

AHA/ASA Scientific Statement

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

*The American Academy of Neurology (AAN) affirms the value of this statement
as an educational tool for neurologists*

*Endorsed by the American Association of Neurological Surgeons (AANS)
and Congress of Neurological Surgeons (CNS)*



American Heart Association | American Stroke Association®

science is why

Authors



Bart M. Demaerschalk, MD, MSc, FAHA, Chair;
Dawn O. Kleindorfer, MD, FAHA, Vice-Chair; Opeolu M. Adeoye, MD,
MS, FAHA; Andrew M. Demchuk, MD; Jennifer E. Fugate, DO; James
C. Grotta, MD; Alexander A. Khalessi, MD, MS, FAHA; Elad I. Levy,
MD, MBA, FAHA; Yuko Y. Palesch, PhD; Shyam Prabhakaran, MD,
MS, FAHA; Gustavo Saposnik, MD, MSc, FAHA;
Jeffrey L. Saver, MD, FAHA; Eric E. Smith, MD, MPH, FAHA;

On behalf of the American Heart Association Stroke Council
and Council on Epidemiology

Slides Prepared by Members of the Stroke Professional Education Committee



Kelly Anderson, MSN, RN
Member – Stroke Council Professional Education committee

Applying classification of recommendations and levels of evidence



		SIZE OF TREATMENT EFFECT													
		CLASS I <i>Benefit >>> Risk</i> Procedure/Treatment SHOULD be performed/administered	CLASS IIa <i>Benefit >> Risk</i> Additional studies with <i>focused objectives needed</i> IT IS REASONABLE to perform procedure/administer treatment	CLASS IIb <i>Benefit ≥ Risk</i> Additional studies with <i>broad objectives needed; additional registry data would be helpful</i> Procedure/Treatment MAY BE CONSIDERED	CLASS III <i>No Benefit</i> or CLASS III <i>Harm</i>										
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Comparative effectiveness phrases [†]		treatment/strategy A is recommended/indicated in preference to treatment B treatment A should be chosen over treatment B	treatment/strategy A is probably recommended/indicated in preference to treatment B it is reasonable to choose treatment A over treatment B												

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I. Introduction



- Recombinant Tissue Plasminogen Activator (alteplase) was first approved by the Food and Drug Administration (FDA) in the United States in 1996 and remains the only medication proven to impact outcomes when given in the hyperacute timeframe after ischemic stroke.
- The most common exclusion for alteplase is dominated by delays in presentation to medical attention. Within a population, only 22-31% of ischemic stroke patients present to an emergency department within three hours from symptom onset.
- However, national estimates of the use of alteplase only range from 3-5%.

I. Introduction



- There are numerous other clinical, radiological, and laboratory-related exclusion criteria for alteplase that are considered standard of care and are listed in the AHA/ASA acute stroke management guidelines.
- Some of these exclusions for alteplase are controversial. Many stroke experts across the country consider some of these exclusion criteria (or contraindications) to be “relative” and others to be “absolute”.
- The intent of this scientific statement is to critically review and evaluate the science behind each of the alteplase eligibility criteria (indications and contraindications alike), as well as explore some popular myths regarding treatment.

I. Introduction



- **Contraindications** — A drug should be contraindicated only in those clinical situations for which the risk from use clearly outweighs any possible therapeutic benefit. Only known hazards, and not theoretical possibilities, can be the basis for a contraindication.
- **Warnings and Precautions** — The Warnings and Precautions section is intended to identify and describe a discrete set of adverse reactions and other potential safety hazards that are serious or are otherwise clinically significant because they have implications for prescribing decisions or for patient management. To include an adverse event in the section, there should be reasonable evidence of a causal association between the drug and the adverse event, but a causal relationship need not have been definitively established.

I. Introduction

- This scientific statement is expected to be an adjunct to, and not a replacement for, the AHA/ASA acute stroke management guidelines.
- This AHA/ASA statement writing group feels strongly that the AHA/ASA acute stroke management guidelines, in combination with the science presented in this statement, should be what clinicians access and apply to their acute ischemic stroke treatment and management decisions. This is especially true as the PI changes were made by the FDA in the context of no substantial new information compared to the rigorous process undertaken by these authors.

II. Age Issues



- A meta-analysis of 6 randomized trials and data from observational studies both suggest a benefit in favor of IV alteplase for both younger (≤ 80 y) and older (>80 y) patients.
- Among patients treated within 3 hours, for every 1,000 patients older than 80 years there would be 96 more patients alive and independent at the end of follow-up (3 months later). Similar findings were observed for those younger than 80 years.
- Mortality data is mixed, with some studies showing no significant difference in death at 3 months between alteplase patients and controls for the same age group and other studies showing a higher mortality rate in those receiving alteplase.
- sICH data is also mixed, with some studies showing no significant difference in risk between alteplase patients and controls for the same age group and other studies showing an increased risk of bleeding in those 80 and older.

II. Age Issues

- The initial diagnosis of stroke in children may be challenging considering the diverse presenting symptoms (e.g. coma, seizures, and hemiparesis) common to non-vascular etiologies.
- At this time, there are no published randomized trials using alteplase in neonates and children. Most of the evidence of alteplase in the pediatric population is from observational studies.
- The AHA/ASA pediatric stroke guidelines do not recommend IV alteplase treatment for children with ischemic strokes outside a clinical trial, with the exception of older adolescents who otherwise meet adult eligibility criteria and for whom consensus is lacking.

II. Age Issues - Recommendations



- For otherwise medically eligible patients 18 years and older, IV alteplase administration within 3 hours is equally recommended for patients younger and older than 80 years. Older age is an adverse prognostic factor in stroke, but does not modify the treatment effect of thrombolysis. Even though older patients have poorer outcomes, higher mortality, and higher rates of sICH than those younger than 80, compared to controls, IV alteplase provides a better chance of being independent at 3 months across all age groups. **(Class I, Level of Evidence A)**
- The efficacy and risk of IV alteplase administration in the pediatric population (neonates, children and adolescents younger than 18 years of age) is not well established. **(Class IIb, Level of Evidence B)**

III. Stroke Severity and the NIHSS



- The authors of the two original NINDS alteplase trials concluded that treatment of severe strokes was warranted, because even though the chances of a good outcome were less overall, severe stroke patients still had a better chance of a good outcome with alteplase treatment than without.
- The original FDA approval of alteplase included a warning statement that patients with NIHSS > 22 be treated “with caution”. This was included in the approval because it was noted that more severe ischemic stroke patients were more likely to have hemorrhagic transformation after receiving alteplase within the two NINDS trials. In fact, higher stroke severity has been associated with increased risk of hemorrhagic transformation, with or without alteplase treatment.
- Based on the available literature, there should be no upper limit of NIHSS for patients otherwise eligible for alteplase presenting to medical attention within 3 hours. Patients with stroke severity greater than 25 in the 3-4.5 hour window will be discussed later.

III. Stroke Severity and the NIHSS



- There was no lower limit of the NIHSS for enrollment into the original two NINDS trials, and investigators were instructed to enroll patients with ischemic stroke “causing a measurable neurologic deficit defined as impairment of language, motor function, cognition, and/or gaze, vision or neglect”.
- A review of the rates of disability among milder stroke patients demonstrates that there is significant disability among patients (defined variably) at 3 months in multiple studies. Some of this disability was related to motor deficits as expected; however, there was a significant component of cognitive dysfunction, fatigue, and depression, deficits that are not captured by the presenting NIHSS.
- Alteplase may be beneficial for milder stroke cases judged as potentially disabling despite low NIHSS scores. However, data are not available regarding the effect of alteplase for milder stroke cases judged as not potentially disabling at presentation. Given that there are relatively few patients enrolled in clinical trials of IV alteplase that included milder cases, the risk/benefit ratio for administration of IV alteplase to milder stroke cases is as of yet unknown and requires further study.

III. Stroke Severity and the NIHSS - Recommendations

- For severe stroke symptoms, IV alteplase is indicated within 3 hours from symptom onset of ischemic stroke. Despite increased risk of hemorrhagic transformation, there is still proven clinical benefit for patients with severe stroke symptoms. **(Class I, Level of Evidence A)**
- For patients with, mild, but disabling stroke symptoms, IV alteplase is indicated within 3 hours from symptom onset of ischemic stroke. There should be no exclusion for patients with, mild, but nonetheless disabling stroke symptoms in the opinion of the treating physician from treatment with IV alteplase, since there is proven clinical benefit for those patients. **(Class I, Level of Evidence A)**
- Within 3 hours from symptom onset, treatment of patients with milder ischemic stroke symptoms that are judged as non-disabling may be considered. Treatment risks should be weighed against possible benefits; however, more study is needed to further define the risk-benefit ratio. **(Class IIb, Level of Evidence C)**

IV. Rapidly Improving



- Rapid clinical improvement has a number of pathophysiologic explanations and can be quite dynamic. Often, improvement can be incomplete with disabling deficits remaining once improvement plateaus. Deterioration can also follow spontaneous improvement due to persistent occlusion or partial recanalization with subsequent re-occlusion and often results in a worsening of deficits back to baseline severity. Lacunar strokes involving the pons commonly fluctuate yet often lead to progressive worsening of deficits later.
- It was the unanimous consensus of “The Re-examining Acute Eligibility for Thrombolysis” (TREAT) task force that patients with moderate to severe stroke who do not improve to a non-disabling state should be treated with IV alteplase unless other contraindications are present. The task force further emphasized that treatment should not be delayed to monitor for improvement beyond the extent of time needed to prepare and administer the IV alteplase bolus.

IV. Rapidly Improving - Recommendations

- IV alteplase treatment is reasonable for patients who present with moderate to severe ischemic stroke and demonstrate early improvement but remain moderately impaired and potentially disabled in the judgment of the examiner.
(Class IIa, Level of Evidence A)
- Since time from onset of symptoms to treatment has such a powerful impact on outcome, delaying treatment with IV alteplase to monitor for further improvement, is not recommended.
(Class III, Level of Evidence C)

V. Time from Symptom Onset - Recommendations

- The time from last seen normal to treatment with IV alteplase should be < 3 hours for eligible patients using standard eligibility criteria. **(Class I, Level of Evidence A)**
- IV alteplase treatment in the 3-4.5 hour time window is also recommended for those patients <80yo, without a history of both diabetes and prior stroke, NIHSS<25, not taking any oral anticoagulants, and without imaging evidence of ischemic injury involving more than one third of the MCA territory. **(Class I, Level of Evidence B)**
- Treatment should be initiated as quickly as possible within the above listed timeframes as time to treatment is strongly associated with outcome. **(Class I, Level of Evidence A)**
- In patients in the 0-4.5 hour time window who meet criteria for treatment with IV alteplase, substantially delaying IV alteplase treatment in order to obtain penumbral imaging prior to treatment is not recommended. **(Class III, Level of Evidence C)**

VI. Acute Intracranial Hemorrhage on CT - Recommendations



- IV alteplase should not be administered to a patient whose CT reveals an acute intracranial hemorrhage.
(Class III, Level of Evidence C)
- Acute intracranial hemorrhage includes intracerebral hemorrhage, subarachnoid hemorrhage, intraventricular hemorrhage, subdural hematoma, epidural hematoma, and acute hemorrhagic transformation of a cerebral infarction.

VII. Pregnancy and Postpartum



- The alteplase label specifies that there are no adequate or well-controlled studies in pregnant women and that alteplase should be used in pregnancy only if the potential benefit justifies the potential risk to the fetus.
- There is minimal experience with IV or IA alteplase for stroke in pregnancy. Our systematic review identified only 12 reported cases of pregnant women with arterial stroke who were treated with IV alteplase or endovascular therapy.
- No studies reported cases of clot aspiration or retrieval.

VII. Pregnancy and Postpartum - Recommendations

- IV alteplase administration for ischemic stroke may be considered in pregnancy when the anticipated benefits of treating moderate to severe stroke outweigh the anticipated increased risks of uterine bleeding. **(Class IIb, Level of Evidence C)**
- The safety and efficacy of IV alteplase in the early post-partum period (<14 days after delivery) have not been well established. **(Class IIb, Level of Evidence C)**
- Urgent consultation with an obstetrician-gynecologist and potentially a perinatologist to assist with management of the mother and fetus is recommended. **(Class I, Level of Evidence C)**

VIII. Platelets

- Out of 9613 patients in pooled trial data, only 10 patients with platelets $<100,000 \text{ mm}^3$ who received IV alteplase despite this contraindication were identified. Overall, the extremely small number of published cases precludes solid conclusions.
- The number of patients with elevated INR levels or prolonged aPTT values who received IV alteplase are also quite small.
- Given that so few patients have been reported and that much of the data comes from large voluntary registries or observational studies in which selection bias and publication bias are likely, no firm conclusions regarding the safety or efficacy of IV alteplase in patients with INR >1.7 , aPTT >40 seconds, or PT >15 seconds can be made.

VIII. Platelets - Recommendations

- The safety and efficacy of IV alteplase for acute stroke patients with platelets $< 100,000/\text{mm}^3$, INR > 1.7 , aPTT > 40 seconds, or PT > 15 seconds is unknown, and IV alteplase is not recommended. **(Class III, Level of Evidence C)**
- Given the extremely low risk of unsuspected abnormal platelet counts or coagulation studies in a population, it is reasonable that urgent IV alteplase treatment not be delayed while waiting for hematologic or coagulation testing, if there is no reason to suspect an abnormal test. **(Class IIa, Level of Evidence B)**

IX. History of Bleeding Diathesis or Coagulopathy - Recommendations



- Potential causes of coagulopathies include liver cirrhosis, end stage renal disease (ESRD), hematologic malignancy, vitamin K deficiency, sepsis, antiphospholipid antibody syndrome and congenital disorders.
- There is a dearth of evidence to support or refute the usefulness of administering IV alteplase to stroke patients with known hematologic disorders. As in other cases, hemorrhagic risks and potential benefits should be considered on an individual basis.
- The safety and efficacy of IV alteplase for acute stroke patients with a clinical history of potential bleeding diathesis or coagulopathy is unknown. IV alteplase may be considered on a case-by-case basis.
(Class IIb, Level of Evidence C)

X. History of Anticoagulant Use - Recommendations

- Intravenous alteplase may be reasonable in patients who have a history of warfarin use and an INR ≤ 1.7 . **(Class IIb, Level of Evidence B)**
- Intravenous alteplase in patients who have a history of warfarin use and an INR > 1.7 is not recommended. **(Class III, Level of Evidence B)**
- Intravenous alteplase in patients who have received a dose of LMWH within the previous 24 hours is not recommended. This applies to both prophylactic doses and treatment doses. **(Class III, Level of Evidence B)**
- The use of intravenous alteplase in patients taking direct thrombin inhibitors or direct factor Xa inhibitors has not been firmly established, but may be harmful. **(Class III, Level of Evidence C)**
- The use of intravenous alteplase in patients taking direct thrombin inhibitors or direct factor Xa inhibitors is not recommended unless laboratory tests such as aPTT, INR, platelet count, ecarin clotting time (ECT), thrombin time (TT), or appropriate direct factor Xa activity assays are normal, or the patient has not received a dose of these agents for > 48 hours (assuming normal renal metabolizing function).

XI. Major Surgery within 14 Days - Recommendations

- Though the rationale behind this contraindication centers on the potential for surgical site or systemic hemorrhage, no Level A or B evidence currently supports this exclusion. The current review affirms the paucity of data supporting major surgery as an absolute contraindication to IV alteplase administration.
- Clinicians must therefore weigh the potential salutary benefit of IV alteplase in the individual stroke patient against the possibility of surgical site hemorrhage. Provided there is availability of clinical services to manage potential surgical site hemorrhages, IV alteplase remains reasonable in select stroke patients.
- Use of intravenous alteplase in carefully selected patients presenting with acute ischemic stroke who have undergone a major surgery in the preceding 14 days may be considered, but the potential increased risk of surgical site hemorrhage should be weighed against the anticipated benefits of reduced stroke-related neurologic deficits. **(Class IIb, Level of Evidence C)**
- Another section of this statement details specific literature regarding cranial and spinal surgery.

XII. Major Trauma within 14 Days and Serious Head Trauma within 3 Months



- Limited data are available on the use IV alteplase after major trauma or serious head trauma.
- Post-traumatic infarction, defined as an ischemic stroke in an arterial distribution, is reported to occur in 2-10% of patients during the acute in-hospital phase of severe head trauma. However, no data are available on treatment of post-traumatic infarction with IV alteplase.
- After major or minor trauma, dissection of the cervical vessels may cause ischemic stroke. In otherwise eligible patients with cervical artery dissection strokes, a meta-analysis of retrospective studies and case reports that involved 121 patients (31 with preceding trauma) treated with IV alteplase found no safety concerns.
- Cervical artery dissection outside of major trauma is not a contraindication to IV alteplase and is discussed later.

XII. Major Trauma within 14 Days and Serious Head Trauma within 3 Months - Recommendations

- In acute ischemic stroke patients with recent major trauma (within 14 days), IV alteplase may be carefully considered, weighing the risks of bleeding from injuries related to the trauma against the severity and potential disability from the ischemic stroke.
(Class IIb, Level of Evidence C)
- In acute ischemic stroke patients with recent severe head trauma (within 3 months), IV alteplase is contraindicated.
(Class III, Level of Evidence C)
- Given the possibility of bleeding complications from the underlying severe head trauma, IV alteplase is not recommended in post-traumatic infarction that occurs during the acute in-hospital phase.
(Class III, Level of Evidence C)

XIII. Cardiac Conditions



- ***Acute MI***
 - A feasible option is to administer the stroke dose (0.9 mg/kg) of alteplase to treat the acute ischemic stroke and then to proceed to percutaneous transluminal coronary angioplasty and stenting (PTCAS), if indicated, for the acute coronary event. Pretreatment with IV alteplase does not decrease the coronary benefit of PTCAS.
- ***History of Recent MI (preceding 3 months)***
 - The published literature on treating acute ischemic stroke patients with recent MI with IV alteplase is limited in scope and varies based on STEMI or non-STEMI, as well as location of the infarct within the heart.

XIII. Cardiac Conditions - Recommendations

- ***Acute MI or History of Recent MI (preceding 3 months)***
 - For patients presenting with concurrent acute ischemic stroke and acute myocardial infarction, treatment with IV alteplase at the dose appropriate for cerebral ischemia, followed by percutaneous coronary angioplasty and stenting if indicated, is reasonable. **(Class IIa, Level of Evidence C)**
 - For patients presenting with acute ischemic stroke and a history of recent myocardial infarction in the past 3 months, treating the ischemic stroke with IV alteplase is reasonable if the recent MI was non-STEMI **(Class IIa, Level of Evidence C)**, is reasonable if the recent MI was STEMI involving the right or inferior myocardium **(Class IIa, Level of Evidence C)**, and may be reasonable if the recent MI was STEMI involving the left anterior myocardium. **(Class IIb, Level of Evidence C)**

XIII. Cardiac Conditions - Recommendations



- ***Pericarditis***

- For patients with major acute ischemic stroke likely to produce severe disability and acute pericarditis, treatment with IV alteplase may be reasonable (**Class IIb, Level of Evidence C**); urgent consultation with a cardiologist is recommended in this situation.
- For patients presenting with moderate acute ischemic stroke likely to produce mild disability and acute pericarditis, treatment with IV alteplase is of uncertain net benefit. (**Class IIb, Level of Evidence C**)

- ***Infective Endocarditis***

- For patients with acute ischemic stroke and symptoms consistent with infective endocarditis, treatment with IV alteplase is not recommended due to the increased risk of intracranial hemorrhage. (**Class III, Level of Evidence C**)

XIII. Cardiac Conditions - Recommendations



- *Left Heart Thrombus*
 - For patients with major acute ischemic stroke likely to produce severe disability and known left atrial or ventricular thrombus, treatment with IV alteplase may be reasonable. **(Class IIb, Level of Evidence C)**
 - For patients presenting with moderate acute ischemic stroke likely to produce mild disability and known left atrial or ventricular thrombus, treatment with IV alteplase is of uncertain net benefit. **(Class IIb, Level of Evidence C)**

XIV. History of Intracranial/Spinal Surgery within 3 Months - Recommendations



- No meaningful Level A or B evidence exists in the literature to support the prohibition of IV alteplase administration based on 3-month cranial or spinal surgery history. However, surgical site bleeding carries the potential threat of neurological insult in this subset of stroke patients and may therefore attenuate the neurological benefit associated with IV alteplase.
- For patients with acute ischemic stroke and a history of intracranial/spinal surgery within the prior 3 months, IV alteplase is potentially harmful. **(Class III, Level of Evidence C)**
- Mechanical thrombectomy remains a strong option in patient's harboring a large vessel occlusion in the setting of recent cranial or spinal surgery.

XV. History of Ischemic Stroke within 3 Months

- The existing evidence on IV alteplase in instances of patients having had a recent stroke < 3 months is limited and overlaps the evidence concerning IV alteplase for patients with a past history of stroke and concomitant diabetes mellitus.
- There is evidence derived from cardio-respiratory literature that repeated administration of systemic thrombolysis is effective and safe. However, repeated administration of IV alteplase for acute ischemic stroke after early recurrence has been reported only infrequently.
- What remains unknown is how soon, post-ischemic stroke, is it relatively safe to administer IV alteplase for a recurrent acute ischemic stroke and how best to quantitatively and qualitatively estimate the potential of increased risk of sICH.
- Further research on risk stratification based on size, severity, location and time would help inform clinicians before recommendations can be adjusted.

XV. History of Ischemic Stroke within 3 Months - Recommendations



- Use of IV alteplase in patients presenting with acute ischemic stroke who have had a prior ischemic stroke < 3 months may be harmful. **(Class III, Level of Evidence B)**
- The potential for increased risk of sICH and associated morbidity and mortality exists but is not well established. **(Class IIb, Level of Evidence B)**
- The potential risks should be discussed during thrombolysis eligibility deliberation and weighed against the anticipated benefits during decision making. **(Class I, Level of Evidence C)**

XVI. Active Internal Bleeding or History of GI/GU Bleeding within 21 Days



- Existing literature is extremely sparse. Though IV alteplase was well tolerated in the few reported patients with recent GI or GU hemorrhagic events, further evidence is needed.
- For clinical purposes, it may be worthwhile to distinguish patients with a known source or structural lesion from those with an occult source of GI or GU bleeding.
- Patients with solid malignancies or defined ulcers or varices may harbor therapeutic targets for sclerotherapy or embolization in the event of systemic hemorrhage.
- Ultimately, the safety of administering IV alteplase to acute stroke patients with recent GI or GU bleeding is uncertain; patients who suffered their hemorrhagic event more than 7 days preceding their acute stroke presentation may carry a lower bleeding risk.

XVI. Active Internal Bleeding or History of GI/GU Bleeding within 21 Days - Recommendations

- Reported literature details a low bleeding risk with IV alteplase administration in the setting of past GI/GU bleeding. Administration of IV alteplase in this patient population may be reasonable. **(Class IIb, Level of Evidence C)**
- Patients with a structural GI malignancy or recent bleeding event within 21 days of their stroke event should be considered high risk, and IV alteplase administration is potentially harmful. **(Class III, Level of Evidence C)**

XVII. Arterial Puncture of Non-Compressible Vessels in the Preceding 7 Days - Recommendations

- Based on expert consensus, arterial puncture of a non-compressible vessel within the week preceding acute stroke symptoms is a contraindication to administering IV alteplase to acute stroke patients.
- The most likely scenario in which this problem would arise is after catheterization of the subclavian or internal jugular veins in critically ill patients, procedures which are complicated by inadvertent adjacent arterial puncture in up to 8% of cases.
- The safety and efficacy of administering IV alteplase to acute stroke patients who have had an arterial puncture of a non-compressible blood vessel in the 7 days preceding stroke symptoms is uncertain. **(Class IIb, Level of Evidence C)**

XVIII. Uncontrolled Hypertension, Severe Hypertension, Repeated BP or Requiring Aggressive Treatment

- Uncontrolled or severe hypertension (greater than 185 mmHg systolic or 110 mmHg diastolic on 2 or more consecutive measurements) has been a common reason to exclude a patient from IV alteplase in real world practice, especially if not quickly brought under control with BP treatment.
- High blood pressure at presentation has been associated with an elevated risk of sICH with IV alteplase in the SITS and Get-With-The-Guidelines Phase 4 registries. The higher the blood pressure, the greater the risk.
- As long as systolic blood pressure can be reduced to 185 mmHg or lower range and diastolic blood pressure can be reduced to 110 mmHg or lower range by whatever means necessary, the patient remains suitable for thrombolysis with IV alteplase.

XVIII. Uncontrolled Hypertension, Severe Hypertension, Repeated BP or Requiring Aggressive Treatment - Recommendations

- IV alteplase is recommended in patients whose blood pressure can be lowered safely (to below 185/110 mm Hg) with antihypertensive agents, with the physician assessing the stability of the blood pressure before starting IV alteplase. **(Class I, Level of Evidence B)**
- 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 alteplase and maintained below 180/105 mm Hg for at least the first 24 hours after IV alteplase treatment. **(Class I, Level of Evidence B)**

XIX. History of Intracranial Hemorrhage



- Similar to earlier reviews of IV alteplase exclusion criteria, the literature only offers a handful of cases in the context of larger retrospective reviews.
- The lack of any data regarding this issue is possibly why the revised FDA label removed any history of ICH as a contraindication and added a warning against “recent” ICH only. It remains unclear how the FDA would define “recent” in such a setting.
- Overall, the risk of sICH likely corresponds with
 - (1) the volume of encephalomalacia from the previous ICH;
 - (2) whether the previous ICH occurred in the same vascular territory as the acute stroke presentation; and
 - (3) how recently the ICH took place.
- The treating clinician should use these factors to stratify the sICH risk for IV alteplase administration in this patient subset. Given the low overall ICH rate in patients with acute cerebral microbleeds, it remains unlikely the sICH rate would swamp the benefits of IV alteplase in the more remote ICH patients.

XIX. History of Intracranial Hemorrhage - Recommendations



- IV alteplase has not been shown to increase symptomatic ICH rates in patients with cerebral microbleeds. IV alteplase administration in these patients is therefore reasonable.
(Class IIa, Level of Evidence B)
- IV alteplase administration in patients who have a history of intracranial hemorrhage is potentially harmful.
(Class III, Level of Evidence C)

XX. Unruptured Intracranial Aneurysm - Recommendations



- Available case series and reports indicate no significant increase in ICH risk among patients with unruptured aneurysms undergoing treatment with IV alteplase, compared with those without aneurysms. Although limited by selection bias, these series suggest that IV alteplase can be safely administered in patients with incidental intracranial aneurysms.
- For patients presenting with acute ischemic stroke who are known to harbor a small or moderate sized (<10 mm) unruptured and unsecured intracranial aneurysm, administration of IV alteplase is reasonable and probably recommended. **(Class IIa, Level of Evidence C)**
- No data are available for evaluation of the safety of IV alteplase in patients with unruptured large or giant aneurysms, which might carry a higher risk for ICH.
- Usefulness and risk of IV alteplase in patients with acute ischemic stroke who harbor a giant unruptured and unsecured intracranial aneurysm are not well established. **(Class IIb, Level of Evidence C)**

XXI. Intracranial Vascular Malformations- Recommendations



- Given the increased risk of hemorrhage in patients with intracranial malformations (including cavernous angiomas, capillary telangiectasias, development venous anomalies, and arteriovenous malformations and fistulas) and limited experience with the use of IV alteplase in this group of patients, no solid conclusions can be made on the safety of thrombolysis in stroke patients with known or incidental malformations.
- For patients presenting with acute ischemic stroke who are known to harbor an unruptured and untreated intracranial vascular malformation, the usefulness and risks of administration of IV alteplase are not well established.
(Class IIb, Level of Evidence C)
- Because of the increased risk of ICH in this population of patients, IV alteplase may be considered in patients with stroke with severe neurologic deficits and high likelihood of morbidity and mortality to outweigh the anticipated risk of ICH secondary to thrombolysis. **(Class IIb, Level of Evidence C)**

XXII. Intracranial Neoplasms - Recommendations

- Though data regarding IV alteplase in the setting of intracranial neoplasms is confined to case reports, systemic thrombolysis appears safe in extra-axial, intracranial neoplasms.
- IV alteplase treatment is probably recommended for patients with acute ischemic stroke who harbor an **extra-axial** intracranial neoplasm. (**Class IIa, Level of Evidence C**)
- IV alteplase treatment for patients with acute ischemic stroke who harbor an **intra-axial** intracranial neoplasm is potentially harmful. (**Class III, Level of Evidence C**)
- The data surrounding sICH rate in intracranial metastases, most notably hemorrhagic metastases including renal cell, cholangiocarcinoma and melanoma, is less available. Ultimately, the histology, location, and baseline bleeding risk of the tumor can inform reasonable IV alteplase administration in these patients.

XXIII. Serious Medical Comorbid Illnesses - Recommendations



- In patients with end-stage renal disease on hemodialysis, and normal aPTT, IV alteplase is recommended. **(Class I, Level of Evidence C)** However, those with elevated aPTT may have elevated risk for hemorrhagic complications.
- Patients with pre-existing dementia may benefit from IV alteplase. **(Class IIb, Level of Evidence B)** Individual considerations such as life expectancy and pre-morbid level of function are important to determine whether or not alteplase may offer a clinically meaningful benefit.
- The safety and efficacy of alteplase in patients with current malignancy is not well established. **(Class IIb, Level of Evidence C)** Patients with systemic malignancy and reasonable (> 6 months) life expectancy may benefit from IV alteplase if other contraindications such as coagulation abnormalities, recent surgery, or systemic bleeding do not co-exist.

XXIV. Pre-existing Disability - Recommendations

- Pre-existing disability does not seem to independently increase the risk of sICH post-IV alteplase, but it may be associated with less neurological improvement and higher mortality.
- The decision of thrombolysis among patients from long-term care facilities or nursing homes is controversial.
- Thrombolytic therapy with IV alteplase for acute stroke patients with pre-existing disability ($mRS \geq 2$) may be reasonable, but decisions should take into account relevant factors other than mRS (including quality of life, social support, place of residence, need for a caregiver after alteplase, patients' and families' preferences, and goals of care). **(Class IIb, Level of Evidence B)**

XXV. Blood Glucose



- The rationale for inclusion in the eligibility criteria derives mostly from a concern that hypo- and hyperglycemia are known to produce acute focal neurologic deficits that can mimic those from acute brain ischemia. In practice, glucose levels account for < 1% of alteplase contraindications in the GWTG-Stroke registry.
- It is reasonable to consider IV alteplase in suspected stroke patients with initial blood glucose levels < 50 mg/dL or > 400 mg/dL after appropriate glycemic management (i.e. dextrose or insulin, respectively) and neurologic re-examination within a short time frame (i.e. 15 minutes).
- If the significant neurologic deficits persist with normalization of glucose levels, IV alteplase may be optional in such patients. However, data on this practice are lacking.

XXV. Blood Glucose - Recommendations



- IV alteplase is recommended in otherwise eligible patients within initial glucose levels > 50 mg/dL. **(Class I, Level of Evidence A)**
- Treating clinicians should be aware that hypoglycemia and hyperglycemia may mimic acute stroke presentations and check blood glucose levels prior to IV initiation. IV alteplase is not indicated for non-vascular conditions.
(Class III, Level of Evidence B)
- Treatment with IV alteplase in acute ischemic stroke patients who present with initial glucose levels > 400 mg/dL which are subsequently normalized and are otherwise eligible may be reasonable. **(Class IIb, Level of Evidence C)**

XXVI. Seizure at Stroke Onset Syndrome



- The evidence for IV alteplase use in patients with seizures at symptom onset is comprised predominantly of retrospective reviews of prospectively collected stroke patients from registries.
- In total, there are almost 300 patients with seizure at onset that received IV alteplase for stroke-like symptoms described in the English literature. Of these, sICH has been reported in only 2 patients, and one of these patients had a remote history of surgical removal of a brain tumor that may have served as a nidus for development of ICH.
- In summary, evidence mostly derived from prospective stroke registries suggests that a seizure at onset of symptoms should not be considered an absolute contraindication to administering IV alteplase to acute stroke patients.

XXVI. Seizure at Stroke Onset Syndrome - Recommendations



- Intravenous alteplase is reasonable in patients with a seizure at the time of onset of acute stroke if evidence suggests that residual impairments are secondary to stroke and not a postictal phenomenon. (Class IIa, Level of Evidence C)

XXVII. Major Early Infarct Size, Large Areas of Ischemic Stroke, Early Ischemic Changes as Measured by ASPECTS and 1/3rd Rule

- Based on current literature, there remains no established extent or severity of early ischemic changes (EIC) which should exclude patients from IV alteplase within the standard approved time window.
- Neither the $>1/3$ MCA rule method nor an ASPECTS threshold has demonstrated a clear treatment interaction with IV alteplase, nor does either method identify a group of patients with uniformly dismal outcome despite IV alteplase. A further practical limitation of the $>1/3$ MCA rule is that, in practice, it cannot be applied reliably.
- Baseline NCCT scan early ischemic change detection is not critical to IV alteplase decision making in the first 6 hours from acute stroke symptom onset. However, RCTs have either enrolled few patients with very extensive EIC (e.g. ASPECTS 0-2) or purposely excluded them (e.g. the ECASS 3 trial); therefore, safety and efficacy of alteplase in this group with very extensive EIC remains poorly defined.

XXVII. Major Early Infarct Size, Large Areas of Ischemic Stroke, Early Ischemic Changes as Measured by ASPECTS and 1/3rd Rule - Recommendations

- Intravenous alteplase administration is recommended in the setting of early ischemic changes of mild to moderate extent (other than frank hypodensity). **(Class I, Level of Evidence A)**
- There remains insufficient evidence to identify a threshold of hypoattenuation severity or extent that affects treatment response to alteplase. However, administering IV alteplase to patients whose CT brain imaging exhibits extensive regions of clear hypoattenuation is not recommended. These patients have a poor prognosis despite IV alteplase, and severe hypoattenuation defined as obvious hypodensity represents irreversible injury. **(Class III, Level of Evidence A)**

XXVIII. Diabetic Hemorrhagic Retinopathy and/or Other Hemorrhagic Ophthalmological Conditions



- Ocular hemorrhage, in general, and intraocular hemorrhage, in particular, after IV alteplase therapy for approved indications, i.e. acute ischemic stroke and acute MI, is extremely uncommon.
- Best estimates of incidence are 0%, 95% CI (0.0% to 0.05%) for patients with diabetes and 0.003%, 95% CI (0.0% to 0.006%) for patients without diabetes. The upper 95% confidence interval limit of 0.05% for the incidence of intraocular hemorrhage in patients with diabetes is very small and quite negligible compared with the proven disability-preventing benefit of IV alteplase in patients with acute ischemic stroke.
- Diabetic retinopathy should not be considered an absolute contraindication to IV alteplase in patients with an acute ischemic stroke.

XXVIII. Diabetic Hemorrhagic Retinopathy and/or Other Hemorrhagic Ophthalmological Conditions - Recommendations

- Use of intravenous alteplase in patients presenting with acute ischemic stroke who have a history of diabetic hemorrhagic retinopathy or other hemorrhagic ophthalmic conditions is reasonable to recommend, but the potential increased risk of visual loss should be weighed against the anticipated benefits of reduced stroke related neurologic deficits.
(Class IIa, Level of Evidence B)

XXIX. Suspicion of SAH on Pretreatment Evaluation - Recommendations

- Suspicion of SAH usually involves a compelling clinical history, such as a sudden severe or “thunderclap” headache or presence of xanthochromia on lumbar puncture. The presence of frank SAH on pre-alteplase CT imaging would be an absolute contraindication for thrombolysis.
- Potentially for a unique scenario of an acute stroke syndrome presentation which includes thunderclap headache, a change in the order sequence may be advisable; with a negative NCCT head being followed by a CTA or MRA (of head and neck) and MRI brain rather than immediately turning to a lumbar puncture.
- Clinicians administering IV alteplase in environments without available, acute arterial imaging should consider the burden of SAH and degree of stroke deficit in weighing risks and benefits of IV alteplase administration.
- IV alteplase is contraindicated in patients presenting with symptoms and signs most consistent with a SAH. **(Class III, Level of Evidence C)**

XXX. Examining The Individual Exclusions to an Extended Time Window from the ECASS-3 Trial - Recommendations

- Despite the fact that the FDA has not approved alteplase use for the extended window in the US, its application in clinical practice has spread.
- Intravenous alteplase is recommended for carefully selected patients who meet ECASS-III criteria and treated in the 3-4.5 hour window. **(Class I, Level of Evidence B)**
- For patients older than 80 years presenting in the 3-4.5 hour window, IV alteplase treatment is safe and can be as effective as in younger patients. **(Class IIa, Level of Evidence B)**
- For patients taking warfarin and with INR < 1.7 who present in the 3-4.5 hour window, IV alteplase treatment appears safe and may be beneficial. **(Class IIb, Level of Evidence B)**
- The benefit of IV alteplase administration for acute stroke patients with baseline NIHSS score > 25 and presenting in the 3-4.5 hour window is uncertain. **(Class IIb, Level of Evidence C)**
- In acute ischemic stroke patients with prior stroke and diabetes presenting in the 3-4.5 hour window, IV alteplase may be as effective as treatment in the 0-3 hour window and may be a reasonable option. **(Class IIb, Level of Evidence B)**

XXXI. Miscellaneous Topics - Recommendations



- *Wake-up/Unclear Onset Time Stroke*

- IV alteplase is not recommended in ischemic stroke patients who awoke with stroke with time last known to be at baseline state > 3 or 4.5 hours. **(Class III, Level of Evidence B)**
- IV alteplase is not recommended in ischemic stroke patients who have an unclear time and/or unwitnessed symptom onset and in whom the time last known to be at baseline state > 3 or 4.5 hours. **(Class III, Level of Evidence B)**
- Use of imaging criteria to select ischemic stroke patients who awoke with stroke or have unclear time of symptom onset for treatment with IV alteplase is not recommended outside of a clinical trial. **(Class III, Level of Evidence B)**

XXXI. Miscellaneous Topics - Recommendations



- ***Menstruation and Menorrhagia***

- Intravenous alteplase is probably indicated in women who are menstruating who present with acute ischemic stroke and do not have a history of menorrhagia. However, women should be warned that alteplase treatment could increase the degree of menstrual flow. **(Class IIa, Level of Evidence C)**
- As the potential benefits of IV alteplase probably outweigh the risks of serious bleeding in patients with recent or active history of menorrhagia without clinically significant anemia or hypotension, intravenous alteplase administration may be considered. **(Class IIb, Level of Evidence C)**
- When there is a history of recent or active vaginal bleeding causing clinically significant anemia, then emergent consultation with a gynecologist is probably indicated prior to decision regarding IV alteplase. **(Class IIa, Level of Evidence C)**
- In patients who are menstruating or have active vaginal bleeding and are treated with alteplase, the degree of vaginal bleeding should be monitored for 24 hours after alteplase. **(Class I, Level of Evidence C)**

XXXI. Miscellaneous Topics - Recommendations



- ***Intracardiac Mass***

- For patients with major acute ischemic stroke likely to produce severe disability and cardiac myxoma, treatment with IV alteplase may be reasonable. (Class IIb, Level of Evidence C)
- For patients presenting with major acute ischemic stroke likely to produce severe disability and papillary fibroelastoma, treatment with IV alteplase may be reasonable. (Class IIb, Level of Evidence C)

XXXI. Miscellaneous Topics - Recommendations

- ***Aortic Arch Dissection; Cervicocephalic Arterial Dissection, Known or Suspected***
 - IV alteplase in acute ischemic stroke known or suspected to be associated with aortic arch dissection is not recommended and is potentially harmful. (Class III, Level of Evidence C)
 - IV alteplase in acute ischemic stroke known or suspected to be associated with extracranial cervical arterial dissection is reasonably safe within 4.5 hours and is probably recommended. (Class IIa, Level of Evidence C)
 - IV alteplase usefulness and hemorrhagic risk in acute ischemic stroke known or suspected to be associated with intracranial arterial dissection remains unknown, uncertain, and not well established. (Class IIb, Level of Evidence C)

XXXI. Miscellaneous Topics - Recommendations

- ***Dural Puncture within 7 Days***
 - IV alteplase may be considered for patients who present with acute ischemic stroke, even in instances when they may have undergone a lumbar dural puncture in the preceding 7 days. (Class IIb, Level of Evidence C)

- ***Psychogenic / Conversion / Malingering Stroke Mimic***
 - The risk of symptomatic intracranial hemorrhage in the stroke mimic population is quite low; thus, starting IV alteplase is probably recommended in preference over delaying treatment to pursue additional diagnostic studies. (Class IIa, Level of Evidence B)

XXXI. Miscellaneous Topics - Recommendations



- ***Cath Lab Environment / Endovascular Complications / Stroke Syndrome***
 - IV alteplase is reasonable for the treatment of acute ischemic stroke complications of cardiac or cerebral angiographic procedures, dependent upon the usual eligibility criteria. **(Class IIa, Level of Evidence A)**

XXXI. Miscellaneous Topics - Recommendations

- ***Consent for the Incompetent Patient***

- Regulatory precedents set by FDA and the Department of Health and Human Services in the US and by the World Medical Association internationally support the use of IV alteplase in patients lacking capacity when an alternative form of consent cannot be obtained within the treatment window.
- In an emergency, when the patient is not competent and there is no immediately available legally authorized representative to provide proxy consent, it is recommended to proceed with IV alteplase in an otherwise eligible patient with acute ischemic stroke. **(Class I, Level of Evidence C)**
- Visual displays which convey the benefits and the risks of IV alteplase can be useful to assist with shared decision making and aid in establishing informed consent. **(Class IIa, Level of Evidence B)**

XXXI. Miscellaneous Topics - Recommendations



- ***Concurrent Antiplatelet Medication***

- The administration of aspirin (or other antiplatelet agents) as an adjunctive therapy within 24 hours of IV alteplase is not recommended.
(Class III, Level of Evidence C)
- The concurrent administration of other intravenous antiplatelet agents that inhibit the glycoprotein IIb/IIIa receptor is not recommended outside of a clinical trial.
(Class III, Level of Evidence B)
- IV alteplase is recommended for patients taking antiplatelet drug monotherapy prior to stroke, based on evidence that the benefit of alteplase outweighs a possible small increased risk of sICH. **(Class I, Level of Evidence A)**
- IV alteplase is recommended for patients taking antiplatelet drug combination therapy (e.g., aspirin and clopidogrel) prior to stroke, based on evidence that the benefit of alteplase outweighs a probable increased risk of sICH.
(Class I, Level of Evidence B)

XXXI. Miscellaneous Topics - Recommendations

- ***Drug Use (Cocaine)***

- Illicit drug use, particularly cocaine use, is a recognized risk factor for acute ischemic stroke in young patients.
- Proposed mechanisms of cocaine-associated ischemic stroke include vasoconstriction, increased platelet aggregation, accelerated atherosclerosis and vascular cell death resulting in vessel weakening and dissection.
- Treating clinicians should be aware that illicit drug use may be a contributing factor to incident stroke. IV alteplase is reasonable in instances of illicit drug use-associated acute ischemic stroke in patients with no other exclusions.
(Class IIa, Level of Evidence C)
- Ischemic strokes in amphetamine and marijuana users have been reported. No published data are available on the use of alteplase in patients using amphetamines or marijuana.

XXXI. Miscellaneous Topics - Recommendations

- ***Sickle Cell Disease (SCD)***

- Acute management of ischemic stroke resulting from SCD should include optimal hydration, correction of hypoxemia, correction of systemic hypotension and blood exchange to reduce the percentage of hemoglobin S levels. **(Class I, Level of Evidence B)**
- IV alteplase for children and adults presenting with an acute ischemic stroke with known sickle cell disease is not well established. **(Class IIb, Level of Evidence C)**

XXXII. Conclusions/Summary

In our review of the current literature, it is clear that the levels of evidence supporting individual exclusion criteria for IV alteplase vary widely. Some exclusions and myths already have extensive scientific study, such as the clear benefit of alteplase treatment in elderly stroke patients, in those with severe stroke, in those with diabetes and hyperglycemia, and in those with minor early ischemic changes evident on CT. Some exclusions are likely based on common sense and very likely will never have a randomized clinical trial to evaluate safety, such as recent intracranial surgery. Most contraindications or warnings range somewhere in between. However, the differential impact of each exclusion factor varies not only with the evidence base behind it, but also with the frequency of the exclusion within the stroke population, the probability of co-existence of multiple exclusion factors in a single patient, and the variation in practice among treating clinicians.

XXXII. Conclusions/Summary



- **High priority research areas**
 - Alteplase treatment of patients with mild ischemic stroke
 - Multimodal cerebral imaging to identify treatment candidates among previously alteplase-ineligible patients
 - International consensus/harmonization of guidelines regarding alteplase inclusion/exclusion
 - Alteplase treatment of patients with ischemic stroke who may be anticoagulated
 - Alteplase treatment of patients with peri-procedural or peri-operative ischemic stroke
 - Alteplase treatment of patients with acute ischemic stroke who have had recent ischemic stroke
 - Alteplase treatment of patients with pre-existing disabilities and dementia who sustain an acute ischemic stroke

A large, stylized orange flame graphic is positioned on the right side of the image, extending from the top right towards the center. The flame has a thick, rounded base and several curved, upward-pointing tongues of fire. The entire image has a solid orange background.

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