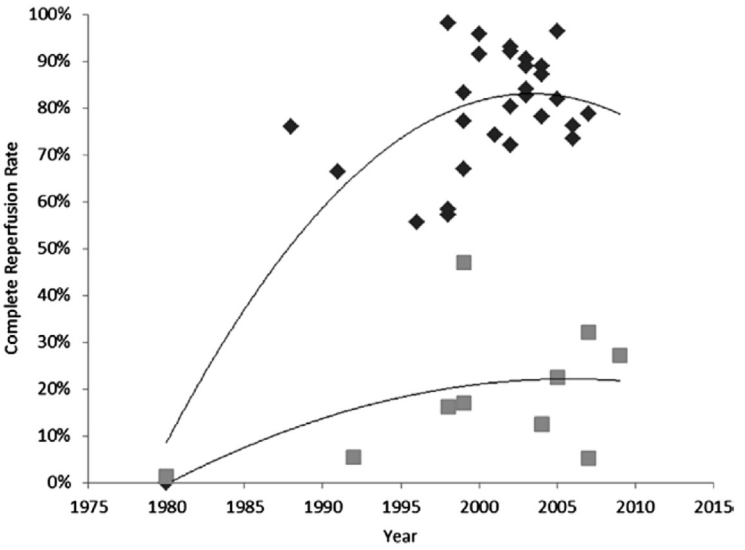


**Fig. 3.** Trends over time in complete reperfusion rates in active arms of coronary (*diamond*) and cerebral (*square*) reperfusion trials. (*From* Patel RD, Saver JL. Evolution of reperfusion therapies for acute brain and acute myocardial ischemia: a systematic, comparative analysis. Stroke 2013;44:94–8; with permission.)

had no mortality or morbidity benefits.[30] The optimal time or BP target to start antihypertensive treatment after acute stroke is also uncertain.

### *Aspirin*

There is a small but statistically significant decline in mortality and unfavorable outcomes with the administration of aspirin (initial dose is 325 mg) within 24 to 48 hours after stroke. Early aspirin treatment leads to a 1% absolute reduction of stroke over the next 2 weeks.[31,32] If IV-tPA or acute endovascular therapy is administered, aspirin is initiated at approximately 24 hours and only after confirmation of no hemorrhagic transformation on 24-h CT head. Data regarding the utility of other antiplatelet agents, including clopidogrel alone or in combination with aspirin, for the treatment of acute ischemic stroke are limited. The Clopidogrel in High-Risk Patients with Acute Non-disabling Cerebrovascular Events trial compared clopidogrel plus aspirin versus aspirin alone started within 24 hours and continued for 21 days in Chinese patients with minor ischemic stroke or transient ischemic attack.[33] Over 90 days, 8.2% of patients in the clopidogrel + aspirin group, compared with 11.7% in the aspirin-only group, had a stroke (hazard ratio [HR] 0.68; 95% CI, 0.57–0.81; $P<.001$). The rate of ICH was 0.3% in each group.[33]

### *Statins*

Statin therapy with intensive lipid-lowering effects is established for primary and secondary stroke prevention.[34,35] There is emerging evidence favoring the neuroprotective effect of statins on ischemic stroke outcomes.[36,37] The only randomized trial on the topic was a small study involving 89 patients already taking chronic statins at the time of ischemic stroke. Patients were randomized within 24 hours of onset to statin withdrawal for 3 days or to continued statin therapy. Patients with statin withdrawal showed a higher frequency of mRS score greater than 2 at the end of follow-up (60.0% vs 39.0%; $P = .043$), which is associated with a 4.66-fold (1.46–14.91) increase in the risk of death or dependency and a 8.67-fold (3.05–24.63) increase in the risk of early neurologic deterioration compared with the nonstatin withdrawal group.[36] Similarly, in a large observation study, statin use before ischemic stroke hospitalization was associated with improved survival (HR 0.85; 95% CI, 0.79–0.93; $P<.001$), and use before and during hospitalization was associated with better rates of survival (HR 0.59; 95% CI, 0.53–0.65; $P<.001$).[37] Therefore, patients already taking statins at the time of ischemic stroke should continue this regimen. Those who are not on statin therapy should be; however, the impact on functional outcome is less certain.

### *Anticoagulation*

Venous thromboembolism is a common but preventable complication of acute ischemic stroke. Without venous thromboembolism prophylaxis, up to 75% of patients with hemiplegia after stroke develop deep vein thrombosis and 20% develop

pulmonary embolism,[38] which is fatal in 1% to 2% of patients with acute ischemic stroke and causes up to 25% of early deaths after strokes.[39] The Prevention of Venous Thromboembolism After Acute Ischemic Stroke (PREVAIL) study gives strong evidence of the superiority of low-molecular-weight heparin (LMWH) in prevention of venous thromboembolism over unfractionated heparin after ischemic stroke.[40] PREVAIL is an open-label, randomized comparison between enoxaparin (40 mg) subcutaneous daily versus unfractionated heparin (5000 U) subcutaneous every12 hours in patients with acute ischemic stroke. Enoxaparin reduced the risk of venous thromboembolism by 43% compared with unfractionated heparin (68 [10%] vs 121 [18%]; relative risk 0.57; 95% CI, 0.44–0.76; $P = .0001$; difference −7.9%, −11.6 to −4.2).[40] Hence, patients with acute ischemic stroke should be on LMWH for deep vein thrombosis prophylaxis on the day of admission or 24 hours after tPA administration.

On the other hand, urgent full anticoagulation for the management of noncerebrovascular conditions (ie, atrial fibrillation) is not recommended for patients with moderate-to-severe stroke because of an increased risk of symptomatic ICH. A meta-analysis of anticoagulants in patients with presumed cardioembolic stroke found that the agents were associated with a nonsignificant reduction in the rate of early recurrent stroke within 7 to 14 days (3.0% vs 4.9%; OR 0.68; 95% CI, 0.44–1.06; $P = .09$), a significant increase in symptomatic intracranial bleeding (2.5% vs 0.7%; OR 2.89; 95% CI, 1.19–7.01; $P = .02$), and a similar rate of death or disability at final follow-up (73.5% vs 73.8%; OR 1.01; 95% CI, 0.82–1.24; $P = .9$).[41]

## STROKE SYSTEMS OF CARE

Rapid evaluation of stroke begins with community education to recognize signs and symptoms of stroke. The call to a 9-1-1 dispatcher is the first link in the stroke chain of survival (see **Fig. 1**).[42] Specific time frames have been established for the Emergency Medical Service System to follow on dispatch, response, and on-scene activities.[43] It then takes an organized system of care that involves EMS personnel, public safety agencies, emergency facilities, and hospital health care personnel, including acute and subacute stroke units, to enable delivery of acute stroke care.[4] Primary Stroke Centers, with certification by the Joint Commission based on demonstration of compliance with recommendations from the Brain Attack Coalition and American Heart Association guidelines,[4,44] are generally associated with lower mortality rates compared with noncertified hospitals.[45,46] Nationwide quality improvement initiatives include the American Heart Association's Get With The Guidelines program and the National Stroke Registry.

Hospitals that have implemented organized stroke care by following the Get With The Guidelines program have demonstrated sustained improvement in multiple measures of stroke care quality, including tPA administration.[47] To evaluate the impact of the Get With The Guidelines and Target: Stroke[48,49] programs on acute stroke care and outcomes, Fonarow and colleagues[50] compared door-to-needle (DTN) times of tPA administration in patients with acute ischemic stroke before (2003–2009; n = 27,319) and after (2010–2013; n = 43,850) the implementation of the initiative in 1030 participating hospitals (52.8% of total). The investigators found improvements in process measures, such as timeliness of tPA administration (DTN times improved from 77 minutes preintervention to 67 minutes postintervention), and the proportion of individuals with DTN times of less than or equal to 60 minutes increased from 26.5% to 41.3% (all $P<.001$). Clinical outcomes also improved: in-hospital mortality decreased from 9.9% to 8.2%, symptomatic ICH within 36 hours decreased fr006Fm 5.7% versus 4.7%, and percentage of patients discharged home increased from 37.6% to 42.7% (all $P<.001$).

## SUMMARY

Rapid evaluation of stroke begins with community education to recognize signs and symptoms of acute ischemic stroke. It then takes an organized system of care that involves EMS personnel, emergency facilities, and hospital health care personnel all striving to achieve a DTN time of IV-tPA administration within less than or equal to 60 minutes. The FDA has approved the use of IV-tPA within 3 hours of symptom onset, and multiple randomized controlled trials have shown benefits up to 3 to 4.5 hours after symptom onset. For patients not eligible for IV-tPA or for those with persistent large-vessel occlusion, endovascular therapy should be considered within up to 6 hours of symptom onset. There are currently 4 devices cleared by the FDA for recanalization of arterial occlusion in patients with ischemic stroke. The IMS III, MR RESCUE, and SYNTHESIS-Expansion studies failed to show clinical outcome differences between endovascular retrieval devices and IV-tPA; therefore, no evidence has currently been presented showing superiority of endovascular clot retrieval over IV-tPA. Endovascular device technology and advanced imaging technology for

patient selection, however, continue to evolve; newer devices have suggested greater recanalization success. Finally, postperfusion therapy care, including BP modulation and antiplatelet and neuroprotective agents (statins), is paramount for successful stroke outcome.

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