Recent Changes in IV TPA Recommendations

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Vascular Neurology
Disclosures

- none
Statistics

- 4th leading cause of death
- Nearly 800,000 cases of stroke annually
- Leading cause of disability in the US
- On Average someone has stroke every 40 seconds
- Every 4 minutes somebody dies from stroke
Pathophysiology

NL CBF 50-55 cc/100ml/min
Classifications of Recommendations and Level of Evidence

<table>
<thead>
<tr>
<th>Classification</th>
<th>Description</th>
<th>Evidence Support</th>
<th>Suggested Phrases</th>
<th>Comparative Effectiveness Phrases</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LEVEL A</strong></td>
<td>Multiple populations evaluated*</td>
<td>Data derived from multiple randomized clinical trials or meta-analyses</td>
<td>Recommendation that procedure or treatment is useful/effective</td>
<td>treatment strategy A is recommended over treatment B</td>
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<td></td>
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<td></td>
<td>Sufficient evidence from multiple randomized trials or meta-analyses</td>
<td>treatment strategy A is probably recommended over treatment B</td>
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<td></td>
<td>Recommendation in favor of treatment or procedure being useful/effective</td>
<td>it is reasonable to choose treatment A over treatment B</td>
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<td>Some conflicting evidence from multiple randomized trials or meta-analyses</td>
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<tr>
<td><strong>LEVEL B</strong></td>
<td>Limited populations evaluated*</td>
<td>Data derived from a single randomized trial or nonrandomized studies</td>
<td>Recommendation that procedure or treatment is useful/effective</td>
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<td>Some conflicting evidence from single randomized trial or nonrandomized studies</td>
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<tr>
<td><strong>LEVEL C</strong></td>
<td>Very limited populations evaluated*</td>
<td>Only consensus opinion of experts, case studies, or standard of care</td>
<td>Recommendation that procedure or treatment is useful/effective</td>
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<td>Only expert opinion, case studies, or standard of care</td>
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<td>Only diverging expert opinion, case studies, or standard of care</td>
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</tbody>
</table>

**Suggested phrases for writing recommendations**

- should
- is recommended
- is indicated
- may/might be considered
- is reasonable
- can be useful/effective/beneficial
- is probably recommended or indicated

**Comparative effectiveness phrases**

- treatment strategy A is recommended over treatment B
- treatment strategy A is probably recommended over treatment B
- it is reasonable to choose treatment A over treatment B

*Note: *This table outlines the classification of recommendations and the level of evidence based on the size of treatment effect. The categories include Level A, Level B, and Level C, each with specific criteria for evidence support and suggested phrases for writing recommendations.
Age Issues

- Medically eligible patients > 18 years old age, IV TPA administration within 3 hours is equally recommended for patients < 80 and those >80 years
- Older age is associated with an adverse prognosis. Older patients have poor outcomes, higher mortality, higher rates of sICH than those less than 80 years of age, compared with control subjects,
- Intravenous alteplase provides a better chance of being independent at 3 months across all age groups
- Class I; Level of Evidence A
Age continued

- Pediatric
- The efficacy and risk of intravenous alteplase administration in the pediatric population is not well established
Stroke Severity and NIHSS

- Previous version of FDA labeled did not recommend alteplase for the treatment of stroke patients with minor deficits
- Also caution should be used with NIHSS >22
- Updated FDA label February 2015 has removed both of these warnings
Stroke Severity
Recommendations

• **For severe stroke symptoms**, intravenous alteplase as 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** intravenous alteplase as indicated within 3 hours from symptom onset. *There should be no exclusion for patient with mild but nonetheless disabling stroke symptoms in the opinion of the treating physician* (Class I; Level Evidence A)
Stroke Severity

- Within 3 hours from symptom onset, treatment of patients with milder ischemic stroke symptoms that are judged nondisabling may be considered. (Class IIB; Level Evidence C)
Rapidly Improving Stroke Patient

- Rapid improvement is one of the most common reasons for exclusion for intravenous alteplase

- The original FDA PI did not recommend alteplase treatment for patients with rapidly improving symptoms.

- The updated FDA label has removed this warning.

- Original rationale in the 2 NINDS trials was to exclude rapidly improving stroke symptoms so that patients with TIA did not receive unnecessary treatment
Intravenous alteplase treatment is reasonable for patients who present with a moderate to severe ischemic stroke and demonstrate *early improvement but remain moderately impaired and potentially disabled* in the judgment of the examiner (Class 2A; Level of Evidence A)

Delaying treatment for intravenous alteplase to monitor for further improvement is not recommended (Class III; Level Evidence C)
Table 12. Task Force Consensus: Definition and Clinical Context of Rapidly Improving Stroke Symptoms as an Exclusion Criterion for Intravenous Alteplase137

Improve to a mild stroke such that any remaining deficits seem non-disabling.

**The following typically should be considered disabling deficits:**

- Complete hemianopsia (≥2 on NIHSS question 3) or severe aphasia (≥2 on NIHSS)
- Visual or sensory extinction (≥1 on NIHSS question 11) or
- Any weakness limiting sustained effort against gravity (≥2 on NIHSS question 6 or 7)

or

- Any deficits that lead to a total NIHSS score >5 or
- Any remaining deficit considered potentially disabling in the view of the patient and the treating practitioner. Clinical judgment is required.

NIHSS indicates National Institutes of Health Stroke Scale.

Modified from Levine et al.137 Copyright © 2013, American Heart Association, Inc.
Time out from the onset of symptoms

- Time from symptom onset is the most important exclusion criteria for intravenous alteplase.

- It is the most frequent reason why patients are ineligible for treatment.

- The scientific rationale for choosing such a restrictive time window was from the original NINDS trials came from models of ischemic stroke in rodents and primates.

- Within an awake primate model they found that after 2-3 hours of occlusion of the MCA lead to permanent, larger infarcts compared with ischemia for 15-30 minutes.
• Time from last seen normal to treatment with IV alteplase should be less than 3 hours for eligible patient’s with the use of standard eligibility criteria (Class I; Level of Evidence A)

• Intravenous alteplase treatment in the 3-4.5 hour time window is also recommended for those patients less than 80 years of age without a history of diabetes and prior stroke, and NIHSS <25, not taking any OAC’s and without imaging evidence of ischemic injury involving more than one third of the MCA territory (class I; level evidence B)
- Treatment should be initiated as quickly as possible within the listed timeframes because time to treatment is strongly associated with outcome (class I; level evidence A)

- In patients in the 0-4.5 hour time window who meet criteria for treatment with IV TPA substantially delaying intravenous alteplase to obtain penumbra imaging before treatment is not recommended (Class III; level evidence C)
Pregnancy and Postpartum

- Alteplase is listed as pregnancy category C, indicating possible embryocidal risk based on animal experiments at high doses.

- Animal studies of alteplase at 1 mg/kg did not show fetal toxicity or teratogenic effects.

- The most relevant risk for alteplase in pregnancy is related to the risk of bleeding.
Pregnancy

- There are 12 reported cases of pregnant women with arterial strokes who were treated with intravenous alteplase or endovascular therapy.

- Of these 12 patients: 8 were in the first trimester, 2 were in the second trimester, and 2 were in the third trimester.

- 6 were treated with intravenous alteplase and 6 were treated with intra-arterial alteplase

- No clot retriever was done on any of these patients
Pregnancy

- 2 sICH and 1 fatal ICH resulting from arterial dissection during angioplasty. And 1 mild sICH after interarterial alteplase resolved with good neurologic outcome.

- 2 patients Systemic bleeding complications of the 6 patients treated with IV alteplase. 1 case of uterine hematoma that required surgical drainage and was associated with medical termination of pregnancy. 1 case of buttock hematoma that was managed conservatively, resulting in the delivery of a healthy infant.
Overall outcomes among the 12 fetuses

- 2 fetal demise
- 2 medical termination of pregnancy
- 8 healthy infants

• Intravenous alteplase administration for ischemic stroke may be considered in pregnancy when the anticipated benefit of treating moderate to severe stroke outweighed the anticipated increased risks of uterine bleeding (Class IIb; Level of Evidence C)

• The safety and efficacy of alteplase in early postpartum. Has not been well established (Class IIb level of evidence C)

• Urgent consultation with OB/GYN and potentially perinatology to assist with further recommendations (Class I level of evidence C)
Platelet and Coagulation Studies

• The safety and efficacy of intravenous alteplase for acute stroke in patients with platelet count less than 100,000, INR greater than 1.7, PTT greater than 40 or PT greater than 15 seconds are unknown and intravenous alteplase is not recommended (Class III; level evidence C)

• Intravenous alteplase treatment should 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)
Hx of Anticoagulation Use

- Federal agency found up 4.2 million Americans aged 18-80 used some type of blood thinner in 2007.
  
  US Department of Health and Human Services.

- It is projected that the number of people in the United States to have Atrial fibrillation will be 5.6-10 million by the year 2050.
• Intravenous alteplase may be reasonable patients who have a history of warfarin use an INR less than or equal to 1.7, PT < 15 seconds. (Class IIb; Level of Evidence B)

• Intravenous alteplase in patients who have a history of warfarin use an INR >1.7 or a PT > 15 seconds it is not recommended (class III; level evidence B)

• Intravenous alteplase in patients who received a treatment dose of LMWH within the previous 24 hours is not recommended (class III; level evidence B)
Anticoagulant Recommendations

- 1 study of 5 Spanish hospitals included 98 patient’s taking anticoagulation received intravenous alteplase.

- Of these 21 were receiving LMWH, 18 of whom had received a dose with in the past 24 hours

- 5 were taking therapeutic doses, 16 were taking prophylactic doses, and all had normal coagulation values.

- 8 had ICH 3 of which were symptomatic
• 7 had favorable outcomes and 6 died

• Patients taking low molecular weight heparin had a higher odds of symptomatic ICH and a 60% lower probability of independence at 3 months compared to those with no anticoagulation

• There are other studies with very small numbers of patients on LMWH receiving thrombolysis in which there was no instances of ICH

Anticoagulant Recommendations

- NOAC

Use of IV TPA and patient is taking direct thrombin inhibitors or direct factor X A inhibitors have not been firmly established but may be harmful. (Class III; Level of Evidence C)
Use of intravenous alteplase in carefully selected patients presenting with acute stroke who underwent 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 benefit of reduced stroke related neurologic deficit.

- Rationale behind this contraindication centers around the potential for surgical site or systemic hemorrhage.

- Guillian et al included 13 patients surgery or trauma in the preceding 3 months

- 2 patients suffered systemic hemorrhage requiring transfusion
• 1 patient had perianal surgery the other pacemaker implantation.

• A third patient with a history of a hip fracture secondary to trauma suffered hemorrhage

• None of these patients suffer neurologic worsening or long-term consequences from her hemorrhage
Major trauma within 14 days and severe head trauma within 3 months

- In acute ischemic stroke patients with recent major trauma 14 days, intravenous alteplase may be carefully considered with the risks of bleeding from injuries related to trauma weighed against the severity and potential disability from ischemic stroke class IIB level evident C

- Acute ischemic stroke patients with recent severe head trauma within 3 months, intravenous alteplase is contraindicated (class III; level evidence C)

- Given the possibly bleeding complications from underlying severe head trauma intravenous alteplase is not recommended in posttraumatic infarction (class III; level evidence C)
The major concerns about giving intravenous alteplase to patients with recent completed MIs is that they may be harboring ventricular thrombi that can be caused to embolize by lytics, post MI pericarditis that may be transformed to pericardial hemorrhage by lytics and cardiac rupture caused by lysis of fibrin clots with necrotic myocardial

Left ventricular thrombi develop typically after anterior wall STEMI within a few days after acute MI
Acute MI or Hx of recent MI

- Percutaneous transluminal coronary angioplasty and stenting of reduce the incidence to approximately 2-8% of left ventricular thrombi after stenting

- Pericarditis after MI appears to have declined after coronary angioplasty and stenting as well with a currency of 7-25%
For patients presenting with concurrent acute ischemic stroke and acute MI treatment with IV TPA at dose appropriate for cerebral ischemia followed by percutaneous coronary angioplasty and stenting if indicated (Class IIa; Level of Evidence C)

For patients presenting with acute ischemic stroke recent history of MI in the past 3 months, treating ischemic stroke with intravenous alteplase is reasonable if the recent MRI was non-STEMI (Class IIa; level of evidence C)

If the recent MI was STEMI involving the right inferior myocardium it may be reasonable it may be reasonable to treat
MI and recent Hx of MI

- It may be reasonable if the recent MI was a STEMI involving the anterior myocardium class IIb level evidence C
Pericarditis was an exclusion criteria in the 2 NIND S trials and is listed as a warning in the current FDA Label

Pericarditis is inflammation of the fibro-elastic pericardial sac. Pericarditis occurs in approximately 5% of patients admitted to the emergency department for nonacute MI chest pain

In western countries most cases of pericarditis occur in immunocompetent patients and are attributed to viral infections or are idiopathic. They can occur also in metabolic disorders, renal failure, autoimmune disorders, neoplastic origin and cardiovascular disorders such as MI or aortic dissection
Pericarditis Recommendations

- For patients with major acute ischemic stroke likely to produce severe disability and acute pericarditis treatment with intravenous alteplase may be reasonable (Class IIB; Level of Evidence C). Urgent consultation cardiologist is recommended in this situation.

- For patients with moderate acute ischemic stroke likely to produce mild disability in acute pericarditis treatment with intravenous alteplase is of uncertain benefit.
Left-sided Heart Thrombus

- Fibrinolysis treatment can cause fragmentation, mobilization, and embolization of pre-existing thrombi in the myocardium.

- Limited data is available in a series of 5 patients with cardiac thrombi treated with systemic alteplase for acute stroke, no early cerebral or systemic embolization occurred.

• For patients with major acute ischemic stroke likely to produce severe disability and known left atrial or ventricular thrombus, treatment with intravenous alteplase may be reasonable (class IIB level of evidence C)

• For patients presenting with moderate acute ischemic likely to produce mild disability and known left atrial and ventricular thrombus treatment with intravenous alteplase is of uncertain benefit (class IIB; level evidence C)
• Patients with acute ischemic stroke and symptoms consistent with infective carditis, treatment with intravenous alteplase is not recommended because increased risk of intracranial hemorrhage (class III; level of evidence C)
Hx of Intracranial/Spinal Surgery within 3 months

- Recent intracranial and intraspinal surgery is listed in the FDA label as a contraindication and in the AHA/ASA guidelines as an exclusion criteria.

- There is no meaningful level of evidence that exists in the literature support the contraindication of intravenous alteplase administration because of three-month cranial or spinal surgery history.

- The scale of the operation, relationship to critical neurologic structures, and availability of neurosurgical backup for potential bleeding complications should be considered in potential intravenous alteplase administration.
Hx of Intracranial/Spinal Surgery within 3 months

Recommendations

• For patients with acute ischemic stroke with a history of intracranial/spinal surgery within 3 months intravenous alteplase is potentially harmful (class III; level evidence C)
Hx of Ischemic Stroke within 3 months

- Previously ischemic stroke within 3 months was listed as a contraindication and exclusion in the original FDA label.

- This has now been removed from the FDA labeled.

- The recommendation to exclude these patients appears to be drawn from trials of thrombolysis patients with acute MI.
Hx of Ischemic Stroke within 3 months

- Karlinski et al analyzed data from Polish centers contributed to SITS and evaluated the safety and effectiveness and intravenous alteplase in patients who were treated off label. Off label thrombolysis was administered in 224 of 946 patient’s (23.7%). Previous stroke criteria was violated in 14 of 942 (1.5%).

Both groups on and off label had similar proportions of sICH

Karlinski M, Kobayashi A, Litwin T, Boblewski P, Frye W. Poland collaborative group. Intravenous trauma lysis for acute ischemic stroke in patients not fully adhering to European license and Poland. Neurol Neurochior Pol 2012, 46; 3-14
Hx of Ischemic Stroke within 3 months

Recommendations

- Use of intravenous alteplase in patient’s presenting with acute stroke who had a prior ischemic stroke within 3 months may be harmful (Class III; level evidence B)

- The potential for increased risk of sICH and associated morbidity and mortality exist but is not well established (Class Iib; level of evidence B)

- The potential risks should be discussed and weighed against anticipated benefit during decision making (class I; level evidence C)
Active Internal Bleeding or Hx of GI/GU Bleeding within 21 days

- Reported literature details a low risk of bleeding with intravenous alteplase administration in the setting of past GI/GU bleeding. Administration of intravenous alteplase in this patient population may be reasonable (class IIb; level evidence C).

- Patients with a structural GI malignancy or recent bleeding events within 21 days their stroke event should be considered high risk, and intravenous alteplase and administration is potentially harmful (class III level evidence C).
Arterial Puncture of Noncompressible Vessels in the preceding 7 days

- On the basis of expert consensus, arterial puncture of a noncompressible vessel within the week preceding an acute stroke is a contraindication to administering intravenous alteplase to patient’s with acute stroke.

- Most likely scenario after catheterization of the subclavian or internal jugular vein there could be inadvertent adjacent arterial puncture which occurs up to 8% of cases
Arterial Puncture of Noncompressible Vessels in the preceding 7 days

Recommendation

- The safety and efficacy of administering intravenous alteplase to acute stroke patients who have had an arterial puncture of a noncompressible blood vessel in the past 7 days are uncertain (class IIb; level evidence B)
Uncontrolled Hypertension

- High blood pressure at presentation has been associated with elevated risk of sICH with intravenous alteplase
- The higher the blood pressure the greater the risk
- Australian streptokinase trial, the only thrombolytic trial that did not exclude subject with systolic blood pressure greater than 185
- A correlation was seen between high blood pressure and very high risk of hemorrhage in the ASK trial
Uncontrolled Hypertension Recommendations

- Intravenous alteplase is recommended in patients whose blood pressure can be safely lowered to <185/110 with antihypertensive agents. The physician must be assessing the stability of blood pressure before starting intravenous alteplase (class I level evidence b).

- If medications are given to lower blood pressure, the clinician should be sure the blood pressure is stabilized at the lower level before beginning treatment with intravenous alteplase and maintained below 180/105 for at least the first 24 hours after intravenous alteplase treatment.
Hx of Intracranial Hemorrhage

- The original FDA labeled 2013 AHA/ASA guidelines excluded patients who had a previous ICH.

- Recent update label only lists recent ICH as a warning and removed a history of ICH as a contraindication.

- The lack of any data on this issue is the possible reason the revised FDA label came about.

- The Bleeding Risk Analysis in Stroke Imaging Before Thrombolysis (BRASIL) study used MRI within 6 hours of stroke onset examine the presence and number of CMBs.
242 CMBs were detected in 510 stroke patients

Here was no statistical difference in sICH rate with alteplase administration between the CMB and non-CMB groups

Hx of Intracerebral Hemorrhage Recommendations

- Intravenous alteplase has not been shown to increase sICH rates patient’s with CMBs. Intravenous alteplase administration in these patients is therefore reasonable (class Iia; level evidence B)

- Intravenous alteplase administration in patients who have a history of intracranial hemorrhage is potentially harmful (class III; level evidence C)
Unruptured Intracranial Aneurysm

- 2013AHA/ASA guidelines with an intracranial aneurysm as a contraindication exclusion for intravenous alteplase for stroke

- It is listed as a warning in the FDA label

- The largest case series included 22 unruptured aneurysms of those 73% were in the anterior circulation and 27% greater than 5 mm


- The rates of ICH were similar for patients with and without aneurysm
Unruptured Intracranial Aneurysm Recommendation

- For patients presenting with acute ischemic stroke who are known to harbor a small or moderate-sized (<10 mm) unruptured and unsecured intra-cranial aneurysm... Administration of intravenous alteplase is reasonable and probably recommended (class IIa level evidence C)

- Usefulness and risk of intravenous alteplase in patients with acute ischemic stroke who harbor a giant unruptured unsecured intracranial aneurysms are not well established (class IIb low evidence C)
• Intravenous alteplase treatment is probably recommended for patients with acute ischemic stroke who harbor an extra-axial intracranial neoplasm (class IIa level evidence C).

• Intravenous alteplase treatment for patients with acute ischemic stroke who harbor an intra-axial neoplasm is potentially harmful (class III level evidence C).
Blood Glucose

- Levels between 50 and 400 mg/dL had previously been recommended for alteplase eligibility.

- Most recent AHA/ASA guidelines mention excluding only patients with glucose less than 50 mg/dL.

- Focal neurologic deficits resulting from hypoglycemia are rare but occur and may be attributable to ischemic vulnerability to low levels of circulating glucose required for aerobic metabolism.
Blood Glucose

- Hyperglycemia may accelerate tissue infarct after ischemia and decrease the chances of unsuccessful recannulization.

- Persistent hyperglycemia may be more important for predicting adverse outcomes.
Blood Glucose Recommendations

- Intravenous alteplase is recommended in otherwise eligible patient’s with initial glucose level greater than 50 mg/dL (class I level of evidence A)

- Treating clinician should be aware that hypoglycemia and hyperglycemia may mimic acute stroke presentations and check blood glucose levels before intravenous initiation. (Class III level of evidence B)

- Treatment with intravenous alteplase in patients with acute ischemic stroke who present with initial glucose > 400 mg/dl and are subsequently normalized. It may be reasonable to treat. (class IIb level evidence C)
Diabetic Hemorrhage Retinopathy or other Ophthalmologic Conditions Recommendations

- Use of intravenous alteplase and patient’s presenting with acute ischemic stroke of a history of diabetic hemorrhagic retinopathy or other hemorrhagic ophthalmic conditions is reasonable to recommend.

- Potential increased risk of vision loss should be weighed against the anticipated benefits of reduced stroke related neurologic deficit (class IIa level evidence b)
The risk of symptomatic intracranial hemorrhage in the psychogenic population is very low. Starting intravenous alteplase is probably recommended in preference over delaying treatment to pursue additional diagnostic studies (class II a level evidence b).
Seizures at the onset recommendation

- Intravenous alteplase is reasonable in patients with a seizure at the onset of acute stroke if evidence suggests that residual impairments are secondary to stroke not a postical phenomenon (class IIa; Level of Evidence C)
<table>
<thead>
<tr>
<th>Study</th>
<th>Study Design</th>
<th>Seizure/Total SMs, n</th>
<th>Average Initial</th>
<th>Any ICH, n</th>
<th>sICH, n</th>
<th>mRS Score of 0–1, %</th>
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</thead>
<tbody>
<tr>
<td>Winkler et al.</td>
<td>Retrospective of prospective registry</td>
<td>6/7</td>
<td>10*</td>
<td>0</td>
<td>0</td>
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<td>Chernyshev et al.</td>
<td>Retrospective of prospective registry</td>
<td>26/69</td>
<td>7</td>
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<td>0</td>
<td>87</td>
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<td>Zinkstok et al.</td>
<td>Multicenter, observational cohort</td>
<td>81/100</td>
<td>6</td>
<td>NA</td>
<td>2</td>
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<td>Tsvigoulis et al.</td>
<td>Retrospective of prospective registry</td>
<td>11/56</td>
<td>6</td>
<td>NA</td>
<td>0</td>
<td>96</td>
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<tr>
<td>Förster et al.</td>
<td>Retrospective of prospective registry</td>
<td>20/42</td>
<td>6.5</td>
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<td>Chang et al.</td>
<td>Retrospective</td>
<td>6/14</td>
<td>6*</td>
<td>0</td>
<td>0</td>
<td>NA†</td>
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</tbody>
</table>

ICH indicates intracerebral hemorrhage; mRS, modified Rankin Scale; NA, not applicable; NIHSS, National Institutes of Health Stroke Scale; rtPA, recombinant tissue-type plasminogen activator; sICH, symptomatic intracerebral hemorrhage; and SM, stroke mimic.

*Average indicates the median except where indicated by an asterisk (mean).
†In that trial, 97% had an mRS score of 0 to 2.
Consent for the Incompetent Patient Recommendations

- In emergency, when the patient is not competent and there is no immediate legal authority represented to provide proxy consent it is recommended to proceed with intravenous alteplase and otherwise eligible patients with acute ischemic stroke class I level evidence c
### Appendix: Comparison of AHA/ASA Acute Stroke Management Guidelines and Previous and New FDA Prescribing Information for Alteplase (Activase) Treatment in Acute Ischemic Stroke

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<tbody>
<tr>
<td>Prior stroke</td>
<td>Exclusion: prior stroke within 3 mo</td>
<td>Contraindication: recent prior stroke &lt; 3 mo</td>
<td>Removed entirely</td>
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<tr>
<td>Seizure at onset</td>
<td>Relative exclusion: seizure at onset with persistent neurological impairments</td>
<td>Contraindication: seizure at onset of stroke</td>
<td>Removed entirely</td>
</tr>
<tr>
<td>Bleeding</td>
<td>Exclusion: Platelet count &lt; 100,000/mm³</td>
<td>Contraindication: known bleeding diathesis including but not limited to:</td>
<td>Bleeding diathesis remains a contraindication, but all laboratory values and specific examples removed</td>
</tr>
<tr>
<td></td>
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<td>Current use of OACs (e.g., warfarin sodium), an INR &gt; 1.7, or a PT &gt; 15 s</td>
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<td>Heparin received within 48 h, resulting in abnormally elevated aPTT</td>
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<tr>
<td></td>
<td></td>
<td>Current use of anticoagulant with INR &gt; 1.7 or PT &gt; 15 s</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Current use of direct thrombin inhibitors or direct factor Xa inhibitors with elevated sensitive laboratory tests</td>
<td></td>
</tr>
<tr>
<td>ICH</td>
<td>Exclusion: history of previous ICH</td>
<td>Contraindication: history of ICH</td>
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</tr>
<tr>
<td>BP</td>
<td>Exclusion: Elevated BP (systolic &gt; 185 mmHg or diastolic &gt; 110 mmHg)</td>
<td>Contraindication: uncontrolled hypertension at the time of treatment (e.g., &gt; 185 mmHg systolic or &gt; 110 mmHg diastolic)</td>
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<tr>
<td>Blood glucose</td>
<td>Exclusion: blood glucose &gt; 50 mg/dL</td>
<td>Warning: because of the increased risk for misdiagnosis of acute ischemic stroke, special diligence is required in making this diagnosis in patients whose blood glucose values are &gt; 50 or &lt; 40 mg/dL</td>
<td>Removed entirely</td>
</tr>
<tr>
<td>Diabetic stroke</td>
<td>Not listed</td>
<td>Warning: patients with severe neurological deficit (NIHSS score &gt; 22) at presentation, there is an increased risk of ICH in these patients</td>
<td>Removed entirely</td>
</tr>
<tr>
<td>Mild stroke</td>
<td>Relative exclusion: only minor or rapidly improving stroke symptoms (clearing spontaneously)</td>
<td>Warning: safety and efficacy in patients with minor neurological deficit or with rapidly improving symptoms have not been evaluated; therefore, treatment of patients with minor neurological deficit or with rapidly improving symptoms is not recommended</td>
<td>Removed entirely</td>
</tr>
<tr>
<td>Neuroimaging findings</td>
<td>Exclusion: CT demonstrates multiblud infarction (hypodensity &gt; 1/3 cerebral hemisphere)</td>
<td>Warning: Major early infarct signs (substantial edema, mass effect, or midline shift on CT)</td>
<td>Removed entirely</td>
</tr>
<tr>
<td>SAH</td>
<td>Exclusion: symptoms suggest SAH</td>
<td>Contraindication: Suspicion of SAH on pretreatment evaluation</td>
<td>Contraindication: subarachnoid hemorrhage</td>
</tr>
<tr>
<td>Use in specific populations</td>
<td>Pregnancy</td>
<td>Warning: pregnancy Category C</td>
<td>No change</td>
</tr>
<tr>
<td></td>
<td>Nursing mothers</td>
<td>Not mentioned</td>
<td>Unknown risk</td>
</tr>
<tr>
<td></td>
<td>Children</td>
<td>Exclusion: &gt; 18 y of age</td>
<td>Indicated for adults</td>
</tr>
<tr>
<td></td>
<td>Elderly</td>
<td>Not listed</td>
<td>Warning: for all indications: advanced age (e.g., &gt; 75 y) may increase risks</td>
</tr>
<tr>
<td>Gastrointestinal or genitourinary bleeding</td>
<td>Warning: gastrointestinal or genitourinary bleeding within the past 21 d</td>
<td>Warning: gastrointestinal or genitourinary bleeding within the past 21 d</td>
<td>Warning: gastrointestinal or genitourinary bleeding</td>
</tr>
</tbody>
</table>

AHASS indicates American Heart Association/American Stroke Association; aPTT, activated partial thromboplastin time; BP, blood pressure; CT, computed tomography; FDA, US Food and Drug Administration; ICH, intracerebral hemorrhage; NIHSS, National Institute of Health Stroke Scale; OAC, oral anticoagulant; PI, prescribing information; PT, prothrombin time; and SAH, subarachnoid hemorrhage.
• Questions??