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COMMENTARY

# The Case Against Thrombolytic Therapy in Stroke

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Lysing clots in brain arteries to reverse an acute ischemic stroke *should* work. Thrombolysis worked in myocardial infarction (MI).

For MI, 14 trials of more than 140,000 patients proved lytic therapy improved outcomes.[1] A 2014 Cochrane review of 27 stroke trials included about 11,000 patients—12-fold fewer.[2]

Before Gina Kolata, a health journalist at the *New York Times*, wrote a story about the decades-long debate between neurology leadership and emergency medicine specialists on the use of lytic therapy for stroke, I, like many cardiologists, accepted the experts' view that tissue plasminogen activator (tPA) is beneficial and "should be given"[3] to eligible patients with stroke.

Kolata clearly sided with the neurologists. She also featured the oft-heard opinion from many in academic medicine that social media, blogs, and podcasts can be used in negative ways to slow uptake of beneficial therapy.

As an electrophysiologist, I often see patients with stroke—both acutely in the hospital and also in follow-up. I did not know about the tPA debate. So I studied the evidence.

What I found was shocking: The evidence for thrombolysis in acute stroke does *not* support its guideline recommendation. The resistance to thrombolysis promoted through social media channels and in emergency medicine literature is rational.

Let me explain the strong case against lytic therapy.

## Dubious Benefits

Unlike thrombolysis for MI, no stroke trial has shown that lytic therapy lowers death rates. In fact, lytic therapy for stroke strongly increases early death, and shows trends towards higher death overall.

Neurologists measure benefit of lytic therapy by estimating function or ability to remain independent, a much more subjective endpoint than death. Trialists use multiple scales (such as the modified Rankin Scale [mRS]) to quantify functional capacity. Attempts to put numbers on qualitative outcomes is the first of many flaws in the lytic trials. Evidence from the neurology literature chronicle "potentially significant interobserver variability in these scales."[4],[5]

Ten randomized clinical trials assessed functional capacity in patients with acute ischemic stroke treated with thrombolysis or placebo. Two streptokinase trials[6],[7] and two tPA trials[8],[9] were stopped early because of harm or futility, and four trials showed no benefit of tPA on functional improvement.[10],[11],[12],[13] That leaves two positive trials: NINDS (Part 2)[14] and ECASS III.[15] The first point to make concerns the distribution of these results. If you did 10 trials of an ineffective treatment, this pattern (most trials negative and outliers showing both harm and benefit) is what you would observe in a normal distribution—or by chance alone.

The second point is that the two positive trials have significant flaws and biases toward tPA.

## Flawed Trials in Favor

In the NINDS (Part 2) trial,[14] patients treated with tPA were at least 30% more likely to have minimal or no disability at 3 months compared with those treated with placebo. In the original *New England Journal of Medicine* publication, the authors listed median baseline National Institutes of Health Stroke Scale (NIHSS) scores of 14 and 15 in the respective treatment groups. This gave readers the impression that baseline characteristics were similar. But they were not.

Five years later, the same authors[16] published a subanalysis of NINDS that brought to light imbalances in the baseline characteristics of the two groups. For example, within the subgroup of patients treated between 91 and 180 minutes, 19% of those given tPA had NIHSS scores of 0 to 5 (mild) compared with only 4.2% of the placebo group. In addition, fewer patients in the tPA subgroup had severe strokes (18% vs 27% with NIHSS score > 20). Because the outcome of stroke depends greatly on the severity of the initial presentation, these imbalances bias the results in favor of tPA.[17]

Using patient-level data from the NINDS trial, which the National Institutes of Health (NIH) placed in the public domain, Jerome Hoffman and David Schriger, from the University of California, Los Angeles, published a reanalysis showing that baseline stroke severity and preexisting disability had a greater association with outcome than did the treatment provided.[18]

Their novel reanalysis centered on the concept of *change* in NIHSS score. Essentially, the original NINDS investigators reported where patients end up at 90 days based on treatment assignment. What's not reported is the change from baseline. If tPA is beneficial, people treated with the drug should end up with a significantly lower score than they started with. When Hoffman and Schriger charted the change in NIHSS, tPA benefit was no longer evident.

Their provocative analysis also refuted the time-is-brain hypothesis. When they analyzed the relationship in 90-day change in stroke scale by time to treatment, the purported advantage of early tPA disappeared. This finding supports the notion that the best predictor of stroke outcomes is the severity of stroke at presentation.

Post hoc analyses challenge Hoffman and Schriger's conclusions and uphold the original findings of NINDS.[19],[20],[21] Crucially, none of these papers use patient-level data to measure the change in stroke score from baseline. Another post hoc study[22] by an independent group of authors convened at the request of the NIH to ascertain whether the subgroup imbalance invalidates NINDS backed up the main trial but added the caveat that their exploratory analysis "was not powered to detect subgroup treatment differences."

The other positive trial, ECASS III,[15] also had statistically significant imbalances in baseline stroke severity that biased toward tPA: The placebo group had more severe strokes (higher NIHSS score) and nearly double the number of patients with previous strokes (14.1% vs 7.7%; *P* = .003).

The most significant flaw in ECASS III involved the subjective primary endpoint. Investigators used the mRS dichotomized at scores of 0 to 1 or 2 to 6 for their primary endpoint. A favorable outcome (mRS score of 0 or 1) occurred in 52.4% of the tPA group vs 45.2% of the placebo group. The absolute difference of 7.2 percentage points just reached statistical significance at a level of *P* = .04. The problem is that the difference between a score of 1 (able to carry out all usual activities, despite some symptoms) and a score of 2 (able to look after own affairs without assistance, but unable to carry out all previous activities) is subjective. Yet in ECASS III, a score of 2 was lumped together with a score of 6 or death. If instead you compared those with a score of 0 to 2 with those with a score of 3 to 6, there was no significant difference between tPA and placebo.

The strongest argument against tPA in stroke came from the negative IST-3 trial[12]— the largest randomized, controlled trial of thrombolysis vs placebo, which included just over 3000 patients. The primary outcome of being alive and independent at 6 months as measured by the Oxford Handicap Score was not statistically different between those in tPA group and those in the placebo group (37% vs 35%, respectively; *P* = .18).

## Certain Harm: Increased Risk for ICH

Every paper published on thrombolysis in stroke reports a higher rate of intracerebral hemorrhage (ICH) with lytic therapy. This statement comes from the American Heart Association/American Stroke Association guidelines[3] for the early management of acute ischemic stroke: "Treatment with intravenous rtPA is associated with increased rates of intracranial hemorrhage, which may be fatal." A Cochrane systematic review found that thrombolytic therapy for stroke increased the risk for symptomatic ICH nearly fourfold (odds ratio [OR]; 3.75, 95% confidence interval [CI], 3.11 - 4.51).[2] It was two- to sixfold higher in ECASS III and NINDS (Part 2).

## Possible Risk for Increased Death

All thrombolytic trials show an increased risk of early death with tPA. Death rates tend to even out over time, but the cumulative mortality signal trends higher with thrombolysis.

A 2012 meta-analysis of tPA trials did not show a significant increase in overall mortality (OR, 1.06; 95% CI, 0.94 - 1.20; *P* = .33).[23] Australian authors, who were not involved in any of the thrombolytic trials, did a systematic review of thrombolysis in stroke and found a 17% higher rate of overall death with lytic therapy vs placebo when they included all thrombolytic trials (OR, 1.17; 95% CI, 1.06 - 1.30; *P* = .003). When they included only tPA trials, overall death did not differ (OR, 1.04; 95% CI, 0.92 - 1.18; *P* = .49).[24] This latter meta-analysis also reported a trend for decreasing mortality rates over the two decades that stroke trials have been done. Because tPA trials came after the streptokinase trials, it's possible the improved mortality in tPA trials occurred not because of drug effects but because of overall improvements in stroke care.

## External Validity of Thrombolytic Trials

Let's say you disagree with this analysis. You ignore the trials stopped early for harm. You ignore the many negative trials. You ignore the higher rate of ICH and possible signal of increased death. And you focus only on the two positive trials, despite their flaws and subjective efficacy endpoint. You still have the problem of translating this evidence to real life.

Diagnosing stroke emergently isn't always easy. A study from the 1990s found that stroke mimics, such as Todd's paralysis, infection, or metabolic disorders, occurred in nearly one in five patients initially diagnosed with stroke.[25] Proponents might argue that the rate of misdiagnosis is lower now because of stroke centers. Maybe, but many patients still receive care outside of specialty centers. What's more, any patient who receives tPA for a nonstroke gains no benefit and is exposed to a real possibility of harm.

In the tPA trials, strict criteria governed enrollment of patients, which is not feasible in regular practice. Cleveland Clinic researchers tallied results from every stroke patient receiving tPA from 29 local hospitals area and found that half of the 70 patients treated with tPA received it inappropriately and that treated patients had a rate of ICH (15.7%), which greatly exceeded that seen in clinical trials.[26]

Supporters of tPA can point to observational studies reporting rates of ICH, early death, and functional independence similar to those in the clinical trials. These studies have significant limitations: In addition to being uncontrolled, they suffer from incomplete case ascertainment and likely selection bias. For example, one such Canadian registry study[27] is not applicable to US practice because the centralized infrastructure of Canada's healthcare system allows for the naturalized development of expert stroke centers. Another registry study (SITS-MOST)[28] had voluntary participation of centers that "promised" to enroll all patients. Also, SITS-MOST represents an idealized situation in that it excluded all patients given tPA in violation of strict eligibility criteria.[29]

## Conclusion

Here I echo Hoffman's analysis[30] of lytic trials from almost two decades ago when he wrote that using a new therapy is reasonable for a condition if four criteria are met:

1. Outcome is almost uniformly bad with standard therapy.
2. The potential benefits of the new therapy are substantial.
3. The proposed treatment is unlikely to cause harm.
4. There is no reason to suspect results will be substantially worse in general practice.

None of these criteria exist for thrombolysis in stroke.

Although we have all seen a patient with stroke defects improve after lytic therapy, the evidence from nearly 10,000 patients in trials shows that the odds of that patient getting better with placebo are similar (eg, spontaneous lysis) whereas the chances of that patient suffering ICH are two- to sixfold higher.

Thrombolytic proponents are wrong to recommend this therapy as something that "should be done." The evidence for harm is greater than the evidence for benefit. You don't have to be a neurologist to see that.

Finally, the fact that a therapy with clear harms and high costs became anointed as beneficial despite dubious evidence argues strongly for the kind of independent critical appraisal that the digital democracy now allows.

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