Novel Treatments for Transient Ischemic Attack and Acute Ischemic Stroke

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KEYWORDS

• Acute ischemic stroke • Intravenous alteplase • Endovascular thrombectomy

KEY POINTS

- Nearly 700,000 people experience a stroke every year and 240,000 experience a transient ischemic attack.
- Primary prevention is important in stroke prevention and includes controlling hypertension, diabetes, cholesterol, weight, and cardiac risk factors, and getting plenty of physical activity, abstaining from cigarette smoking and alcohol, and eating a nutritious diet.
- In patients who are not candidates for reperfusion therapy, treatment involves perfusing the ischemic penumbra to prevent worsening of the infarcted region.

INTRODUCTION

Each year, nearly 700,000 people will suffer an acute ischemic stroke (AIS)[1] and an additional 240,000 people will experience a transient ischemic attack (TIA).[2] Before the coronavirus disease-19 outbreak, stroke was the fifth leading cause of death in the United States and remains a leading cause of long-term disability. Over the last 25 years, researchers have been searching for novel ways of treating TIA and AIS that are both effective and safe. Although researchers have yet to identify better treatments, recent trials have shown better patient selection to extend the time window for some beyond the standard 3-hour window.

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EVALUATION

Any patient with suspected AIS should have a focused assessment aimed at identifying ongoing, functionally disabling focal neurologic deficits. Prehospital and emergency department professionals may use any number of validated stroke screening and severity grading tools (discussed elsewhere in this article) to aid in efficient stroke detection.[3] The use of prehospital stroke screens have been linked with improved thrombolytic treatment rates and faster door-to-needle times, whereas severity scales aid in the identification of patients with large vessel occlusion (LVO) stroke for faster door-to-groin times for endovascular candidates. The National Institutes of Health Stroke Scale (NIHSS) is a standardized and commonly used assessment of neurologic deficits intended to be easily reproducible, using 11 items to produce a score of 0 to 42. Generally speaking, the higher the NIHSS, the larger the area of infarction and the worse the outcome for patients. Documentation of the NIHSS at the time of the initial evaluation and before stroke treatment is a quality performance metric. NIHSS training and certification is available to EM clinicians and is encouraged, particularly where neurologic expertise is unavailable.

Establishing the time that the patient was "last known well" (LKW), that is, without symptoms, is of paramount importance. It is distinct from the time of symptom discovery and should be used as the presumed time of stroke onset in all cases when the patient cannot clearly recall the precise time symptoms began. The patient's premorbid functional status (level of independence immediately before the stroke) should also be assessed. The modified Rankin Scale (mRS) is a 6-point ordinal measurement of functional disability and is commonly used as an outcome measure in stroke treatment trials (**Table 1**).[4]

Early Stabilization and Resuscitation

All emergency department patients should first have their airway, breathing, and circulation assessed and standard resuscitative measures enacted to ensure hemodynamic stability. The role of the emergency clinician in immediate assessment of suspected stroke patients upon arrival is key, because a minority may lose protective airway reflexes and require emergent endotracheal intubation before ascertaining diagnostic imaging. Hypotension should be avoided and corrected immediately if present. Unless the patient is to receive intravenous (IV) thrombolysis, permissive

Table 1
The mRS

Score	Description
0	No symptoms at all
1	No significant disability despite symptoms; able to carry out all usual duties and activities
2	Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance
3	Moderate disability; requiring some help, but able to walk without assistance
4	Moderately severe disability; unable to walk without assistance, unable to attend to needs without assistance
5	Severe disability; bedridden, incontinent, and requiring constant nursing care and attention
6	Dead

hypertension (up to 220 mm Hg systolic) should be allowed. Patients receiving thrombolytics should have their blood pressure maintained at or below 185/110 mm Hg in accordance with the American Heart Association/American Stroke Association (AHA/ASA) recommendations.[5]

Primary Stroke Prevention

Because 76% of patients with stroke are experiencing this for the first time,[1] primary prevention is an important factor in treatment. The top 10 modifiable risk factors for strokes include[6]:

- Hypertension
- Diabetes
- Dyslipidemia
- Cigarette smoking
- Obesity
- Poor diet
- Physical inactivity
- Stress or depression
- Alcohol intake
- Cardiac causes such as atrial fibrillation and valvular disease

Controlling these risk factors reduces the risk of first stroke. **Table 2** shows the current recommendations for primary prevention of stroke based on the AHA/ASA guidelines for primary prevention of stroke.[7]

Non–stroke-related visits to the emergency department are important opportunities for screening, counseling, and referring patients with conditions such as asymptomatic hypertension, undiagnosed or uncontrolled diabetes, obesity, and cigarette smoking.

INTRAVENOUS THROMBOLYSIS

History

Thrombolytic therapies for AIS have been under investigation since the 1950s, preceding computed tomography (CT) technology. The predominant risk of treatment is hemorrhagic conversion of the area of infarction leading to intracerebral hemorrhage (ICH) and high rates of mortality. Early studies predominantly used streptokinase and urokinase, which shifted to recombinant tissue plasminogen activator (rt-PA) in the 1990s. In 1995, the European Cooperative Acute Stroke Study (ECASS)-I was the first randomized trial of alteplase (an rt-PA) for AIS patients within 6 hours of LKW and enrolled 620 patients throughout Europe. No difference in outcomes (disability or mortality) were found in the intention-to-treat population, but after accounting for protocol violations in more than 17% of the study population, rt-PA treatment showed an overall benefit.[14] Later the same year, the National Institute of Neurological Disorders and Stroke (NINDS)-II trial of 624 stroke patients showed a significant improvement in clinical outcome at 3 months for AIS patients treated with t-PA within 3 hours, despite an increased risk of symptomatic ICH of 6.4%.[15] Overall, the NINDS trial found that t-PA treated patients were 30% more likely to have minimal or no disability at 3 months. One year later, the US Food and Drug Administration approved t-PA for the treatment of AIS up to 3 hours after symptom onset.

ECASS III, published in 2008, was the next trial to show clinical efficacy of patients receiving rt-PA up to 4.5 hours of LKW. This study randomized 821 patients to treatment between 3.0 and 4.5 hours from LKW (as treatment within 3 hours had become

Table 2
Recommendations for primary stroke prevention based on the 2014 AHA/ASA guidelines[7]

	Recommendation for Primary Stroke Prevention
Physical inactivity	Moderate-intense aerobic physical activity 3–4 times/wk for 40 min/d[8]
Dyslipidemia	Treatment with a statin medication in patients for a goal LDL $\leq$70 or a high 10-y risk for cardiovascular events[9,10]
Diet and nutrition	Reduced intake of sodium and saturated fat Increased intake of potassium, fruits, vegetables, and low-fat dairy products
Hypertension	Regular blood pressure screening, diet modification for patients with prehypertension (120–139/80–89 mm Hg), and medical treatment of patients with hypertension for a goal BP of <140/90 mm Hg[11]
Obesity	Weight reduction for overweight (BMI = 25–29 kg/m^2) and obese (BMI >30 kg/m^2) patients[12]
Diabetes	In addition to controlling diabetes, patients with type I or type II diabetes should have control of hypertension to a goal of <140/90 mm Hg and treated with a statin medication for a goal LDL $\leq$70[13]
Cigarette smoking	Smoking cessation with the use of drug therapy or nicotine replacement[10]
Atrial fibrillation	Long-term anticoagulation in patients without hemorrhagic risk factors for patients with a high risk for stroke, defined as a CHA2DS2-VASc score of $\geq$2
Other cardiac conditions	
Valvular disease	Long term aspirin therapy for patients with bioprosthetic valves and long term anticoagulation in patients with mitral stenosis, left atrial thrombus, and after mechanical valve replacement therapy
CHF	Aspirin or anticoagulation can be used if no previous thromboembolic events.
MI	Anticoagulation can be considered in patients with asymptomatic left ventricular mural thrombi and for patients with STEMI and anterior apical akinesis or dyskinesis if no contraindications.
PFO	Antithrombotic treatment and catheter-based closure are not recommended in patients with PFO if no history of thromboembolic events

Abbreviations: BMI, body mass index; BP, blood pressure; CHF, congestive heart failure; LDL, low-density lipoprotein cholesterol; MI, myocardial infarction; PFO, patent foramen ovale; STEMI, ST-elevation myocardial infarction.

standard of care) and a favorable outcome was observed in 52.4% of treated patients versus 45.2% of controls.[16]

The International Stroke Trial-3 trial enrolled a total of 3035 out of an intended 6000 patients in a 1:1 open controlled design and is the largest clinical trial to date investigating rt-PA efficacy. This study was conducted after thrombolysis had become the standard of care for patients up to 4.5 hours from LKW, so only patients meeting the "uncertainty principle" for whom clinical equipoise remained were enrolled (e.g., 53% of patients treated with rt-PA were >80 years old). Although this trial did not

achieve its primary outcome measure (proportion alive and independent at 6 months), there was a significant ordinal decrease in disability at 6 months, and those treated within 3 hours of onset showed significant benefit. Overall, this trial further reinforced the use of rt-PA.

In the subsequent 25 years since the NINDS publication, the debate regarding the clinical efficacy of fibrinolysis in stroke has continued.[17] Some trials following NINDS, including ECASS II (0–3 hours and 3–6 hours from LKW)[18] and Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke (ATLANTIS) B (3–5 hours from LKW)[19] did not demonstrate a similar benefit of rt-PA therapy. In addition, other trials have shown higher percentages of hemorrhages, but these are likely due to a large number of protocol deviations including treatment beyond the 3-hour time window, administration of antiplatelets or anticoagulants in the first 24 hours, or uncontrolled blood pressures, all of which have been shown to increase the risk of ICH.[20–22]

Several pooled analyses have explored the overall efficacy of rt-PA[23] and, although subject to methodologic heterogeneity, the collective evidence from these analyses supports a time-dependent treatment effect of rt-PA.[24]

Current Recommendations

Although the US Food and Drug Administration has approved the use of rt-PA for AIS only up to 3 hours from LKW, multiple organizations including the AHA/ASA, American College of Emergency Physicians, American College of Cardiology, European Stroke Organization, National Stroke Foundation, and National Institute for Health and Care Excellence have endorsed its use up to 4.5 hours of LKW, which is widely considered the international standard of care. Of note, some groups including the Canadian Association of Emergency Physicians and Australasian College for Emergency Medicine have called for more research before considering rt-PA standard of care based on conflicting available evidence, and it is anticipated that the recent reanalysis of ECASS-III may lead to others following suit.[25]

Although the lack of consensus regarding the use of rt-PA in AIS may leave the emergency clinician hesitant to administer and/or recommend it, it is clear that rt-PA should not be considered life saving, but rather autonomy preserving. The decision to pursue thrombolysis should be based on individual patient wishes, and made using shared decision making after a brief discussion of risks and benefits (American College of Emergency Physicians Level C recommendation).[26] Written informed consent is generally not required, but documentation of a discussion of risks and benefits with the patient and/or health care proxy should be reflected in the medical record.

Thrombolytic treatment should be reserved for only those patients with ongoing, disabling, focal neurologic deficits not meeting any exclusion criteria.[27] Treatment of minor and nondisabling symptoms has been a source of debate, but the Phase IIIB, Double-Blind, Multicenter Study to Evaluate the Efficacy and Safety of Alteplase in Patients With Mild Stroke: Rapidly Improving Symptoms and Minor Neurologic Deficits (PRISMS) trial recently explored this and was halted after enrollment of only 313 of an intended 948 subjects. In this study, patient with an NIHSS of 0 to 5 with symptoms described as “not clearly disabling” were randomized to rt-PA versus control. Although halted prematurely, there was no significant difference in 90-day mRS between groups, yet the treated group had a much higher rate of symptomatic ICH (3.2% vs 0%).[28]

Recent Advances

In an effort to maximize the likelihood of a good patient outcome, significant effort has been made to expedite door-to-needle times for AIS patients receiving rt-PA.

One such initiative has been to bring stroke reperfusion therapies to the scene, bypassing the emergency department all together. Mobile stroke units have emerged in many metropolitan areas as an innovative way to improve stroke treatment efficiency. Patients are met on scene by an ambulance equipped with a portable CT scanner, many of which have full CT angiography capabilities to detect LVO stroke. To date, approximately 20 locations around the world deploy mobile stroke units, despite their high initial investment and operating costs.[29] The overall clinical benefits and broader generalizability of mobile stroke units are undetermined, but likely dependent on individual geographic and treatment factors.[30]

Telestroke has emerged as a practical way to bring cerebrovascular neurologic expertise to rural and resource-conservative settings in an effort to improve acute stroke treatment, and small hospitals using telestroke have been associated with reduced door-to-needle times.[31] Regardless of the technology used, a coordinated stroke system of care that emphasizes efficient diagnosis to minimize onset-to-treatment time is encouraged (AHA/ASA Class I, Level A recommendation).[32]

Extended window thrombolysis has been demonstrated with some success, despite the ongoing debate about the efficacy of rt-PA in the currently endorsed time window (0–4.5 hours from LKW). The Efficacy and Safety of MRI-Based Thrombolysis in Wake-Up Stroke (WAKE-UP) trial enrolled 503 of an intended 800 acute stroke patients in whom the time LKW could not be determined. Patients were randomized to receive rt-PA or not if MRI showed an area of restricted diffusion without changes on T2 fluid attenuated inversion recovery imaging. Patients treated with rt-PA were more likely to have a favorable outcome (mRS of 0–2 at 90 days), despite a trend toward increased risk of symptomatic ICH (2.0% vs 0.4%; $P = .15$).[33] The Extending the Time for Thrombolysis in Emergency Neurological Deficits (EXTEND) trial randomized 225 of a planned 310 subjects between 4.5 and 9.0 hours from LKW with a mismatch on CT scan or MR perfusion imaging and also favored rt-PA treatment despite increased symptomatic ICH.[34] The cautious selective use of rt-PA in patients with a favorable imaging pattern with LKW beyond 4.5 hours has been given a weak level of recommendation by the AHA/ASA, and further studies are warranted.

Alternative fibrinolytic agents have been explored to improve the safety and efficacy of thrombolysis in AIS. Although alteplase remains the treatment standard, its short half-life and need for continuous infusion over 1 hour after an initial bolus make it less ideal. Other agents such as tenecteplase have been shown to be more fibrin-specific and have a longer half-life after a bolus-only dose. Because tenecteplase causes less hypofibrinogenemia than alteplase, it is thought to cause less hemorrhagic transformation, which was demonstrated in a recent meta-analysis.[35] Tenecteplase has demonstrated noninferiority to alteplase in AIS and LVO patients undergoing endovascular treatment.[36,37] It is currently being investigated in multiple extended window trials.[38]

Sonothrombolysis is the concept of augmenting clot-dissolving capabilities of systemic fibrinolysis through ultrasound-induced mechanical agitation. Continuous transcranial Doppler examinations performed concurrently with t-PA administration seems to be a noninvasive way to promote fluid motion around a thrombus and increase rt-PA concentration within the clot.[39] Studies have been mixed in terms of clinical benefit, although most have shown an increased rate of vessel recanalization without an increased risk of mortality or symptomatic ICH.[40] The greatest potential benefit seems to be in proximal LVO stroke of the middle cerebral artery, where rt-PA alone is unlikely to be efficacious.[41]

ENDOVASCULAR STROKE CARE

A revolution in interventional stroke treatment occurred in 2015 with the publication of 5 prospective, randomized, multicenter trials that enrolled patients from around the world using confirmed LVO stroke. Each showed overwhelming benefit of mechanical thrombectomy with modern generation stent retrieval devices.[42–46] The Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute. Ischemic Stroke in the Netherlands (MR CLEAN) trial was the first of this group to report its results and the other trials were subsequently closed prematurely citing lack of equipoise in light of other positive trials. Using pooled data from the Highly Effective Reperfusion Evaluated in Multiple Endovascular Stroke Trials (HERMES) collaboration of endovascular trials, the number needed to treat to decrease 90-day functional disability by 1 point on the mRS is 2.6,[47] and mechanical thrombectomy is now considered the standard of care for eligible patients with LVO stroke of less than 6 hours duration.[5]

It should be noted that the majority of patients in all 5 of the landmark endovascular trials also received IV rt-PA, wherein mechanical thrombectomy was an adjuvant therapy used in conjunction with systemic thrombolysis. Although this remains the current treatment standard, 1 head-to-head trial comparing combination therapy (IV rt-PA + thrombectomy) with thrombectomy alone reported noninferiority of endovascular treatment alone,[48] and multiple additional studies are currently underway.

Although the efficacy of endovascular reperfusion decreases over time, some patients have been shown to benefit from mechanical thrombectomy as far out as 24 hours from LKW. Careful selection of patients using advanced neuroimaging is key for patients in an LVO and LKW greater than 6 hours. The Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke 3 (DEFUSE 3) trial identified patients 6 to 16 hours from LKW with an LVO and a diffusion/perfusion mismatch using CT- or MR-based perfusion imaging. A computer algorithm generated mismatch ratio (core/penumbra) of greater than 1.8 was needed for eligibility. Patients receiving endovascular therapy were much more likely than those who did not to have a mRS of -2 at 90 days (45% vs 17%).[49] The Diffusion Weighted Imaging (DWI) or Computerized Tomography Perfusion (CTP) Assessment With Clinical Mismatch in the Triage of Wake Up and Late Presenting Strokes Undergoing Neurointervention (DAWN) trial selected patients 6 to 24 hours from stroke onset using a mismatch of infarct volume on MRI to severity of clinical deficit. The likelihood of having a mRS of 0 to 2 at 90 days was 49% in those receiving thrombectomy and 13% in those who did not.[50] Collectively, the number needed to treat to restore 1 patient with LVO with a favorable imaging pattern presenting beyond 6 hours from LKW to functional independence at 90 days is between 3 and 4.

NEUROPROTECTIVE THERAPY

The ischemic cascade progresses from initially oligemic tissue to irreversible infarction, but increasing evidence suggests this sequence occurs at different rates among individuals experiencing a stroke. Strategies to slow and disrupt this progression have been the subject of numerous investigational studies. Apoptotic and excitatory pathway inhibitors, anti-inflammatory agents and free radical scavengers are among the most studied candidate agents, but to date none has demonstrated clear benefit. The subset of stroke patients that seems to be most likely to benefit includes those with large penumbral areas of tissue at risk, such as LVO patients awaiting thrombectomy. The recently published Efficacy and Safety of Nerinetide for the Treatment of Acute Ischaemic Stroke (ESCAPE-NA1) trial of IV nerinetide in patients with LVO within 12 hours of onset did not show any significant difference in clinical outcomes between

treatment groups, but did not find an improved outcome in patients who did not receive rt-PA.[51] The Field Administration of Stroke Therapy–Magnesium (FASTMAG) trial of early IV magnesium administration was also negative in improving functional outcomes, but did pave the way for prehospital neuroprotective studies.[52] Adjuvant neuroprotective strategies are likely to remain an appealing and exciting area of acute stroke research for the foreseeable future.

CONTRAINDICATIONS TO REPERFUSION STRATEGIES

Whereas the primary goal in AIS is reperfusion of the occluded vessel, there are patients in whom IV thrombolytics and endovascular thrombectomy is contraindicated. For these patients, the goal must be focused on saving the at-risk surrounding ischemic region via improving cerebral perfusion, antiplatelet medications, and preventing cerebral hypoxia.

Blood Pressure

When blood flow is cut off from a region of the brain, there is infarcted tissue immediately downstream to the occluded vessel causing a core infarct area. Surrounding that region is an area of at-risk brain in which there is low blood flow and hypoxia, resulting in an ischemic penumbra (**Fig. 1**). This tissue is perfused by collateral vessels from other nonoccluded branches and, given these are smaller vessels and circumvent the standard flow, hypotension and hypovolemia should be avoided.[53–55] Given the paucity of data to determine the optimal blood pressure, the goal is not known and may be different for every patient. Therefore, in patients who did not receive IV alteplase or mechanical thrombectomy and have no comorbid conditions requiring urgent

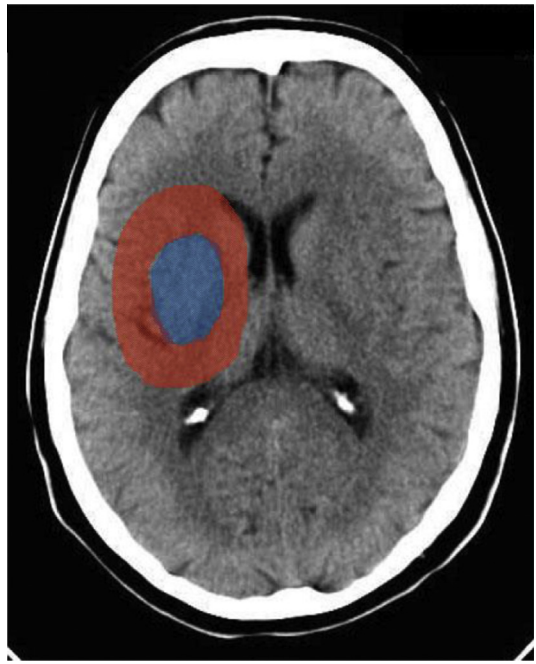

Fig. 1. A noncontrast CT scan of the head showing representation of a core infarct (*blue*) and surrounding ischemic penumbra (*red*). (Image source: Rhonda Cadena, MD)

antihypertensive treatment, allowing the blood pressure to rise up to 220/120 mm Hg might be reasonable. If there are signs of end-organ damage that need emergent treatment such as acute myocardial infarct, heart failure, aortic dissection, or eclampsia, a decrease of 15% of initial pressure is warranted.[34]

Twenty-fourhour blood pressure goals include:

- Before IV alteplase: less than 185/110 mm Hg
- After IV alteplase: ≤180/105 mm Hg
- After mechanical thrombectomy (0–6 h): ≤180/105 mm Hg
- After mechanical thrombectomy (6–24 h): ≤140/90 mm Hg
- No IV alteplase or mechanical thrombectomy: ≤220/120 mm Hg

Antiplatelet Therapy

In patients without contraindications, aspirin should be given within 24 hours of symptom onset. The initial dose should be at least 160 mg, because doses of 160 to 300 mg have been shown to be effective in decreasing the recurrence of stroke.[56,57] In patients who are deemed unsafe to swallow or who have not yet passed a dysphagia screening, rectal or nasogastric aspirin can be given. In patients with small strokes (NIHSS ≤3) who did not receive IV alteplase or mechanical thrombectomy, treatment with dual antiplatelet therapy (aspirin and clopidogrel) started within 24 hours of stroke may be effective in decreasing recurrent ischemic stroke.[58,59]

Cerebral Edema

The most life-threatening complication of large cerebral and cerebellar strokes is malignant cerebral edema and herniation (**Fig. 2**). Studies have shown a reduction in mortality if a decompressive hemicraniectomy is performed within 48 hours in patients 60 years of age or younger who experience neurologic decline.[60] Therefore, for patients with large strokes, intensive care unit admission in a facility with neurosurgery consultation should be considered.[61]

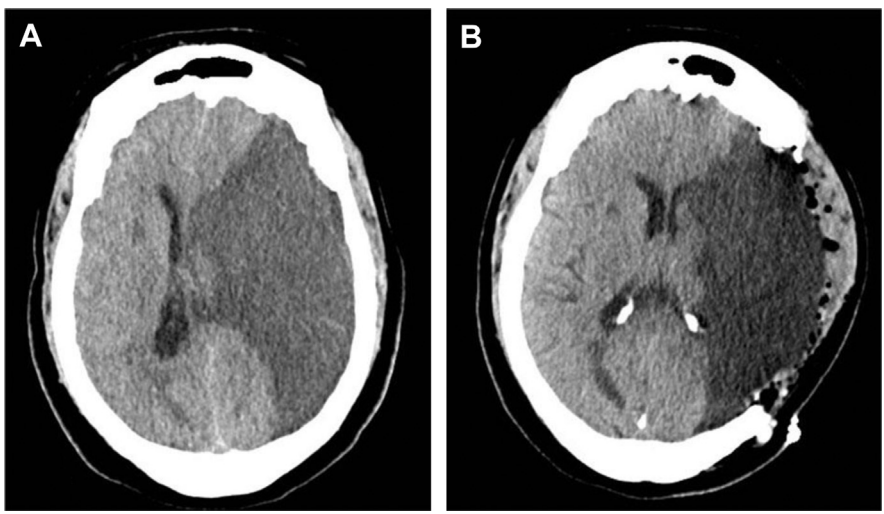

Fig. 2. (*A*) A CT scan of the head showing a malignant left middle cerebral artery stroke with cerebral edema and midline shift and (*B*) The same patient after a decompressive hemicraniectomy. (Images: Rhonda Cadena, MD.)

In patients with intracranial hypertension and clinical signs of herniation, hyperventilation (goal P_{CO_2} 30–34 mm Hg) or hyperosmolar therapy can be used to temporarily reduce intracranial pressures as a bridge to surgical intervention. Hypothermia or barbiturates in the setting of malignant cerebral or cerebellar edema are not recommended owing to limited data supporting benefit.[62] Corticosteroids have not been shown to be beneficial in the treatment of cerebral edema owing to AIS and may be associated with increased risk of infection; therefore, they are not currently recommended.[63]

Cerebellar infarction with brain stem compression and fourth ventricle effacement can lead to obstructive hydrocephalus. In these patients, ventriculostomy is recommended and suboccipital decompressive craniectomy may or may not be necessary on the basis of factors such as the size of the infarction, neurologic condition, degree of brainstem compression, and effectiveness of medical management.[63]

SPECIAL CIRCUMSTANCES

Cervical Artery Dissection

Stroke prevention with antithrombotic therapy remains the mainstay of treatment for patients with cervical artery dissections. Although there has not been a randomized trial of antithrombotic therapy versus placebo in patients with acute cervical artery dissection, observational studies and expert opinion suggest that it is reasonable to initiate antithrombotic therapy in the acute setting to prevent early thromboembolic events.[64] The ideal antithrombotic agent has not yet been determined but an antiplatelet agent is reasonable over anticoagulation if there are no contraindications.

In patients who present to the emergency department with an AIS owing to an extracranial or intracranial dissection without rupture, despite limited evidence on this specific population with regard to IV alteplase, a subgroup analysis in this population indicates it as effective and safe in patients without dissection.[65,66] Therefore, in a patient with neurologic deficits concerning for stroke, after an initial CT scan of the head without contrast is performed to rule out hemorrhage, IV alteplase is recommended in accordance with published guidelines if there are no contraindications, followed by endovascular treatment, if indicated. After treatment, further testing with CT angiography of the head and neck could be performed for evaluation of a dissection if suspicion exists.

Posterior Circulation Strokes

Posterior circulation strokes account for up to 19% of all strokes treated with IV alteplase,[67–69] but have been excluded from recent studies regarding treatment beyond the standard time windows owing to the risk of hemorrhage. A recent retrospective review of an ongoing prospective database of strokes reported that in the 14.6% of posterior circulation strokes that received IV alteplase, their bleeding risk was one-half of what was seen in anterior circulation strokes.[70] Current stroke guidelines suggest that mechanical thrombectomy is reasonable for posterior circulation occlusions up to 6 hours but do not guide further recommendations.[63] Currently there is a paucity of data guiding treatment outside of the 6-hour time window.

Small Strokes

The benefits of IV alteplase in patients with mild stroke (NIHSS 0–5) are unclear given various analyses of the data showing benefit in some and no benefit in others.[19,26,71] A recent randomized controlled trial looked at the efficacy of IV alteplase in patients with and NIHSS 0 to 5 with nondisabling symptoms.[30] In those patients, there was no benefit of treatment when given within 3 hours of onset because the risk of the IV

alteplase may be more than the benefit. However, in patients with disabling mild strokes, such that would affect the ability to talk or perform activities of daily living, IV alteplase is recommended.[63]

TRANSIENT ISCHEMIC ATTACK

Much like AIS, the mainstay of treatment of TIA is to identify the underlying etiologic trigger and prevent a recurrent event. Both stroke and TIA should be regarded as cerebrovascular emergencies, warranting an early and frontloaded diagnostic evaluation. A TIA warns of impending stroke in 12% to 30% of patients experiencing a stroke and the risk is highest within the first 24 to 48 hours of the sentinel event.[72,73] When presenting to the emergency department, patients should undergo brain and cervicocephalic vascular imaging to differentiate stroke and nonstroke mimics and to identify high-risk vascular lesions (such as severe stenosis or dissection), and be assessed for common causes of cardiac embolism.[74]

Differentiating true ischemic events from mimics can prove diagnostically challenging because patients most often have a normal neurologic examination at the time of their index visit. A careful history focusing on the differentiation of symptoms that suggest irritative phenomenon like seizure or complex migraine can be helpful. A noncontrast CT scan is of low yield in patients with TIA and diffusion-weighted MRI is strongly preferred, but oftentimes logistically not feasible in the emergency department setting given the majority of US emergency departments do not have 24/7 access to MRI.[75] Perfusion imaging modalities (both CT scans and MRI) have been shown to identify patients with focal perfusion abnormalities in 30% to 42% of patients after a TIA, some of whom had no abnormalities detected on diffusion-weighted MRI.[76–78] Although this strategy may identify an additional subset of patients at risk of early progression to infarct, it is not commonly performed on patients with TIA on the whole.

Clinical risk prediction scores such as the ABCD2 score[79] have been shown to estimate short-term stroke risk after TIA with moderate accuracy, but should not alone drive disposition decisions from the emergency department. Imaging-enhanced tools such as the ABCD3-I score[80] have superior predictive ability compared with clinical tools, but add advanced diagnostic testing (such as diffusion-weighted MRI and vessel imaging), which make them less useful as clinical decision aids in the emergency department. The Canadian TIA Score provides a practical alternative, showing good discriminative capability in differentiating low, moderate and high-risk TIA patients in terms of 7-day subsequent stroke risk after emergency department presentation.[81] This score was recently validated in 14 emergency departments across Canada, with findings supporting the early discharge of patients deemed low risk, additional testing and secondary prevention initiation with close follow-up for those of moderate risk, and specialist consultation for those of high risk.[82]

If a cardioembolic source is identified, then patients should generally be started on anticoagulation unless contraindicated. For most other patients, antiplatelet therapy is recommended. Dual antiplatelet therapy with aspirin and clopidogrel (300 mg loading dose followed by 75 mg/d) for a total of 21 days is currently recommended by the AHA/ASA for high-risk patients with an ABCD2 score of greater than 4. Otherwise, the same secondary prevention strategies used in AIS are applicable to TIA with a focus on mitigating risk factors and adopting a healthy lifestyle.

DISCLOSURE

I have no commercial or financial conflicts.

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