Acute Ischemic Stroke Controversies

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Using the term "controversy" loosely, there remain a number of uncertainties in the care of patients with acute ischemic stroke. In particular, there exist ambiguities surrounding patient selection for acute interventions including intravenous tPA and intra-arterial thrombectomy. While multiple randomized trials and meta-analyses have demonstrated that intravenous recombinant tissue plasminogen activator (tPA) is associated with improved neurologic outcomes for select patients with acute ischemic stroke, it remains challenging to translate the inclusion/exclusion criteria used in trials to individual patients being cared for in the Emergency Department.[1-3] In the past, the FDA labeling and clinical practice guidelines have restricted tPA use, or provided warnings, for outlier patients who may have been excluded from early tPA studies. However, over the past decade the FDA has been broadly attempting to simplify labels and reduce limiting physician autonomy by removing contraindications if they are not directly backed up by evidence of inefficacy or harm. As a result, the FDA updated the prescribing information for IV tPA in 2015 allowing for a great deal more clinician judgment in who should be treated (see Table 1).

Table 1. Specific changes to the FDA labeling for recombinant tissue plasminogen activator (Alteplase, Activase, Genentech, inc).

Contraindications removed: • Seizure at onset • Prior stroke in patients with acute ischemic stroke • Specific lab tests under bleeding diathesis • Specific blood pressure cutoffs • History of ICH was moved to "warnings and precautions"
Warnings and precautions removed: • Minor neurological deficit or rapidly improved symptoms • Blood glucose levels • Severe stroke • Major early infarct signs

In addition to the FDA label change, there has been an accumulation of randomized and observational evidence suggesting that some patients excluded from, or not well represented in, early tPA trials may also be safely and appropriately treated. Prior guidelines or hospital policies have provided warnings or exclusions for patients with mild or severe stroke symptoms, and for elderly patients as well, but these groups often should receive treatment.

Mild or rapidly improving symptoms

Mild or rapidly improving symptoms are the most common reasons for not treating with IV tPA among otherwise eligible patients.[4] However, multiple studies have found that up to 1/3 of patients with mild stroke symptoms at presentation will have poor long term outcomes.[5, 6] Subgroup analysis from the International Stroke Trial 3 demonstrated a benefit for patients with NIHSS<5 when treatment was given within 3 hours.[7 8] The most recent meta-analysis of randomized tPA studies including IST3 similarly suggests a potential benefit in mild stroke.[3] Given this evidence, it is highly likely that patients with a low NIHSS and clearly disabling symptoms—such as a visual field deficit or isolated aphasia—benefit from tPA. There remains uncertainty about the efficacy of tPA in mild non-disabling strokes. Phase III trials testing IV tPA in mild stroke patients are currently enrolling in the US (clinicaltrials.gov NCT02072226), and to test IV tenecteplase in transient ischemic attacks or mild stroke patients with visualized intracranial occlusion in Canada (clinicaltrials.gov NCT02398656).

Severe strokes

Only a small percentage of patients in the original NINDS rt-PA Stroke Trials had severe strokes with National Institutes of Health Stroke Scale> 20. However, subgroup analysis from that trial suggested that patients with severe stroke were still more likely to achieve a good outcome when treated with tPA compared to those patients who were given placebo. [9] Subsequently, the large meta-analysis of tPA trials confirmed this finding and it is clear that severe strokes benefit from tPA use despite an increased risk of symptomatic ICH, given that untreated patients do so poorly. [3]

Elderly patients

Older patients are more likely to experience poor outcomes from stroke compared to younger patients and thus early studies evaluating tPA often excluded patients over 80. Only 69 patients (11%) included in the original NINDS rt-PA Stroke Study were over 80 years of age. No other randomized study of tPA for acute stroke allowed patients over 80 years of age to be enrolled until the IST-3 study was published in 2012.[7] This trial included 1617 octogenarians, accounting for over half of the patients in the study, and there was a clear benefit for this cohort when treated within the 3 hour window. Importantly, the meta-analysis of randomized tPA trials found that older patients were just as likely to benefit as younger patients and the window for treatment was not reduced (p=0.08, with a point estimate suggesting longer rather than shorter timeframe) suggesting that treatment in the 3 to 4.5 hour window remains appropriate for this population. [3]

The American Heart Association/American Stroke Association recently recently published a statement reviewing the literature and providing guidance on the scientific rationale for tPA inclusion and exclusion criteria. This comprehensive advisory goes far beyond prior guidelines allowing physicians to make the most informed decisions for the wide variety of patients they encounter in clinical practice.[10]. Table 2 provides a summary of the many recommendations for tPA use with specific patient characteristics and scenarios.

Table 2. Select recommendations from the AHA/ASA Statement on tPA inclusion/exclusion criteria

Patient characteristic	Recommendation	Size of Treatment effect	Level of evidence	Comments
>80 years of age	Treat	Class I	A	tPA increases likelihood of independence at 3 months across all age groups
Severe stroke symptoms	Treat within 3 hours	Class I	A	Despite increased hemorrhage risk, there is still proven clinical benefit
Mild but disabling stroke symptoms	Treat within 3 hours	Class I	A	There is proven clinical benefit
Mild but non-disabling stroke symptoms	Neutral	Class IIb	C	More study is required to define the risk-benefit ratio
Rapidly improving symptoms with ongoing impairment	Treat	Class IIa	A	Because time from onset to treatment is so strongly associated with response to treatment, delaying treatment to monitor for improvement is not recommended
Active pregnancy or post-partum<14 days	Neutral	Class IIb	C	tPA may be considered if anticipated benefit of treating moderate-to-severe stroke outweigh the anticipated risk of uterine bleeding. Emergent OB consultation is indicated
Coagulopathy (defined as platelets < 100k, INR>1.7, aPTT >40 seconds, or PT >15	Do not treat	Class III	C	Given the low risk of unsuspected abnormal platelet or coagulation studies, treatment should not be delayed while awaiting these results
History of bleeding diathesis/coagulopathy including renal failure, liver failure, hematologic malignancy	Neutral	Class IIb	C	tPA should be considered on a case-by-case basis

History of warfarin, INR ≤1.7	Treat	Class IIb	B	No evidence for increased bleeding risk
History of warfarin, INR >1.7	Do not treat	Class III	B	
History of low molecular weight heparin within 24 hours	Do not treat	Class III	B	Prophylactic or therapeutic treatment
History of factor Xa or direct thrombin inhibitor	Do not treat	Class III	C	tPA is not recommended unless appropriate lab tests including aPTT, INR, ecarin clotting time, thrombin time or appropriate direct factor Xa activity are normal, or it has been > 48 hours since last dose (assuming normal renal function)
Major surgery within 14 days	Neutral	Class IIb	C	Treatment may be considered, potential increased surgical site bleeding should be weighed against the anticipated benefit in stroke-related disability
Major trauma within 14 days	Neutral	Class IIb	C	Treatment may be considered weighing risk of trauma-related bleeding against potential disability from stroke
Severe head trauma within 3 months	Do not treat	Class III	C	Not recommended for post-traumatic infarction during in-hospital phase
Concurrent acute myocardial infarction and stroke	Treat	Class IIa	C	Use stroke dosing (0.9mg/kg, 90 mg max, 10% over 1 minute, the rest infused over an hour), followed by percutaneous coronary intervention in indicated
Recent myocardial infarction within past 3 months	Treat	Class IIa	C	Reasonable if Non-STEMI or STEMI involving right or inferior myocardium. May be reasonable if STEMI involving left anterior myocardium
Pericarditis or left-sided cardiac thrombus	Neutral	Class IIb	C	If severe stroke, treatment may be reasonable. Emergent cardiology consult recommended. If stroke symptoms are moderate, treatment is of uncertain net benefit
Infective endocarditis	Do not treat	Class III	C	Due to increased risk of hemorrhage with mycotic aneurysms
Intracranial or intrasprinal surgery within 3 months	Do not treat	Class III	C	
Dural puncture within 7 days	Treat	Class IIb	C	tPA may be considered
Recent ischemic stroke within 3 months	Do not treat	Class III	B	
Recent GI/GU bleeding within 3 weeks	Do not treat	Class III	C	
History of GI/GU bleeding, > 3 weeks and without a structural malignancy	Treat	Class IIb	C	
Puncture of non-compressible arterial puncture within 7 days	Neutral	Class IIb	C	

Elevated BP able to be lowered to < 185/110 mm Hg	Treat	Class I	B	Ensure that the BP remains stable at the lower level before beginning treatment, and maintained throughout first 24 hours
Cerebral microbleeds on MRI	Treat	Class IIa	B	
History of intracranial hemorrhage	Do not treat	Class III	C	
Unruptured intracranial aneurysm, small or moderate sized	Treat	Class IIa	C	
Unruptured intracranial aneurysm, giant	Neutral	Class IIb	C	
Unruptured, untreated intracranial vascular malformation	Neutral	Class IIb	C	tPA may be considered in patients with severe deficits
Extra-axial intracranial aneurysm	Treat	Class IIa	C	
Intra-axial intracranial aneurysm	Do not treat	Class III	C	
End-stage renal disease on hemodialysis with normal aPTT	Treat	Class I	C	
Pre-existing dementia	Treat	Class IIb	B	Life expectancy and premorbid function should be considered
Current malignancy	Treat	Class IIb	C	If there is a reasonable life expectancy (>6 months) and no coagulopathy, recent surgery, or systemic bleeding
Pre-existing disability (mRS≥2)	Treat	Class IIb	B	Consider quality of life, social support, place of residence, patient and family preferences, and goals of care
Glucose > 50 mg/dL	Treat	Class I	A	Be aware that hypo- and hyper-glycemia may mimic stroke
Initial glucose > 400 mg/dL that are subsequently normalized	Treat	Class IIb	C	
Seizure at onset	Treat	Class IIa	C	Treat if evidence suggests residual symptoms are due to stroke
Early ischemic change on head CT, mild-to-moderate extent	Treat	Class I	A	Without frank hypodensity
Extensive areas of clear hypoattenuation on head CT	Do not treat	Class III	A	
History of hemorrhagic diabetic retinopathy	Treat	Class IIa	B	Increased risk of vision loss should be weighed against stroke disability
Suspicion for subarachnoid hemorrhage	Do not treat	Class III	C	
Suspicion for aortic arch dissection	Do not treat	Class III	C	
Suspicion for extracranial cervical arterial dissection	Treat	IIa	C	
Suspicion for intracranial arterial dissection	Neutral	IIb	C	
Wake up stroke or unknown time of onset	Do not treat	Class III	B	

with last known normal > 4.5 hours				
Women who are menstruating	Treat	IIa	C	Warn patient that tPA may increase menstrual bleeding
Recent or active vaginal bleeding causing significant anemia	Neutral	IIa	C	Emergent Gynecologist consultation is indicated
Cardiac myxoma or fibroelastoma	Treat	IIb	C	Treatment reasonable if severe symptoms
Patient taking a single medication or dual antiplatelet medications prior to stroke onset	Treat	I	A	There may be a small increased risk of ICH but benefit of treatment remains. Do not provide an antiplatelet within 24 hours after tPA
Patient took cocaine prior to stroke	Treat	IIa	C	
History of sickle cell disease	Neutral	IIb	C	Blood exchange should also be performed
For patients within the 3- to 4.5 hour window				
Symptoms onset within 3 to 4.5 hour, if eligible for ECASS III	Treat	Class I	B	
Patients >80 years of age	Treat	Class IIa	B	
Patients taking warfarin with INR <1.7	Treat	Class IIb	B	
Severe stroke with NIHSS > 25	Neutral	Class IIb	C	
History of prior stroke and diabetes	Treat	Class IIb	B	

Intra-arterial thrombectomy

In the past few years, six randomized trials have demonstrated a robust and clinically important benefit of IA thrombectomy for stroke.[11] [12] The number needed to treat to achieve one more patient who remains independent at 3 months ranged from 3 to 7 depending on the specific inclusion exclusion criteria used. While the maximal time from onset ranged from 4.5 to 12 hours, the vast majority of patients were treated within 6 hours. Some studies utilized high level imaging to insure the presence of a meaningful volume of ischemic penumbra while others merely insured that the irreversible injury was not too extensive by restricting the . All studies insured that there was a proximal large vessel occlusion present before randomizing and taking patients to the angio suite. Given the clear benefit of treatment, it raises the question of whether clinicians should expand the criteria for who could be treated with thrombectomy. The AHA provides a strong statement for use within 6 hours, but labels treatment beyond that timepoint as experimental.[13] Additional randomized trials are being performed in the 6 to 16 hour window using high level imaging patient selection. One additional controversy for patients undergoing IA thrombectomy is whether they should be given general anesthesia and intubated, to insure that they remain still while the catheter is being manipulated, or can the procedure be safely be performed under light sedation without intubation? Observational studies including data from the MR CLEAN trial suggest that avoiding general anesthesia is associated with improved outcomes.[14] This potential benefit may be related to faster treatment times and reduced blood pressure variability. However, a randomized trial of conscious sedation compared to general anesthesia in patients undergoing thrombectomy for stroke did not show a benefit for conscious sedation and thus it is reasonable to utilize general anesthesia if it can be performed rapidly with close attention to blood pressure to avoid hypotension. [15]

Conclusion

The specific patients who benefit from IV tPA likely extend well beyond those included in early IV tPA trials. As the FDA label has become less proscriptive by minimizing explicit exclusions, clinician judgment is of paramount importance. Careful consideration of the potential disability if left untreated, should be weighed against the potential risk of bleeding that may occur. Patient and family education should occur when able, but consent is

not required if the patient is unable to provide it and there is no surrogate decision maker available. Careful documentation of the rationale for tPA use, or non-use, is also essential. The recent AHA guideline does provide comprehensive and well-reasoned advice to help guide decision making though clinician judgment at the bedside is always paramount. Finally, the robust benefit of intra-arterial thrombectomy for stroke patients with proximal large vessel occlusions seen in a number of positive trials is a huge advance for stroke care. It is important to note that the vast majority of patients in these IA trials also received IV tPA, and thus a plan to undergo IA intervention does not preclude thrombolysis. That said, in patients where IV tPA is of uncertain safety or efficacy (such as the conditions with a neutral recommendation for IV tPA treatment in Table 2) IA thrombectomy alone may be a preferable alternative if the patient has a vessel occlusion amenable to thrombectomy.

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