Update on Treatment of Acute Ischemic Stroke

By Alejandro A. Rabinstein, MD, FAAN

EDITOR’S NOTE
The article “Update on Treatment of Acute Ischemic Stroke” by Dr Rabinstein was first published in the February 2017 Cerebrovascular Disease issue of Continuum: Lifelong Learning in Neurology as “Treatment of Acute Ischemic Stroke” and has been updated by Dr Rabinstein for this issue at the request of the Editor-in-Chief.

ABSTRACT
PURPOSE OF REVIEW: This article provides an update on the state of the art of the treatment of acute ischemic stroke with particular emphasis on the indications for reperfusion therapy.

RECENT FINDINGS: In addition to the previously established indications for intravenous (IV) thrombolysis with recombinant tissue plasminogen activator (rtPA) within 4.5 hours of stroke symptom onset and endovascular therapy with mechanical thrombectomy for patients with large artery occlusion who can be treated within 6 hours of symptom onset, recent randomized controlled trials have now established new indications for emergency reperfusion in patients with wake-up stroke or delayed presentation (up to 24 hours from last known well in the case of mechanical thrombectomy). Identification of patients who may benefit from acute reperfusion therapy within this extended time window requires screening with perfusion brain imaging or, in the case of IV thrombolysis for wake-up strokes, emergency brain MRI. Collateral status and time to reperfusion remain the primary determinants of outcome.

SUMMARY: Timely successful reperfusion is the most effective treatment for patients with acute ischemic stroke. Recent evidence supports the expansion of the time window for reperfusion treatment in carefully selected patients.

INTRODUCTION
Over the past 2 decades, the therapeutic approach to acute ischemic stroke has been deeply transformed. Long gone is the nihilism of former times, now replaced by the excitement of proven treatment options that can reverse ischemia and bring back function to patients who were otherwise destined to death or severe disability. The wide adoption of IV thrombolysis that began 25 years ago has recently been followed with clear evidence that the addition of endovascular...
treatment with mechanical thrombectomy can further improve outcomes in patients with severe neurologic deficits from a proximal intracranial vessel occlusion. Furthermore, growing evidence now supports the expansion of the therapeutic window for emergency reperfusion, thus increasing the proportion of patients with acute ischemic stroke who might be considered candidates for these highly effective treatments.

Acute reperfusion is by far the most effective treatment for acute ischemic stroke. Yet, the treatment of acute stroke also includes adequate hemodynamic management, monitoring and management of ischemic brain edema, and early recognition of and therapy for systemic complications (such as infections, cardiac arrhythmias, heart failure, and venous thromboembolism) in a stroke unit staffed by specially trained personnel.

The management of acute ischemic stroke starts with the prompt recognition of the diagnosis in the field, and attention is aimed at optimizing the time to reperfusion in the emergency department and the angiographic suite. However, what happens in the stroke unit or intensive care unit after hospitalization is also very important to maximize the chances of good recovery. Comprehensive guidelines offer useful advice in these additional areas.1

This article is an update of the one published in the previous Cerebrovascular Disease issue of Continuum in February 2017.2 Its objective is to present the most current general approach to the emergency evaluation and treatment of patients with acute ischemic stroke. This issue of Continuum includes additional articles fully devoted to the discussion of acute neuroimaging and endovascular therapy. Therefore, these important topics will only be mentioned briefly in this updated review.

**PRINCIPLES OF ACUTE STROKE CARE**

The three main principles of acute stroke care are: (1) achieve timely recanalization of the occluded artery and reperfusion of the ischemic tissue, (2) optimize collateral flow, and (3) avoid secondary brain injury.

Recanalization and reperfusion are the mainstays of acute stroke treatment and can reduce infarct size and reverse neurologic deficits. Recanalization is defined by the degree of reopening of the occluded artery. Reperfusion is measured by the degree of flow reaching the previously hypoperfused brain region. Opening the occluded artery works because in most cases when the occlusion occurs, an area of brain tissue becomes hypoperfused but is initially not infarcted. This tissue represents the ischemic penumbra that can be salvaged if adequate blood flow is promptly reestablished. Advanced brain imaging with CT perfusion or magnetic resonance (MR) diffusion/perfusion can visualize this tissue at risk (penumbra imaging).3 Chemical thrombolysis with recombinant tissue plasminogen activator (rtPA), also known as alteplase, and mechanical embolectomy with a retrievable stent are the two evidence-based strategies to achieve reperfusion.

Collateral flow is responsible for keeping the ischemic penumbra viable. It provides enough flow to prevent critical ischemia and infarction but not sufficient flow to maintain normal cellular function. This explains why the acute neurologic deficits exceed what would be expected for the established infarct core at the time of presentation and why neurologic function can improve after reperfusion. This collateral flow, however, is often tenuous and can sustain viability only for a limited period of time. Thus, without recanalization, the ischemic penumbra is destined to progress to infarction. Collateral flow can be

**KEY POINTS**

- Prompt reperfusion is the most effective treatment for patients with acute ischemic stroke.
- The three principles of acute stroke therapy are to achieve recanalization of the occluded vessel (and reperfusion of the ischemic tissue), to optimize collateral flow, and to avoid secondary brain injury.
- The ischemic penumbra is the region of hypoperfused brain that can still be viable with prompt recanalization of the occluded artery.
- Collateral flow is responsible for the temporary preservation of the ischemic penumbra.
protected by avoiding blood pressure drops and supported by the administration of IV fluids. The value of keeping the head of the bed flat for patients with acute ischemic stroke should be weighed against the risk of aspiration, and it was investigated in the HeadPoST (Head Position in Stroke Trial). In this trial, keeping the patients in a laying-flat position for 24 hours after hospital admission did not affect the likelihood of disability at 90 days when compared with patients who had the head of the bed elevated to at least 30 degrees. It is still unknown if this intervention could be beneficial for a more selected subset of patients (eg, patients with large vessel occlusion). Hemodynamic augmentation with vasopressors may be beneficial in well-selected cases (such as patients with cervical internal carotid artery occlusion without tandem intracranial occlusion), but the safety and efficacy of this strategy are otherwise unknown. Invasive interventions to improve collateral flow remain investigational. Blood pressure targets should be individualized based on several factors, including history of chronic hypertension, administration of IV thrombolysis, location and persistence of the vessel occlusion, and degree of collaterals. These targets should be dynamic depending on the evolution of the patient (eg, in a patient with a proximal artery occlusion, it is reasonable to keep a higher blood pressure target until recanalization and then lower the target after successful recanalization to avoid reperfusion injury).

Despite promising results in basic and translational experiments, numerous neuroprotective agents have failed to improve outcomes in clinical trials. Yet, avoidance of secondary insults is a form of neuroprotection. Hypoglycemia can exacerbate energy failure and should be strictly averted. Hyperglycemia is also associated with worse outcomes after an ischemic stroke, but no solid evidence exists that its correction improves outcomes. The SHINE (Stroke Hyperglycemia Insulin Network Effort) trial was a randomized controlled trial comparing tight glycemic control with IV insulin to maintain a glucose level between 80 mg/dL and 130 mg/dL versus standard glycemic control using subcutaneous insulin dosed according to a sliding scale to keep the glucose level lower than 180 mg/dL in patients with acute ischemic stroke within 12 hours of symptom onset. Intensive treatment of hyperglycemia was not associated with improved 90-day outcomes and resulted in more episodes of hypoglycemia. Fever is associated with worse clinical results; thus, treating fever may be beneficial. The value of hypothermia continues to be investigated, but currently there is no indication for inducing hypothermia in patients with acute ischemic stroke. Preventing infections (which notably includes dysphagia assessment before any oral intake) and early recurrent strokes are additional priorities in the care of the patient with acute stroke.

**ACUTE REPERFUSION TREATMENTS**

There is incontrovertible evidence that IV thrombolysis with rtPA and endovascular thrombectomy with a retrievable stent improve neurologic outcomes in patients with acute ischemic stroke. These treatments should be administered as quickly as possible after stroke onset, can be combined, and are safe in appropriately selected candidates.

IV thrombolysis and mechanical thrombectomy can produce reperfusion injury after recanalization. Reperfusion injury can manifest with hemorrhage and edema. It is more severe when the area of established infarction is larger. Good patient selection (ie, absence of a large ischemic core) and prompt treatment are crucial to avoid this complication.
Intravenous Thrombolysis

IV thrombolysis with rtPA is proven to be effective in improving functional outcomes after an ischemic stroke up to 4.5 hours after symptom onset. Randomized controlled trials followed by large observational studies confirming the rates of recovery noted in these trials and meta-analyses support this therapeutic indication (FIGURE 2-1). The US Food and Drug Administration (FDA) has only approved rtPA for use within 3 hours of stroke onset, but regulatory agencies in most other countries (including those in the European Union) have approved its administration within 4.5 hours of stroke onset, and 4.5 hours is the recommended time window in the guidelines from the American Heart Association (AHA)/American Stroke Association.

The initial evaluation of a patient with a possible acute stroke in the emergency department should focus on establishing whether the patient is eligible for reperfusion therapy. Necessary information includes the time the patient was last known to be well, medical conditions or recent surgery that could contraindicate thrombolysis, neurologic examination to calculate the National Institutes of Health Stroke Scale (NIHSS) score, a capillary glucose level, blood pressure, and brain imaging (CT scan with or without a CT angiogram depending on whether endovascular therapy is being considered).

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<td>≥22</td>
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FIGURE 2-1

Results of meta-analysis of individual data from major randomized trials of IV recombinant tissue plasminogen activator (rtPA) (alteplase) for acute ischemic stroke showing that thrombolysis increases the chances of achieving a modified Rankin Scale score of 0 to 1 (no symptoms or mild symptoms with no disability) at 90 days. Notice that the benefit is time dependent and no longer significant when the drug is administered more than 4.5 hours after symptom onset, though more recent evidence suggests that there may be patients with persistent ischemic penumbra on perfusion imaging for whom IV rtPA may still be beneficial up to 9 hours after symptom onset. Treatment is beneficial in patients older than 80 years, and the benefit is fairly consistent across all degrees of initial stroke severity.

The indications and contraindications for IV rtPA have been revisited in the most recent version of the AHA guideline for the management of acute stroke and modified by the FDA in the package insert for the drug (TABLE 2-1). As a result, more patients can be considered for IV thrombolysis in clinical practice. IV thrombolysis should not be withheld because of advanced age, and mild but disabling deficits justify treatment. Individualized clinical judgment is necessary when deciding whether to recommend thrombolysis to patients with weaker indications (such as nondisabling deficits) or relative contraindications. The safety and efficacy of IV thrombolysis in pediatric patients (younger than 18 years of age) is not well established.

IV rtPA infused within 3 hours of symptom onset increases the chances of functional independence at 3 months by one-third. The benefit is time dependent and much stronger when the drug is administered within the first 90 minutes after symptom onset (estimated number necessary to treat to help one more patient achieve functional independence is 3.6 within the first 90 minutes).
90 minutes and 4.3 between 91 and 180 minutes (CASE 2-1). Older patients and those with a very severe stroke at presentation have worse prognosis but can still benefit from IV rtPA. The benefit is less robust for patients treated between 3 and 4.5 hours, but rtPA is still beneficial in this extended window (number necessary to treat, 5.9).^{10,15}

The standard dose of IV rtPA for acute ischemic stroke is 0.9 mg/kg, with 10% administered as a bolus and the remainder infused over 1 hour. The total dose should not exceed 90 mg. In emergency departments of medical centers with more limited capabilities, patients can receive the bolus of rtPA and then be transferred to a primary stroke center or comprehensive stroke center while the rest of the dose of the drug is being infused (the drip-and-ship strategy). A lower dose of IV rtPA was investigated in the phase 3 ENCHANTED (Enhanced Control of Hypertension and Thrombolysis Stroke Study) that enrolled 3310 predominantly Asian patients to receive either 0.9 mg/kg or 0.6 mg/kg of IV rtPA within 4.5 hours of stroke onset.^{17} The reduced dose was inferior to the

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<th>American Heart Association Guideline 2019</th>
<th>US Food and Drug Administration (FDA) Package Insert 2015</th>
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<td>CT showing extensive hypodensity (eg, &gt;1/3 of the cerebral hemisphere)</td>
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</tr>
</tbody>
</table>

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a Updated from Rabinstein AA, Continuum (Minneap Minn). © 2017 American Academy of Neurology.
b In other situations listed in the guideline, the risk and benefit need to be individually assessed. Some of these situations include major extracranial trauma or major surgery within the previous 14 days, intradural arterial dissection, untreated giant intracranial aneurysm, intracranial arteriovenous malformation, multiple cerebral microbleeds on MRI (count >10), recent but not concomitant anterior wall ST-elevation myocardial infarction, pregnancy, and early puerperium.
c Last known well.
d Evidence also exists that perfusion imaging can be used to select candidates with stroke presenting upon wake up or between 4.5 and 9 hours of last known well, but these studies were published after the evidence review for the 2019 American Heart Association guidelines.
e The term removed is used to denote a change compared with the previous version of the package insert (2009).
f Activated partial thromboplastin time, INR, platelet count, ecarin clotting time, thrombin time, factor Xa activity assays.

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standard dose for the end point of death or any degree of disability at 90 days, although it was associated with a lower risk of symptomatic intracerebral hemorrhage (which was low in both treatment groups).

No other thrombolytic agent has been approved for use in ischemic stroke. Yet, there is growing information on the value of tenecteplase for treating patients with acute cerebral ischemia. Tenecteplase is a bioengineered variant of rtPA that has a longer half-life, greater fibrin specificity, and increased resistance against tissue plasminogen inhibitor-1 than rtPA. Therefore, it is administered as a single IV bolus. The NOR-TEST (Norwegian Tenecteplase Stroke Trial) tested the safety and efficacy of tenecteplase 0.4 mg/kg (up to 40 mg) versus standard-dose rtPA within 4.5 hours of acute ischemic stroke onset.¹⁸ Most patients had mild stroke severity (median NIHSS score of 4). The proportions of patients with serious adverse events, including symptomatic intracerebral hemorrhage (ICH), and functional independence at 3 months were similar in the tenecteplase and rtPA groups. However, the authors could not conclude that the two treatments were equivalent because the trial had been designed to test only for superiority. The EXTEND-IA TNK (Tenecteplase Versus Alteplase Before Endovascular Therapy for Ischemic Stroke) trial randomly assigned patients with acute ischemic stroke and a proximal intracranial artery occlusion eligible for mechanical thrombectomy to receive tenecteplase (0.25 mg/kg, up to 25 mg) or standard-dose rtPA within 4.5 hours of symptom onset.¹⁹ Patients treated with tenecteplase had higher rates of recanalization/reperfusion at the time of initial assessment by conventional angiography (22% versus 10% with rtPA) and better functional outcomes at 3 months with similarly low rates of symptomatic ICH (1% in both groups). Thus, tenecteplase may become a preferred alternative to rtPA if future studies confirm these promising results.

CASE 2-1

A 62-year-old man presented with the sudden onset of right-sided weakness and dysarthria. The patient promptly arrived by ambulance to the emergency department 25 minutes after symptom onset. His National Institutes of Health Stroke Scale (NIHSS) score was 8. Noncontrast brain CT showed no hemorrhage, acute ischemic changes, or hyperdense vessel sign. He had no contraindications for IV thrombolysis. IV recombinant tissue plasminogen activator (rtPA) was started 46 minutes after symptom onset. CT angiography was performed after initiation of IV rtPA and showed no evidence of large artery occlusion. The patient improved rapidly within the following 3 hours, and by the following day, he had no residual symptoms.

COMMENT

The benefit from IV thrombolysis for patients with acute ischemic stroke is highly dependent on time to administration. Administration of the bolus within 60 to 90 minutes affords maximal chances of improvement. In order to treat patients within this short time window, it is essential to optimize the efficiency of early evaluation, CT scanning, and drug delivery. In the United States, stroke centers are expected to be able to consistently administer IV rtPA within 60 minutes of patient arrival to the emergency department.
Hemorrhage is the most dangerous complication after thrombolysis. The reported rates of symptomatic intracerebral hemorrhage (sICH) have varied (between 1.9% and 6.4%), depending on its definition and the design of the study.20 However, most cases of sICH are caused by reperfusion injury and worsen strokes that were already severe and destined to be disabling. Hemorrhagic transformation of a large infarction can increase the risk of death, but sICH rarely negates what would have otherwise been a good recovery. In fact, the number needed to harm for IV rtPA has been estimated to be 126 for the combined end point of disability or death.21 The risk of sICH is increased with old age, diabetes mellitus, severe hyperglycemia, uncontrolled hypertension, and larger hypodensity on baseline CT scan.22 The risk of sICH might also be higher in patients with cerebral microbleeds (only visible on hemosiderin-sensitive MRI sequences and, therefore, most often not known at the time of thrombolysis), although this association is not entirely certain.23

When sudden neurologic decline occurs during rtPA infusion, the infusion should be immediately stopped and a CT scan should be obtained emergently. Whenever post-thrombolysis sICH is diagnosed, treatment consists of control of hypertension (systolic target 140 mm Hg to 160 mm Hg) and reversal of the fibrinolytic effect with cryoprecipitate (10 units) or an antifibrinolytic agent (tranexamic acid 10 mg/kg to 15 mg/kg IV over 20 minutes or ε-aminocaproic acid 5 g IV followed by an infusion of 1 g over 1 hour if necessary). Additional cryoprecipitate may be given if the serum fibrinogen level remains below 150 mg/dL.24

Orolingual angioedema is a rare but potentially serious complication of rtPA administration. The risk is higher in patients taking angiotensin-converting enzyme inhibitors. It is typically asymmetric and tends to involve the hemiparetic side. The most severe cases can compromise airway patency; thus, careful monitoring is indispensable. Treatment consists of a combination of diphenhydramine (50 mg IV), ranitidine (50 mg IV), and dexamethasone (10 mg IV).

While IV thrombolysis is the standard of care for eligible patients with acute ischemic stroke, this treatment has limitations. In addition to its short time window and contraindication in patients with increased bleeding risk, IV rtPA often fails to recanalize proximal artery occlusions caused by large clots. These are the most disabling strokes, and strong evidence now exists that these patients should be considered for endovascular therapy.

Mechanical Thrombectomy
Endovascular mechanical thrombectomy must be considered the standard of care for patients with disabling symptoms caused by acute cerebral ischemia related to occlusion of the intracranial carotid artery or M1 segment of the middle cerebral artery (CASE 2-2). The value of mechanical thrombectomy is supported by multiple randomized controlled trials that showed substantial improvement in functional outcomes with this treatment, with numbers necessary to treat ranging from 3 to 7 across these trials.25-30 Furthermore, since the benefit conferred by mechanical thrombectomy spanned the entire range of functional outcome, the number necessary to treat to reduce disability by one level on the modified Rankin Scale was only 2.6. This benefit was confirmed across multiple subgroups (including patients older than 80 years and those with very severe strokes as indicated by a baseline NIHSS score greater than 20).31 Mechanical

KEY POINTS
- Most cases of symptomatic intracerebral hemorrhage are caused by reperfusion injury causing hemorrhagic transformation of an already severe stroke.
- Endovascular therapy with mechanical thrombectomy substantially improves functional outcomes in patients with acute stroke from a proximal intracranial artery occlusion (internal carotid artery or M1 segment) especially when the intervention is performed within 6 hours of symptom onset.
- Some previously cited contraindications for IV thrombolysis have been revisited, thus expanding the pool of patients who can be considered good candidates for this treatment.
- Benefit from IV thrombolysis is much greater in the first 90 minutes from symptom onset.
thrombectomy was also proven to be quite safe, with a pooled rate of sICH of 4.4% across all patients treated in the intervention arms of the five trials.31

The main features of the randomized controlled trials establishing the benefit of mechanical thrombectomy are summarized in TABLE 2-2. All of them enrolled patients with severe neurologic deficits and good prestroke functional status who presented mostly within 6 hours of symptom onset. Major early ischemic changes on the baseline CT were a reason for exclusion. The great majority of patients in both arms were treated with IV rtPA. The characteristics of the ideal candidates for acute endovascular therapy are listed in TABLE 2-3. However, other patients may also benefit, including those presenting beyond 6 hours (see section on Wake-up Strokes and Strokes of Unknown Time of Onset below), patients with M2 branch occlusions, some patients with extensive early ischemic

CASE 2-2

A 62-year-old man without significant past medical history collapsed in his bathroom. The noise alerted his son, who found his father on the ground, mute and unable to move the right side of his body. He immediately called an ambulance. Paramedics in the field noted a blood pressure of 180/100 mm Hg and an irregularly irregular pulse.

In the emergency department, the patient had a fluctuating level of alertness, forced left gaze deviation, a right visual field deficit, global aphasia with mutism, right hemiplegia, and severe right hypoesthesia. His National Institutes of Health Stroke Scale (NIHSS) score was 22. Noncontrast head CT showed a hyperdense left middle cerebral artery sign, but his ASPECTS (Alberta Stroke Program Early CT Score) was 10 (FIGURE 2-2A). CT angiogram showed a flow gap in the left middle cerebral artery with good collateral flow distal to it (FIGURE 2-2B).

IV thrombolysis was started 55 minutes after symptom onset, and the patient was taken to the angiographic suite for endovascular therapy. Groin puncture took place 67 minutes after symptom onset. Initial injection of contrast into the left internal carotid artery showed that this vessel was occluded at the top of its supraclinoid segment (FIGURE 2-2C). Complete recanalization with full reperfusion was rapidly achieved with mechanical thrombectomy using a retrievable stent (FIGURE 2-2D). The patient began improving on the angiographic table and continued to improve overnight. By the next morning, his NIHSS score was 3. Repeat CT showed a small infarction in the left lenticular nucleus (FIGURE 2-2E). At 3 months, the patient had full function and no residual symptoms.

COMMENT

Thanks to technologic advances, endovascular therapy with mechanical thrombectomy is highly effective in achieving reperfusion in patients with proximal intracranial artery occlusions. It is usually combined with IV thrombolysis. However, endovascular recanalization is also beneficial in patients with contraindications for IV rtPA. Adequate patient selection (in this case, the patient had no evidence of ischemic changes on CT scan and good collaterals on CT angiogram) and prompt intervention are crucial to optimize the chances of therapeutic success.
changes on CT scan or large cores on CT perfusion, patients with acute vertebrobasilar occlusions (see section on Posterior Circulation Strokes below), and patients with moderate preexistent disability. Also, the best imaging modality to select patients for acute endovascular intervention remains to be determined. Evaluation of early ischemic changes on a noncontrast CT is indispensable, but the relative value of collateral flow assessment by noninvasive angiography and degree of perfusion deficit by CT or MRI perfusion scans continues to be debated for patients presenting within the first 6 hours after symptom onset. Perfusion imaging is necessary to identify candidates for endovascular therapy after 6 hours from symptom onset. Imaging selection and endovascular stroke therapy are discussed in detail in, respectively, the article “Neuroimaging in Acute Stroke” by Bijoy K. Menon, MD, DM, MSc, FRCPC, and the article “Endovascular Treatment of Acute

**FIGURE 2-2**
Imaging of the patient in CASE 2-1. A, CT of the brain showing hyperdensity in the left middle cerebral artery consistent with acute thrombus (arrow). B, CT angiogram showing a focal area of left middle cerebral artery occlusion (arrow) with good collateral flow in the vessels distal to the occlusion. C, Digital subtraction angiogram demonstrating occlusion of the distal segment of the left internal carotid artery as well as intact collaterals supplying the peripheral middle cerebral artery branches. D, Full recanalization and reperfusion after mechanical thrombectomy. E, Repeat CT showing a small residual infarction in the left basal ganglia (arrow).

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Ischemic Stroke” by Gisele S. Silva MD, MPH, PhD, and Raul G. Nogueira, MD, in this issue of Continuum.

SPECIAL SITUATIONS
Special clinical situations remain for which the evidence is insufficient to determine the best course of action. Until more definite data become available, these cases should be approached considering individual factors and what is known from collective experience.

Wake-up Strokes and Strokes of Unknown Time of Onset
Patients whose neurologic deficits are first noticed upon their awakening represent a particular challenge to the clinician. The same applies to those with

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</table>

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unclear time of onset (such as when the patient is aphasic and the onset of symptoms was not witnessed). Although these situations were formerly considered contraindications for acute reperfusion treatment, evidence exists that carefully selected patients with wake-up stroke or stroke of unknown onset can definitely benefit from endovascular therapy and some might benefit from IV thrombolysis. All trials showing benefit of acute reperfusion treatment in patients with wake-up stroke or stroke of unknown onset enrolled patients who had a baseline CT scan without evidence of extensive early ischemic changes and with advanced imaging showing salvageable hypoperfused tissue.

DAWN (the DWI or CTP Assessment With Clinical Mismatch in the Triage of Wake-Up and Late Presenting Strokes Undergoing Neurointervention) randomly assigned patients with acute ischemic stroke from a large intracranial

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<table>
<thead>
<tr>
<th>Study Variable</th>
<th>MR CLEAN</th>
<th>ESCAPE</th>
<th>EXTEND-IA</th>
<th>SWIFT PRIME</th>
<th>REVASCAT</th>
<th>THRACE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset to groin puncture, median (minutes)</td>
<td>260</td>
<td>185</td>
<td>210</td>
<td>224</td>
<td>269</td>
<td>250</td>
</tr>
<tr>
<td>Onset to reperfusion, median (minutes)</td>
<td>Not reported</td>
<td>241</td>
<td>248</td>
<td>250</td>
<td>355</td>
<td>303</td>
</tr>
<tr>
<td>M1 occlusion, %&lt;sup&gt;b&lt;/sup&gt;</td>
<td>66.1 versus 62</td>
<td>68.1 versus 71.4</td>
<td>57 versus 51</td>
<td>67 versus 77</td>
<td>64.7 versus 64.4</td>
<td>86 versus 79</td>
</tr>
<tr>
<td>TICI score 2b–3, %</td>
<td>58.7</td>
<td>72.4</td>
<td>86</td>
<td>88</td>
<td>65.7</td>
<td>69</td>
</tr>
<tr>
<td>mRS 0 to 2 at 90 days, %&lt;sup&gt;b&lt;/sup&gt;</td>
<td>32.6 versus 19.1</td>
<td>53 versus 29.3</td>
<td>71 versus 40</td>
<td>60.2 versus 35.5</td>
<td>43.7 versus 28.2</td>
<td>53 versus 42</td>
</tr>
<tr>
<td>OR 1.8</td>
<td>OR 4.2</td>
<td>OR 1.7</td>
<td>OR 1.7</td>
<td>OR 2.1</td>
<td>OR 1.55</td>
<td>(95% CI 1.05–2.30)</td>
</tr>
<tr>
<td>(95% CI 1.4–2.4)</td>
<td>(95% CI 1.4–12)</td>
<td>(95% CI 1.2–2.3)</td>
<td>(95% CI 1.1–4.0)</td>
<td>(95% CI 1.05–2.30)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>mRS 0 to 2 at 90 days, NNT</td>
<td>7.1</td>
<td>4.2</td>
<td>3.2</td>
<td>4.0</td>
<td>6.3</td>
<td>9.1</td>
</tr>
<tr>
<td>sICH, %&lt;sup&gt;b&lt;/sup&gt;</td>
<td>6 versus 5.2</td>
<td>3.6 versus 2.7</td>
<td>0 versus 6</td>
<td>1 versus 3</td>
<td>1.9 versus 1.9</td>
<td>2 versus 2</td>
</tr>
</tbody>
</table>

<sup>a</sup> Updated from Rabinstein AA, Continuum (Minneap Minn).<sup>2</sup> © 2017 American Academy of Neurology.

<sup>b</sup> Values in this row are representative of patients who were treated with endovascular thrombectomy versus those who were not.

<sup>c</sup> 84% within 6 hours.

<sup>d</sup> 67% of MR CLEAN subjects and 81% of SWIFT PRIME subjects had CT perfusion.
artery occlusion who had last been known well within the previous 6 to 24 hours to thrombectomy versus standard care alone.\(^{34}\) To be eligible for the trial, patients must have had a mismatch between the severity of the clinical deficits and the volume of the ischemic core as defined by diffusion-weighted imaging or by CT perfusion criteria. Meanwhile, the DEFUSE 3 (Diffusion and Perfusion Imaging Evaluation for Understanding Stroke Evolution 3) randomly assigned patients with large intracranial artery occlusion between 6 and 16 hours after symptom onset and selected them exclusively by radiologic criteria indicating mismatch between the areas of ischemic core and ischemic penumbra.\(^{35}\) Both trials showed a very dramatic benefit from thrombectomy, with numbers necessary to treat between 2 and 4 and no major safety concerns. This evidence strongly supports endovascular thrombectomy for patients with wake-up stroke or stroke of unknown time of onset presenting within 24 hours with a large intracranial artery occlusion and ischemic cores that do not fully explain the deficits or are surrounded by an extensive penumbra.

Evidence, albeit much weaker, also supports the use of IV thrombolysis for selected patients with wake-up stroke or stroke of unknown time of onset. The WAKE-UP (Efficacy and Safety of MRI-Based Thrombolysis in Wake-Up Stroke) trial randomly assigned patients with unknown time of symptom onset who had a lesion on MRI–diffusion-weighted imaging but not on fluid-attenuated inversion recovery (FLAIR) to receive IV rtPA or placebo.\(^{36}\) Although enrollment had to be stopped prematurely because of insufficient funding, the results showed a modest but significant benefit from thrombolysis (modified Rankin Scale score of 0 to 1 at 90 days, 53.3% versus 41.8% with placebo; adjusted odds ratio, 1.61; 95% confidence interval [CI], 1.09 to 2.36; \(P=0.02\)) at the expense of nonsignificant but notable increases in symptomatic ICH (2% with IV rtPA versus 0.4% with placebo) and death (4.1% with IV rtPA versus 1.2% with placebo). Other randomized trials tested IV thrombolysis for patients with stroke symptoms between 4.5 and 9 hours from symptom onset or wake-up stroke who had salvageable brain tissue identified by MRI or CT perfusion.\(^{12,37,38}\) When taken in conjunction, the results from these trials indicated that IV thrombolysis may increase the chances of excellent functional outcome at 3 months (adjusted odds ratio, 1.86; 95% CI, 1.15 to 2.99; \(P=0.01\)) but also increase the risk of symptomatic ICH (adjusted odds ratio, 9.7; 95% CI, 1.23 to 76.55; \(P=0.03\)).

**TABLE 2-3 Candidates for Acute Endovascular Stroke Therapy**

- Age \(\geq 18\) years
- National Institutes of Health Stroke Scale score \(\geq 6\)
- Time from symptom onset to groin puncture \(< 6\) hours (up to 24 hours if evidence of sizable ischemic penumbra is seen on perfusion imaging)
- Good prestroke functional status
- Alberta Stroke Program Early CT Score \(\geq 6\) on baseline CT scan
- Presence of proximal intracranial artery occlusion
Intravenous Thrombolysis in Patients Taking Newer Anticoagulants

IV rtPA can be administered within 3 hours of symptom onset to patients taking warfarin whose international normalized ratio (INR) is 1.7 or less. However, no adequate safety data with the newer anticoagulants (the direct thrombin inhibitor dabigatran and the factor Xa inhibitors rivaroxaban, apixaban, and edoxaban) exist. Readily available laboratory studies cannot quantify the degree of anticoagulation. Thus, it is most prudent to withhold thrombolysis in patients taking these agents. However, patients with proximal intracranial artery occlusion may benefit from mechanical thrombectomy.

Minor and Rapidly Improving Deficits

Although thrombolysis is often withheld because the symptoms are considered mild or patients appear to be rapidly improving, several observational studies have shown that up to one-third of patients who are otherwise eligible for thrombolysis but do not receive it for these reasons are disabled at 3 months. Thus, one must be very careful when assessing these patients. IV rtPA might be justified when the NIHSS score is low but the symptoms are nonetheless disabling for the patient (eg, hemianopia in a professional driver). Improving deficits that are still disabling at the time of the neurologic evaluation may similarly warrant thrombolysis. Patients with mild deficits that are not disabling may require a more conservative approach. The value of IV rtPA within 3 hours of symptom onset in patients with mild deficits (NIHSS score of 5 or less) that were judged nondisabling was investigated in the PRISMS (Potential of rtPA for Ischemic Strokes With Mild Symptoms) trial. Enrollment was stopped very early because of slow recruitment, but available results did not suggest a benefit from thrombolysis in these patients with minor, nondisabling stroke.

Posterior Circulation Strokes

Randomized trials of IV thrombolysis and mechanical thrombectomy (except for very few patients enrolled in the THRACE [Trial and Cost Effectiveness Evaluation of Intra-arterial Thrombectomy in Acute Ischemic Stroke] trial) have been restricted to patients with anterior circulation strokes. Yet, clinical experience with treating posterior circulation infarctions with these therapies exists. Basilar artery occlusions can be devastating unless recanalization is achieved. Registry data indicate that IV rtPA and mechanical thrombectomy can result in functional independence at 3 months in 30% to 40% of cases; these rates of favorable outcome are clearly greater than those reported without reperfusion therapy. The value of endovascular therapy for acute basilar occlusion is currently being investigated in BASICS (the Basilar Artery International Cooperation Study). Even among patients who are treated with reperfusion strategies, mortality remains high (30% to 35%). Therefore, some consider it reasonable to extend the therapeutic window for IV thrombolysis beyond 4.5 hours and for mechanical thrombectomy even beyond 24 hours in patients with basilar artery occlusion who do not have a large established pontine or cerebellar infarction, especially if they have fluctuating deficits.

FUTURE DIRECTIONS

Current efforts are focused on increasing the efficiency of systems of care and investigating new strategies for acute stroke therapy. The common objective is to...
increase the number of patients with acute ischemic stroke who can regain perfusion of the ischemic tissue before infarction is established.

Mobile stroke units are rapidly gaining acceptance. These are special ambulances equipped with a portable CT scanner and digital technology to enable telecommunication with a stroke specialist. They have been shown to allow safe initiation of IV thrombolysis while en route to the stroke center. This option, although expensive, can be a very welcome solution for some heavily populated urban communities. Dispatchers and paramedics must receive specific stroke education to optimize the efficiency and safety of these mobile units. For more information about these mobile units, refer to the article “Innovations in Prehospital Stroke Management Utilizing Mobile Stroke Units” by Anne W. Alexandrov, PhD, AGACNP-BC, ANVP-BC, FAAN, and Andrei V. Alexandrov, MD.

As mentioned earlier, tenecteplase offers the advantage of practicality over rtPA and is the thrombolytic agent of choice for patients with acute myocardial infarction. Results of available trials suggest that it could also replace rtPA for acute stroke. Further studies will probably answer this question in the near future.

Once systems of care are optimized to guarantee fast access to the angiographic suite for patients with acute stroke, it will be necessary to perform a trial comparing IV thrombolysis followed by mechanical thrombectomy versus primary mechanical thrombectomy for patients with severe stroke and proven proximal artery occlusion. For now, optimizing triaging mechanisms by refining the identification of patients with large intracranial artery occlusion in the field remains a priority.

Efforts continue to expand indications for endovascular therapy, both within the early and extended time windows. Observational data suggest that further research is warranted to determine if patients with more distal arterial occlusions, mild deficits at risk of decline from collateral failure, and large cores might benefit from mechanical thrombectomy and, if so, how these patients should be optimally selected for therapy. Other areas of active research to maximize benefit from endovascular therapy include the comparison of general anesthesia versus local anesthesia or conscious sedation and the determination of the optimal blood pressure target during and after the endovascular treatment.

Collateral flow augmentation is another proposed strategy. In current practice, this is sometimes attempted with vasopressors. Evidence is restricted to small case series and one pilot feasibility study. Yet, hemodynamic augmentation with vasopressors can occasionally work, in particular in patients with proximal vessel occlusions who are not deemed candidates for endovascular recanalization or in whom the recanalization attempt was unsuccessful. Mechanical techniques for collateral recruitment (such as external counterpulsation and intraaortic inflation devices) have been shown feasible and safe, but their efficacy remains to be proven.

**CONCLUSION**

Acute ischemic stroke is a medical emergency in which every minute counts. Achievement of reperfusion can reverse neurologic deficits, even if severe, and allow patients to regain function. Two reperfusion strategies are now proven: IV thrombolysis...
rtPA and mechanical thrombectomy (FIGURE 2-3). They are both safe and effective for the right candidates. Patient selection is crucial to optimize outcomes, but the attitude of the clinician should be that treatment should be given unless a solid contraindication exists.

At this juncture, efforts should be concentrated on refining systems of care to allow more patients to have access to reperfusion treatment. Expanding the number of candidates for intervention will require continuous education of the community to recognize signs of stroke, improving the initial triage of patients with stroke, and speeding evaluation and treatment in the hospital.

REFERENCES


