Acute Treatment of Ischemic Stroke

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KEYWORDS

• Acute ischemic stroke • Thrombolysis • Endovascular treatment

KEY POINTS

- Intravenous alteplase is safe and effective when given within 4.5 hours of stroke symptom onset.
- Endovascular treatment within 6 hours is safe and effective for acute ischemic stroke due to anterior circulation proximal large vessel occlusion with aspects ≥6.
- Endovascular treatment within 6 to 24 hours from symptom onset is safe and effective in patients who meet dawn or defuse-3 trial criteria.
- Further research is needed in the area of endovascular treatment in patients with low NIHSS, large core infarction, and middle vessel occlusions.

INTRODUCTION

Every year close to 700,000 people experience a new or recurrent ischemic stroke in the United States, and 3% of the total US population is affected by stroke. Stroke is the leading cause of severe disability and the fifth leading cause of death in the nation. Owing to the widespread impact of stroke in patients' individual lives and the tremendous financial cost on the economy, there are many efforts to improve stroke care. Acute therapies are available to decrease the morbidity associated with ischemic stroke and include intravenous thrombolysis and endovascular treatment.

INTRAVENOUS THROMBOLYSIS

Intravenous (IV) recombinant tissue-type plasminogen activator (alteplase) has been approved by the United States Food and Drug Administration (USFDA) for the treatment of acute ischemic stroke within 3 hours of witnessed symptom onset or last known well since 1996.[1] Patients older than 18 years are eligible to receive this treatment if they have a disabling deficit, which is often quantified using the National Institutes of Stroke Severity Scale (NIHSS), and those deficits are presumed to be due to an ischemic stroke with no evidence of an acute hemorrhage on a noncontrast head

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computed tomography (CT). This includes patients with rapidly improving symptoms who continue to have deficits, seizure at onset with disabling symptoms not due to a postictal state, large NIHSS scores, and age more than 80 years. Blood pressure must be kept less than 185/110 before and during the infusion and less than 180/105 for 24 hours after the infusion. Blood pressure parameters may be achieved however the treating physician sees fit, though labetalol, nicardipine, and clevidipine are commonly used agents. Patients treated with alteplase have been shown to be 30% more likely to have minimal or no disability at 3 months compared to patients treated with placebo.[2] This favorable outcome helped lead to widespread practice implementation.

Extended Window for Intravenous Alteplase

Intravenous alteplase can also be given within 3 to 4.5 hours of witnessed symptom onset or last known well, although the odds ratio for a favorable outcome compared with placebo during this time frame is 1.28, and its use during this time frame is not approved by the USFDA.[3,4] The European Cooperative Acute Stroke Study (ECASS) III trial showed that alteplase was safe and effective in this time window with strict inclusion criteria that included patients $\leq$80 years of age, without a history of both diabetes mellitus and prior stroke, with an NIHSS score $\leq$25, not taking any oral anticoagulation, and without imaging evidence of ischemic injury involving more than one-third of the middle cerebral artery (MCA) territory.[3] Further published data indicate that not all these exclusion criteria are justified. The 2019 American Heart Association/American Stroke Association (AHA/ASA) guideline for the early management of acute ischemic stroke states that alteplase treatment in the 3- to 4.5-hour window may be safe and reasonable in patients who are older than 80 years, or have a history of diabetes mellitus and stroke, or are on warfarin with an international normalized ratio (INR) less than 1.7.[4] However, the benefit remains uncertain in patients with an NIHSS greater than 25.

Current Evidence and Guidelines for Intravenous Alteplase Thrombolysis

Although the original National Institute of Neurologic Disorders and Stroke (NINDS) trial had an extensive list of exclusion criteria, the AHA/ASA committees have revised this list based on documented scientific evidence of harm or lack of benefit with the use of data repositories and clinical expertise. A list of contraindications, based on either a benefit of treatment that equals the risk of treatment or a greater risk of treatment than benefit, are provided in a bulleted list below.[2]

In patients without a known coagulopathy, IV alteplase can be begun before the availability of the platelet count, INR, activated partial thromboplastin time (aPTT), or prothrombin time (PT). This is due to the overall low rates of unsuspected abnormal platelet counts or coagulation studies in the population of acute stroke patients.[5,6] However, if the platelet count returns and is less than 100,000/mm^3 or the INR is greater than 1.7 or the PT is abnormally elevated, alteplase should be discontinued.[7] In addition, if a patient is on a direct thrombin inhibitor or a direct factor Xa inhibitor, and the appropriate laboratory test such as aPTT, INR, ecarin clotting time, thrombin time, or direct factor Xa activity assay is normal, alteplase could be considered. Obtaining these additional coagulation tests may cause delays, so practitioners should be aware of the availability of and the time required to obtain results at their institution.

There is an important emphasis on whether a patient's symptoms are disabling. If a patient presents within 4.5 hours of last known well and has a mild deficit that is judged by the examiner to be disabling, then treatment with IV alteplase is recommended, regardless of a "low" NIHSS score. This assessment should be based on the impact

the deficit has on the patient's livelihood and lifestyle. For example, if a patient scores a 1 for aphasia on the NIHSS and is a reporter, they may be judged to have a disabling deficit despite a low NIHSS. However, if a patient presents within 4.5 hours from last known well and has mild, *non-disabling* deficits, treatment with IV alteplase is not recommended. The Potential of tPA for Ischemic Strokes with Mild Symptoms (PRISMS) trial affirmed this recommendation. It randomized patients with mild symptoms, defined as an NIHSS 0 to 5, where the neurologic deficits were not felt to interfere with activities of daily living or prevent return to work, to aspirin and IV alteplase, and found no benefit from treatment with IV alteplase.[8]

It is also important to understand limitations of the NIHSS. The scoring paradigm is heavily weighted toward left MCA infarcts. A patient can have a disabling posterior circulation stroke, but have a low score because the NIHSS does not quantify symptoms of posterior circulation strokes such as axial ataxia, dysphagia, and diplopia.

Intravenous alteplase contraindications

- Mild *non-disabling* symptoms (NIHSS 0–5)
- Head CT with extensive regions of hypoattenuation
- Prior ischemic stroke within 3 months
- Head CT with acute intracranial hemorrhage
- Subarachnoid hemorrhage
- Intra-axial intracranial neoplasm
- Intraspinal or intracranial surgery or serious head trauma within 3 months
- History of intracranial hemorrhage
- Gastrointestinal malignancy or gastrointestinal bleed within 21 days
- Known coagulopathy, including platelets less than 100,000/mm^3, INR greater than 1.7, aPTT greater than 40s, or PT greater than 15s
- Low-molecular-weight heparin full treatment dose received within 24 hours
- Current use of direct thrombin inhibitors or direct factor Xa inhibitors within 48 hours
- Infective endocarditis
- Aortic arch dissection

Expanded inclusion criteria

Although patients with the following conditions were historically excluded from receiving alteplase, further evidence has shown that IV alteplase is reasonable in patients with[9]:

- Extracranial arterial dissection
- Unruptured intracranial aneurysm $\leq$10 mm
- 1 to 10 cerebral microbleeds demonstrated on a prior MRI
- Menstruating women without a history of menorrhagia
- Extra-axial intracranial neoplasms
- Acute myocardial infarction
- Non-ST-segment myocardial infarction (STEMI) and STEMI involving the right or inferior myocardium within 3 months
- Acute ischemic stroke as a complication of cardiac or cerebral angiographic procedures
- History of diabetic hemorrhagic retinopathy or other hemorrhagic ophthalmic condition while weighing the potential increased risk of visual loss against the benefit of treatment
- Suspected stroke mimic but obtaining additional confirmatory studies would delay treatment

- Illicit drug use
- Sickle cell anemia

Intravenous alteplase may be considered, with careful weighing of the risks and benefits, in individuals with disabling acute stroke symptoms and the following known conditions[2]:

- Initial blood glucose values less than 50 or greater than 400 that have normalized, yet clinical deficits remain
- Dural puncture in the previous 7 days
- Major nonhead trauma within the previous 14 days
- Major surgery in the previous 14 days
- History of previous (greater than 21 days prior) gastrointestinal or genitourinary bleeding
- Active menstruation with a history of menorrhagia without anemia or hypotension
- Pre-existing dementia
- Warfarin use and an INR $\leq$1.7 or a PT less than 15 seconds
- Myocardial infarction within 3 months involving the left anterior myocardium
- Acute pericarditis and stroke symptoms likely to produce severe disability (cardiology consultation is recommended)
- Left atrial or ventricular thrombus and stroke symptoms likely to produce severe disability
- Cardiac myxoma or papillary fibroelastoma and stroke symptoms likely to produce severe disability
- Pregnancy and moderate to severe stroke
- Pre-existing disability with a modified Rankin score $\geq$2
- Systemic malignancy and reasonable (>6 months) life expectancy

Patient conditions where the benefit of and risk associated with intravenous alteplase remain uncertain are[2]:

- Arterial puncture at a noncompressible site in the previous 7 days
- Intracranial arterial dissection
- Giant unruptured intracranial aneurysms
- Unruptured, untreated intracranial vascular malformations
- High burden (>10) of cerebral microbleeds on a previous MRI
- Acute pericarditis and stroke symptoms likely to produce mild disability
- Left atrial or ventricular thrombus and stroke symptoms likely to produce mild disability
- Early postpartum period (<14 days after delivery)
- History of bleeding diathesis or coagulopathy

Complications of Treatment

Life-threatening complications of intravenous alteplase therapy include orolingual angioedema and symptomatic intracerebral hemorrhage. **Box 1** includes treatment algorithms for orolingual angioedema management and alteplase reversal in patients with a symptomatic intracranial hemorrhage.

Further Expansion of Treatment with Intravenous Thrombolysis: Fluid-Attenuated Inversion Recovery/Diffusion Weighted Imaging Mismatch

Approximately, 30% of acute ischemic stroke patients who present to the emergency department have an unclear stroke symptom onset time,[10] making it difficult to determine intravenous thrombolysis eligibility. The WAKE-UP and MR WITNESS trials

Box 1
Management of IV alteplase complications

A. Orolingual Edema
   1. Maintain airway
      a. Intubation may not be necessary if the edema is limited to the anterior tongue and lips
      b. Edema involving larynx, palate, floor of mouth, or oropharynx with rapid progression within 30 minutes may require intubation
      c. Awake fiberoptic intubation is optimal as nasal-tracheal intubation my pose risk of epistaxis post-IV alteplase.
   2. Discontinue IV alteplase infusion and hold any angiotensin-converting enzyme inhibitors
   3. Administer IV methylprednisolone 125 mg x1
   4. Administer IV diphenhydramine 50 mg x1
   5. Administer famotidine 20 mg IV x1
   6. If there is further increase in angioedema:
      a. Administer epinephrine 1 mg/mL 0.3 mL intramuscular injection x1 OR racemic epinephrine 2.25% orally inhaled solution 0.5 mL nebulization x1
      b. Plasma-derived C1 esterase inhibitor (Berinert) 20 international units/kg IV infusion may be considered in refractory cases

B. Symptomatic Intracranial Bleeding within 12 hours of IV Alteplase
   1. Stop alteplase infusion
   2. Obtain CBC, PT (INR), aPTT, fibrinogen level, and type and cross-match
   3. Obtain an emergent nonenhanced head CT
   4. If intracranial hemorrhage is confirmed:
      a. Cryoprecipitate (includes factor VIII): 10 U infused over 10 to 30 minutes (onset in 1 hour, peaks in 12 hours); administer an additional dose for fibrinogen level of less than 200 mg/dL
      b. Consider Tranexamic acid 1000 mg IV infused over 10 minutes OR ε-aminocaproic acid 4 to 5 g over 1 hour, followed by 1 g IV/h if cryoprecipitate is unavailable, or other blood products are contraindicated
   5. Supportive care to include blood pressure, intracranial pressure, cerebral perfusion pressure, and mean arterial pressure management

Abbreviations: aPTT, activated partial thromboplastin time; CBC, complete blood count; CT, computed tomography; INR, international normalized ratio; IV, intravenous; PT, prothrombin time.

enrolled 503 patients and 80 patients, respectively, between the ages of 18 and 85 years, who either awoke with stroke symptoms or had unclear time of symptom onset, but remained within 4.5 hours of symptom recognition. These trials enrolled patients in whom MRI demonstrated ischemia on diffusion-weighted imaging (DWI) but no visible change on fluid-attenuated inversion recovery (FLAIR), thereby identifying patients with recent stroke onset. Patients were excluded if there was a DWI lesion larger than one-third of the MCA territory, NIHSS greater than 25, contraindication to treatment with alteplase, or if thrombectomy was planned.[11,12]

In MR WITNESS, which was an observational study in which all subjects were treated with IV alteplase, rates of symptomatic hemorrhage were similar to those in the ECASS III trial. This helped to establish that the use of intravenous alteplase in patients with unwitnessed stroke that have a DWI-FLAIR mismatch is safe.[11] The WAKE-UP trial helped establish a functional outcome benefit in patients who receive alteplase. More specifically, the primary end-point of a modified Rankin scale (mRS; **Box 2**) of 0 to 1 at 90 days was achieved in 53.3% of patients in the alteplase arm as compared to 41.8% in the placebo arm ($P = .02$).[12] The median NIHSS was 7 in MR WITNESS and 6 in WAKE-UP, exhibiting that the majority of patients had minor strokes compared to the median NIHSS of 16 to 17 seen in landmark endovascular studies. Wake-up strokes accounted for 94% of the WAKE-UP study population. As a result, their study

Box 2
Modified Rankin scale (mRS)

0—No symptoms

1—No significant disability, despite symptoms; able to perform all usual duties and activities

2—Slight disability; unable to perform all previous activities but able to look after own affairs without assistance

3—Moderate disability; requires some help, but able to walk without assistance

4—Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance

5—Severe disability; bedridden, incontinent, and requires constant nursing care and attention

6—Death

population was a representative sample and, ultimately, helped expand treatment options to patients with unclear symptom onset.

Following these trials, the 2019 AHA/ASA Acute Ischemic Stroke Guideline stated that intravenous alteplase treatment in this patient population can be beneficial.[9] Consequently, some institutions have created rapid MRI protocols with limited

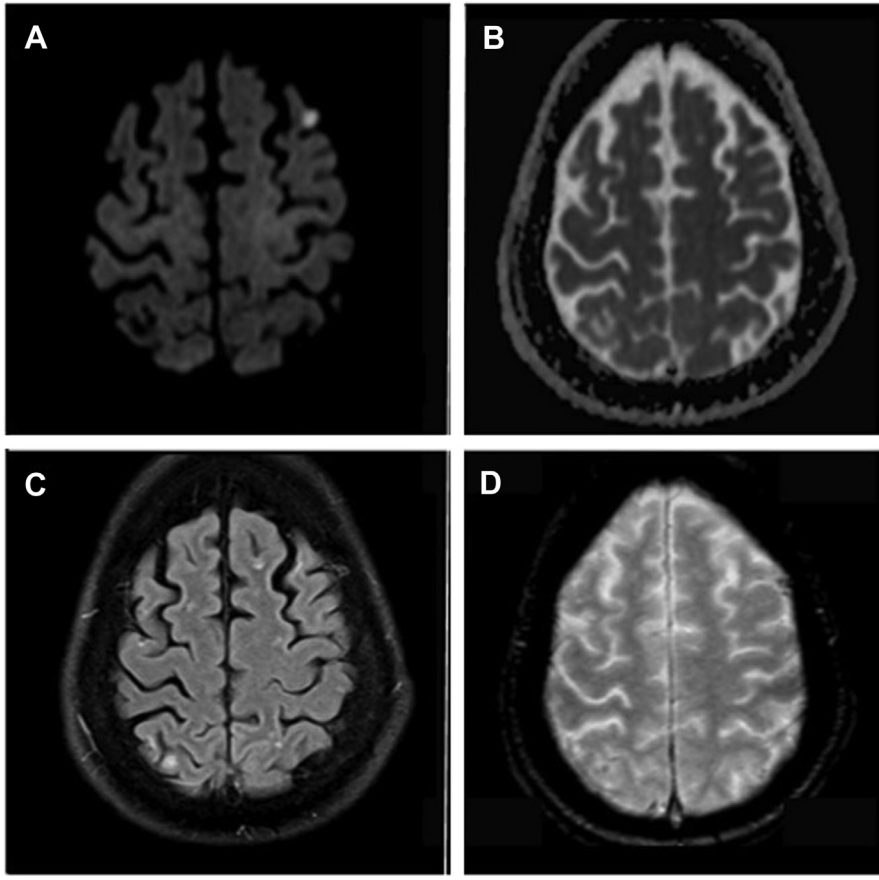

Fig. 1. MRI brain without contrast shows an area of restricted diffusion on DWI sequence (*A*) in the left frontal lobe with apparent diffusion coefficient correlate (*B*) and no evidence of correlating hyperintensity on FLAIR sequence (*C*), suggesting an acute infarct. Gradient echo sequence (*D*) was negative for acute hemorrhage.

sequences, such as DWI, FLAIR, apparent diffusion coefficient and gradient echo, or susceptibility-weighted imaging, to rapidly assess this patient demographic for thrombolysis candidacy. **Fig. 1** provides an illustrative case with a radiographic example.

Case presentation

A 62-year-old male with type II diabetes, hypertension, and hyperlipidemia awoke with expressive aphasia and impaired executive function. NIHSS was 1 for aphasia. He reported concern that his deficits would impair his ability to work as a contractor and operate heavy machinery. He was taken for rapid MRI brain—completed in 8 minutes—with the limited sequences shown below. After informed consent, the patient was treated with IV alteplase based on DWI-FLAIR mismatch and his concern for disabling symptoms. The following day his symptoms had improved with an NIHSS of 0.

Current Evidence for Tenecteplase Thrombolysis

Although intravenous alteplase is currently the only agent approved by the USFDA for the treatment of acute ischemic stroke, a second fibrinolytic, tenecteplase, may be as effective. Tenecteplase is a variant of alteplase bioengineered to have higher fibrin specificity and increased resistance to plasminogen activator inhibitor-1, and is administered via a single intravenous bolus. In the largest trial comparing tenecteplase to alteplase in minor stroke patients (median NIHSS 4) without a major intracranial occlusion, tenecteplase at 0.4 mg/kg failed to demonstrate superiority, but had a safety and efficacy profile similar to that of alteplase.[13] Current guidelines recommended that tenecteplase may be considered as an alternative treatment for patients with a minor stroke without a large vessel occlusion at a class IIb level recommendation.[9] A more recent meta-analysis of 5 tenecteplase stroke trials demonstrated that tenecteplase has noninferior safety and efficacy relative to alteplase for the primary endpoint of freedom from disability (mRS of 0–1) at 3 months.[14] Because of the shorter time to prepare and administer tenecteplase and the lack of requirement for an IV infusion pump during interfacility transfer, some institutions have adopted its use.[15]

ENDOVASCULAR MANAGEMENT OF ACUTE ISCHEMIC STROKE WITH LARGE VESSEL OCCLUSION

Proximal occlusion of a major intracranial vessel accounts for roughly one-third of all anterior circulation acute ischemic strokes. Unfortunately, intravenous alteplase is successful at recanalization of these occluded arteries only one-third of the time.[16] Before 2015, randomized thrombectomy trials in this patient population used inefficacious thrombectomy devices and had long delays from onset to treatment, leading to poor outcomes and lack of support for this treatment modality. In 2015, 5 clinical trials using newer devices were published showing clear benefit of endovascular therapy in the treatment of acute ischemic stroke with a large vessel occlusion from 0 to 6 hours from symptom onset.[17–21] In these studies, patients eligible for IV alteplase before embolectomy were still treated with thrombolysis. The Highly Effective Reperfusion Using Multiple Endovascular Devices (HERMES) meta-analysis published in 2016 included patient-level data from these 5 trials for a total of 1287 patients.[22] For the primary outcome of mRS score reduction by 1 point at 90 days, the authors found a common odds ratio of 2.49 favoring intervention.[22] This equated to a number needed to treat of 2.6. Following the publication of these studies, endovascular treatment became the standard of care for this patient population. **Box 3** outlines the inclusion criteria for such treatment when initiated within 6 hours from symptom onset.

Imaging studies required to determine eligibility for endovascular therapy include a noncontrast head CT and CT angiogram of the head and neck. CT perfusion (CTP) is not required. Some institutions may use MRI and magnetic resonance angiography (MRA) based on their local accessibility to such imaging. The ASPECTS is a 10-point topographic score used to assess early ischemic stroke changes on noncontrast CT scans in patients with MCA occlusions. As noted in **Box 3**, it is used as part of the inclusion criteria for endovascular therapy up to 6 hours from symptom onset. Because hypoattenuation on CT indicates infarcted tissue and injury that is more likely irreversible, treatment is no longer beneficial with lower ASPECTS. To calculate this score, 10 segmental areas in the MCA territory are each given 1 point, as visualized in **Fig. 2**. One point is subtracted from the total of 10 for each area that exhibits early ischemic changes with loss of gray-white differentiation.

Tenecteplase Before Endovascular Therapy

The Tenecteplase Versus Alteplase Before Endovascular Therapy for Ischemic Stroke (EXTEND-IA TNK) trial investigated intravenous tenecteplase, 0.25 mg/kg as a single bolus, versus intravenous alteplase at standard dosing in patients presenting within 4.5 hours of symptom onset and eligible for endovascular therapy.[23] The primary outcome was reperfusion of greater than 50% of the involved ischemic territory or an absence of retrieval thrombus at the time of the initial angiographic assessment. This primary outcome was reached in 22% of the tenecteplase treated patients versus 10% of those treated with alteplase ($P = .002$ for noninferiority, $P = .03$ for superiority).[23] The tenecteplase group had a median mRS of 2 at 90 days versus a median mRS of 3 in the alteplase group ($P = .04$). An obvious critique of this trial is that the primary outcome was a radiologic outcome and not a clinical one. Regardless, the 2019 AHA/ASA guideline for the early management of acute ischemic stroke states that it may be reasonable to choose tenecteplase over alteplase in patients without contraindications for IV fibrinolysis who are eligible for mechanical thrombectomy.[9] A follow-up open-label trial comparing 2 doses of tenecteplase (0.4 mg/kg and 0.25 mg/kg) in patients with ischemic stroke due to large vessel occlusion did not find a radiographic or clinical advantage of the higher dose.[24]

Basilar Occlusion

Basilar artery occlusion carries very high fatality rates.[25] Treatment approaches to basilar artery occlusion have been heterogeneous, and the pivotal endovascular trials

Box 3
Inclusion criteria for endovascular therapy from 0 to 6 hours from symptom onset

Prestroke mRS of 0 to 1

Causative occlusion of the internal carotid artery or MCA segment 1 (M1)[a]

Age ≥18 years

NIHSS score of ≥6

Alberta Stroke Program Early Computed Tomography Score (ASPECTS) of ≥6

Treatment (groin puncture) can be initiated within 6 hours of symptom onset

[a]M1 is defined as the horizontal or sphenoidal segment of the MCA from the internal carotid terminus until the bifurcation.

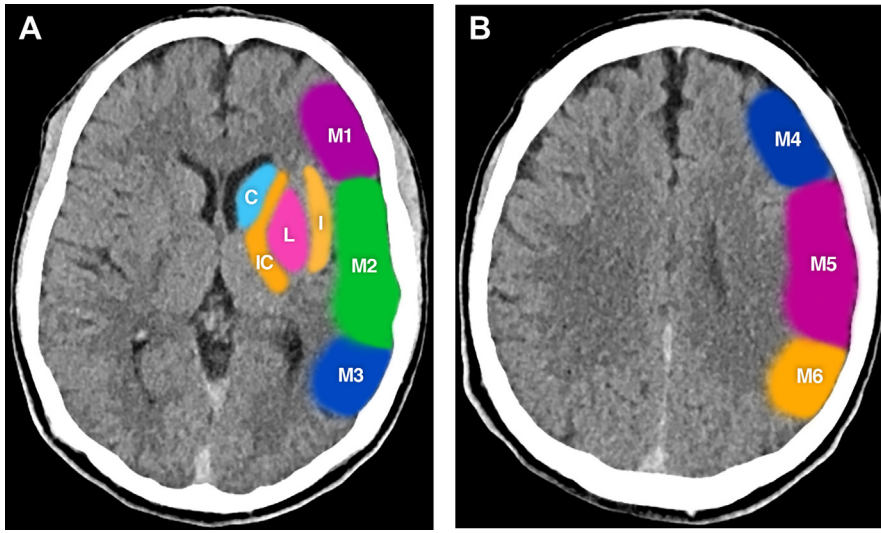

Fig. 2. (*A*) C = caudate, L = lentiform nucleus, IC = internal capsule, I = insular cortex, M1 = anterior MCA cortex, M2 = MCA cortex lateral to insular ribbon, M3 = posterior MCA cortex. (*B*) M4 = anterior MCA territory immediately superior to M1, M5 = lateral MCA territory immediately superior to M2, M6 = posterior MCA territory immediately superior to M3.

from 2015 included only small numbers of patients with basilar occlusion.[17–21] Despite the lack of evidence, due to the near-universal poor outcome in the absence of thrombectomy,[26] many institutions include basilar artery occlusion in their endovascular treatment protocol up to 24 hours from symptom onset.

Thrombectomy Beyond 6 Hours

Eligibility for mechanical thrombectomy was broadened beyond 6 hours in 2018 following the publication of the DWI or CTP Assessment with Clinical Mismatch in the Triage of Wake-Up and Late Presenting Strokes Undergoing Neurointervention with Trevo (DAWN) and Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke (DEFUSE 3) trials. Each of these trials used different methods to identify patients with a mismatch between infarcted tissue and ischemic penumbra, selecting patients most likely to benefit from late endovascular therapy. The DAWN trial evaluated patients with a high NIHSS relative to a small infarct core (using CTP or DWI) in the setting of a proximal MCA or internal carotid artery occlusion, who presented between 6 and 24 hours from last known well. The primary outcome of an mRS score 0 to 2 at 90 days was seen in 49% of the thrombectomy group versus 13% in the standard medical group, which reached statistical significance and corresponds to a number needed to treat of 2.8. The rate of symptomatic intracranial hemorrhage and mortality did not differ between the 2 groups.[27] **Box 4** includes the DAWN eligibility criteria.

The DEFUSE 3 trial differed in that it selected patients with a proximal MCA or internal carotid artery occlusion who presented 6 to 16 hours from last known well with a perfusion-core mismatch ratio greater than 1.8 and maximum core size less than 70 mL. Specialized perfusion imaging software is required to assess infarct-perfusion mismatch. A core infarct area is usually depicted by reduction in cerebral

Box 4
DAWN eligibility criteria

Symptoms attributable to acute ischemic stroke

Patient belongs to one of the following:
a. Failed IV t-PA therapy (defined as a confirmed persistent occlusion 60 min after administration)
b. Contraindication for IV t-PA

Age ≥18 years

Baseline NIHSS ≥10 (assessed within 1 hour before measuring core infarct volume)

Patient randomization could occur within 6 to 24 hours after time last known well

Prestroke mRS of 0 or 1

Anticipated life expectancy of at least 6 months

Patients receiving heparin or low-molecular-weight heparin or an intravenous direct thrombin inhibitor within the last 24 hours from screening were eligible to participate if their coagulation profile was acceptable

Subjects on factor Xa inhibitors or direct thrombin inhibitors were eligible for participation

Less than 1/3 MCA territory involved, as evidenced using noncontrasted CTH or DWI sequence on MRI

Occlusion of the intracranial ICA and/or MCA-M1, as evidenced by MRA or CTA

Achievement of one of the following measures of Clinical-Imaging Mismatch on CTP or MRI
a. 0 to 20 cc core infarct and NIHSS ≥ 10 (and age ≥ 80 years)
b. 0 to 30 cc core infarct and NIHSS ≥ 10 (and age < 80 years)
c. 31 cc to less than 50 cc core infarct and NIHSS ≥ 20 (and age < 80 years)

Data from Nogueira RG, Jadhav AP, Haussen DC, et al. Thrombectomy 6 to 24 Hours after Stroke with a Mismatch between Deficit and Infarct. N Engl J Med. 2018;378(1):11-21. https://doi.org/10.1056/NEJMoa1706442.

blood flow (CBF) less than 30% of normal. Hypoperfused brain is a brain that is at risk for progression to infarction and could be salvageable with reperfusion. It is depicted by the prolonged or delayed time it takes for contrast to reach areas of the brain. There are different thresholds with the most common being a time to maximum (Tmax) greater than 6 seconds. Tmax and CBF are the main parameters to determine core and penumbra. A penumbra or mismatch volume can be calculated by subtracting the infarct core volume from the total area of hypoperfused brain.

At 90 days, an mRS score of 0 to 2 was seen in 44.6% of the thrombectomy group versus 16.7% in the standard medical therapy group ($P < .0001$). The endovascular group was also found to have a favorable mortality rate at 14% compared to 26%, and there was no significant difference in the frequency of intracranial hemorrhage.[28] **Box 5** includes a detailed list of the DEFUSE 3 eligibility criteria.

As these are the only 2 randomized controlled trials that have demonstrated safety and efficacy for thrombectomy greater than 6 hours from symptom onset, only patients who meet the eligibility criteria for either DAWN or DEFUSE 3 should receive mechanical thrombectomy in this time window.[9] **Fig. 3** describes a case using RAPID© software to help assess for the radiographic Target Mismatch Profile.

CONTROVERSIES AND ONGOING CLINICAL TRIALS IN ENDOVASCULAR THERAPY

Large Core

It is unclear if patients with medium to large core infarctions could benefit from thrombectomy, as patients with large baseline ischemic infarctions (ASPECTS ≤6 and 7)

Box 5
DEFUSE 3 eligibility criteria

Symptoms attributable to acute ischemic stroke

Age 18 to 90 years

NIHSS score of ≥6

Treatment (groin puncture) within 6 to 16 hours after time last known well

Prestroke mRS of 0, 1, or 2

Occlusion of the intracranial ICA and/or MCA-M1, as evidenced by MRA or CTA

Achievement of all of the following radiographic measures (Target Mismatch Profile) on CTP or MRI
a. Ischemic core volume is < 70 mL
b. Mismatch ratio is ≥ 1.8
c. Mismatch volume[a] is ≥ 15 mL)

[a]Alternative neuroimaging inclusion criteria if perfusion imaging or CTA/MRA was technically inadequate:

a. If CTA (or MRA) was technically inadequate:
   - Tmax>6s perfusion deficit consistent with an ICA or MCA-M1 occlusion AND Target Mismatch Profile was met

b. If MRP was technically inadequate:
   - Occlusion of the intracranial ICA and/or MCA-M1 by MRA (or CTA, if MRA was technically inadequate and a CTA was performed within 60 minutes before the MRI) AND DWI lesion volume less than 25 mL

c. If CTP was technically inadequate:
   - Patient could be screened with MRI and randomized if Target Mismatch Profile was met.

Data from Albers GW, Marks MP, Kemp S, et al. Thrombectomy for Stroke at 6 to 16 Hours with Selection by Perfusion Imaging. N Engl J Med. 2018;378(8):708-718. https://doi.org/10.1056/NEJMoa1713973.

have been excluded from many of the thrombectomy clinical trials.[18–21] These patients were excluded based on prior evidence that large initial infarct volume was an independent predictor of poor outcome, mortality, and hemorrhagic transformation.[22,29–34] Subgroup analyses and meta-analyses have attempted to address this question. A subgroup analysis within the MR CLEAN trial failed to show benefit with thrombectomy in patients with an ASPECTS of 0 to 4.[17] However, this subgroup represented only 6% of the study population and was likely underpowered. Another meta-analysis assessed the impact of thrombectomy in patients with pretreatment ASPECTS 0 to 6 and found that 30.1% of patients achieved an mRS of 0 to 2 in the thrombectomy arm as compared to 3.2% in the medical management. On further subdivision, patients with an ASPECTS 5 and 6 achieved good outcome (33% and 38%, respectively) as compared to patients with ASPECTS of 0 to 4 (17%).[35] The HERMES meta-analysis also found that only 25% of the 126 patients with an ASPECTS 0 to 4 achieved an mRS of 0 to 2 at 90 days following thrombectomy.[22] Several clinical trials are currently planned to determine if endovascular thrombectomy is efficacious in these patients.[36–38]

Low National Institutes of Stroke Severity Scale

Currently, there is insufficient data to help with decision-making in patients with low NIHSS and proximal large vessel occlusions. Consequently, there are ongoing trials

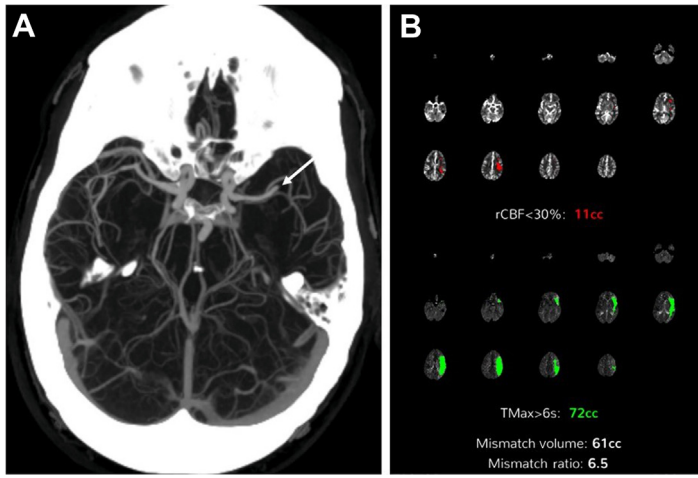

Fig. 3. Case presentation: A 31-year-old male with a prior left hemispheric stroke and alcohol use disorder presented to the emergency department 7 hours from last known well after he awoke with aphasia and right-sided hemiparesis. NIHSS was 15. CT angiogram of the head and neck showed an occlusion of the left middle cerebral artery at the M2 segment (*A*). CT perfusion showed a large perfusion deficit (*B*). Patient's imaging was felt to be favorable, given the core size of 11 cc was less than 70 cc, the mismatch ratio at 6.5 was above 1.8, and the mismatch volume at 61 cc was above 15 cc, meeting the radiographic parameters of the DEFUSE 3 trial. Consequently, the patient was taken for mechanical thrombectomy in the extended time window. A TICI 3 revascularization was achieved. Patient's NIHSS at 90 days was 1 for aphasia with an mRS of 1. The arrow is pointing to the occluded left middle cerebral artery.

investigating the efficacy of endovascular thrombectomy in these patients.[39,40] Some argue that the low NIHSS reflects sufficient collateral vascular supply to perfuse the ischemic territory, but others report cases where patients have robust, acute collateral compensation that later fails, leading to increased infarction. It is difficult to understand the appropriate intervention given these factors, thus necessitating further clinical trials.

Medium Vessel Occlusions

For patients with an occlusion of the MCA segment 2 (M2), the direction of treatment effect has been found to be positive, but not statistically significant.[22] The 2019 AHA/ASA Acute Ischemic Stroke Guidelines[9] state the benefits are uncertain in this patient population but treatment may be reasonable. Inadequate numbers of patients with MCA segment 3 (M3), anterior cerebral, vertebral, basilar, and posterior cerebral artery occlusions have been enrolled in clinical trials of endovascular therapy, so benefit in this patient population is also uncertain, yet may be reasonable in carefully selected patients. Further clinical trials are needed to assess patients presenting with medium vessel occlusions.

Telemedicine

Telemedicine has become a major tool for care delivery during the COVID-19 pandemic. However, telemedicine utilization in stroke care has been in place for many years before 2020.

The STRokEDOC trial assessed the efficacy of telemedicine versus telephone consultation regarding treatment decisions with IV alteplase. This prospective trial randomized

patients to telemedicine or telephone consultation with a primary outcome of correct thrombolytic decision making. Secondary outcomes included IV alteplase use-rate, 90-day functional outcomes, postalteplase hemorrhage, and technical complications. It found that an accurate alteplase decision was made in 98.2% of telemedicine consultations versus 82% of telephone consultations (OR 10.9; 95% CI 2.7–44.6; $P = .0009$). No difference was found in 90-day functional outcomes, mortality, or post-tPA hemorrhage. There was an increase in alteplase use rate in the telemedicine group compared to the telephone consultation group (28% vs 23%, respectively; OR 1.3; 95% CI 0.7–2.5; $P = .4248$). Low technical complications and favorable assessment time were also found in the telemedicine group. This trial was pivotal in providing an evidence-based foundation for telemedicine implementation within stroke neurology.[41]

Use of telemedicine to direct thrombolysis treatment has also been shown to have similar complication rates as those reported in the National Institute of Neurologic Disorders and Stroke Trial,[1,42] helping to assert the safety of using telemedicine in this capacity. Telemedicine stroke care networks are also a means to increase the use of thrombolysis in rural and underserved areas.[43] Improved treatment rates have been attributed to increased access to neurologic expertise. It is presumed that with increased use of thrombolysis in appropriately selected candidates, there would be a positive effect on patient outcomes. However, further clinical trials are needed to formally assess the use of telestroke and outcome.

SUMMARY

There are many therapies available to reduce disability after acute ischemic stroke. When approaching a patient with symptoms consistent with acute ischemic stroke, the first step is to obtain a last known well time, an onset of symptoms time, and an NIHSS as the patient is taken for imaging. If the patient was last known well less than 6 hours before presentation, obtain a noncontrasted head CT to rule out intracranial hemorrhage, and CTA head and neck to assess for a large vessel occlusion. If the patient has a disabling deficit, normal glucose, and a last known well less than 4.5 hours, assess for alteplase candidacy. If the patient has disabling deficits, symptom onset time is unknown and has no contraindication to alteplase, obtain a rapid MRI brain to determine if there is a DWI-FLAIR mismatch and no hemorrhage to determine alteplase candidacy. If the patient is found to have a proximal large vessel occlusion, has an ASPECTS score $\geq$6 and an NIHSS $\geq$6, proceed to endovascular intervention. If, however, the patient is eligible for both alteplase and endovascular reperfusion, treat with alteplase first if it does not delay endovascular intervention. In patients with a last known well greater than 6 hours and less than 24 hours, obtain a noncontrasted head CT, CTA head and neck, and CT perfusion or rapid MRI brain with MRA head and neck to determine if a patient has a large vessel occlusion and is an endovascular candidate using the DAWN or DEFUSE-3 inclusion criteria.

DISCLOSURE

The authors have nothing to disclose.

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