Redefining Exclusionary/Inclusionary Criteria for IV tPA Use
Live Program: June 20, 2012

A few more questions from attendees—answered by the faculty

1. Even if we strictly follow the guideline, the risk of symptomatic intracerebral hemorrhage is still 6% with half fatal. Would giving tPA in mild or rapidly improving stroke increase this risk even more?

I do not believe that the risk of bleeding with IV tPA would be higher in mild or rapidly improving stroke. In fact, the literature would indicate that the lower the NIHSS score, the lower the risk of symptomatic ICH. An analysis of the ICH rates in tPA-treated patients demonstrated that those patients with NIHSS scores less than 10 had a symptomatic ICH rate less than the 6%. While the rate of symptomatic ICH may be lower than the 6%, the issue to consider is that we do not know the benefit to treating mild or rapidly resolving symptoms, so the benefit is not clear but the risk is still significant. —Dr. Pancioli

2. In your practice, do you routinely use CTA in acute stroke work-up in the emergency department?

Yes. The evaluation of the stroke patient must include imaging of the head and neck vasculature, and CTA provides that more rapidly and accurately and with less risk than any other test, so more often than not the acute stroke patient will get a CTA in the emergency department. It is important not to delay tPA in order to get the CTA, but often it can be obtained at the same time as the head CT before tPA, or else immediately after tPA. CTA is particularly valuable if considering the patient for additional therapies such as intra-arterial therapy or carotid surgery or stenting. Almost all patients also get an MRI of their brain. If we get a CTA, then we don’t need an MRA. If the patient has renal insufficiency, or does not present in the first hours after a stroke, we will usually not get the CTA, and just get an MRA with the MRI. —Dr. Grotta

3. What are your thoughts if tPA is given after 3 hours in mild or rapidly improving symptoms, since this is clearly associated with high risk of bleeding as well?

Treating patients after 3 hours, while potentially beneficial, does generally offer less benefit than treating earlier. Therefore this reduced potential for benefit added to the unknown potential for benefit of treating mild or rapidly resolving symptoms is hard to justify against the very real risk of ICH. Therefore my enthusiasm for treating mild or spontaneously improving symptoms is low beyond 3 hours. —Dr. Pancioli
4. Does a TEG study help in the decision to give tPA to the patient on new oral anticoagulants?

I am not aware of any strong data to support using the TEG results to guide such therapy. An elevated PTT is an indicator that there is a dabigatran effect in that patient. An elevated thrombin time would mean the same type of effect. —Dr. Alberts

5. Do you use MRI for acute stroke imaging?

See comments about CTA. We do not usually get an MRI in the ED in most patients because we can obtain most of the information we need for decision making in the ED using CT, CTA and CT perfusion. In the emergency setting, the most valuable MRI sequence is the DWI, which can help confirm the presence of stroke in questionable cases and also tell us if the established infarct core is so large that any further intervention would be dangerous. Other centers use MRI more routinely in the emergency setting to look for "perfusion/diffusion mismatch" thought to be a surrogate for salvageable ischemic penumbra. We find that we can get similar information from CT blood volume and CT perfusion studies much more quickly. The value of such "advanced" imaging in the ED remains to be proven but should be elucidated somewhat in the MR Rescue trial data to be released later this year. Although we don't often get an MRI in the ED, we will get an MRI on most stroke patients within the first 24 hours so in order to understand stroke location, size, configuration and pathology, which give a clue as to stroke etiology, thereby helping to plan secondary prevention. —Dr. Grotta

6. I like the concept of more to gain than lose in tPA for mild or rapidly improving stroke. How much weight do you put in considering major comorbidities in reaching a decision to give tPA?

Whenever one considers the risk benefit ratio for thrombolysis in a stroke patient you do have to consider co-morbidities. If you keep in mind that tPA only provides a 10-12% absolute benefit for an excellent outcome, then any significant co-morbidity that could increase the risk significantly can easily overwhelm the potential benefit. With all that remains unknown about treating a rapidly improving stroke, it does not take a lot to dissuade me from treating a patient if the co-morbidity is significant. —Dr. Pancioli

7. Do you consider the Thrombin Time an indicator for considering IV thrombolytics when patients are on dabigatran?

An elevated thrombin time would certainly indicate that the patient is taking or was taking dabigatran. If the thrombin time was elevated I would not administer IV TPA to that patient. —Dr. Alberts
8. When do you mobilize post tPA patients? Do you wait 24 hours?

It really depends on their clinical status. Most of the time the patient will still have a deficit so will not be fully mobilized in the first 24 hours. But it is still reasonable to allow PT to assess the patient on the first day. If the patient has fully recovered and is able to stand and walk without difficulty, and has been cleared by PT, I will let them mobilize around the room as long as someone can watch them and help if needed. —Dr. Grotta

9. What time guideline do you follow for giving tPA to a patient who is taking an untestable oral anticoagulant? If they have taken it in the last 2 days, you don't give tPA? Or another timeframe?

Based on a half-life of about 12 hours for dabigatran and 9 hours for rivaroxaban, a 48-hour safety buffer for dabigatran and 36 hours for rivaroxaban seems prudent. All of this is assuming normal or near normal renal function. Keep in mind that the Activase package insert does state that taking an oral anticoagulant is a contraindication to Activase therapy for stroke. —Dr. Alberts

10. In what situations would you consider intra-arterial intervention after giving IV tPA?

The benefit of intra-arterial therapy (IAT) over conservative management remains unproven but I think it is likely that some patients benefit. I think the same basic principles apply to IAT as IV tPA—“Time is brain.” Data from Khatri et al. suggest that up to 80% of patients will have a good outcome (modified Rankin score of 2 or less) if the artery can get opened by 4 hours after symptom onset. But this requires excellent teamwork and a skilled team to get the patient on the table, the IAT team mobilized and the artery opened so quickly. Newer devices such as the stentriever may also help. More delayed treatment out to 6-8 hours may also be useful in some patients, but has even less data to support it. One of the biggest questions is how to select such patients. Some would argue that we should use the “mismatch” criteria mentioned in response to the previous question in order to select patients who will respond. Data in support of this approach are mixed, and are mainly obtained from trials of intravenous treatment, not IAT. As mentioned previously, the MR Rescue trial will shed light on the value of such imaging for selecting patients for IAT. Another approach would be to simply exclude the patients most unlikely to benefit. We have found that patients with early CT changes in more than 1/3 of the MCA, advanced age, elevated blood glucose and very high NIHSS score are least likely to benefit from delayed IAT. —Dr. Grotta

11. Could you utilize CT perfusion and do you utilize this in your practice with seizure patients?

See previous comments on the use of CT. I use CT perfusion in cases where I am trying to decide about delayed treatment with IV TPA or IAT. In some cases of questionable stroke, the CTP will help confirm a cortical branch infarct when the arterial occlusion can't be seen on CTA. But in these circumstances, and in suspected stroke patients presenting with a seizure, I think MRI (DWI) would be more useful to determine if a stroke is present. —Dr. Grotta
12. Do you think for patients in all of the situations that you spoke on today would you consider IA-tPA with or without endovascular intervention if they qualify?

During the webinar, we focused on patients presenting with seizure, minor or improving stroke, and patients on anti-thrombotic drugs. I see no reason why IAT would be any better than IV tPA for patients with seizure or minor/improving stroke. However, for patients on antithrombotic drugs, it is possible that mechanical clot extraction without the use of lytics might be safer, but this is unproven. —Dr. Grotta

13. In terms of rapidly improving symptoms, what is your lowest NIHSS number where you will still go ahead and treat?

I do not think that the absolute number is as important as the perceived disability of the deficit at hand. For example, an NIHSS score of 2 based on an isolated hemianopsia is vastly different than a similar score for minimal weakness and minimal sensory loss both in one extremity. Therefore I would make my decision to treat or not to treat a “mild” stroke or “rapidly improving” stroke entirely on the clinical deficit and trajectory of the patient when I was evaluating them. —Dr. Pancioli

14. Do you routinely take informed consent when you give tPA for those patients presenting in the 3 to 4 1/2 hour window?

We had not been getting a written consent in such patients. But with the recent FDA ruling on IV TPA in the 3-4.5 hour time window, we are changing our hospital protocol to obtain some type of formal consent for patients just in the 3-4.5 hour time window. —Dr. Alberts

15. You said some patients may benefit from being treated in the 3-4.5 hour window---who are these particular patients?

I believe that the ECASS III trial offers adequate science and in general I have translated those findings into my clinical practice. Therefore, the additional exclusion criteria of the ECASS III trial, such as age over 80, severe stroke with NIHSS score > 25 and the combination of previous stroke and diabetes should be included in tPA decision making for patients being considered between 3 and 4.5 hours. —Dr. Pancioli

16. What are your thoughts on treating wake-up strokes with IV tPA?

In general we do not use IV TPA in patients with a wake-up stroke, unless the time last known normal would qualify the patient within the usual TPA time window. There are various studies that have used different imaging techniques to determine if such patients might qualify for such therapy. The overall validity of these techniques, as well as the safety and efficacy of IV TPA in such therapy remains an open question, in my opinion. —Dr. Alberts
17. Please discuss the issue of "restarting" the TPA clock when a patient reported he had symptoms ~12 hours ago but which improved/resolved per patient report and then the symptom returned. What is the evidence regarding this "resetting" of the clock?

If the patient’s symptoms totally resolve and a detailed neurologic examination is back to baseline, then it is reasonable to restart the TPA time clock. We do this routinely in our practice and generally it has worked out quite well. —Dr. Alberts

18. Post tPA, how long should we expect to see progress in patients?

We have seen some patients who responded within a matter of minutes or hours. Other patients improve over a 2-5 day time window. Still others have a more gradual improvement over weeks to months. Remember that the NINDS TPA study used a 3-month time frame to assess the primary endpoint for improvement. An immediate response should not be expected in all patients. —Dr. Alberts

19. Do you know of any articles of treating patients with TPA who stroke during a heart cath procedure?

Not any formal studies, but I know that my colleagues and I have used IV TPA in this setting in many cases. The overall efficacy and safety is similar to that seen in larger studies. There are a few reports of groin hematomas and more serious hemorrhages (retroperitoneal) in this setting. —Dr. Alberts

20. Are there any risk/benefit current trials since the NINDS trial?

The studies that provide significant new information include ECASS III which showed benefit is greater than risk of IV TPA out to 4.5 hrs. When the ECASS data were pooled with other previous IV TPA trials including NINDS, there was gradually decreasing benefit with increasing time to treatment, but no increased risk. However, after 4.5 hours there was no benefit, and possibly increased risk. The recently completed IST study evaluated treatment out to 6 hours in patients whom the treating physician was "uncertain" would benefit. While overall results were neutral, benefit greater than risk was confirmed in patients treated within 3 hours, including those over 80 years of age. —Dr. Grotta

21. I'm not clear about the risk of using tPA when Todd's paralysis is suspected.

The risk of symptomatic ICH in patients that do NOT have an ongoing stroke likely mirrors the risk in other non-neurologic clinical uses of tPA. The best example of this is the trials of myocardial infarction. Keeping in mind that in the cardiac trials the tPA doses are slightly higher than in the NINDS trial for stroke and typically included heparin, the risk is likely to be less than 0.6% in the setting of a Todd’s. Notably this assumes that there is not some underlying lesion that would be the cause of the seizure, such as a previously unknown tumor. The risk in that setting is unknown. —Dr. Pancioli
22. I have seen several patients with second stroke at less than 90 days after first stroke. How strict are you with waiting 90 days from first stroke before administering tPA?

We have had the same experience, and within our group have established the following consensus for standard of care. I want to emphasize that this is our UT SOC and assumes a highly experienced group of stroke specialists making the decision. In these cases where we treat “off label,” we document at least verbal informed consent from patient or family member. If a previous ischemic stroke has occurred within the previous 3 weeks, we will not treat with IV tPA. If a stroke occurred between 3 weeks and 3 months previously, treatment is OK if no edema or blood is present on CT. If there is uncertainty, we consider contrast CT or MRI to see if any evidence of BBB breakdown. —Dr. Grotta

23. During the lecture this morning, the MDs made reference to the FDA’s ruling against the expansion of the window for IV tPA. Can I get a resource for that?

To the best of my knowledge, the FDA has not publically released any formal documents at this time. We are hopeful these will be forthcoming in the near future. —Dr. Alberts

24. Do you know of any articles of treating patients with TPA who stroke during a heart catheterization procedure (with intervention versus simply angiogram)?

This is certainly something that we have treated many times. The most recent article I have seen on this is below under references. My personal practice is to attempt IV tPA unless contraindicated in combination with an endovascular approach. These patients have the advantage of already being in a hospital and already have arterial access for the potential for endovascular reperfusion therapies. Despite these advantages, time delays are frequent and good outcomes are far from assured. —Dr. Grotta

25. Seizures and tPA perspective?

In general the reason for excluding patients with seizures is that the odds that the stroke-like symptoms are due to the seizure as opposed to an underlying stroke are quite high. Thus in the setting of a likely “non-stroke” the potential benefit of tPA would be quite low. The challenge is that there may be more true strokes in this group that we previously recognized. Currently, two camps of thought are evolving. One group of clinicians believes that any significant stroke-like symptoms should be treated without delay to maximize potential benefit. This group would argue that the risk of bleeding is so low in the non-stroke patients that it is best to simply treat. Another camp of thinkers would prefer to get definitive imaging (MRI DWI) and prove stroke before treatment. This discussion will evolve over time and any case should be discussed with local experts to optimize the patient’s potential. —Dr. Pancioli
References:

Kidwell CS. MR and REcanalization of Stroke Clots Using Embolectomy (MR RESCUE). Available at: clinicaltrials.gov; NCT00389467.


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