Acute Ischemic Stroke

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LEARNING OBJECTIVES

1. Design a patient-specific pharmacotherapeutic regimen to treat adverse events associated with intravenous alteplase, including hemorrhage and angioedema.
2. Distinguish key differences between the most recent guidelines for early management of acute ischemic stroke and the previous guidelines.
3. Assess a patient's candidacy for intravenous fibrinolytic therapy on the basis of updated inclusion and exclusion recommendations.
4. Evaluate the role of thrombolysis and thrombectomy with respect to eligibility criteria, efficacy, complications, and post-intervention considerations.
5. Devise an evidence-based, patient-specific antiplatelet plan for early secondary prevention after minor ischemic stroke or high-risk transient ischemic attack.
6. Justify the pharmacist's role as an integral part of the stroke response team for acute ischemic stroke.

ABBREVIATIONS IN THIS CHAPTER

AIS	Acute ischemic stroke
DAPT	Dual antiplatelet therapy
DTN	Door-to-needle time
EVT	Endovascular therapy
ICH	Intracranial hemorrhage
LVO	Large vessel occlusion
MCA	Middle cerebral artery
mRS	Modified Rankin Scale
NIHSS	National Institutes of Health Stroke Scale
NINDS	National Institute of Neurological Disorders and Stroke
TIA	Transient ischemic attack
TICI	Thrombolysis in Cerebral Infarction

Table of other common abbreviations.

INTRODUCTION

Stroke is the leading cause of serious long-term disability and the fifth leading cause of death for Americans. On average, someone in the United States has a stroke every 40 seconds, resulting in about 795,000 strokes per year. Ischemic strokes account for 87% of cases, whereas 10% are intracerebral hemorrhage and 3% are subarachnoid hemorrhage. The burden of stroke in the United States resulted in direct and indirect costs that averaged $33.9 billion annually in 2013 (Benjamin 2017).

Acute ischemic stroke (AIS) can affect the anterior circulation, the posterior circulation, or both. The internal carotid arteries supply oxygenated blood to the anterior circulation of the brain (i.e., middle cerebral arteries [MCAs] and anterior cerebral arteries), and the posterior circulation is supplied by the vertebral arteries that merge into the basilar artery, which feeds into the posterior cerebral and posterior communicating arteries. These anterior and posterior arteries that make up the circle of Willis (Figure 1) are called proximal arteries, given their proximity to the circle itself. Anterior circulation strokes involving the internal carotid artery and MCA are more common than posterior infarcts.

The vascular territory and the volume of ischemic brain tissue determine the type and severity of deficits. Patients with anterior strokes may present with focal deficits such as aphasia, neglect, hemiplegia, hemisensory loss, or visual field deficits. Patients with posterior strokes usually have a broad range of symptoms, including gait disturbances, unilateral or bilateral ataxia, visual field disturbances, optic ataxia, nystagmus, and even unresponsiveness and

respiratory arrest in the case of a complete, proximal basilar artery occlusion. Proximal arterial occlusions tend to result in larger volumes of ischemic brain tissue (and therefore a broader array and increased severity of stroke symptoms), whereas occlusions more distally or in small arteries typically produce an isolated deficit of lower severity.

Acute ischemic stroke can be categorized into five subtypes depending on the cause, as described by the TOAST investigators (Adams 1993). These subtypes are large-artery atherosclerosis, cardioembolic, small vessel occlusion (lacunar), stroke of other determined cause, and stroke of undetermined cause. Table 1 outlines the definitions, incidence, and survival rates from a population-based epidemiology study (Kolominsky-Rabas 2001). The TOAST categorization is useful to both clinicians and researchers. For clinicians, this categorization helps classify the cause in order to formulate a therapeutic plan to mitigate risk factors and potentially prevent future stroke events. For researchers, this classification defines different stroke subtypes to more clearly identify risk factors and to evaluate the safety and efficacy of potential new therapies.

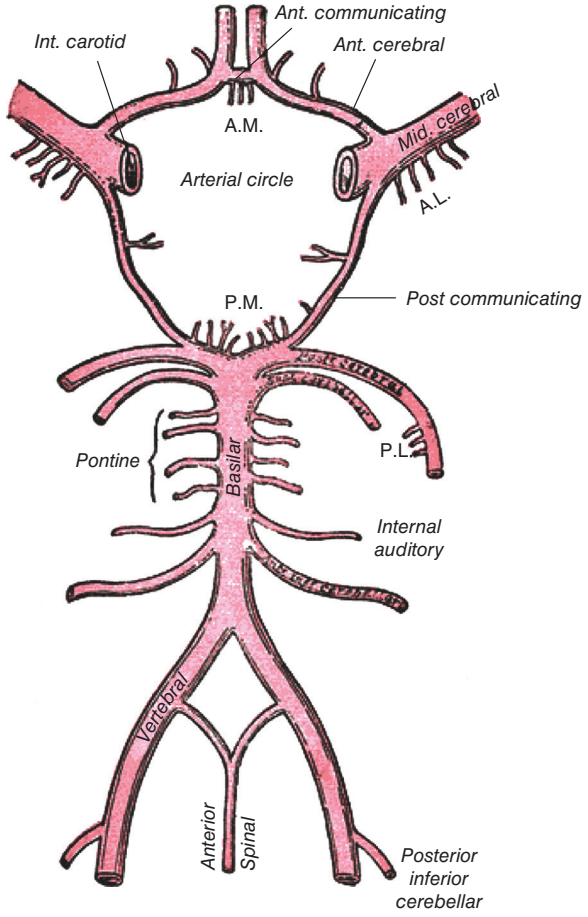

Figure 1. Arterial circulation at the base of the brain, "the circle of Willis."

A.L. = anterolateral ganglionic branches; A.M. = anteromedial ganglionic branches; Ant. = anterior; Int. = internal; arterial circle = "the circle of Willis"; P.L. = posterolateral ganglionic branches; P.M. = posteromedial ganglionic branches; Post = posterior.

Image reprinted from: Gray H. Anatomy of the Human Body. Philadelphia: Lea & Febiger, 1918; Figure 519.

BASELINE KNOWLEDGE STATEMENTS

Readers of this chapter are presumed to be familiar with the following:

- General knowledge of the pathophysiology of AIS
- Understanding of the pharmacology of aspirin, fibrinolytics, and $P2Y_{12}$ receptor inhibitors
- Knowledge of pharmacotherapy for secondary prevention of stroke

Table of common laboratory reference values

ADDITIONAL READINGS

The following free resources have additional background information on this topic:

- Powers WJ, Rabinstein AA, Ackerson T, et al. Guidelines for the early management of patients with acute ischemic stroke: 2019 update to the 2018 guidelines for the early management of acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2019;50:e344-e418.
- Demaerschalk BM, Kleindorfer DO, Adeoye OM, et al. Scientific Rationale for the Inclusion and Exclusion Criteria for Intravenous Alteplase in Acute Ischemic Stroke: A Statement for Healthcare Professionals From the American Heart Association/American Stroke Association. Stroke 2016;47:581-641.
- Yaghi S, Willey JZ, Cucchiara B, et al. Treatment and Outcome of Hemorrhagic Transformation After Intravenous Alteplase in Acute Ischemic Stroke: A Scientific Statement for Healthcare Professionals From the American Heart Association/American Stroke Association. Stroke 2017;48:e343-e61.
- Frontera JA, Lewin JJ, Rabinstein AA, et al. Guideline for Reversal of Antithrombotics in Intracranial Hemorrhage: A Statement for Healthcare Professionals from the Neurocritical Care Society and Society of Critical Care Medicine. Neurocrit Care 2016;24:6-46.

Table 1. TOAST Classifications

TOAST Classification	Incidence	Definition	Support for Diagnosis	2-Yr Survival	2-Yr Recurrence
Undetermined causes	31%	a. Two or more causes identified, b. Negative evaluation, OR c. Incomplete evaluation	Diagnosis of exclusion	61%	14%
Cardioembolic	29%	Arterial embolism of cardiac origin	High-risk cardiac sources: Mechanical prosthetic valve, atrial fibrillation, left atrial appendage thrombus, left ventricular thrombus, and dilated cardiomyopathy	55%	22%
Small-artery "lacunar"	21%	No recognizable lesion on CT or MRI or a subcortical or brain stem lesion < 1.5 cm diameter	Lacunar syndrome (e.g., pure motor hemiparesis, pure sensory stroke, sensorimotor stroke, or ataxic hemiparesis) History of diabetes mellitus and/or hypertension	85%	11%
Large-artery atherosclerosis	15%	> 50% stenosis of a large artery with a > 1.5-cm atherosclerotic lesion, no cardioembolic source	History of intermittent claudication, carotid bruit, TIAs, or diminished pulses	58%	10%
Stroke of other cause	5%	Identified source of stroke different fromearlier classifications	Examples include hypercoagulable states, vasculopathies, hematologic disorders	Variable	Variable

CT = computed tomography; TIA = transient ischemic attack.

Information from: Adams HP Jr, Bendixen BH, Kappelle LJ, et al. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST Trial of Org 10172 in Acute Stroke Treatment. Stroke 1993;24:35-41; Kolominsky-Rabas PL, Weber M, Gefeller O, et al. Epidemiology of ischemic stroke subtypes according to TOAST criteria: incidence, recurrence, and long-term survival in ischemic stroke subtypes: a population-based study. Stroke 2001;32:2735-40; Krishnamurthi RV, Barker-Collo S, Parag V, et al. Stroke incidence by major pathological type and ischemic subtypes in the Auckland Regional Community Stroke Studies: changes between 2002 and 2011. Stroke 2018;49:3-10.

THERAPEUTIC GOALS

Therapeutic goals for ischemic stroke can be categorized as acute versus chronic. Although chronic management goals focus towards secondary prevention of ischemic events, initial acute treatment goals focus on reducing infarct size and stroke severity to ultimately return a patient to baseline functional status. Acute treatment aims for timely restoration of blood flow to ischemic areas to limit the volume of unsalvageable brain tissue, known as the ischemic core. Acute treatment also focuses on preserving the penumbra, which is an area of salvageable, ischemic neurons surrounding the core infarct that can be recovered by timely reperfusion.

Outcomes from landmark AIS trials focus on eliminating or reducing the severity of stroke-related deficits and improving functional status at 90 days. The 2019 guidelines prefer the National Institutes of Health Stroke Scale score (NIHSS), a validated scoring tool for measuring stroke deficits (Brott 1989, Powers 2019). The NIHSS generates a value of 0–42, with 0 representing the absence of ischemic stroke deficits and 42 representing the highest severity of deficits (Table 2). The NIHSS is rapidly performed and is valuable for its ability to determine stroke severity while serving as a tool for measuring changes in clinical status (Table 3).

Varying definitions of stroke severity have been defined in the literature, with severe strokes usually identified as an NIHSS score of more than 15 to 20 points. Although clinicians and researchers also use varying thresholds for defining clinically relevant changes in the NIHSS, differences in NIHSS scores of 1, 4, or 8 are used most in thrombolytic trials (Kwah 2014; Schlegel 2003). Besides stroke severity, the NIHSS score also predicts long-term outcomes. Despite some limitations, the NIHSS is the most widely used rating scale for identifying candidates for reperfusion therapies such as thrombolysis and thrombectomy.

The modified Rankin Scale (mRS) is the gold standard tool for categorizing functional status in patients with stroke (van Swieten 1988). The mRS ranges from 0 to 6, with 0 representing the absence of disability and 6 representing death

Table 2. NIHSS Score

Category	Score/Description	Category	Score/Description
1a. LOC	0 = Alert 1 = Drowsy 2 = Stuporous 3 = Coma	6a. Motor leg – Left 6b. Motor leg – Right	0 = No drift 1 = Drift 2 = Cannot resist gravity 3 = No effort against gravity 4 = No movement X = Untestable
1b. LOC questions	0 = Answers both correctly 1 = Answers one correctly 2 = Incorrect		
1c. LOC commands	0 = Obeys both correctly 1 = Obeys one correctly 2 = Incorrect	7. Limb ataxia	0 = No ataxia 1 = Present in one limb 2 = Present in two limbs
2. Gaze	0 = Normal 1 = Partial gaze palsy 2 = Forced deviation	8. Sensory	0 = Normal 1 = Partial loss 2 = Severe loss
3. Visual fields	0 = No visual loss 1 = Partial hemianopia 2 = Complete hemianopia 3 = Bilateral hemianopia	9. Language	0 = No aphasia 1 = Mild to moderate aphasia 2 = Severe aphasia 3 = Mute X = Untestable
4. Facial paresis	0 = Normal 1 = Minor 2 = Partial 3 = Complete	10. Dysarthria	0 = Normal articulation 1 = Mild to moderate slurring of words 2 = Near to unintelligible or worse X = Intubated or other physical barrier
5a. Motor arm – Left 5b. Motor arm – Right	0 = No drift 1 = Drift 2 = Cannot resist gravity 3 = No effort against gravity 4 = No movement X = Untestable	11. Extinction/ inattention	0 = No neglect 1 = Partial neglect 2 = Complete neglect

LOC = level of consciousness; NIHSS = National Institutes of Health Stroke Scale.

Information from: Richardson J, Murray, D, House CK, et al. Successful implementation of the National Institutes of Health Stroke Scale on a stroke/neurovascular unit. J Neurosci Nurs 2006;38:309-15.

(Table 4). Disability status, as measured by the mRS, is generally determined at discharge and again at 90 days because most patients who achieve functional recovery do so within this timeframe (Duncan 2000). The clinical significance of a 1-point change in mRS depends on the baseline value of the mRS. For example, a change from 0 to 1 indicates a low impact on daily activities, whereas a change in mRS from 3 to 4 indicates that the patient can no longer ambulate without assistance.

INTRAVENOUS FIBRINOLYTICS

Alteplase

Alteplase is a recombinant tissue-type plasminogen activator (rtPA) that exerts its therapeutic effect through initiating fibrinolysis (also referred to as *thrombolysis*). Specifically, rtPA cleaves plasminogen at the Arg561-Val562 peptide bond, forming plasmin. Plasmin is an endogenous protease enzyme that cleaves the cross-links between fibrin molecules, thus disrupting the mesh-like structure of a fibrin-based blood clot. Alteplase's FDA-approved labeling includes treatment of AIS at a dose of 0.9 mg/kg intravenously once with a maximum total dose of 90 mg. Ten percent of the dose (0.09 mg/kg) is given as a bolus over 1 minute, with the remaining 90% (0.81 mg/kg) infused over 1 hour. The biggest concern with administering intravenous alteplase for AIS is the risk of symptomatic intracranial hemorrhage (ICH), which occurs in 2 to 7 percent of patients (Frontera 2016). ICH is usually the result of hemorrhagic conversion within the infarcted territory. Providing broad clinical guidance on alteplase use is a delicate balance. Liberal interpretation of relative contraindications may increase the risk of ICH, whereas conservative approaches may limit how many patients benefit from this therapy.

Table 3. NIHSS Definitions of Severity and Relationship with Hospital Discharge Disposition

NIHSS Score	Stroke Severity	Discharge Disposition
0 or 1	Normal	Discharge home
1–4	Mild	
5–14	Mild to moderately severe	Acute inpatient rehabilitation
15–25	Severe	Long-term acute care
> 25	Very severe	

NIHSS = National Institutes of Health Stroke Scale.

Information from: Schlegel D, Kolb SJ, Luciano JM, et al. Utility of the NIH Stroke Scale as a predictor of hospital disposition. Stroke 2003;34:134-7.

Acute Blood Pressure Management

About 70% of patients presenting with stroke have a blood pressure of 170/110 mm Hg or greater (Britton 1986). Severe hypertension must be managed acutely if a patient is otherwise eligible to receive intravenous alteplase. The goal of acute management of blood pressure is to achieve a blood pressure less than 185/110 mm Hg to initiate alteplase and maintain a blood pressure of less than 180/105 mm Hg while alteplase is being infused and for the 24 hours after administration (Powers 2019). If the patient is not a candidate for intravenous fibrinolysis or mechanical thrombectomy, permissive hypertension, up to 220/120 mm Hg, is recommended to maintain cerebral perfusion to the penumbra. In these patients with no other indication for urgent hypertension treatment, the benefit of treatment of hypertension in the first 48 to 72 hours is uncertain (Powers 2019). The guidelines state it may be reasonable to lower the blood pressure by fifteen percent in the first 24 hours after onset of strokes in this select population. Ideal agents for acute control of blood pressure have a rapid onset, are available for intravenous administration, have a short half-life, and have a predictable blood pressure lowering to dose response. There is no evidence that one antihypertensive is preferred to another in the setting of AIS. Common blood pressure–lowering agents are labetalol, nicardipine, clevidipine, and hydralazine (Table 5).

The optimal target for blood pressure during and after intravenous alteplase was recently evaluated. Published in February 2019, the ENCHANTED trial randomized 2196 patients with hypertension receiving alteplase to a systolic blood pressure (SBP) goal of 130–140 mm Hg within 1 hour (intensive blood pressure–lowering cohort) or to a goal SBP of less than 180 mm Hg (guideline-based blood pressure cohort) (Anderson 2019). Functional outcome (shift in mRS) at 90 days was the primary efficacy end point, and the primary safety outcome was any ICH. The incidence of ICH was lower in the intensive-lowering group (14.8% vs. 18.7%; OR 0.75; 95% CI, 0.60–0.94; p=0.0137); however, the primary outcome of functional status at 90 days did not differ between the groups (unadjusted OR 1.01; 95% CI, 0.87–1.17; p=0.8702). Despite reduced rates of ICH, no change in functional outcome was shown. These findings call into question the benefit of intensive blood pressure lowering, and subsequent editorials from stroke experts, including the authors of this study, advise caution in interpreting the lower rates of ICH as a positive indicator of this therapy. The positive outcomes associated with the lower rate of ICH could have been negated by the negative impact on cerebral perfusion with intensive blood pressure lowering, possibly leading to the net neutral effect on functional outcomes at 90 days. According to this study alone, intensive blood pressure lowering post-alteplase may not be necessary or beneficial.

Table 4. Modified Rankin Scale

	Value	Description
Independent	0	No symptoms
	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
Dependent	3	Moderate disability; requiring 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 requiring constant nursing care and attention
	6	Dead

Information from: van Swieten JC, Koudstaal PJ, Visser MC, et al. Interobserver agreement for the assessment of handicap in stroke patients. Stroke 1988;19:604-7.

Table 5. Options for Antihypertensive Agents in Acute Stroke

Medication	Dose	Onset	Duration
Labetalol	10–20 mg slow IV push q5min, doubling dose until effect. May follow with an IV infusion at 2 mg/min. Titrate to max of 8 mg/min.	Within 5 min	16–18 hr (dose dependent)
Nicardipine	5 mg/hr IV continuous, titrate by 2.5 mg/hr q5–15min. Max 15 mg/hr	Within 5 min; 50% of max effect at 45 min with continuous infusion	50% decrease in effect by 30 min after discontinuation
Clevidipine	1–2 mg/hr IV continuous, titrate by doubling dose q2–5min. Max 21 mg/hr	2–4 min	5–15 min
Hydralazine	10–20 mg IV push q4–6hr, max single dose 40 mg	10–80 min	Up to 12 hr
Enalaprilat	1.25 mg slow IV push over 5 min q6hr	Within 15 min, peak effect 1–4 hr	6 hr

IV = intravenous(ly); q = every.

Information from: Powers WJ, Rabinstein AA, Ackerson T, et al. Guidelines for the early management of patients with acute ischemic stroke: 2019 update to the 2018 guidelines for the early management of acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2019;50:e344-e418.

Management of Adverse Events

The incidence of ICH after alteplase administration for AIS depends on several factors, including age, weight, history of hypertension, current antiplatelet therapy, baseline NIHSS score, blood glucose, SBP, and time since symptom onset (Mazya 2012). This complication can be devastating, with rates of hematoma expansion of up to 40% and 3-month mortality as high as 60%. "Reversal" of intravenous thrombolytics is usually indicated for symptomatic ICH with decline in neurologic function within the first 24 hours after administration. This may seem counterintuitive, given that the plasma half-life of alteplase is only 4 minutes; however, the terminal half-life is 72–100 minutes, and studies have noted a decrease in fibrinogen concentrations at 24 hours after administration. Treatment of thrombolytic-related ICH has great uncertainty, and guidance is limited to theoretical mechanisms, a heterogeneous mix of case series, and a few small, underpowered retrospective studies. Recommendations for managing ICH after alteplase in patients with AIS are available from the 2019 American Heart Association/American Stroke Association (AHA/ASA) guidelines for the early treatment of patients with AIS (Powers 2019) and the Neurocritical Care Society (NCS) guideline for reversal of antithrombotics in ICH (Frontera 2016). A summary of these recommendations is listed in Table 6.

The recommendation for cryoprecipitate administration after alteplase-related ICH is based on a single, multicenter, retrospective study. This trial evaluated risk factors for patients with symptomatic ICH after receiving alteplase for AIS (Yaghi 2015). In this study, a fibrinogen concentration of less than 150 mg/dL was the only statistically significant predictor of hematoma expansion. Because cryoprecipitate contains fibrinogen 200 mg/unit (and can increase fibrinogen concentrations by about 70 mg/dL after 10 units given to a patient weighing 70 kg), administration of this blood product to target a fibrinogen concentration of greater than 150 mg/dL is theorized to decrease the risk of further expansion. This theory, however, has never been prospectively evaluated, and retrospective studies have been underpowered to detect a treatment benefit.

Antifibrinolytics such as tranexamic acid and ε-aminocaproic acid have less efficacy data in the setting of ICH after alteplase administration. Mechanistically, these agents competitively bind to plasminogen, blocking its conversion to plasmin and inhibiting fibrin degradation (Frontera 2016). Supporting data analyses for recommending these agents are limited to case reports and small, retrospective case series. Given the slightly stronger evidence for cryoprecipitate, the NCS guidelines recommend cryoprecipitate over antifibrinolytics unless there is a contraindication to using or significant delay in obtaining this product. The authors state that an antifibrinolytic such as tranexamic acid or ε-aminocaproic acid can be used as an alternative to cryoprecipitate if these conditions exist. Alternatively, the 2019 AHA/ASA guidelines for the early treatment of patients with AIS are less direct about this recommendation, suggesting that using both agents together could be considered, but certainly antifibrinolytics would have a specific benefit in situations where cryoprecipitate was unavailable or otherwise contraindicated.

Transfusing platelets for the treatment of ICH associated with alteplase remains controversial as well. No data have supported the use of platelet transfusion, regardless of Plt. In fact, in one retrospective study, platelet transfusion was associated with a risk of hematoma expansion; however, given the study's retrospective design, the authors could not

Table 6. Management of Symptomatic ICH Within 24 Hr After IV Thrombolytic Administration

AHA/ASA 2019	NCS 2016
Discontinue alteplase	Discontinue thrombolytic infusion when ICH is present or suspected
Obtain CBC, PT (INR), PTT, fibrinogen concentration, type, and cross-match	No recommendation made for pretreatment laboratory tests
Cryoprecipitate 10 units infused over 10–30 min. Administer additional dose if fibrinogen concentration < 200 mg/dL	Cryoprecipitate 10 units initially for patients with thrombolytic administration within previous 24 hr. Administer additional dose if fibrinogen concentration < 150 mg/dL
Tranexamic acid 1000 mg IV over 10 min OR ε-aminocaproic acid 4–5 g IV over 1 hr, followed by 1 g IV until bleeding controlled (Potential for benefit in all patients, but particularly when blood products are contraindicated or declined by patient/family or if cryoprecipitate is not available in a timely manner)	When cryoprecipitate contraindicated or unavailable in a timely fashion, suggest tranexamic acid 10–15 mg/kg IV over 20 min or ε-aminocaproic acid 4–5 g IV as an alternative to cryoprecipitate
No recommendation for platelet transfusion	Unclear whether platelet transfusion is useful; therefore, no recommendation offered
Hematology and neurosurgery consultation and supportive therapy, BP management, ICP, CPP, MAP, temperature, and glucose control	No recommendation made for consultations or supportive therapies

AHA/ASA = American Heart Association/ American Stroke Association; BP = blood pressure; CPP = cerebral perfusion pressure; ICH = intracranial hemorrhage; ICP = intracranial pressure; MAP = mean arterial pressure; NCS = Neurocritical Care Society.

Information from: Powers WJ, Rabinstein AA, Ackerson T, et al. Guidelines for the early management of patients with acute ischemic stroke: 2019 update to the 2018 guidelines for the early management of acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2019;50:e344-e418; Frontera JA, Lewin JJ, Rabinstein AA, et al. Guideline for reversal of antithrombotics in intracranial hemorrhage: a statement for health-care professionals from the Neurocritical Care Society and Society of Critical Care Medicine. Neurocrit Care 2016;24:6-46.

conclude whether this finding was because of selection or even outcome bias (Yaghi 2015). Regardless, given the paucity of data with this intervention in ICH after alteplase, the NCS guidelines recommend against the routine use of platelets and make no recommendation about platelet transfusion in known thrombocytopenia.

Additional supportive therapy for ICH after thrombolysis is essentially extrapolated from the management of spontaneous ICH. In-depth discussion is beyond the scope of this chapter. Briefly, SBP should be lowered to a target of less than 160 mm Hg to decrease the risk of further hematoma expansion. Administration of anticoagulation reversal agents such as 4-factor prothrombin complex concentrate and vitamin K should be reserved for patients who were receiving anticoagulants at the time of alteplase administration (Frontera 2016). Administration of hyperosmolar solutions such as hypertonic saline or mannitol may be necessary if cerebral edema or increased intracranial pressure is present or if the patient has signs of impending herniation.

Orolingual angioedema is a rare but important adverse reaction associated with alteplase therapy after AIS. Alteplase is thought to cause angioedema in AIS through several pathways activated by the conversion of plasminogen into plasmin, resulting in both histamine release and an increase in circulating bradykinin (Hill 2000). The 2019 AHA/ASA guidelines provide treatment recommendations for alteplase-induced angioedema as outlined in Figure 2.

The incidence of orolingual angioedema is 1%–5%, and concurrent use of angiotensin-converting enzyme inhibitors (ACEIs) is associated with up to 65% of cases. This is thought to be propagated by an already elevated bradykinin in patients receiving ACEI therapy. In most cases associated with alteplase, angioedema is self-limiting and typically does not require an advanced airway. A recent, prospective analysis of 923 patients treated with intravenous alteplase for AIS in a single center in France found an overall incidence of angioedema of 2.2%, with no patients requiring an advanced airway or epinephrine (Myslimi 2016). Outcomes, including 90-day mRS and ICH, did not differ between those who had angioedema and those who did not. The risk of angioedema increased significantly in those receiving ACEI therapy (OR 3.8; 95% CI, 1.6–9.3). No single anatomic site of stroke was linked to the development of angioedema.

The AHA/ASA guidelines recommend blood pressure checks, neurologic examinations, and angioedema screenings every 15 minutes for the first 2 hours after initiating

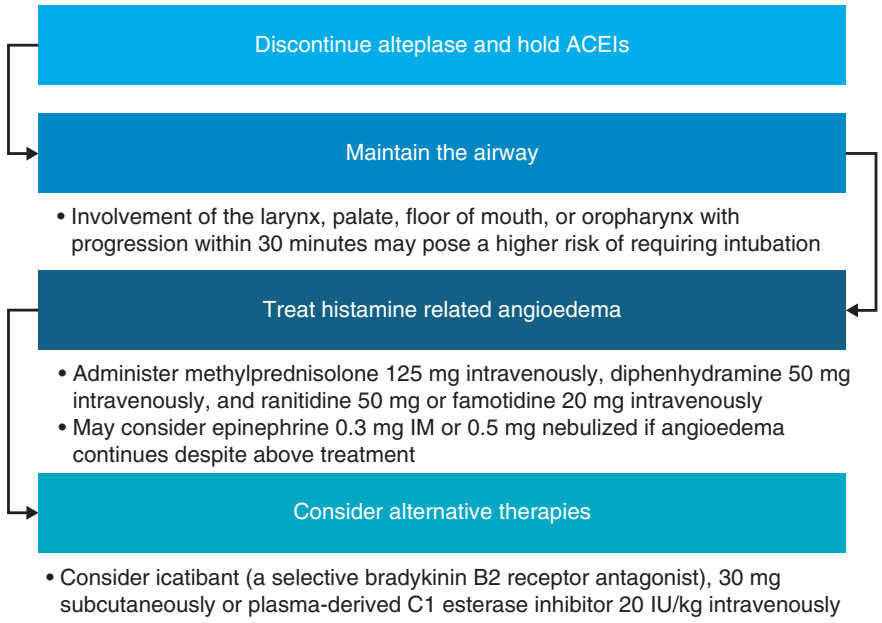

Figure 2. Treatment of alteplase-induced angioedema.

C1 = complement 1; IM = intramuscular(ly).

Information from: Powers WJ, Rabinstein AA, Ackerson T, et al. Guidelines for the early management of patients with acute ischemic stroke: 2019 update to the 2018 guidelines for the early management of acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2019;50:e344-e418.

alteplase and then every 30 minutes for the next 6 hours, followed by every hour until 24 hours after administering intravenous alteplase (Powers 2019; Miller 2010). The AHA/ASA guidelines also recommend a computed tomography (CT) scan or magnetic resonance imaging (MRI) about 24 hours after alteplase, prior to initiating anticoagulant or antiplatelet agents.

Tenecteplase

Tenecteplase is a 3-point-mutated (T-threonine, N-asparagine, K-lysine) variant of alteplase, resulting in an agent with the same mechanism of action but a longer half-life (22 minutes vs. 4 minutes), a 14-fold increased specificity toward fibrin, and an 80-fold increased resistance to plasminogen activator inhibitor-1 compared with alteplase (Logallo 2015). These pharmacokinetic differences allow tenecteplase to be given as a single intravenous push injection rather than as an infusion and create greater specificity of the agent for fibrin-rich clots. These features provide tenecteplase with a more potent and faster fibrinolysis than alteplase. Furthermore, tenecteplase causes less consumption of fibrinogen, plasminogen, and α_2-antiplasmin, leading to a lower systemic fibrinolytic effect than that produced by alteplase and, theoretically, a lower bleeding risk (Logallo 2015). The aforementioned pharmacokinetic and pharmacodynamic properties of tenecteplase make it appealing for AIS treatment. To date, three phase II clinical trials and one phase III randomized clinical trial evaluating tenecteplase in AIS have been published (Table 7). Three additional phase III studies are under way: TASTE (Australian New Zealand Clinical Trials Registry number ACTRN12613000243718), TEMPO-2 (ClinicalTrials.gov 2019b; NCT02398656), and TWIST (NCT03181360).

The NOR-TEST study was a phase III, randomized, multicenter, open-label, blinded end point superiority trial in Norway (Logallo 2017). Patients presenting within 4.5 hours of onset or awakening with suspected AIS received either intravenous tenecteplase 0.4 mg/kg (maximum dose 40 mg) or alteplase 0.9 mg/kg (maximum dose 90 mg). Patients awakening with symptoms were eligible to receive tenecteplase on the basis of advanced MRI techniques, to identify a low risk-benefit. The study enrolled 1100 patients, and the baseline demographics did not differ between groups. Patients enrolled had an average age of 71 years, were primarily male, and had mild (NIHSS score 0–7) stroke. Median door-to-needle times (DTNs) were 32 and 34 minutes in the tenecteplase and alteplase groups, respectively. The primary outcome of excellent functional outcome (mRS score of 0 or 1 at 3 months) was achieved at similar rates in patients receiving tenecteplase and alteplase (see Table 7). The rate of ICH did not differ, which occurred in 3% and 2% of patients in the tenecteplase and alteplase groups, respectively (OR 1.16; 95% CI, 0.51–2.68; p=0.70).

Table 7. Phase II and III Studies Evaluating TNK in AIS

Study	TNK Dose (mg/kg)	Alteplase Control	Window (hr)	Baseline NIHSS (median)	Primary End Point	Results	sICH with TNK (%)
TEMPO (2015)	0.1	No	< 12	2.5	sICH	Recanalization: 39% complete and 17% partial	0
	0.2					Recanalization: 52% complete and 9% partial	4
ATTEST (2015)	0.25	Yes	< 4.5	11.5	Salvaged penumbra at 24–48 hr	Salvaged penumbra: 68% [SD 28] for the TNK group vs. 68% [23] for the alteplase group; mean difference 1.3% [95% CI, -9.6 to 12.1]; p=0.81	5.8
NOR-TEST (2017)	0.4	Yes	< 4	4	mRS score 0 or 1 at 3 mo	Primary outcome: 64% in TNK group vs. 63% in alteplase group (OR 1.08; 95% CI, 0.84–1.38; p=0.52)	3
EXTEND-IA TNK (2018)	0.25	Yes	< 4.5	17	Pre-thrombectomy reperfusion in > 50% of territory	Primary outcome in 22% with TNK and 10% with alteplase (incidence ratio 2.2; 95% CI, 1.1–4.4; p=0.002 for noninferiority; p=0.03 for superiority)	1

AIS = acute ischemic stroke; sICH = symptomatic intracranial hemorrhage; TNK = tenecteplase.

Information from: Logallo N, Novotny V, Assmus J, et al. Tenecteplase versus alteplase for management of acute ischaemic stroke (NOR-TEST): a phase 3, randomised, open-label, blinded endpoint trial. Lancet Neurol 2017;16:781-8; Campbell BCV, Mitchell PJ, Churilov L, et al. Tenecteplase versus alteplase before thrombectomy for ischemic stroke. N Engl J Med 2018;378:1573-82; Huang X, Cheripelli BK, Lloyd SM, et al. Alteplase versus tenecteplase for thrombolysis after ischaemic stroke (ATTEST): a phase 2, randomised, open-label, blinded endpoint study. Lancet Neurol 2015;14:368-76; and Coutts SB, Dubuc V, Mandzia J, et al. Tenecteplase-tissue-type plasminogen activator evaluation for minor ischemic stroke with proven occlusion. Stroke 2015;46:769-74.

The EXTEND-IA TNK is the most recent phase II tenecteplase study published (Campbell 2018). The primary outcome was the reperfusion rate of greater than 50% of the involved ischemic territory or the absence of a retrievable thrombus on initial angiographic assessment after a confirmed thrombus by computed tomography angiography (CTA). Patients presenting within 4.5 hours of symptom onset were randomly assigned to receive either tenecteplase 0.25 mg/kg intravenously (maximum dose 25 mg), or alteplase 0.9 mg/kg intravenously (maximum dose 90 mg). The primary outcome occurred significantly more often in the tenecteplase group than in the alteplase group (Table 7). Functional outcome was significantly better at 90 days in the tenecteplase group than in the alteplase group (median mRS score of 2 vs. 3; OR 1.7; 95% CI, 1.0–2.8; p=0.04), and symptomatic hemorrhage occurred in 1% of patients in each group (RR 1.0; 95% CI, 0.1–15.9; p=0.99). This study showed that tenecteplase is at least noninferior and may be superior in achieving early reperfusion over alteplase in patients with confirmed large vessel occlusion (LVO) who are thrombectomy candidates. The EXTEND-IA TNK part 2 is a phase II study under way to compare tenecteplase 0.25 mg/kg and 0.4 mg/kg in a similar patient population.

GUIDELINES FOR THE EARLY MANAGEMENT OF PATIENTS WITH ACUTE ISCHEMIC STROKE: AHA/ASA

Recognizing the vast amount of high-quality evidence published since the 2013 guidelines for the early treatment of patients with AIS (Jauch 2013), the AHA published an update in 2018 (Powers 2018). This new guideline summarized advances in prehospital care, emergency care, treatment with intravenous and intra-arterial therapies, and in-hospital management. The authors limited their recommendations to the period up to 2 weeks after the onset of stroke. In 2019 the AHA/ASA published an update to these guidelines recognizing practice changing studies published in 2018 and early 2019 (Powers 2019). For this chapter, only new or significantly revised recommendations that affect pharmacotherapy or pharmacists' practice in the acute hospital setting will be discussed. The updates that will be discussed in the rest of this chapter are briefly summarized in Table 8. A link to the full version of these new guidelines is in the additional readings section of this chapter.

Table 8. Comparison of the AHA/ASA Acute Ischemic Stroke Guidelines

	2013 Guideline	2018 Guideline	2019 Guideline
Door-to-needle times for IV thrombolysis	Goal < 60 minutes	• Establish internal goals • Primary goal of < 60 minutes in 50% of patients, secondary goal of < 45 minutes in 50% of patients	• Establish internal goals • Thrombolysis and thrombectomy should be performed as fast as possible
Tenecteplase instead of alteplase for AIS	Usefulness is unknown, should only be used in the setting of a clinical trial	May consider in minor neurological impairment without LVO	• Reasonable to consider over alteplase in patients who are candidates for thrombectomy with LVO • May consider in minor neurological impairment without LVO
Alteplase eligibility recommendations	Listed as inclusion, exclusion and relative exclusion criteria	Listed as indications, contraindications and additional recommendations, significantly more inclusive	Listed as indications, contraindications and additional recommendations, slight modifications to recommendations
Alteplase extended 3- to 4.5-hr window	Contraindicated in warfarin use regardless of INR, age >80, history of both stroke and diabetes, or NIHSS >25	• Beneficial in warfarin use with INR <1.7, age >80 or history of both stroke and diabetes • Uncertain benefit in NIHSS >25	• Beneficial in warfarin use with INR <1.7, age >80 or history of both stroke and diabetes • Uncertain benefit in NIHSS >25
Alteplase for mild non-disabling stroke	Reasonable to consider	Reasonable to consider	Contraindicated
Neuroimaging for thrombolysis guidance	No recommendation	No recommendation	MRI to identify diffusion-positive and FLAIR-negative lesions can be used to identify candidates for IV thrombolysis
DAPT	No recommendation	In patients with mild stroke, not receiving IV fibrinolysis, 21 days of aspirin and clopidogrel started within the first 24 hr may reduce risk of recurrent ischemic stroke	In patients with mild stroke, not receiving IV fibrinolysis, 21 days of aspirin and clopidogrel started within the first 24 hr is effective in reducing the risk of recurrent ischemic stroke
Thrombectomy	No recommendation	Extended time window to 24 hr in patients meeting eligibility criteria	Extended time window to 24 hr in patients meeting eligibility criteria

AIS = acute ischemic stroke; DAPT = dual antiplatelet therapy; FLAIR = fluid-attenuated inversion recovery; INR = international normalized ratio; IV = intravenous(ly); LVO = large vessel occlusion; MRI = magnetic resonance imaging; NIHSS = National Institutes of Health Stroke Scale.

Information from: Jauch EC, Saver JL, Adams HP, et al. Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2013;44:870-947; Powers WJ, Rabinstein AA, Ackerson T, et al. 2018 guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2018;49:e46-e110; Powers WJ, Rabinstein AA, Ackerson T, et al. Guidelines for the early management of patients with acute ischemic stroke: 2019 update to the 2018 guidelines for the early management of acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2019;50:e344-e418.

DTN Recommendations

The 2013 AIS guidelines recommended that health systems establish a primary goal DTN of 60 minutes and that this DTN be achieved by at least 50% of patients. The AIS 2019 guidelines state that thrombolysis and thrombectomy should be performed as fast as possible, and it can be beneficial for institutions to establish and monitor target time goals for DTN and implement performance improvement measures to decrease times to these treatments. "Target: Stroke" is a national quality improvement initiative developed and implemented by the AHA/ASA to improve AIS treatment by reducing DTN (AHA 2019). Phase III of Target: Stroke has recently proposed more aggressive national goals, including more stringent targets for DTN: 50% within 30 minutes, 75% within 45 minutes, and 85% within 60 minutes. Meeting these new targets will require diligence to ensure the resolution of all systemic, staffing, and educational barriers to rapid alteplase administration.

Eligibility Recommendations for Intravenous Alteplase

Many have questioned some of the relative and absolute contraindications to intravenous alteplase therapy, most of which were based on the inclusion and exclusion criteria from the original NINDS study (NINDS 1995). Similarly, the additional contraindications to alteplase use in the 3- to 4.5-hour window were entirely based on additional exclusion criteria introduced by the ECASS III trial (Hacke 2008). Since publication of these landmark trials, several studies have assessed the validity of many different aspects of these contraindications.

In 2016, the AHA/ASA published the "Scientific Rationale for the Inclusion and Exclusion Criteria for Intravenous Alteplase in Acute Ischemic Stroke" (Demaerschalk 2016). This review addressed the available data analyses and provided guidance on clinical decision-making when faced with a relative or absolute contraindication to intravenous alteplase. This drove major changes in the newly termed "eligibility recommendations for IV alteplase" in the 2018 AIS guidelines. These recommendations for the use of alteplase in patients with AIS were carried forward to the 2019 guidelines, with a few minor updates. The contraindications and additional recommendations from the 2019 guideline update for intravenous alteplase are summarized in Box 1.

One notable change to the contraindications to alteplase is the elimination of the restrictive verbiage assigned to the extended window of 3–4.5 hours. Patients presenting in the 3- to 4.5-hour window can now be considered for intravenous alteplase therapy if they are older than 80, have a history of stroke and diabetes, or are receiving warfarin anticoagulation, given that their INR is 1.7 or less. In patients who present in the extended window with severe stroke symptoms (NIHSS score greater than 25), the benefit of intravenous alteplase remains uncertain. Another notable change in the 2019 AIS guidelines is the new contraindication in mild non-disabling stroke for both the 0- to 3-hour and 3- to 4.5-hour time windows. This recommendation is based on findings from the PRISMS randomized controlled trial (Kharti 2018). This study evaluated patients experiencing AIS with an NIHSS of 0 to 5 whose deficits were judged not to interfere with activities of daily living or prevent return to work. They found no benefit of treatment with alteplase over aspirin within 3 hours of onset in this patient population. The guidelines still recommend treatment of mild, disabling stroke, in patients presenting within 4.5 hours of last known well. Indications for intravenous alteplase include patients with AIS symptoms presenting within 4.5 hours of onset whose blood pressure can safely be lowered to less than 185/110 mm Hg with antihypertensive agents and whose blood glucose is greater than 50 mg/dL. Intravenous alteplase should be initiated as quickly as possible because a shorter time to treatment is strongly associated with improved outcomes.

Tenecteplase in Practice

The 2018 AHA/ASA AIS guidelines were the first to add tenecteplase as an alternative to alteplase for the treatment of mild AIS (class IIb recommendation) (Powers 2018). These guidelines, and the 2019 guidelines, note that tenecteplase has not been proven superior or noninferior to alteplase in this patient population; however, current data analyses show that tenecteplase is similar to alteplase in safety. Thus, the guidelines state that tenecteplase can be considered in patients with minor neurologic deficits and no major intracranial occlusion, given the low baseline NIHSS score (median NIHSS score 4) of patients in the NOR-TEST study. Citing the positive results from the EXTEND-IA TNK study mentioned above, the 2019 guidelines added a recommendation for tenecteplase in place of alteplase prior to thrombectomy. The guidelines state that it may be reasonable to choose tenecteplase 0.25-mg/kg intravenously (with a maximum of 25 mg) over intravenous alteplase in patients without contraindications to IV fibrinolysis who are also eligible to undergo mechanical thrombectomy (Class of recommendation – IIb, moderate-quality evidence) (Powers 2019). With ongoing phase III studies of tenecteplase in AIS, this will almost certainly be an evolving topic and potentially an evolving recommendation as more data analyses are published.

Tenecteplase has not yet gained FDA approval for the indication of AIS; thus, any use in the United States is off-label. Nevertheless, some centers are moving toward using tenecteplase for minor stroke, and potentially now for pre-thrombectomy fibrinolysis based on the earlier discussion. Optimal candidacy for and contraindications to tenecteplase in AIS remain uncertain, and the 2019 guidelines simply state tenecteplase could be used in "patients without contraindications for intravenous fibrinolysis", suggesting providers refer to the same contraindications and considerations for intravenous alteplase. Use of tenecteplase may provide both logistical benefits and drawbacks. Benefits, as previously mentioned, include fewer steps to reconstitution and its administration by intravenous push. However,

Box 1. 2019 AHA/ASA Guidelines: Eligibility for IV Alteplase Treatment in Patients with AIS

Contraindications

- Mild non-disabling stroke
- Acute head trauma (posttraumatic infarction during acute in-hospital phase)
- Acute intracranial hemorrhage on imaging
- Aortic arch dissection
- Blood pressure > 185/110 mm Hg (must be lowered prior to administration)
- Coagulopathy including Plt < 100,000/mm^3, INR > 1.7, aPTT > 40 s, or PT > 15 s
- Concomitant use of abciximab
- Concomitant administration of IV aspirin
- Extensive regions of clear hypoattenuation on CT brain imaging
- GI malignancy or recent bleeding event within 21 days
- History of intracranial hemorrhage
- Infective endocarditis
- Intra-axial intracranial neoplasm
- Intracranial or intraspinal surgery within 3 mo
- Low-molecular-weight heparin treatment dose within the previous 24 h (deep venous thrombosis prophylaxis dosing is NOT a contraindication)
- Prior ischemic stroke within 3 mo
- Symptoms and signs most consistent with subarachnoid hemorrhage
- Severe head trauma within 3 mo
- Use of direct thrombin inhibitors or direct factor Xa inhibitors unless pertinent laboratory tests such as aPTT, INR, ecarin clotting time, platelet count, thrombin time or direct factor Xa activity assays are normal or patient has not received a dose in > 48 hr (assuming normal clearance)

Additional Recommendations

In the 3- to 4.5-hr window:

- Alteplase may be reasonable for patients with mild, disabling stroke
- Benefit of alteplase is uncertain in patients with severe stroke symptoms (NIHSS score > 25)
- Treatment appears to be safe and may be beneficial in: patients > 80, patients with INR ≤ 1.7, and patients with both a prior stroke and diabetes

Alteplase is reasonable in patients with:

- Acute MI or MI within the past 3 mo
- AIS as a complication of cardiac or cerebral angiographic procedures
- AIS known or suspected to be associated with extracranial arterial cervical artery dissection within 4.5 h
- Baseline mRS score ≥ 2 or patients with dementia
- Early improvement, but persisting symptoms causing moderate impairment or disability
- Extra-axial intracranial neoplasm
- GI or genitourinary bleeding > 21 days ago
- History or active menorrhagia without clinically significant anemia or hypotension
- History of hemorrhagic ophthalmic conditions
- Hyperdense MCA sign
- Illicit drug use–associated AIS given no other exclusions
- Initial blood glucose concentrations < 50 or > 400 mg/dL that are normalized and patients remain otherwise eligible for treatment
- Low burden of CMBs (1–10) on MRI
- Lumbar dural puncture in the preceding 7 days
- Malignancy and a reasonable life expectancy (> 6 mo) without contraindications
- Sickle cell disease
- Small or moderate (< 10 mm) unruptured and unsecured aneurysm
- Seizure at onset of AIS if impairment appears to be caused by stroke rather than postictal phenomenon
- Severe stroke leading to severe disability and acute pericarditis, left atrial or ventricular thrombus, cardiac myxoma, or papillary fibroelastoma
- Stroke mimics, given the low risk of intracranial hemorrhage
- Wake up stroke, and stroke of unclear time of onset >4.5 h since last known well who have a diffusion-weighted MRI lesion smaller than 1/3 the MCA territory and no visible signal change on FLAIR

Weigh risk-benefit in patients with:

- Arterial puncture at a non-compressible blood vessel in the preceding 7 days
- Bleeding diathesis or coagulopathy
- Pregnancy when treating moderate or severe strokes
- Recent or active vaginal bleeding causing clinically significant anemia; recommend an emergency consultation with a gynecologist
- Recent major trauma or recent major surgery, not involving the head, within 14 days
- Unruptured and untreated intracranial vascular malformation

Safety and efficacy of alteplase are not well established in patients with:

- Acute pericarditis or left atrial or ventricular thrombus and moderate stroke with mild disability
- Concomitant use of tirofiban or eptifibatide
- Current active malignancy
- Giant unruptured and unsecured intracranial aneurysm
- High burden of CMBs (> 10)
- Intracranial arterial dissection
- Recent postpartum status (<14 d after delivery)

AIS = acute ischemic stroke; aPTT = activated partial thromboplastin time; CMB = cerebral microbleed; FLAIR = fluid-attenuated inversion recovery; INR= international normalized ratio; IV = intravenous(ly); mRS = modified Rankin Scale; MCA = middle cerebral artery; MI = myocardial infarction; MRI = magnetic resonance imaging; NIHSS = National Institutes of Health Stroke Scale.

Information from: Powers WJ, Rabinstein AA, Ackerson T, et al. Guidelines for the early management of patients with acute ischemic stroke: 2019 update to the 2018 guidelines for the early management of acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2019;50:e344-e418.

having two different medications available for use with different dosing, administration instructions, and reconstitution instructions may introduce confusion and medication errors. These errors and unfamiliarity with tenecteplase may increase the DTN and lead to poor outcomes. Thorough education of team members and involvement of a clinical pharmacist may reduce the chances of these errors.

Alteplase and Imaging Sequence of Events

Neuroimaging strategies for AIS should follow a defined sequence to minimize DTN and door-to-endovascular therapy (EVT) times. The non-contrast head CT should be performed within 20 minutes of hospital arrival. In current practice, multimodal neuroimaging is usually not necessary for deciding to administer alteplase within the standard 3- or 4.5-hour DTN windows. If all contraindications have been ruled out, intravenous alteplase should be administered immediately after ruling out ICH on the initial CT and not delayed for additional imaging according to the 2019 guideline update. Alterations in this sequence will prolong DTN (Powers 2019). Based on this recommended sequence, it would be optimal for administration of intravenous thrombolysis to take place while the patient is still in the CT scanner, as not to further delay the administration of alteplase. Because alteplase requires a dedicated intravenous line and these patients may also receive intravenous contrast and antihypertensive infusions concurrently, preemptively placing two or three intravenous access sites may be beneficial.

Patient Care Scenario

T.J. is an 81-year-old man with a medical history of atrial fibrillation, heart failure, type 2 diabetes, morbid obesity, and hypertension. He has no surgical history. He presents to your hospital with right upper and right lower-extremity hemiparesis, right facial droop, aphasia, and dysarthria. The patient is in atrial fibrillation with a ventricular rate of 120 beats/minute. His blood pressure is 190/95 mm Hg. His wife witnessed the onset of these symptoms about 4 hours before ED arrival. The patient takes many home medications, including rivaroxaban. His wife states that he was scheduled to have a procedure later today and that his physician told him to stop taking rivaroxaban 4 days ago. She notes that his weight this week at the physician's office was 130 kg. His NIHSS score is 19, as determined by the neurologist. T.J. is rushed to a non-contrast head CT that reveals no acute intracranial abnormality. Laboratory results, including a basic metabolic panel and a CBC, are unremarkable, and a bedside INR performed in the ED shows an INR of 1.0. The CTA is unrevealing for a large vessel occlusion. Determine his therapeutic plan, including doses, goal times to therapy, and eligibility for interventions.

ANSWER

T.J. has a large left MCA territory infarction, likely of cardioembolic origin, which matches with the right-sided hemiparesis and language difficulty. The infarction is likely caused by the abrupt discontinuation of rivaroxaban in a patient with a relatively high stroke risk. He has been prescribed an anticoagulant; however, given that it has been more than 48 hours, his renal function is unremarkable, and his INR is not elevated, this should not exclude him from receiving intravenous thrombolysis. He would otherwise be considered a candidate for intravenous thrombolysis because he is within the 4.5-hour window and no other contraindications are present. Therefore, his blood pressure should be managed until it is below the goal of 185/110 mm Hg before initiating alteplase. This should be recognized by the pharmacist within minutes of patient arrival and aggressively managed with 10 or 20 mg of labetalol, administered intravenously over 2 minutes. If the initial labetalol dose does not decrease the blood pressure to meet this goal, a second dose of labetalol at double the initial dosage should be administered and a nicardipine or clevidipine infusion initiated. This should all be done within 10–15 minutes of the patient's arrival. Before advancing to the CT imaging suite, the patient should be placed on a zeroed weigh bed or his weight estimated independently by two different providers. Once his blood pressure is controlled and the CT head is negative for bleeding or other intracranial pathology, the decision to administer alteplase should be made by the neurologist, and the pharmacist should be ready to reconstitute alteplase immediately. A dose of 0.9 mg/kg should be calculated. In this patient, because he is weighs more than 100 kg, a maximum dose of 90 mg should be used. Ten percent of this dose should be provided as a bolus over 1 minute, followed by an infusion over 1 hour. The pharmacist primes the tubing and sets up the pre-programmed pump to deliver the medication as previously described. This administration should be achieved as fast as possible, and new guidance suggests that at least 50% of patients presenting should have a DTN of less than 30 minutes. The goal should be to initiate the alteplase infusion between the non-contrast CT and advanced imaging such as CTA or CTP, given the delay in DTN that may ensue while waiting for these tests; however, systemic or situational delays in administering alteplase should not create significant delays in acquiring advanced imaging. Given the CTA findings, the patient is not a candidate for thrombectomy.

1. Powers WJ, Rabinstein AA, Ackerson T, et al. Guidelines for the early management of patients with acute ischemic stroke: 2019 update to the 2018 guidelines for the early management of acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2019;50:e344-e418.
2. American Heart Association. Introducing Target: Stroke Phase III. 2019.

Neuroimaging for Thrombolysis Guidance

Neuroimaging is essential in AIS management and has become increasingly important for stroke response pharmacists to understand as contributors to thrombolytic decision-making. Since 1995, the value of traditional, non–contrast-enhanced head CT scans has been recognized for quickly ruling out ICH in patients who may be candidates for intravenous alteplase (NINDS 1995), and MRI has long been recognized as the gold standard for diagnosing ischemic stroke (Powers 2019). Using neuroimaging techniques besides the standard non-contrast head CT to determine acute reperfusion therapy eligibility is termed *imaging-based patient selection*. After publication of the 2015 thrombectomy trials, advanced neuroimaging techniques became popular for identifying thrombectomy candidates. Evidence has recently emerged for using advanced imaging to select optimal patients for thrombolytic therapy when the time of symptom onset is unknown such as when patients wake up with stroke.

In contrast to previous AIS guideline versions, the 2019 recommendation updates recognize the benefits of advanced, multimodal imaging in addition to the routine non-contrast CT for select patients with unclear time of stroke onset. A key difference between neuroimaging used for selecting thrombectomy candidates versus thrombolytic candidates is that vessel angiography (CTA or MRA) is not required for identifying thrombolytic candidates (Table 9).

Time Windows and Tissue Windows

The 0 to 3- and 4.5-hour windows are general approximations of the window in which the benefits of thrombolysis outweigh the risks in eligible patients; however, thrombolytic benefits could continue to outweigh risks beyond this window in many patients (Schwamm 2018). Many patients presenting beyond 3 to 4.5 hours from symptom onset still have salvageable brain tissue as a result of high-integrity collateral circulation. The extent of collateral circulation varies between patients and can sustain the viability of ischemic brain tissue for a period that depends on collateral integrity and can be longer than the typical 4.5-hour treatment window.

Unwitnessed AIS with symptoms on awakening (wake-up stroke) represents about 15%–25% of all AIS cases (Urrutia 2018). Patients with unwitnessed strokes from LVO may be candidates for thrombectomy, given more recent literature. However, most of these patients present without an LVO leading to a large cohort that, prior to the 2019 guidelines, would not receive reperfusion therapy for AIS (Albers 2018; Nogueira 2018; Schwamm 2018). Using neuroimaging

Table 9. Comparison of Advanced, Multimodal Neuroimaging Strategies to Identify Extended Window Reperfusion Candidates[a]

Type of Reperfusion Therapy	CT-Based Imaging			MRI Based Imaging		
	CTA Determines presence of LVO	CTP Estimates core and salvageable tissue volumes		MRA Determines presence of LVO	DW-MRI Estimates ischemic volume	FLAIR MRI Estimates core volume
Thrombolysis Required imaging for treatment greater than 4.5 hours from last known well (including wake up stroke)	-	+	OR	-	+	+
Thrombectomy Required imaging for treatment within 6 to 24 hours of stroke onset	+	+	OR	+	+	-

[a]Minus sign = not applicable; Plus sign = required as part of either the CT-based or the MR-based imaging strategy.

[b]MR-based strategy is recommended by current guidelines for identifying thrombolytic candidates. The recent EXTEND trial supports a CTP-based strategy.

[c]Providers may use a CT-based strategy or an MR-based strategy to identify thrombectomy candidates according to current guidelines.

CTA = Computed tomography angiography; CTP = computed tomography perfusion; DW = diffusion weighted; FLAIR = fluid attenuated inversion recovery; LVO = large vessel occlusion; MR = magnetic resonance; MRA = magnetic resonance angiography; MRI = magnetic resonance imaging;

Information from: Ma H, Campbell BCV, Parsons MW, et al. Thrombolysis Guided by Perfusion Imaging up to 9 Hours after Onset of Stroke. N Engl J Med 2019;380:1795-803; Powers WJ, Rabinstein AA, Ackerson T, et al. Guidelines for the early management of patients with acute ischemic stroke: 2019 update to the 2018 guidelines for the early management of acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2019; October 30:[ePub ahead of print].

for imaging-based patient selection, some patients with unknown time of stroke onset can now be treated with thrombolytic therapy (Powers 2019).

To safely and effectively provide reperfusion therapies to more patients, a paradigm shift is occurring toward identifying patient-specific "tissue windows" (or tissue clock) rather than chronologic time windows to assess eligibility for both thrombectomy and thrombolysis. Recent publications demonstrate a net benefit for good functional outcome at 90-days when imaging is used to select candidates for thrombolysis when time of stroke onset is unknown (Schwamm 2018; Logallo 2017). The MR WITNESS, WAKE UP, and EXTEND trials (discussed below) represent the beginning of this paradigm shift (Ma 2019; Schwamm 2018; Thomalla 2018; Bivard 2017).

MRI-Based Imaging

Besides being the gold standard for diagnosing ischemic stroke, different types of MRI studies can be used to select patients for thrombectomy or thrombolysis according to the 2019 guideline recommendations (Powers 2019). The MRI is more sensitive than CT imaging, can visualize brain tissue and brain vasculature, and can identify a stroke within minutes of onset. At many hospitals, rapidly obtaining an MRI during acute stroke response is limited by resources, accessibility, and logistics. Routine use of MRI in place of the initial CT has not been deemed cost-effective (Powers 2019).

MRI for Thrombolytic Patient Selection

In advanced MRI evaluations, penumbral volume is estimated by comparing two different types of MRIs (diffusion-weighted MRI images vs. fluid-attenuated inversion recovery [FLAIR] images). A mismatch in these two types of MRIs represents penumbra. If there is no mismatch, the interpretation is that the area has fully infarcted and reperfusion therapies would not be beneficial. Published in 2018, MR WITNESS was a multicenter phase IIa trial evaluating the safety and efficacy of intravenous alteplase when administered to unwitnessed strokes, including wake-up strokes (Schwamm 2018). Using predefined eligibility criteria for alteplase (except for the defined treatment window), patients were enrolled if they presented within 4.5 hours of the discovery of symptoms and within 4.5 to 24 hours of the last known well. Patients were enrolled only if they had a diffusion-weighted MRI/FLAIR mismatch on imaging. This was an open-label trial of 80 patients (70% with wake-up strokes) with the results compared with those of ECASS-3 (Hacke 2008). Patients were enrolled with a median of around 11 hours from the last known well. The primary end point of symptomatic ICH occurred in one patient (1.3%) compared with 5.3% in ECASS-3 (p=0.07). About 40% of patients had an mRS score of 0 or 1 at 90 days, reflecting a good outcome. Outcomes and mortality findings compared with the results of ECASS-3 were not statistically different.

Also published in 2018, the WAKE UP trial evaluated a similar patient population. Unlike MR WITNESS, WAKE UP was a randomized, double-blind, placebo-controlled phase III trial (Thomalla 2018). About 500 patients were enrolled. These patients met the standard alteplase eligibility criteria except for time from onset within 3–4.5 hours. About 90% of these patients were considered to have wake-up strokes. Significantly more patients receiving alteplase had a more favorable outcome (mRS score of 0 or 1) than did patients who received no treatment. The median time between the patient's last known well and alteplase administration was 10.3 hours. Mortality did not differ; however, there were more symptomatic ICHs in the alteplase group than in placebo (4% vs. 0.4%; p=0.03). The WAKE UP trial provides evidence for alteplase administration on the basis of a tissue clock versus a chronologic clock; however, the results must be interpreted in the context of the trial's limitations. This trial was terminated prematurely because of a lapse in funding and did not achieve the target enrollment (Thomalla 2018).

MRI-based selection was indirectly evaluated in the NORTEST trial with tenecteplase (Logallo 2017) and is being used in two currently enrolling phase III tenecteplase trials (TEMPO-2, NCT02398656; and TWIST, NCT03181360).

CT-Based Imaging

Computed tomography angiography (CTA) and computed tomography perfusion (CTP) are two types of advanced neuroimaging techniques for patients with a suspected LVO who may be thrombectomy candidates. A proximal LVO is the optimal target for a thrombectomy procedure, given its size and location. The primary purpose for performing a CTA is for the clinician to confirm or deny the presence of an LVO. Patients without LVO are not candidates for thrombectomy (Powers 2019). CTP may be used to determine if there is perfusion – core mismatch which indicates the presence of salvageable tissue and may be particularly useful in the setting of extending the time window for reperfusion therapies when mismatch is present. The EXTEND study is the most recent trial evaluating wake-up strokes (Ma 2019). This trial also included patients with unknown onset times, and treatment was administered in the 4.5- to 9-hour window from stroke onset or awakening. Eligibility was based on presence of perfusion-core mismatch by advanced CT perfusion (87%) or MRI perfusion (13%) imaging to identify appropriate thrombolytic candidates (Ma 2019). The trial was terminated early after the publication of WAKE UP, but the available results were similar.

Updates in Antiplatelet Therapy for Secondary Prevention

Alternative $P2Y_{12}$ Inhibitors

The risk of recurrent ischemic stroke is as high as 12% in the first 2 weeks after AIS or transient ischemic attack (TIA) and then declines. Up to 80% of recurrent strokes occur within the first 14 days of the index stroke or TIA (Wang 2019). Although aspirin/extended-release dipyridamole and clopidogrel are effective for secondary prevention after AIS or TIA, aspirin monotherapy has long been the cornerstone of antiplatelet therapy for chronic prevention, given its cost-effectiveness. Aspirin monotherapy has both short- and long-term benefits.

Prasugrel and ticagrelor are two additional antiplatelet options available in the United States, though neither is FDA approved for secondary prevention after ischemic stroke. These agents have the same mechanism of action through inhibition of the $P2Y_{12}$ receptor. Prasugrel is contraindicated in patients with a history of stroke or TIA, given the post hoc results of the TRITON-TIMI trial. Patients with a history of cerebrovascular events enrolled in the trial had no clinical benefit with respect to secondary prevention of stroke, and there was a trend toward an increased risk of major bleeding, including ICH, in patients treated with prasugrel compared with clopidogrel (Wiviott 2007). The FDA labeling includes a black box warning regarding prasugrel use in patients with stroke or TIA.

The SOCRATES trial was a large, international, randomized, controlled, double-blind study comparing ticagrelor monotherapy with aspirin in patients with non-severe acute stroke or high-risk TIA deemed of atherosclerotic origin. Antiplatelet treatment began within 24 hours after symptom onset and continued for 90 days. This trial showed no difference in the incidence of ischemic stroke or ICH between the cohorts (Johnston 2018). Although the trial evaluated monotherapy, not dual antiplatelet therapy (DAPT), this is the only randomized controlled trial showing the safety and efficacy of ticagrelor for secondary prevention of AIS. Thus, providers may use ticagrelor judiciously in patients needing DAPT who are hyporesponsive to clopidogrel. According to these results, however, ticagrelor is not recommended over aspirin for treatment of patients with minor stroke (Powers 2019). Antiplatelet options for DAPT other than ticagrelor or clopidogrel are limited by safety concerns.

Dual Antiplatelet Therapy

Initial trials comparing DAPT with aspirin alone after ischemic stroke failed to show net benefit. These findings were likely a result of heterogeneity from the inclusion of strokes with diverse causes and severities. Furthermore, early DAPT trials randomized patients to treatment weeks after the index event. The SPS3 trial compared clopidogrel plus aspirin with aspirin monotherapy in patients with a lacunar stroke or TIA. The median time from ischemic event to DAPT initiation was 2 months (Benavente 2012). Critics of the trial believe that initiating DAPT after the acute phase is one reason the trial showed an increased risk of major bleeding without a reduction in the rate of stroke or TIA. In contrast, initiating short-term DAPT in the acute setting (within 24 hours of the event) has shown net benefit in patients with mild stroke (NIHSS score less than 4) or high-risk TIA (greater than 3 on the $ABCD^2$ score) (Venturelli 2018).

The CHANCE trial compared aspirin and clopidogrel with aspirin alone. Therapy was initiated within 24 hours of stroke or TIA onset and continued for 21 days. After enrolling over 5000 patients in China, the study showed that DAPT was superior to aspirin monotherapy for secondary prevention of stroke within 90 days. There were no differences in hemorrhagic complications between the treatment interventions (Wang 2013).

DAPT was most recently evaluated in the POINT trial. Almost 5000 patients with minor stroke or TIA were randomized to begin antiplatelet therapy within 12 hours of symptom onset. Dual antiplatelet therapy was superior to aspirin monotherapy for preventing recurrent events at the expense of an over 2-fold increased risk of major hemorrhage (p=0.02), leading to early trial termination by the data and safety monitoring board (Johnston 2018). The increased hemorrhagic risk in POINT, but not CHANCE, may have resulted from the longer duration of DAPT in the POINT trial (90 days vs. 21 days) (Wang 2019). The net benefit from DAPT diminishes beyond the initial 10 days (Wang 2019, 2013). A comparison of CHANCE and POINT is included in Table 10.

DAPT with clopidogrel plus aspirin is recommended to be initiated in patients with minor, noncardioembolic stroke (NIHSS < 4) or high-risk TIA within 24 hours after symptom onset in patients who did not receive IV alteplase. DAPT has been shown to reduce the occurrence of non-fatal stroke, functional disability, and poor quality of life at 90 days post-event. Some evidence of an increased risk of bleeding (minor, moderate, and severe) has been observed with DAPT in this patient population within 90 days of the index event, so the risk-benefit profile of DAPT must be weighed for each patient before initiating therapy (Prasad 2018). When DAPT is prescribed, experts favor a loading dose of 300 mg of clopidogrel followed by 75 mg daily together with 75–81 mg of aspirin daily, continuing for up to 21 days (Wang 2019). Longer durations are not preferred because of increased bleeding risks that outweigh any benefits beyond 21 days (Wang 2019). These expert recommendations are consistent with the 2019 AHA/ASA guidelines (Powers 2019). The THALES trial, which will compare ticagrelor plus aspirin with aspirin alone after minor stroke or TIA, is expected to enroll 13,000 patients across 450 centers worldwide. Treatment will begin within 24 hours of stroke and continue for 30 days (ClinicalTrials.gov 2019a).

In addition to minor strokes and TIAs, DAPT may be considered in other AIS scenarios, including in patients with severe intracranial atherosclerotic disease without stents or in patients with intra- or extracranial stents. Evidence for DAPT in these settings is limited to nonrandomized evaluations, extrapolation of cardiac literature, and clinical equipoise. The optimal DAPT regimens and durations for these clinical scenarios are unknown.

Triple antiplatelet therapy is not recommended because of the TARDIS study, in which clopidogrel, dipyridamole, and aspirin increased the risk of bleeding (20% vs. 9%; p<0.001) with no difference in efficacy compared with guideline-recommended antiplatelet therapy with aspirin/dipyridamole or clopidogrel alone (Bath 2018).

Table 10. Comparison of CHANCE and POINT Trials

	CHANCE	POINT
Year of publication	2013	2018
Methodology	Randomized, double-blind, placebo controlled; thrombolysis excluded	
Cohort size	5170	4881
Location	China	Europe, New Zealand, Australia, North America (80% enrolled in the United States)
Stroke vs. TIA	TIA: 28% Minor stroke: 72%	TIA: 43% Minor stroke: 57%
Intervention	Clopidogrel LD: 300 mg once MD: 75 mg daily Aspirin LD: 75–300 mg once MD: 75 mg daily	Clopidogrel LD: 600 mg once MD: 75 mg daily Aspirin LD: None MD: 50–325 mg daily
Control	Clopidogrel LD: 300 mg once MD: 75 mg daily	Aspirin LD: None MD: 50–325 mg daily
Stroke onset to randomization (hr)	≤ 24	≤ 12
DAPT duration (days)	21	90
Efficacy result	Stroke DAPT: 8.2% Monotherapy: 11.7% (HR 0.68; 95% CI, 0.57–0.81; p<0.001)	Major ischemic events DAPT: 5.0% Monotherapy: 6.5% (HR 0.75; 95% CI, 0.59–0.95; p=0.02)
Safety result	Moderate or severe hemorrhage: DAPT: 7 (0.3%) Monotherapy: 8 (0.3%) (p=0.73) Hemorrhagic stroke was 0.3% in each group	Major hemorrhage: DAPT: 23 (0.9%) Monotherapy: 10 (0.4%) (HR 2.32; 95% CI, 1.10–4.87; p=0.02)
Comments	After 21 days, clopidogrel was continued as monotherapy until day 90	• Most ischemic events occurred within the first week • Secondary analysis: Net benefit in first 10 days but benefit offset by bleeding risk from 10 to 90 days

DAPT = dual antiplatelet therapy; LD = loading dose; MD = maintenance dose; TIA = transient ischemic attack.

Information from: Wang Y, Zhao X, Liu L, et al. Clopidogrel with aspirin in acute minor stroke or transient ischemic attack. N Engl J Med 2013;369:11-9; Wang Y, Johnston SC, Bath PM, et al. Acute dual antiplatelet therapy for minor ischaemic stroke or transient ischaemic attack. BMJ 2019;364:l895; Johnston SC, Easton JD, Farrant M, et al. Clopidogrel and aspirin in acute ischemic stroke and high-risk TIA. N Engl J Med 2018;379:215-25; Tillman H, Johnston SC, Farrant M, et al. Risk for major hemorrhages in patients receiving clopidogrel and aspirin compared with aspirin alone after transient ischemic attack or minor ischemic stroke: a secondary analysis of the POINT randomized clinical trial. JAMA Neurol 2019;76:774-82.

THROMBECTOMY

Thrombectomy procedures are performed under continuous x-ray imaging and require insertion of a femoral or radial artery catheter that is threaded through the arteries into the posterior or anterior circulation near the site of the thrombus. Intravenous contrast media is administered as needed throughout the procedure to visualize the vascular anatomy, location of the thrombus, and patency of the vessels. In addition, access sites for the procedure are often infused with low, flush-like concentrations of unfractionated heparin after an initial, low-dose unfractionated heparin intravenous bolus. Procedural angiography requires higher intravenous contrast

loads than traditional CT-based imaging. Higher contrast loads have been associated with an increased risk of renal injury, though the risk is low in the absence of other risk factors such as hypotension or nephrotoxic drugs.

Digital subtraction angiography (DSA), the imaging technique used during thrombectomies in a neurointerventional suite, provides more detailed imaging of a patient's vasculature than the CTA or MRI. Modern DSA techniques generate 3D vascular images in real-time during the procedure.

The sophistication of mechanical thrombectomy devices has evolved since 2004. The currently utilized third-generation thrombectomy devices (stent retrievers) remove thrombi by insertion of a mesh stent into the thrombus. When the stent is deployed, it engages the thrombus from within, and the entire stent plus thrombus is pulled back into the catheter to recanalize the vessel.

Quantification of vessel patency and more importantly, reperfusion can be described using the thrombolysis in cerebral infarction score (TICI). This scoring tool is typically determined by neurointerventionalists before and after thrombectomy to describe procedural success with respect to vessel recanalization and perfusion. Scores range from 0 to 3, with 0 indicating complete occlusion of the vessel and 3 indicating complete patency. The modified TICI score (mTICI) (Table 11) is the assessment tool of choice according to the 2019 guidelines for AIS, and the goal of the thrombectomy procedure should be reperfusion to mTICI of 2b/3 as quickly as possible (Gerber 2014, Powers 2019). Clinicians use the TICI scoring systems for prognosticating and to determine blood pressure targets and the risk of complications. Expanded TICI scoring systems have been developed to further define reperfusion within the 2b category (Liebeskind 2019).

Table 11. Modified TICI Scoring System

mTICI Grade	Description of Grade
0	No reperfusion
1	Clot reduction with no change in reperfusion of distal arteries
2a	Partial filling < 50% territory
2b	Partial filling 50%–99% of territory
3	Complete reperfusion (100%)

mTICI = modified thrombolysis in cerebral infarction

Information from: Gerber JC, Miaux YJ, von Kummer R. Scoring flow restoration in cerebral angiograms after endovascular revascularization in acute ischemic stroke patients. Neuroradiology 2015;57:227-40.

Box 2. Guideline-Based Criteria for Mechanical Thrombectomy Within 6 Hr of Stroke Onset

- Age ≥ 18 yr
- ASPECTS of ≥ 6
- LVO demonstrated on CTA or MRA
- NIHSS score ≥ 6
- Prestroke mRS score of 0 to 1 is ideal, but patients with mRS may undergo thrombectomy
- Treatment can be initiated within 6 hours of symptom onset

ASPECTS = Alberta Stroke Program Early Computed Tomography Score; CTA = computed tomography angiography; LVO = large vessel occlusion; MRA = Magnetic resonance angiography; mRS = modified Rankin scale; NIHSS = National Institute of Health Stroke Scale.

Information from: Powers WJ, Rabinstein AA, Ackerson T, et al. Guidelines for the early management of patients with acute ischemic stroke: 2019 update to the 2018 guidelines for the early management of acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2019;50:e344-e418.

2015 Thrombectomy Trials

The superiority of mechanical thrombectomy plus usual care to usual care alone was shown in several randomized controlled trials in 2015. In most of these trials, EVT was initiated within 6 hours of stroke onset, and all used strategies (e.g., advanced imaging, scoring tools) to select for large vessel strokes with small cores and relatively large penumbra volumes (Pierot 2015). These trials have shown a 2-fold greater odds of achieving a good outcome with thrombectomy with no increased risk of harm in patients meeting specific selection criteria.

Current guidelines strongly recommend intravenous alteplase for eligible patients in addition to mechanical thrombectomy if patients also meet the EVT criteria (Box 2) (Powers 2019). Of note, some exceptions to the criteria in Box 2 can be considered according to the 2019 guideline statements although the recommendations for exceptions to the usual criteria are not as strong. For example, mechanical thrombectomy may be reasonable for select patients with mRS score greater than 1 or NIHSS < 6 (Powers 2019).

The Alberta Stroke Program Early CT Score (ASPECTS) is a 10-point scoring tool that assesses early ischemic changes on the patient's initial non-contrast head CT. Lower scores indicate greater degree of ischemic changes while higher scores indicate minimal early changes. A score of 10 indicates no ischemic changes. Increasing early ischemic changes is a surrogate for greater amounts of core volume. Perfusion imaging can be deferred in patients with ASPECTS greater than or equal to 6 within the 6-hour window from stroke onset (Powers 2019).

Box 3. DAWN Criteria for Mechanical Thrombectomy Within 24 Hr of Last Known Well

- Anticipated life expectancy of at least 6 mo
- LVO in ICA or MCA
- One of the following:
  - Age ≥ 80 and NIHSS ≥ 10 and core infarct < 21 mL
  - Age < 80 and NIHSS ≥ 10 and core infarct < 31 mL
  - Age < 80 and NIHSS ≥ 20 and core infarct 31–51
- Prestroke mRS score of 0 to 1

ICA = internal carotid artery; LVO = large vessel occlusion; MCA = middle cerebral artery; mRS = modified Rankin scale; NIHSS = National Institute of Health Stroke Scale.

Information from: Powers WJ, Rabinstein AA, Ackerson T, et al. Guidelines for the early management of patients with acute ischemic stroke: 2019 update to the 2018 guidelines for the early management of acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2019;50:e344-e418.

Extension of the Time Window for Thrombectomy

Despite differences in imaging-based inclusion criteria, the DEFUSE 3 and DAWN trials further revolutionized EVT by extending the thrombectomy time window to 16 and 24 hours, respectively (Albers 2018; Nogueira 2018; Powers 2019). Both landmark trials were multicenter, randomized and controlled and compared usual AIS care with thrombectomy within an extended time window. Both trials demonstrated that the percentage of patients with functional independence at 90 days was significantly greater in the thrombectomy cohort, with no significant difference in symptomatic ICH (Albers 2018; Nogueira 2018). Given these results, the current guidelines support thrombectomy up to 24 hours from the last known well in patients meeting the criteria on the basis of age, NIHSS score, and advanced imaging as defined in the DAWN trial (Box 3) (Nogueira 2018; Powers 2019).

Post-thrombectomy Complications and Considerations

The rate of thrombectomy-related complications can be as high as 30% (Balami 2018). Symptomatic ICH is the most severe complication. Access site complications including infection or damage to the vessel or nerve are more common than other complications, which include those resulting from anesthesia, intravenous contrast, radiation exposure, and the device itself. Routine monitoring of the patient's access site for surrounding hematoma is warranted, together with routine neurologic monitoring in an ICU.

Reperfusion injury after recanalization is a concern. Reperfusion injury can occur after thrombolysis or thrombectomy, but mitigation post-thrombectomy may be more clinically achievable because the exact time of recanalization is known. Infarction, edema, or hemorrhagic transformation is possible. Blood pressure management post-thrombectomy in patients with a TICI score of 2b or 3 may reduce the risk of reperfusion injury.

The optimal strategy for blood pressure management post-thrombectomy remains unclear and likely depends on the degree of reperfusion achieved. In patients undergoing thrombectomy, it is reasonable to maintain blood pressure less than or equal to 180/105 mm Hg during and for 24 hours after the procedure. In patients with successful reperfusion (mTICI score 2b–3), lowering the blood pressure further may be considered. Some experts recommend a goal SBP of lower than 140 or 160 mm Hg for 24 hours, based on the correlation of elevated blood pressures and worse outcomes post-thrombectomy (Blech 2019; Vitt 2019). Based on this information, the DAWN trial protocol included a systolic blood pressure target of less than 140 mm Hg for 24 hour after successful reperfusion. In addition, blood pressure reductions to less than 160/90 mm Hg predict improved 3-month mortality with successful reperfusion (Blech 2019).

In contrast, permissive hypertension up to 180/105 mm Hg may be warranted with partly successful recanalization (TICI score of 1 or 2a) to support circulation to the penumbra. Thrombectomy studies provide minimal guidance within the published protocols for blood pressure management. The 2019 AHA/ASA guidelines for the early treatment of patients with AIS recommend maintaining blood pressure less than 180/105 mm Hg post-procedure; however, lower targets after successful reperfusion may be reasonable (Powers 2019).

Intra-arterial Fibrinolytics

Although once more common, intra-arterial fibrinolytics applied directly at the site of thrombus during neuroendovascular procedures have largely fallen out of favor as a first-line reperfusion strategy. This change resulted from the robust data analyses in support of thrombectomy as the preferred EVT for AIS. Intra-arterial fibrinolytics, primarily alteplase, may still be used on a case-by-case basis as salvage therapy to achieve successful reperfusion during complex EVT cases (Powers 2019). Alteplase is not FDA approved for intra-arterial administration, and optimal dosing has not been established.

PHARMACISTS' ROLE IN ACUTE STROKE CARE

Time to reperfusion in AIS has independently been associated with improved stroke outcomes in several studies. For every minute of large territory MCA occlusion, about 1.9 million neurons, 14 billion synapses, and 7.5 miles of myelinated fibers are destroyed because of ischemia (Saver 2006). Therefore, "time is brain" has become a commonly used adage to emphasize rapid intervention. One study showed that each 1-minute reduction in onset to intravenous thrombolytic therapy led to a 1.8-day increase in disability-free living; thus, "save a minute, save a day" (Meretoja 2014). Furthermore, as time from stroke onset increases, the number needed to

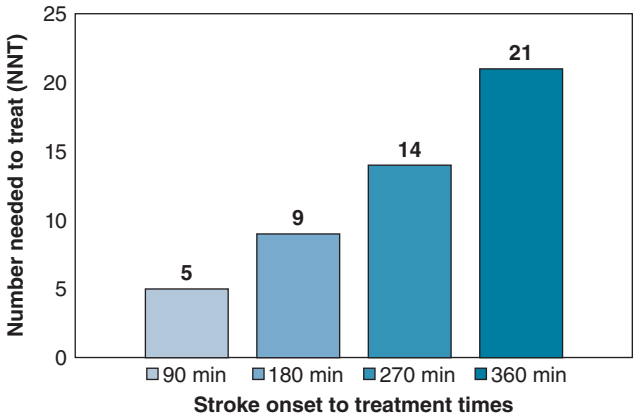

Figure 3. Time to alteplase from symptom onset and number needed to treat to achieve good outcome (mRS score of 0 to 1).

Information from: Lees KR, Bluhmki E, von Kummer R, et al. Time to treatment with intravenous alteplase and outcome in stroke: an updated pooled analysis of ECASS, ATLANTIS, NINDS, and EPITHET trials. Lancet 2010;375:1695-703.

treat with alteplase to achieve a good outcome also increases (Figure 3).

Pharmacists have shown their impact on reducing DTN when directly involved in acute stroke teams (Jacoby 2018; Rech 2017; Gosser 2016; Montgomery 2016) and can substantially affect several aspects of the acute management of stroke. A primary contributor to reducing DTN in AIS is rapid access to alteplase itself, which must be reconstituted before administration because of an 8-hour stability period once mixed (alteplase package insert). Emergency stroke "kits" have been devised by institutions to incorporate all necessary tools to ensure timely and accurate alteplase administration. Common contents of these kits can be found in Box 4.

The pharmacist's proficiency in reconstitution, knowledge of appropriate dosing, and ability to quickly screen for contraindications can lead to faster and potentially safer intravenous thrombolytic administration. In the acute environment, pharmacists provide recommendations for, and access to, acute blood pressure–lowering agents for appropriate candidates for thrombolytic therapy. Pharmacists can also develop or streamline smart pump settings and optimize protocols and order sets for treating patients with AIS. Smart pumps can be programmed to automatically deliver the bolus of alteplase over 1 minute and then immediately start the infusion over the next hour, obviating the need to pull the bolus out into a separate syringe and have the nurse or provider hand push this medication. The automatic bolus followed by infusion can be administered without a person at the bedside, allowing the team to continue obtaining the CTA or CTP scan while the bolus is running. Smart pumps can also be programmed to automatically calculate the dose and volume of alteplase to be administered based solely on a weight input. Furthermore, clinical pharmacists can positively influence stroke care through education of the stroke team and by being directly involved in performance review and subsequent performance improvement initiatives. Pharmacists

Box 4. Common Contents of an Emergency Stroke Kit

- 10-mL syringes
- 18-gauge needles
- 50-mL normal saline bag
- 60-mL syringes
- 100-mg alteplase box (box includes sterile water diluent, transfer spike, and powder alteplase)
- Alcohol pads
- Dosing chart
- Labels for bolus and infusion
- Labetalol premixed syringes
- Mixing instructions
- Nicardipine vial and 250 mL of normal saline bag (or premixed bag)[a]
- Non-vented tubing set
- Vented tubing set
- Smart pump[a]
- Syringe caps

[a]Space within kit may prohibit these items, in which case these should be stored in other locations in the ED.

Box 5. Strategies Associated with a Reduced DTN

- EMS prehospital stroke-screening tool
- Advanced hospital notification by EMS
- Rapid triage protocol and stroke team notification
- Single-call activation system
- A timer or clock attached to a chart, clipboard, or the patient's bed to track time
- Transport of patients by EMS directly to the CT/MRI scanner
- Written informed consent is not required before alteplase administration
- INR and Plt results are not required before alteplase administration
- Brain imaging is interpreted immediately by stroke team members
- Treatment decision made by neurologist attending or trainee after in-person evaluation
- Mix alteplase ahead of time, when appropriate
- Initiation of IV alteplase bolus while the patient is still in the brain imaging suite
- Prompt patient-specific data feedback to the ED staff and stroke team
- Prompt patient-specific data feedback to EMS providers

CT = computed tomography; DTN = door-to-needle time; ED = emergency department; EMS = emergency medical services; IV = intravenous; MRI = magnetic resonance imaging.

Information from: American Heart Association. Introducing Target: Stroke Phase III. 2019.

Practice Points

From the 2019 guidelines for the treatment of patients with AIS:

- **Much is known about the role of intravenous thrombolytics and their complications, but studies continue to push the boundaries of eligibility and optimal use.**
- **Eligibility criteria and recommendations for intravenous alteplase have been liberalized since the previous publication, placing the onus on the health care team to make more decisions depending on individualized risk.**
- **Use of tenecteplase is gaining interest, and several phase III trials are ongoing.**
- **Complications from alteplase are rare; treatment of complications is fraught with uncertainty because of a paucity of data analyses. Recommendations are based primarily on expert consensus.**

Expansion of the treatment time window has been evaluated in several recent articles:

- **An expanded window of 24 hours for thrombectomy in patients meeting the imaging mismatch criteria is supported by the DAWN trial.**
- **The DEFUSE 3 trial provides evidence for expanding the thrombectomy window to 16 hours after the onset of stroke in patients meeting the imaging criteria.**
- **EXTEND, WAKE UP, and NOR-TEST provide evidence for thrombolysis in extended or unknown time windows in patients with positive imaging mismatch in core and penumbra volumes.**

DAPT is becoming increasingly popular in select AIS populations.

- **A growing body of evidence supports DAPT with clopidogrel and aspirin in patients with minor stroke or high-risk TIA.**
- **Net benefit for DAPT after stroke or high-risk TIA is greatest when initiated within 24 hours and continued for up to 21 days, at which point the patient should be continued on single antiplatelet therapy for secondary prevention.**

Clinical pharmacists should strive to become integral members of the stroke response team. Pharmacists can positively affect patient outcomes by reducing DTNs through the following activities:

- **Quickly assessing and treating hypertension in otherwise eligible alteplase candidates.**
- **Rapidly and accurately assessing patients within the 4.5-hour treatment window for contraindications to alteplase.**
- **Ensuring that alteplase and all administration materials are readily available, quickly reconstituted at the bedside, and immediately administered, ideally while the patient is in the imaging suite.**

should be an empowered voice of the acute stroke response team and advocate the streamlining of other processes that may reduce DTN (Box 5).

The pharmacist's role in early AIS management continues after fibrinolytic decision-making, DTN, and early antiplatelet therapy. Neuroendovascular thrombectomies are increasingly common, now that more patients can be treated in an extended time window. The clinical pharmacist should be aware of several periprocedural medication considerations with thrombectomy. The first is identifying and maintaining an appropriate blood pressure target post- fibrinolysis and/or thrombectomy depending on the amount of recanalization achieved. The pharmacist can help select a patient-specific antihypertensive regimen. Second, thrombectomy involves intravenous contrast, heparin, and anesthesia. A pharmacist's understanding of the pharmacokinetics, pharmacodynamics, and adverse effects of periprocedural medications will enable proper monitoring for complications such as contrast-related adverse effects, bleeding, and oversedation. Furthermore, clinical pharmacists may be called on for expertise with antithrombotic medications, including intra-arterial antiplatelet agents and fibrinolytics that may be used as salvage therapy during complex cases. For patients not treated with alteplase, the pharmacist should ensure that aspirin has been administered periprocedurally or as soon as possible after the procedure.

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Self-Assessment Questions

1. A 40-year-old right-handed man presents to the ED with new-onset aphasia and left upper-extremity weakness. The patient entered the ED 10 minutes ago and appears to be a good candidate for intravenous thrombolysis. As the patient is taken to the CT scanner, the ED physician asks you whether there are any new recommendations for goal door-to-needle time (DTN). Your institution recently published your median DTN as 40 minutes, and 75% of patients were treated in less than 60 minutes. According to the Target: Stroke phase III recommendations, which one of the following statements, in response to the physician, would best describe this patient's goal DTN?

   A. "The newest recommendations suggest we should strive for a DTN of less than 30 minutes. This patient has been here for only 10 minutes, so we can take our time because we still have 20 minutes to decide on alteplase."
   B. "We should be striving to reduce our median DTN to less than 30 minutes, with at least 75% of our patients being treated in less than 45 minutes. We should work on processes to reduce our DTNs because this will improve outcomes in these patients. The team should prioritize administration of alteplase as soon as possible after contraindications have been ruled out."
   C. "Our new goal DTN for alteplase in acute ischemic stroke (AIS) has been reduced to less than 45 minutes. We are already achieving a median of 40 minutes, and 75% of our patients are being treated in less than 60 minutes; therefore, our process is working."
   D. "Goal DTN for alteplase remains less than 60 minutes; as long as we are within this time interval because our median goal to needle time is 40 minutes, we are succeeding at treating strokes."

2. A 75-year-old right-handed man presents with right upper- and lower-extremity weakness starting 4 hours before arrival. The patient has a history of hypertension, right MCA stroke 3 years ago, intracranial hemorrhage (ICH) 5 years ago, type 2 diabetes, and atrial fibrillation, for which he takes apixaban 5 mg twice daily; however, he has not taken it for the past 3 days. His basic metabolic panel, CBC, and PT/INR are within normal limits. His symptoms are now rapidly improving, with his NIHSS score falling from a 9 to a 3. He still has residual weakness in his right hand. Which one of the following would most likely be a contraindication to alteplase use in this patient?

   A. His resolution of stroke symptoms from an NIHSS 9 to an NIHSS 3
   B. His apixaban prescription
   C. His history of both diabetes and stroke
   D. His history of ICH

3. An 85-year-old woman (weight 70 kg) presents with right facial droop, right upper-extremity hemiplegia, and right lower-extremity paraesthesia. Her last known normal was 2.5 hours before her ED presentation. She takes no antithrombotics, and no other contraindications to fibrinolysis are found. Intravenous alteplase is administered. One hour after the end of the infusion, she has sudden worsening of her right upper-extremity weakness, develops aphasia, and becomes progressively more somnolent. A noncontrast head CT obtained immediately reveals a hemorrhagic conversion of her left MCA stroke. Laboratory values show normal coagulation parameters except for a fibrinogen concentration of 90 mg/dL. Which one of the following is the best single agent to recommend for this patient's ICH?

   A. Cryoprecipitate 10 units
   B. Fresh frozen plasma 4 units
   C. Tranexamic acid 1000 mg intravenously over 10 minutes
   D. Four-factor human prothrombin complex concentrate 50 units/kg

4. A 55-year-old woman (weight 80 kg) is currently receiving alteplase for left MCA syndrome. She suddenly develops altered mental status. The alteplase infusion is discontinued immediately, and a repeat head CT reveals a large ICH in the area of the suspected infarct. Cryoprecipitate 10 units is ordered, and transfusion is now completed. Her mental status has neither improved nor worsened. No other medications have been administered. Repeat laboratory tests show fibrinogen 100 mg/dL and Plt 125,000/mm^3. Which one of the following would be the best next intervention for this patient's ICH?

   A. Tranexamic acid 1000 mg intravenously over 10 minutes
   B. 10 units of cryoprecipitate intravenously, given her fibrinogen concentration
   C. 2 units of platelets intravenously, given her thrombocytopenia
   D. No further intervention necessary; laboratory values suggest she has reached her therapeutic goals with therapy

5. Which one of the following patients is most likely to be a candidate for tenecteplase, according to the 2019 AHA/ASA guideline recommendations?

   A. 64-year-old woman with right-sided hemiparesis, presumed to be a lacunar stroke by the neurologist. Her last known normal was 2.5 hours before presentation. Her NIHSS score is 4, and she has no

other identified contraindications to intravenous thrombolytic therapy.

B. 90-year-old man who presents with right sided paralysis and aphasia. He was last seen normal 1 hour before arrival. His NIHSS score is 10 according to neurology. CTA demonstrates no large vessel occlusion (LVO).

C. 56-year-old man with left-sided weakness and neglect. Last known normal was 2 hours before arrival. Head CT reveals right MCA territory hemorrhagic conversion. The patient's medical history consists of hypertension and diabetes.

D. 65-year-old woman who presented with a presumed lacunar stroke with left upper- and lower-extremity weakness and ataxia. She was last seen by her daughter 6.5 hours prior to arrival. Her NIHSS score is 3.

6. A 69-year-old man with a medical history that includes hypertension and diabetes presents to emergency medical services with right upper- and lower-extremity weakness for the past 3 hours. The patient's home medications include lisinopril and metformin. He has no known contraindications to intravenous fibrinolytic therapy; therefore, he is treated with intravenous alteplase. The patient develops unilateral orolingual swelling 30 minutes after alteplase is initiated. He is not having any respiratory distress, throat tightness, throat swelling, or difficulty swallowing. The alteplase infusion is discontinued immediately. Which one of the following is the best initial intervention for this patient's angioedema?

   A. Administer icatibant (selective bradykinin B2 receptor antagonist) 30 mg subcutaneously.
   B. Administer C_1 esterase inhibitor 20 units/kg intravenously.
   C. Administer diphenhydramine, famotidine, and methylprednisolone.
   D. Prepare medications for intubation because orolingual swelling often leads to airway compromise, and patients typically require empiric intubation to secure their airway.

7. Which one of the following pharmacist interventions will most significantly reduce DTNs in acute stroke response?

   A. Bedside mixing of alteplase to allow administration between CT and multimodal neuroimaging
   B. Designing and implementing "smart order sets" that optimize the ordering of alteplase.
   C. Immediately reconciling medications and reviewing the patients chart to rule out contraindications
   D. Providing performance assessment, feedback, and improvement projects

8. A 72-year-old man presents with stroke symptoms and an NIHSS score of 16. The stroke response team is determining the patient's eligibility for acute interventions. Which one of the following best describes the relationship between intravenous alteplase and thrombectomy during AIS management?

   A. If the patient receives alteplase, he will not be a candidate for thrombectomy, given the need to obtain arterial access to perform the procedure.
   B. If the patient is eligible for both alteplase and thrombectomy, he should receive alteplase after the thrombectomy if the procedure is unsuccessful.
   C. If the patient is found to have an LVO in a proximal artery, he will be a candidate for alteplase followed by a thrombectomy if he meets all the other eligibility criteria.
   D. If the patient is eligible for both alteplase and thrombectomy, he should undergo a thrombectomy because it is preferred to alteplase according to the recent literature.

9. Which one of the following patients with stroke symptoms is most likely a candidate for thrombectomy but not alteplase?

   A. 49-year-old receiving warfarin (INR 2.1) presenting 8 hours from last known well with an NIHSS score of 18 and LVO with large core volume on advanced imaging. mRs is 0.
   B. 61-year-old presenting with an NIHSS score of 2 whose symptoms resolved shortly after ED arrival. The non-contrast head CT is negative for ICH, and advanced imaging is deferred. mRs is 1.
   C. 82-year-old with an NIHSS score of 18 on aspirin presenting 3.5 hours from the last known well whose MRI reveals small core and large penumbra in the absence of LVO. mRS is 4.
   D. 77-year-old with an NIHSS score of 24 on warfarin (INR 1.9) presenting 2.5 hours from the last known well with CTA positive for LVO and ASPECTS of 7. mRs is 0.

10. A 54-year-old man with new-onset stroke symptoms presents by ambulance to the ED. He receives intravenous alteplase and undergoes a thrombectomy without complications. His mTICI score changes from 0 preprocedure to 3 postprocedure. According to the 2019 guideline updates for early management of AIS, which one of the following SBP goals is best to recommend for this patient immediately post-thrombectomy?

    A. Less than 180 mm Hg
    B. Less than 185 mm Hg
    C. Less than 200 mm Hg
    D. Less than 220 mm Hg

11. A 68-year-old woman presents to the ED with focal neurologic deficits and an NIHSS score of 15. The patient's family reports that she woke up with deficits about 1 hour ago and that her last known well was 10 hours ago. Her baseline mRS score is 0, and her ASPECTS score is 8. Her non-contrast head CT is negative for ICH. She is otherwise healthy at baseline and does not take any medications. According to the guideline recommendations, which one of the following is best to recommend for this patient?

    A. Advanced imaging can be considered to determine whether the patient is eligible for alteplase based on the presence of LVO on CTA
    B. Advanced imaging can be considered to determine whether the patient is eligible for alteplase based on the presence of DW-MRI and FLAIR mismatch.
    C. Advanced imaging can be considered to determine whether the patient is eligible for alteplase and a thrombectomy if CT perfusion demonstrates core volume of 55 mL.
    D. The patient is not a candidate for alteplase or a thrombectomy. No further imaging is necessary.

12. A 45-year-old man with AIS and an NIHSS score of 2 is a candidate for short-term dual antiplatelet therapy (DAPT) for secondary stroke prevention after a mild stroke. Which one of the following DAPT regimens is best to recommend initiating for this patient?

    A. Ticagrelor 180 mg followed by 90 mg twice daily; aspirin 81 mg daily
    B. Ticagrelor 90 mg twice daily; aspirin 325 mg followed by 81 mg daily
    C. Clopidogrel 300 mg followed by 75 mg daily; aspirin 81 mg daily
    D. Clopidogrel 75 mg daily; aspirin 325 mg followed by 81 mg daily

13. Which one of the following best represents the 2019 AHA/ASA guideline recommendations for AIS regarding the initiation and duration of DAPT after minor stroke or transient ischemic attack (TIA)?

    A. 21-day course beginning within 24 hours
    B. 21-day course beginning within 2 weeks
    C. 90-day course beginning within 24 hours
    D. 90-day course beginning within 48 hours

14. When comparing complications of intravenous fibrinolytics with those of thrombectomy, which one of the following best depicts the complication that is unique to thrombectomy procedures?

    A. Reperfusion injury
    B. Anesthetic complications
    C. ICH
    D. Angioedema

15. Your institution's stroke response team has asked you to review the literature pertaining to acute interventions for wake-up strokes. Which one of the following best reflects current evidence?

    A. MR WITNESS showed improved outcomes when patients with wake-up strokes received fibrinolytics compared with no fibrinolytic therapy.
    B. WAKE UP provides evidence for improved functional outcomes with thrombectomy in the wake-up stroke population.
    C. DAWN showed improved outcomes with thrombectomy performed within 24 hours of the last known well.
    D. EXTEND provided evidence for improved outcomes at the expense of an increased 90-day mortality for alteplase administration to wake-up strokes in the 4.5- to 9-hour window.