

## Updated Recommendations for Using Alteplase (TPA) in Acute Ischemic Stroke

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## Disclosures

Dr. Alberts is a speaker and consultant for Genentech

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## Outline

- \* Discuss new FDA labeling rules
- \* Review new alteplase recommendations and guidelines
- \* Practical implications
- \* Questions/Answers

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## Eligibility for IV TPA

- \* In general, only 6% to 8% of patients with acute ischemic stroke are eligible to receive IV TPA within 3 hours of stroke onset
- \* Major reason is that only 22% to 31% of patients present within 3 hours of stroke onset
- \* Many other medical exclusion criteria
- \* Infrastructure limitations
- \* There are very few other medical treatment options

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## What is in the name?

- \* IV TPA is no longer preferred term
- \* Sounds too much like 'TNK'
- \* Chance for confusion
- \* Preferred term is Alteplase of Activase
- \* Change orders and protocols
- \* Educate care providers, pharmacy personnel, etc.

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## New Alteplase Guidelines

**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 affirms the value of this statement as an educational tool for neurologists.*

*Endorsed by the American Association of Neurological Surgeons and Congress of Neurological Surgeons*

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 Eric E. Smith, MD, MPH, FAHA; on behalf of the American Heart Association  
 Stroke Council and Council on Epidemiology and Prevention

Stroke, Feb, 2016

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## Alteplase Inclusion Criteria

Table 4. Inclusion and Exclusion Characteristics of Patients With Ischemic Stroke 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 treatment begins
Age ≥18 y

Most clinicians expand the time window to 4.5 hours

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## Guideline Alteplase Exclusion Criteria

Exclusion criteria
Significant head trauma or prior stroke in the previous 3 mo
Symptoms suggest SAH
Arterial puncture at noncompressible site in previous 7 d
History of previous intracranial hemorrhage
Intracranial neoplasm, AVM, or aneurysm
Recent intracranial or intraspinal surgery
Elevated blood pressure (systolic >185 mmHg or diastolic >110 mmHg)
Active internal bleeding
Acute bleeding diathesis, including but not limited to
Platelet count <100,000/mm <sup>3</sup> <75,000
Heparin received within 48 h resulting in abnormally elevated aPTT above the upper limit of normal
Current use of anticoagulant with INR >1.7 or PT >15 s
Current use of direct thrombin inhibitors or direct factor Xa inhibitors with elevated sensitive laboratory tests (eg, aPTT, INR, platelet count, 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)

Demaerschalk et al., Stroke, Feb 2016

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## Other Protocol Changes

- \* Serious head trauma within past 3 months
  - \* Stroke within past 6 weeks is excluded
- \* Cerebral hemorrhage within past 3 months
- \* AVM without bleeding in past 4 weeks OK
- \* Aneurysm < 10 mm without bleeding OK
- \* CT with ischemic changes OK (I would question timing)

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## Alteplase Use in 3.0 – 4.5 Hr Time Window

2. Intravenous alteplase treatment in the 3- to 4.5-hour time window is also recommended for those patients <80 years of age without a history of both diabetes mellitus and prior stroke, NIHSS score <25, not taking any OACs, and without imaging evidence of ischemic injury involving more than one third of the MCA territory (Class I; Level of Evidence B).

Many medical center largely ignore these special limitations for 3-4.5 hour time frame

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## TPA Exclusion for Anticoagulant Use

### Anticoagulant Use: Recommendations

1. Intravenous alteplase may be reasonable in patients who have a history of warfarin use and an INR  $\leq 1.7$  (Class IIb; Level of Evidence B).
2. 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).
3. 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).
4. 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, thrombin time, 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).

Some say this is OK if just prophylactic dose

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## Special Considerations Should these be in Informed Consent?

- \* Consider risks vs benefits in each case
  - \* Minor Sx or rapidly improving
  - \* Ischemic stroke between 6 weeks and 3 months
  - \* Major surgery or trauma within 14 days
  - \* GI or GU hemorrhage within 21 days
  - \* MI within 3 months
  - \* Arterial puncture at non-compressible site in prior 7 days
  - \* Neurologic deficit after correction of hypoglycemia
  - \* Meningioma
  - \* Unruptured or untreated intracranial vascular malformation

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## Updated Treatment Recommendations

Clinical Feature	Recommendation	Level of Evidence	Comment
Age > 80	Use	I A	Benefits > Risks
Age < 18	Unclear	II b B	Limited data
Severe Stroke	Use	I A	Evidence of benefit
Mild but disabling	Use	I A	Evidence of benefit
Mild, non-disabling	Use	I A	Evidence of benefit
Improving but impairment	Use	II a A	Beneficial

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## Updated Recommendations

Clinical Feature	Recommendation	Level of Evidence	Comment
Pregnancy, Post-partum	Use	II b B	Likely safe in most cases
Renal, Liver disease	Use	II b B	Likely safe in most cases
Major surgery w/i 14 days	Consider	II b C	Case by case decision
Major trauma w/i 14 days	Consider	II b C	Case by case decision
Severe head trauma w/i 3 months	Contraindicated	III C	Bleeding concerns

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## Use of IV TPA with Coagulopathy

- \* IV TPA NOT recommended in the following conditions:
  - \* Platelet count < 100,000 *we changed this to < 75,000*
  - \* INR > 1.7 or PT > 15 sec
  - \* PTT > 40 seconds
- \* Class III, Level C recommendation

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## Use of IV Alteplase in patients taking NOACs

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, thrombin time, 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).

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## Updated Recommendations: Use with Various CNS Lesions

Lesion Type	Recommendation	Level of Evidence	Comment
Aneurysm < 10 mm	Reasonable to use	Ila C	Unruptured and unsecured
Vascular malformation	Reasonable to use	IIb C	Consider stroke severity
Extra-axial neoplasm	Recommended	Ila C	Likely low risk
Intra-axial neoplasm	Avoid	III C	Potentially harmful
Systemic malignancy	Consider	IIb C	Consider life expectancy, coagulopathy

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## Practical Implications

1. Provides us more flexibility in terms of using alteplase in specific patients
2. This means we have more responsibility for patient selection
3. Make sure you use an informed consent that outlines risks, benefits, and alternative therapies

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## Real Issues/New Issues

- \* Despite the success of EVT, IV Alteplase is still the easiest and most widely available treatment to use for acute ischemic stroke in many areas
- \* Time is still = to brain; administer Alteplase ASAP in all cases
- \* Some/many patients who intend to get EVT never end up being Rx for a variety of reasons
- \* EVT should NOT be viewed as a alternative to Alteplase
- \* Thus IV Alteplase remains the most feasible therapy in many cases

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## Conclusions

- \* New guidelines for the use of IV-Alteplase provide more flexibility in terms of inclusion and exclusion criteria
- \* Use of clinical judgment mirrors what we should do in clinical practice
- \* Remember to get informed consent that provides treatment options
- \* Consider endovascular therapy as an alternative if available at your institution or a nearby hospital

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