Guidelines For The Evaluation And Management Of Acute Cerebrovascular Syndromes Part II: Evaluation And Management Of Acute Ischemic Stroke

This issue reviews 2 new guidelines that address the management of acute ischemic stroke. The joint American College of Emergency Physicians (ACEP)/American Academy of Neurology (AAN) guideline sought to answer the question of whether intravenous (IV) tissue plasminogen activator (tPA) is safe and effective for acute ischemic stroke patients if given within 3 hours or 4.5 hours after symptom onset. The joint American Heart Association (AHA)/American Stroke Association (ASA) guidelines were broader in scope, covering the emergency identification, evaluation, and management of patients with acute ischemic stroke in the prehospital, emergency department (ED), and inpatient setting. The role of tPA in acute ischemic stroke has been controversial, but it is important that emergency clinicians be aware of these impactful new guidelines.

**Practice Guideline Impact**

- Either noncontrast enhanced computed tomography (CT) or magnetic resonance imaging (MRI) must be performed before administration of IV tPA in order to exclude intracranial hemorrhage.
- Patients with acute stroke who meet inclusion/exclusion criteria and present up to 4.5 hours after symptom onset may be candidates for IV tPA.
- Minor or rapidly improving symptoms, as well as seizure at time of onset of symptoms are not absolute contraindications to tPA.
- Arrival in the ED to the start of IV tPA time should be ≤ 1 hour.
- Limited laboratory testing is recommended during the initial evaluation; only the measurement of blood glucose must precede tPA administration.
- It is critical that systems be in place to support the safe administration of tPA.
Introduction To The Guidelines: Acute Ischemic Stroke

This issue of EM Practice Guidelines Update reviews 2 recently published guidelines on the evaluation and management of acute ischemic stroke. These are:


Stroke is a major healthcare issue in the United States, as it not only is one of the top causes of mortality, but it is also a leading cause of functional impairment. The AHA/ASA guideline is comprehensive, providing recommendations not only about the clinical management of stroke, but also about systems needed to support the care of stroke patients (AHA/ASA). The ACEP/AAN guideline focuses specifically on the indications for IV tPA (ACEP/AAN). The use of IV tPA is well studied, but there is still active debate about what conclusions should be drawn from this data. Reluctance to use tPA because of questions about its benefits in improving long-term outcomes as well as concern over increasing the risk of intracranial hemorrhage are reflected in a poll of emergency physicians (conducted before the publication of these new guidelines).

The purpose of this publication is not to reopen the debate, but rather to inform clinicians about the new recommendations and present the rationale provided by the guideline development groups. Both guidelines concluded with a high level of certainty that stroke patients who meet NINDS criteria and present within 0 to 3 hours after symptom onset are eligible for IV tPA. Both guidelines also recommended an extended time frame for the consideration of tPA of up to 4.5 hours, as long as patients meet specified inclusion and exclusion criteria.

Abbreviations Of Study Trials Referenced In This Issue

ASK: Australian Streptokinase Trial
ATLANTIS A and B: Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke
CASES: Canadian Alteplase for Stroke Effectiveness Study
DIAS-2: Desmoteplase in Acute Ischemic Stroke Trial
ECASS I, II and III: European Cooperative Acute Stroke Study
EPITHET: Echoplanar Imaging Thrombolytic Evaluation Trial
MAST-I: Multicentre Acute Stroke Trial - Italy
MAST-E: Multicenter Acute Stroke Trial - Europe
NINDS: National Institute of Neurological Disorders and Stroke
SITS-MOST: Safe Implementation of Treatments/Thrombolysis in Stroke Monitoring Study
SITS-ISTR: Safe Implementation of Treatments in Stroke – International Stroke Thrombolysis Registry
Mention thrombolytics for stroke in a group of emergency medicine physicians and you are bound to incite controversy. ACEP stirred the pot again in January 2013 when they published a joint guideline with the AAN on the use of thrombolytics for stroke. If you have been digging your heels in against the use of alteplase (tissue plasminogen activator, or tPA) for stroke, you may no longer have a leg to stand on. The ACEP 2013 clinical policy marks a full pendulum shift in organized emergency medicine’s stance on this issue. The protectionist policy statements of the 2000s are now dust in the wind. Ten years ago, the Society for Academic Emergency Medicine (SAEM), the American Academy of Emergency Medicine (AAEM) and ACEP were unanimous in declaring that there was insufficient evidence to endorse the use of tPA. Fast-forward to 2013, and we find that SAEM has rescinded its statement; AAEM posits that tPA is one possible treatment for ischemic stroke; and, after contemplating the evidence for a number of years, ACEP now encourages thrombolysis.

IV thrombolysis for stroke is one of the most well-studied questions in our field. Randomized controlled trials inform us which drug to choose (MAST-I, MAST-E, ASK, DIAS-2), at what dose (ECASS I) and when to treat (ATLANTIS A and B, ECASS I, II and III, EPITHET, and NINDS). The patients that have been shown to benefit from IV thrombolysis receive alteplase, are younger, and have shorter onset-to-treatment times (NINDS, number needed to treat [NNT] = 8; ECASS III, NNT = 14).

Critics only see 2 positive trials in a sea of negative studies. One can sympathize with their skepticism, given how seemingly once-proven therapies (eg, drotrecogin alfa and steroids for spinal cord injury) have fallen out of favor. However, it is unlikely that the NINDS and ECASS III trials will be repeated. Supplementing our knowledge, large observational registries (CASES, SITS-MOST, and SITS-ISTR) demonstrate that the beneficial effects of thrombolysis remain intact without an increased risk of hemorrhage even under real-world conditions. This body of evidence has led the ACEP policy committee to recommend with a high degree of certainty that patients meeting the NINDS trial inclusion criteria should be offered tPA. ACEP goes on to recommend (with a moderate degree of certainty) considering tPA for patients meeting the ECASS III study criteria. These recommendations favoring the use of alteplase bring ACEP in line with the AHA/ASA and the American College of Chest Physicians (ACCP). The house of medicine and—more importantly—the public have long ago given us the mandate to consider and offer tPA to stroke patients; now ACEP has codified this with level A and B recommendations.

The United States Food and Drug Administration (FDA) approved alteplase for lysis of stroke in 1996, and, since then, emergency medicine clinicians have been on the front lines of burgeoning regional systems of stroke care. It is becoming increasingly common for emergency medical services (EMS) agencies to preferentially route presumed stroke victims to stroke-capable hospitals and 24 states now have laws defining stroke centers. (An additional 10 states have appointed task forces to define best practice.) There is clearly considerable blood and treasure behind the mandate to give tPA and the push to establish stroke systems to support this therapy. The point at which this mandate becomes the “standard of care” is a delicate issue and, like religion and politics, it is best avoided at the dinner table. It should be noted that the most important text in the ACEP policy is not the Level A or Level B guideline but the caveat to the recommendations:

"The effectiveness of tPA has been less well established in institutions without the systems in place to safely administer the medication."

Organized emergency medicine has been calling for these safeguards for the patient and the ED physician from the beginning. The goal is to offer the same care to the real-world patient as the subjects enrolled in randomized controlled trials. At a minimum, this requires consultation with a stroke expert and a neuroradiologist. Moreover, ED pharmacists, nurses, and physicians must be familiar with the diagnosis and
management of acute stroke and best practice should be ensured by rigorous quality review and performance improvement. The AHA/ASA now sees eye-to-eye with ACEP on this point, and they call for systems to be in place to improve the accuracy of diagnosis, avoid protocol violations, and provide optimal acute stroke care.

Given that most of us do not practice in a department that can meet this ideal, how are we to proceed when the AHA/ASA, ACCP, ACEP, the house of medicine, and the public encourage the use of tPA? Asked another way, "What is the standard of care at my shop?" Our college recommends that we offer or consider tPA for a narrowly defined group of stroke patients when supported by systems of care. If we cannot meet that directive, then it seems we are now obligated to transfer the patient somewhere that can...quickly. The best defense is a good offense: preemptively define your standard of care locally. Several strategies (short of becoming a stroke center) have emerged that meet the objectives of the ACEP policy: (1) hospital bypass, (2) immediate transfer, (3) drip-and-ship with remote decision support (telemedicine), or (4) investing in 24-7 access to stroke and radiology consultants. The key is that your group should have a clear plan on how you will manage your next patient presenting with an acute ischemic stroke.

—Christopher Hopkins, MD
Assistant Professor, Department of Emergency Medicine, Interim Medical Director, Neuroscience Intensive Care Unit, University of Florida College of Medicine-Jacksonville, Jacksonville, FL
The AHA/ASA guideline was written by a committee appointed by the American Stroke Council’s Scientific Statement Oversight Committee. The AHA/ASA definition of the levels and classes of evidence are noted in Table 1.

The ACEP clinical policy was developed by joint review of stroke literature by the ACEP and the AAN. Of note, Sigrid Hahn, one of the Editors of *EM Practice Guidelines Update* (and a coauthor of this issue) of is a member of the ACEP Clinical Policy Committee; she was not on the writing subcommittee for this guideline.

<table>
<thead>
<tr>
<th>Level of Evidence</th>
<th>Description</th>
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<tbody>
<tr>
<td>A</td>
<td>Data derived from multiple sources</td>
</tr>
<tr>
<td>B</td>
<td>Data derived from a single randomized trial or nonrandomized studies</td>
</tr>
<tr>
<td>C</td>
<td>Consensus opinion of experts</td>
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<table>
<thead>
<tr>
<th>Classes of Recommendation</th>
<th>Description</th>
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<tbody>
<tr>
<td>Class I</td>
<td>Conditions for which there is conflicting evidence for and/or general agreement that the procedure or treatment is useful and effective</td>
</tr>
<tr>
<td>Class II</td>
<td>Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure or treatment</td>
</tr>
<tr>
<td>Class IIa</td>
<td>The weight of evidence or opinion is in favor of the procedure or treatment</td>
</tr>
<tr>
<td>Class IIb</td>
<td>Usefulness/efficacy is less well established by evidence or opinion</td>
</tr>
<tr>
<td>Class III</td>
<td>Conditions for which there is evidence and/or general agreement that the procedure or treatment is not useful/effective and in some cases may be harmful</td>
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</table>
Selected Guideline Recommendations, With Discussion

The recommendations excerpted here are presented as they appeared in the original guidelines, including the strength of recommendation and the level of evidence. Where possible, recommendations on a given topic from the 2 guidelines are presented side-by-side to facilitate comparison and discussion. Although emergency clinicians are closely involved with emergency medical services (EMS) systems, only selected recommendations related to prehospital care are presented here, with a focus on clinical care. Similarly, only selected recommendations relating to the establishment of stroke systems are presented here, with a focus on those that are most relevant to the practicing clinician in a community setting. Invasive therapies that would likely be decided upon by a stroke team (such as endovascular interventions) or therapies that are recommended only in the setting of clinical trials (such as drug-induced hypertension or induced hypothermia) are discussed in the AHA/ASA guideline but are not presented here. Similarly, inhospital management recommendations are beyond the scope of this emergency medicine guideline update.

Prehospital Clinical Care

- Prehospital care providers should use prehospital stroke assessment tools such as the Los Angeles Prehospital Stroke Screen or Cincinnati Prehospital Stroke Scale (Class I; Level of Evidence B). (Unchanged from the previous guideline)
- EMS personnel should begin the initial management of stroke in the field, as outlined in Table 2. (Class I; Level of Evidence B). Development of a stroke protocol to be used by EMS personnel is strongly encouraged. (Unchanged from the previous guideline)
- Patients should be transported rapidly to the closest available certified primary stroke center (PSC) or comprehensive stroke center (CSC) or, if no such centers exist, the most appropriate institution that provides emergency stroke care as described in the statement (Class I; Level of Evidence A). In some instances, this may involve air medical transport and hospital bypass.

Table 2. Recommendations For Prehospital Evaluation And Management of Potential Stroke Patients

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Support</th>
</tr>
</thead>
<tbody>
<tr>
<td>Assess and manage ABCs; do not initiate interventions for hypertension unless directed by medical command</td>
<td>Class I</td>
</tr>
<tr>
<td>Initiate cardiac monitoring</td>
<td>Class I</td>
</tr>
<tr>
<td>Provide supplemental oxygen to maintain oxygen saturation &gt; 94%</td>
<td>Class I</td>
</tr>
<tr>
<td>Establish IV access per local protocol; do not administer excessive IV fluids</td>
<td>Class I</td>
</tr>
<tr>
<td>Determine blood glucose level and treat accordingly; do not administer dextrose-containing fluids in nonhypoglycemic patients</td>
<td>Class I</td>
</tr>
<tr>
<td>Do not administer medications by mouth (maintain NPO)</td>
<td>Class I</td>
</tr>
<tr>
<td>Determine time of symptom onset or last known normal, and obtain family contact information, preferably a cell phone</td>
<td>Class I</td>
</tr>
<tr>
<td>Triage and rapidly transport patient to nearest most appropriate stroke hospital; do not delay transport for prehospital interventions</td>
<td>Class I</td>
</tr>
<tr>
<td>Notify hospital of pending stroke patient arrival</td>
<td>Class I</td>
</tr>
</tbody>
</table>

Abbreviations: ABCs, airway, breathing, circulation; IV, intravenous; NPO, nil per os (nothing by mouth).

Prehospital Clinical Care Recommendations: Editorial Comment, Sigrid Hahn, MD And Christie Lech, MD

Table 2 highlights what clinical care prehospital providers should provide (including treating hypoxia if oxygen saturation is < 94% and managing hypoglycemia) as well as what they should not do (including the routine treatment of hypertension, the administration of excess IV fluids, and the administration of dextrose-containing fluids). For more information about prehospital stroke systems, readers are referred to the AHA’s policy statement “Implementation Strategies for Emergency Medical Services Within Stroke Systems of Care” at: http://www.heart.org/idc/groups/heart-public/@wcm/@adv/documents/downloadable/ucm_301705.pdf
Stroke Care Systems—Teleradiology And Telestroke Care

• For sites without in-house imaging interpretation expertise, teleradiology systems approved by the FDA or equivalent organization are recommended for timely review of brain CT and MRI scans in patients with suspected acute stroke (Class I; Level of Evidence B). (New recommendation)

• When implemented within a telestroke network, teleradiology systems approved by the FDA (or equivalent organization) are useful in supporting rapid imaging interpretation in time for fibrinolysis decision making (Class I; Level of Evidence B). (New recommendation)

• Implementation of telestroke consultation in conjunction with stroke education and training for healthcare providers can be useful in increasing the use of IV rtPA at community hospitals without access to adequate onsite stroke expertise (Class IIa; Level of Evidence B). (New recommendation)

Stroke Care Systems Recommendations: Editorial Comment, Sigrid Hahn, MD and Christie Lech, MD

The ASA task force on the development of stroke systems has defined key components of a regional stroke system of care, and this section outlines the necessary hospital stroke capabilities, including defining PSCs, CSCs, and acute stroke-ready hospitals. As noted earlier, we excerpted only the recommendations most directly relevant to a practicing clinician in a community setting, as they may see increasing use of telemedicine to support the delivery of stroke care even if they are working in settings without local stroke expertise.

Emergency Evaluation Of Acute Ischemic Stroke

• An organized protocol for the emergency evaluation of patients with suspected stroke is recommended (Class I; Level of Evidence B). The goal is to complete an evaluation and to begin fibrinolytic treatment within 60 minutes of the patient’s arrival in an ED. Designation of an acute stroke team that includes physicians, nurses, and laboratory/radiology personnel is encouraged. Patients with stroke should have a careful clinical assessment, including neurological examination. (Unchanged from the previous guideline)

• The use of a stroke rating scale, preferably National Institutes of Health Stroke Scale (NIHSS), is recommended (Class I; Level of Evidence B). (Unchanged from the previous guideline)

• A limited number of hematologic, coagulation, and biochemistry tests are recommended during the initial emergency evaluation, and only the assessment of blood glucose must precede the initiation of IV rtPA. (See the diagnostic studies table in the AHA/ASA guideline, linked here.) (Class I; Level of Evidence B). (Revised from the previous guideline)

• Baseline electrocardiogram assessment is recommended in patients presenting with acute ischemic stroke but should not delay initiation of IV rtPA (Class I; Level of Evidence B). (Revised from the previous guideline)

• Baseline troponin assessment is recommended in patients presenting with acute ischemic stroke but should not delay initiation of IV rtPA (Class I; Level of Evidence C). (Revised from the previous guideline)

• The usefulness of chest radiographs in the hyperacute stroke setting in the absence of evidence of acute pulmonary, cardiac, or pulmonary vascular disease is unclear. If obtained, they should not unnecessarily delay administration of fibrinolysis (Class IIb; Level of Evidence B). (Revised from the previous guideline)

Emergency Evaluation Of Acute Ischemic Stroke Recommendations: Editorial Comment, Sigrid Hahn, MD and Christie Lech, MD

The guideline authors emphasize the importance of a rapid—but accurate—history and physical examination (including a standardized stroke scale) to establish the time of onset, suspected etiology, and nature and severity of the neurologic deficit. The authors cite data that found that stroke mimics were ultimately diagnosed in approximately 3% of patients who were treated with tPA, but they emphasize the lack of apparent harm of giving tPA to this group of patients whose deficits are most commonly due to seizures.

A recommendation that was revised from the prior guideline and that may alter current practice is that fibrinolytic therapy should not be delayed while awaiting the results of the prothrombin time (PT), activated partial thromboplastin time (aPTT), or platelet count unless a bleeding abnormality or thrombocytopenia is suspected, the patient has been taking warfarin and heparin, or anticoagulation use is uncertain. The acquisition of laboratory tests and their results (except the glucose level) should not impede administration of tPA.
Brain And Vascular Imaging

- Emergency imaging of the brain is recommended before initiating any specific therapy to treat acute ischemic stroke (Class I; Level of Evidence A). In most instances, noncontrast enhanced CT (NECT) will provide the necessary information to make decisions about emergency management. (Unchanged from the previous guideline)
- Either NECT or MRI is recommended before IV rtPA administration to exclude intracranial hemorrhage (absolute contraindication) and to determine whether CT hypodensity or MRI hyperintensity of ischemia is present (Class I; Level of Evidence A). (Revised from the 2009 imaging scientific statement)
- A noninvasive intracranial vascular study is strongly recommended during the initial imaging evaluation of the acute stroke patient if either intra-arterial fibrinolysis or mechanical thrombectomy is contemplated for management, but it should not delay IV rtPA, if indicated (Class I; Level of Evidence A). (Revised from the 2009 imaging scientific statement)
- CT perfusion and MRI perfusion and diffusion imaging, including measures of infarct core and penumbra, may be considered for the selection of patients for acute reperfusion therapy beyond the time windows for IV fibrinolysis. These techniques provide additional information that may improve diagnosis, mechanism, and severity of ischemic stroke and allow more informed clinical decision making (Class IIb; Level of Evidence B). (Revised from the 2009 imaging scientific statement)
- In IV fibrinolysis candidates, the brain imaging study should be interpreted within 45 minutes of patient arrival in the ED by a physician with expertise in reading CT and MRI studies of the brain parenchyma (Class I; Level of Evidence C). (Revised from the previous guideline)

Brain And Vascular Imaging Recommendations: Editorial Comment, Sigrid Hahn, MD and Christie Lech, MD

The use of NECT definitely excludes parenchymal hemorrhage in a patient with suspected stroke. In addition, NECT can identify other contraindications for tPA use including frank hypodensity involving more than one-third of the middle cerebral artery (MCA) territory (discussed more in tPA section, beginning on page 9).

Diffusion-weighted magnetic resonance imaging (DWI) has emerged as the most sensitive and specific imaging technique for acute infarct, better than NECT or any other MRI sequence. Studies have also demonstrated that MRI is as accurate as NECT in the detection of hyperacute intraparenchymal hemorrhage in patients with acute stroke presenting within 6 hours of symptom onset. Practicing clinicians are well aware of the disadvantages of MRI, however, which include the often limited availability of the test, the length of time it takes to complete it, increased vulnerability to motion artifact, and patient contraindications such as claustrophobia, cardiac pacemakers, or metal implants. For these reasons, we think that MRI is unlikely to replace NECT in the near future as the usual first imaging test for suspected stroke patients. Emergency physicians will likely make the decision to get an MRI or other imaging (including vascular imaging) in conjunction with the stroke consultants.
Intravenous tPA Administration

ACEP Recommendations:

- **Level A Recommendation:** In order to improve functional outcomes, IV tPA should be offered to acute ischemic stroke patients who meet NINDS inclusion/exclusion criteria and can be treated within 3 hours after symptom onset.*

- **Level B Recommendation:** In order to improve functional outcomes, IV tPA should be considered in acute ischemic stroke patients who meet ECASS III inclusion/exclusion criteria and can be treated between 3 to 4.5 hours after symptom onset.*

*The effectiveness of tPA has been less well established in institutions without the systems in place to safely administer the medication.

Note: Within any time window, once the decision is made to administer IV tPA, the patient should be treated as rapidly as possible. As of this writing, tPA for acute ischemic stroke in the 3- to 4.5-hour window is not FDA approved.

AHA Recommendations:

- IV rtPA (0.9 mg/kg, maximum dose 90 mg) is recommended for selected patients who may be treated within 3 hours of onset of ischemic stroke (Class I; Level of Evidence A). Physicians should review the criteria outlined in Table 3 (see page 10) and Table 4 (see page 11) (which are modeled on those used in the NINDS Trial) to determine the eligibility of the patient. A recommended regimen for observation and treatment of patients who receive IV rtPA is described in Table 5 (see page 11). (Unchanged from the previous guideline)

- IV rtPA (0.9 mg/kg, maximum dose 90 mg) is recommended for administration to eligible patients who can be treated in the time period of 3 to 4.5 hours after stroke onset (Class I; Level of Evidence B). The eligibility criteria for treatment in this time period are similar to those for people treated at earlier time periods within 3 hours, with the following additional exclusion criteria: patients > 80 years old, those taking oral anticoagulants regardless of international normalized ratio (INR), those with a baseline NIHSS score > 25, those with imaging evidence of ischemic injury involving more than one-third of the MCA territory, or those with a history of both stroke and diabetes mellitus. (Revised from the 2009 IV rtPA Science Advisory)

- For patients who can be treated in the time period of 3 to 4.5 hours after stroke but have 1 or more of the following exclusion criteria: (1) patients > 80 years old, (2) those taking oral anticoagulants, even with international normalized ratio ≤1.7, (3) those with a baseline NIHSS score > 25, or (4) those with a history of both stroke and diabetes mellitus, the effectiveness of IV treatment with rtPA is not well established, (Class IIb, Level of Evidence C), and requires further study. (Revised from the 2009 IV rtPA Science Advisory)

- In patients eligible for IV rtPA, benefit of therapy is time dependent, and treatment should be initiated as quickly as possible. The door-to-needle time (time of bolus administration) should be within 60 minutes from hospital arrival (Class I; Level of Evidence A). (New recommendation)

- IV fibrinolytic therapy is recommended in the setting of early ischemic changes (other than frank hypodensity) on CT, regardless of their extent (Class I; Level of Evidence A). (Revised from the 2009 imaging scientific statement)

- Frank hypodensity on NECT may increase the risk of hemorrhage with fibrinolysis and should be considered in treatment decisions. If frank hypodensity involves more than one-third of the MCA territory, IV rtPA treatment should be withheld (Class III; Level of Evidence A). (Revised from the 2009 imaging scientific statement)

- Use of IV fibrinolysis in patients with conditions of mild stroke deficits, rapidly improving stroke symptoms, major surgery in the preceding 3 months, and recent myocardial infarction may be considered, and potential increased risk should be weighed against the anticipated benefits (Class IIb; Level of Evidence C). These circumstances require further study. (New recommendation)

- IV rtPA is reasonable in patients with a seizure at the time of onset of stroke if evidence suggests that residual impairments are secondary to stroke and not a postictal phenomenon (Class IIa; Level of Evidence C). (Unchanged from the previous guideline)

[Continued on page 11 >>]
Table 3. Inclusion And Exclusion Criteria For Intravenous tPA Administration For Patients Who Could Be Treated With Intravenous rtPA Within 3 Hours From Symptom Onset

Inclusion Criteria
- Diagnosis of ischemic stroke causing measurable neurological deficit
- Onset of symptoms < 3 h before beginning treatment*
- Aged ≥ 18 y

Exclusion Criteria
- Significant head trauma or prior stroke in previous 3 mo
- Symptoms suggest subarachnoid hemorrhage
- Arterial puncture at noncompressible site in previous 7 days
- History of previous intracranial hemorrhage
- Intracranial neoplasm, arteriovenous malformation, or aneurysm
- Recent intracranial or intraspinal surgery
- Elevated blood pressure (systolic > 185 mm Hg or diastolic > 110 mm Hg)
- Active internal bleeding
- Acute bleeding diathesis, including but not limited to:
  - Platelet count < 100,000/mm\(^3\)
  - Heparin received within 48 h, resulting in abnormally elevated aPTT greater than the upper limit of normal
  - Current use of anticoagulant with INR > 1.7 or PT > 15 sec
  - Current use of direct thrombin inhibitors or direct factor Xa inhibitors with elevated sensitive laboratory tests (such as aPTT, INR, platelet count, and ECT; TT; or appropriate factor Xa activity assays)
- Blood glucose concentration < 50 mg/dL (2.7 mmol/L)
- CT demonstrates multilobar infarction (hypodensity > 1/3 cerebral hemisphere)

Relative Exclusion Criteria
Recent experience suggests that under some circumstances (with careful consideration and weighting of risk-to-benefit) patients may receive fibrinolytic therapy despite 1 or more relative contraindications. Consider risk-to-benefit of IV rtPA administration carefully if any of these relative contraindications are present:
- Only minor or rapidly improving stroke symptoms (clearing spontaneously)
- Pregnancy
- Seizure at onset* with postictal residual neurological impairments
- Major surgery or serious trauma within previous 14 days
- Recent gastrointestinal or urinary tract hemorrhage (within previous 21 days)
- Recent acute myocardial infarction (within previous 3 mo)

*Onset time is defined as either the witnessed onset of symptoms or the time last known normal if symptom onset was not witnessed.

In patients without recent use of oral anticoagulants or heparin, treatment with IV rtPA can be initiated before availability of coagulation test results but should be discontinued if INR is > 1.7 or PT is abnormally elevated by local laboratory standards. In patients without history of thrombocytopenia, treatment with IV rtPA can be initiated before availability of platelet count but should be discontinued if platelet count is < 100,000/mm\(^3\).

The checklist includes some United States FDA-approved indications and contraindications for administration of IV rtPA for acute ischemic stroke. Recent guideline revisions have modified the original FDA-approved indications. A physician with expertise in acute stroke care may modify this list.

Abbreviations: aPTT, activated partial thromboplastin time; CT, computed tomography; ECT, ecarin clotting time; FDA, Food and Drug Administration; INR, international normalized ratio; IV, intravenous; PT, partial thromboplastin time; rtPA, recombinant tissue plasminogen activator; TT, thrombin time.
• Patients who have elevated blood pressure and are otherwise eligible for treatment with IV rtPA should have their blood pressure carefully lowered so that their systolic blood pressure is < 185 mm Hg and their diastolic blood pressure is < 110 mm Hg (Class I; Level of Evidence B) before fibrinolytic therapy is initiated. (See the approaches to hypertension in the AHA/ASA guideline, linked here.) If medications are given to lower blood pressure, the clinician should be sure that the blood pressure is stabilized at the lower level before beginning treatment with IV rtPA and maintained below 180/105 mm Hg for at least the first 24 hours after IV rtPA treatment. (Unchanged from the previous guideline)

• In patients undergoing fibrinolytic therapy, physicians should be aware of and prepared to emergently treat potential side effects, including bleeding complications and angioedema that may cause partial airway obstruction (Class I; Level of Evidence B). (Revised from the previous guideline)

• The usefulness of IV administration of tenecteplase,reteplase,desmoteplase,urokinase,or other fibrinolytic agents and the IV administration of ancrod or other defibrinogenating agents is not well established, and they should only be used in the setting of a clinical trial (Class IIb; Level of Evidence B). (Revised from the previous guideline)

• The IV administration of streptokinase for treatment of stroke is not recommended (Class III; Level of Evidence A). (Revised from the previous guideline)

• The use of IV rtPA in patients taking direct thrombin inhibitors or direct factor Xa inhibitors may be harmful and is not recommended unless sensitive laboratory tests such as aPTT, INR, platelet count, and ECT, TT, or appropriate direct factor Xa activity assays are normal, or the patient has not received a dose of these agents for > 2 days (assuming normal renal metabolizing function). Similar consideration should be given to patients being considered for intra-arterial rtPA (Class III; Level of Evidence C). (New recommendation) Further study is required.

• IV fibrinolytic therapy is recommended in the setting of early ischemic changes other than frank hypodensity) on CT, regardless of their extent (Class I; Level of Evidence A). (Revised from the 2009 imaging scientific statement)

Table 4. Additional Inclusion and Exclusion Characteristics of Patients With Acute Ischemic Stroke Who Could Be Treated With IV rtPA Within 3 to 4.5 Hours From Symptom Onset

Inclusion Criteria
• Diagnosis of ischemic stroke causing measurable neurological deficit
• Onset of symptoms within 3 to 4.5 hours before beginning treatment
Relative Exclusion Criteria
• Age > 80 years
• Severe stroke (NIHSS > 25)
• Taking an oral anticoagulant, regardless of INR
• History of both diabetes and prior ischemic stroke

Abbreviations: INR, international normalized ratio; IV, intravenous; NIHSS, National Institutes of Health Stroke Scale; rtPA, recombinant tissue plasminogen activator.

Table 5. Treatment Of Acute Ischemic Stroke: Intravenous Administration Of rtPA

• Infuse 0.9 mg/kg (maximum dose, 90 mg) over 60 min, with 10% of the dose given as a bolus over 1 min.
• Admit the patient to an intensive care or stroke unit for monitoring.
• Discontinue the infusion (if IV rtPA is being administered) and obtain emergent CT scan if the patient develops any of the following:
  ◦ Severe headache,
  ◦ Acute hypertension,
  ◦ Nausea or vomiting, or
  ◦ Has a worsening neurological examination.
• Measure blood pressure and perform neurological assessments every 15 min during and after IV rtPA infusion for 2 h, then every 30 min for 6 h, then hourly until 24 h after IV rtPA treatment.
• Increase the frequency of blood pressure measurements if systolic blood pressure is > 180 mm Hg or if diastolic blood pressure is > 105 mm Hg; administer antihypertensive medications to maintain blood pressure at or below these levels.
• Delay placement of nasogastric tubes, indwelling bladder catheters, or intra-arterial pressure catheters if the patient can be safely managed without them.
• Obtain a follow-up CT or MRI scan at 24 h after IV rtPA before starting anticoagulants or antiplatelet agents.

Abbreviations: CT, computed tomography; IV, intravenous; MRI, magnetic resonance imaging; rtPA, recombinant tissue plasminogen activator.
Intravenous tPA Administration Recommendations: Editorial Comment, Sigrid Hahn, MD and Christie Lech, MD
The role of IV tPA has been debated extensively, and readers interested in reviewing narrative summaries of published thrombolysis for stroke trials are referred to the discussions in the guidelines themselves, as well as independent evidence-based medicine sources and other reviews. The ACEP/AAN guideline authors based their recommendation for tPA within 3 hours on the results of the NINDS trial, citing the consistent effect of IV tPA on favorable outcomes at 90 days. Note that the wording chosen by the ACEP/AAN does not mandate that tPA be given, rather that it should be “offered” to patients, reflecting the importance of physician and patient discussion about the potential risks and benefits of this therapy.

Despite concerns that there was an imbalance in stroke severity favoring better outcomes in the tPA group, the guideline authors felt that the supporting evidence from an independent re-analysis of the NINDS data as well as a patient-level meta-analysis was strong enough to support a level A recommendation. They reasoned that other studies failed to show benefit (ASK trial, MAST-I, MAST-E, and ECASS-I) because of different thrombolytic agents, longer treatment times, higher doses of tPA, or concomitant use of other antithrombotics. Similarly, the AHA/ASA guideline authors base their recommendation on the NINDS trial (also referencing the independent re-analysis that addressed the imbalance in stroke severity), as well as subgroup analysis of patients treated within 3 hours in the ECASS-I, ECASS-II, and ATLANTIS-A and ATLANTIS-B trials.

The ACEP/AAN recommendation for consideration of the use of tPA in the 3- to 4.5-hour window is weaker (Level B), while the AHA/ASA recommendation is Class I but based on a lower level of evidence than that supporting tPA’s use within 3 hours (which the authors refer to as a Grade B recommendation). This recommendation was based largely on ECASS-III study, which was designed explicitly to evaluate tPA in this “extended time window” and it found a modest but still positive treatment effect. It was supported by a meta-analysis of patient-level data from multiple other trials as well. Interestingly, the FDA declined to approve tPA for the 3- to 4.5-hour window after a confidential review process.

The ACEP/AAN recommendations are explicitly tempered with the caveat that the effectiveness of tPA has been less well established in institutions without the systems in place to safely administer the medication, and the AHA/ASA guideline cautions that the risk of intracranial hemorrhage complicating tPA treatment is proportional to the degree to which the NINDS protocol is not followed. Both recommendations, therefore, refer to the study inclusion and exclusion criteria, and this underlies the focus by the AHA/ASA on stroke systems development. The practice of withholding tPA from patients with mild or rapidly improving symptoms has been questioned, as studies have reported that about one-third of this particular subset of patients had poor final stroke outcome. There are no data cited showing a positive outcome in this group, though, and the guideline authors appear to be using this platform to push for further study of this issue.
Other Medical Management Recommendations For Acute Ischemic Stroke

• Cardiac monitoring is recommended to screen for atrial fibrillation and other potentially serious cardiac arrhythmias that would necessitate emergency cardiac interventions. Cardiac monitoring should be performed for at least the first 24 hours (Class I; Level of Evidence B). (Revised from the previous guideline)
• Airway support and ventilatory assistance are recommended for the treatment of patients with acute stroke who have decreased consciousness or who have bulbar dysfunction that causes compromise of the airway (Class I; Level of Evidence C). (Unchanged from the previous guideline)

Role Of Supplemental Oxygen

• Supplemental oxygen should be provided to maintain oxygen saturation > 94% (Class I; Level of Evidence C). (Revised from the previous guideline)
• Supplemental oxygen is not recommended in nonhypoxic patients with acute ischemic stroke (Class III; Level of Evidence B). (Unchanged from the previous guideline)

Blood Pressure Management

• The management of arterial hypertension in patients not undergoing reperfusion strategies remains challenging. Data to guide recommendations for treatment are inconclusive or conflicting. Many patients have spontaneous declines in blood pressure during the first 24 hours after onset of stroke. Until more definitive data are available, the benefit of treating arterial hypertension in the setting of acute ischemic stroke is not well established (Class IIb; Level of Evidence C). Patients who have malignant hypertension or other medical indications for aggressive treatment of blood pressure should be treated accordingly. (Revised from the previous guideline)
• No data are available to guide selection of medications for the lowering of blood pressure in the setting of acute ischemic stroke. The antihypertensive medications and doses in Table 9 of the AHA/ASA guideline (linked here) are reasonable choices based on general consensus (Class IIA; Level of Evidence C). (Revised from the previous guideline)
• Until other data become available, consensus exists that the previously described blood pressure recommendations should be followed in patients undergoing other acute interventions to recanalize occluded vessels, including intra-arterial fibrinolysis (Class I; Level of Evidence C). (Unchanged from the previous guideline)
• In patients with markedly elevated blood pressure who do not receive fibrinolysis, a reasonable goal is to lower blood pressure by 15% during the first 24 hours after onset of stroke. The level of blood pressure that would mandate such treatment is not known, but consensus exists that medications should be withheld unless the systolic blood pressure is > 220 mm Hg or the diastolic blood pressure is > 120 mm Hg (Class I; Level of Evidence C). (Revised from the previous guideline)

Hyperthermia, Hypovolemia, And Hypo- And Hyperglycemia

• Sources of hyperthermia (temperature > 38°C) should be identified and treated, and antipyretic medications should be administered to lower temperature in hyperthermic patients with stroke (Class I; Level of Evidence C). (Unchanged from the previous guideline)
• Hypovolemia should be corrected with IV normal saline, and cardiac arrhythmias that might be reducing cardiac output should be corrected (Class I; Level of Evidence C). (Revised from the previous guideline)
• Hypoglycemia (blood glucose < 60 mg/dL) should be treated in patients with acute ischemic stroke (Class I; Level of Evidence C). The goal is to achieve normoglycemia. (Revised from the previous guideline)
• Evidence indicates that persistent inhospital hyperglycemia during the first 24 hours after stroke is associated with worse outcomes than normoglycemia, and thus, it is reasonable to treat hyperglycemia to achieve blood glucose levels in a range of 140 to 180 mg/
dL and to closely monitor to prevent hypoglycemia in patients with acute ischemic stroke (Class IIa; Level of Evidence C). (Revised from the previous guideline)

Seizure Management
• Prophylactic use of anticonvulsants is not recommended (Class III; Level of Evidence C).

Adjunct Anticoagulants And Antiplatelet Agents
• Oral administration of aspirin (initial dose is 325 mg) within 24 to 48 hours after stroke onset is recommended for treatment of most patients (Class I; Level of Evidence A). (Unchanged from the previous guideline)
• Aspirin is not recommended as a substitute for other acute interventions for treatment of stroke, including IV rtPA (Class III; Level of Evidence B). (Unchanged from the previous guideline)
• The usefulness of clopidogrel for the treatment of acute ischemic stroke is not well established (Class IIb; Level of Evidence C). Further research testing the usefulness of the emergency administration of clopidogrel in the treatment of patients with acute stroke is required. (Revised from the previous guideline)
• The efficacy of IV tirofiban and eptifibatide is not well established, and these agents should be used only in the setting of clinical trials (Class IIb; Level of Evidence C). (New recommendation)
• The administration of other IV antiplatelet agents that inhibit the glycoprotein IIb/IIIa receptor is not recommended (Class III; Level of Evidence B). (Revised from the previous guideline) Further research testing the usefulness of emergency administration of these medications as a treatment option in patients with acute ischemic stroke is required.
• The administration of aspirin (or other antiplatelet agents) as an adjunctive therapy within 24 hours of IV fibrinolysis is not recommended (Class III; Level of Evidence C). (Revised from the previous guideline)
• Urgent anticoagulation, with the goal of preventing early recurrent stroke, halting neurological worsening, or improving outcomes after acute ischemic stroke, is not recommended for treatment of pa-

• Urgent anticoagulation for the management of noncerebrovascular conditions is not recommended for patients with moderate-to-severe strokes because of an increased risk of serious intracranial hemorrhagic complications (Class III; Level of Evidence A). (Unchanged from the previous guideline)
• Initiation of anticoagulant therapy within 24 hours of treatment with IV rtPA is not recommended (Class III; Level of Evidence B). (Unchanged from the previous guideline)

Other Medical Management Recommendations: Editorial Comment, Sigrid Hahn, MD and Christie Lech, MD
The recommendations about medical management of stroke in the acute phase are as much about what not to do as what to do. Treat hypoxia (oxygen saturation < 94%), but don’t administer supplemental oxygen routinely. Manage blood pressure if the patient has malignant hypertension, but, otherwise, the role of antihypertensives in acute stroke management are not well established. Do not give empiric, prophylactic treatment for seizure prevention. Give aspirin, but not if the patient has received tPA. Do not give other antiplatelet agents, as their benefit is unproven. Do not anticoagulate most patients in the acute phase, whether or not they have received tPA, because of risk of serious bleeding. The guidelines do emphasize normalizing several physiologic parameters that are known to impact brain health; ie, treat hyperthermia, and hyper or hypoglycemia to keep glucose within the range of 140 to 180 mg/dL.
References


CME Questions

To take the CME test, visit: www.ebmedicine.net/CME or scan the QR code below with a smartphone:

1. Oxygen saturation in patients with acute stroke should be maintained at a level that is greater than
   a. 88%
   b. 90%
   c. 94%
   d. 99%

2. The following laboratory test is the only one required to be obtained prior to administration of tPA in acute stroke patients:
   a. Glucose
   b. Sodium
   c. Calcium
   d. Potassium

3. The recommended maximum door-to-tPA time in patients with suspected acute stroke is:
   a. 15 minutes
   b. 30 minutes
   c. 45 minutes
   d. 60 minutes

4. Besides bleeding, a complication of tPA use is:
   a. Hypotension
   b. Orolingual edema
   c. Pulmonary edema
   d. Hyperglycemia
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