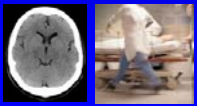




FERNE/EMRA Session:

Treating Ischemic Stroke Patients Using a 3 to 4.5 Hour tPA Window




Edward P. Sloan, MD, MPH




2009 ACEP Scientific Assembly & EMRA Semi-Annual Meetings

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Disclosures

- FERNE Chairman and President
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- ACEP Clinical Policy Committee
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- No specific disclosures related to this topic.

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Personal Experience

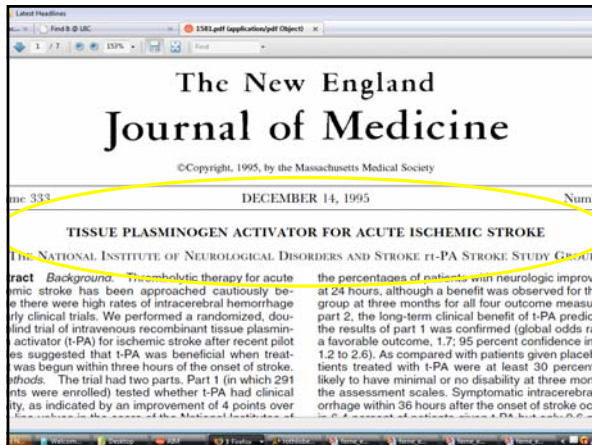

- 10 years, ~20 lectures Re: tPA use
- Preparing clinicians for optimal care of ischemic stroke patients
- Explaining the standard of care as seen by patients and society
- Participation in medico-legal cases
- Awareness of both perspectives

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The Initial tPA Data

Edward P. Sloan, MD, MPH, FACEP



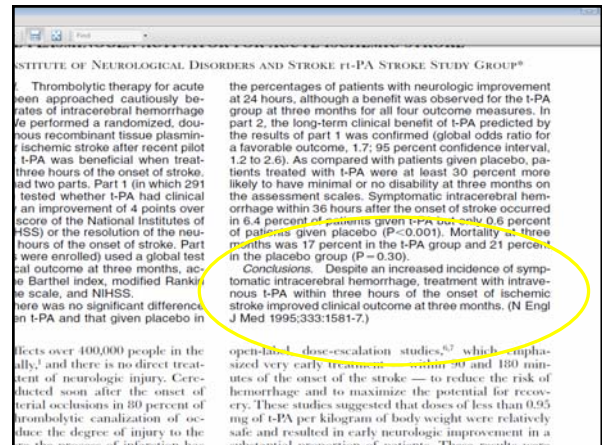
The New England Journal of Medicine

DECEMBER 14, 1995

TISSUE PLASMINOGEN ACTIVATOR FOR ACUTE ISCHEMIC STROKE

THE NATIONAL INSTITUTE OF NEUROLOGICAL DISORDERS AND STROKE t-PA STROKE STUDY GROUP

Abstract. Background. Thrombolytic therapy for acute ischemic stroke has been approached cautiously because there were high rates of intracerebral hemorrhage in early clinical trials. We performed a randomized, double-blind trial of intravenous recombinant tissue plasminogen activator (t-PA) for ischemic stroke after recent pilot studies suggested that t-PA was beneficial when treatment was begun within three hours of the onset of stroke. Methods. The trial had two parts. Part 1 (in which 291 patients were enrolled) tested whether t-PA had clinical efficacy, as indicated by an improvement of 4 points over

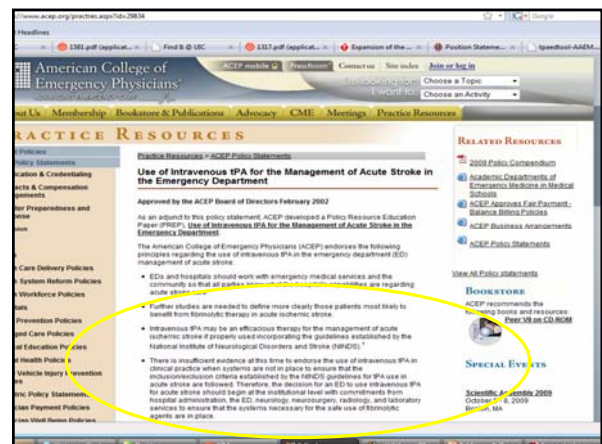


...the percentages of patients with neurologic improvement at 24 hours, although a benefit was observed for the group at three months for all four outcome measures. In part 2, the long-term clinical benefit of t-PA predicted by the results of part 1 was confirmed (global odds ratio for a favorable outcome, 1.7; 95 percent confidence interval, 1.2 to 2.6). As compared with patients given placebo, patients treated with t-PA were at least 30 percent more likely to have minimal or no disability at three months on the assessment scales. Symptomatic intracerebral hemorrhage within 36 hours after the onset of stroke occurred in 6.4 percent of patients given t-PA and only 0.6 percent of patients given placebo (P<0.001). Mortality at three months was 17 percent in the t-PA group and 21 percent in the placebo group (P=0.50).

Conclusions. Despite an increased incidence of symptomatic intracerebral hemorrhage, treatment with intravenous t-PA within three hours of the onset of ischemic stroke improved clinical outcome at three months. (N Engl J Med 1995;333:1581-7.)

Responses by Our Medical Societies

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American College of Emergency Physicians

Use of Intravenous tPA for the Management of Acute Stroke in the Emergency Department

Approved by the ACEP Board of Directors February 2002

As an adjunct to this policy statement, ACEP developed a Policy Resource Education Paper (PREP), *Use of Intravenous tPA for the Management of Acute Stroke in the Emergency Department*.

- EDs and hospitals should work with emergency medical services and the community so that all patients who are eligible for tPA are receiving acute stroke care.
- Further studies are needed to define more clearly those patients most likely to benefit from thrombolytic therapy in acute ischemic stroke.
- Intravenous tPA may be an efficacious therapy for the management of acute ischemic stroke if patients used incorporating the guidelines established by the National Institute of Neurological Disorders and Stroke (NINDS).
- There is insufficient evidence at this time to endorse the use of intravenous tPA in clinical practice when systems are not in place to ensure that the inclusion/exclusion criteria established in the NINDS guidelines for tPA use in acute stroke are followed. Therefore, the decision for an ED to use intravenous tPA for acute stroke should begin at the institutional level with commitments from hospital administration, the ED, neurology, neurosurgery, radiology, and laboratory services to ensure that the systems necessary for the safe use of thrombolytic agents are in place.

order to maximize recovery from an acute stroke. Availability of thrombolytics is only one component of acute stroke care, but it is nonetheless a component that must be included in the protocols for a hospital to qualify for certification. The published literature demonstrates that when protocols are not in place (and adhered to) outcomes from the use of thrombolytics are worse than if no intervention is provided. However, thrombolytics aside, other components of acute stroke care such as blood pressure management, prophylaxis against aspiration and DVT, and early rehabilitation, can make stroke centers the preferred environment in which to receive care.

There are several reasons why certifying hospitals as stroke centers is controversial. One is the use of t-PA, whose effectiveness in the treatment of acute stroke continues to be met with skepticism by some physicians. The ACEP Clinical Policy Statement on t-PA published in 2001 states "There is insufficient evidence at this time to endorse the use of IV t-PA in clinical practice when systems are not in place to ensure that the inclusion/exclusion criteria established by the NINDS guidelines for tPA use in acute stroke are followed." The SAEM Policy Statement on acute stroke published in 2003 states, "Currently insufficient data exist to mandate thrombolytic therapy as the standard of care for acute ischemic stroke for all patients across all medical treatment settings".

There is also significant concern that designated stroke centers will lead to redistribution of patient volumes in major urban areas and contribute to overcrowding, potentially

American Academy of Emergency Medicine

Position Statements

Position Statements are not to be construed as dictating an exclusive course of action nor are they intended to replace the medical judgment of healthcare professionals. The unique circumstances of individual patients and environments are to be taken into account in any diagnosis and treatment plan. AEM statements reflect clinical and scientific advances as of the date of their publication and are subject to change.

Link to AEM Educational Tool: tPA for Stroke – Potential Benefit, Risk and Alternatives (PDF) (5/3/07)

Position Statement on the Use of Intravenous Thrombolytic Therapy in the Treatment of Stroke

AEM Comment by Robert Mittleman, MD, FACEP

The AEM position statement represents a collective great deal of support from our primary constituency, the practicing emergency clinician. However, some in academic centers are not happy with this statement because of their opinion that the NINDS trial is definitive. AEM expected both reactions and understands each view point. We are aware of lawsuits against community emergency physicians alleging a deviation from the standard of care for failure to administer thrombolytics in stroke. This statement should assist in such matters. It is important to note that AEM is not the first organization to care about the widespread use of thrombolytics in stroke. The Canadian Association of Emergency Physicians in their position statement make several recommendations including having an expert in neurology read the CT scan first, having a

Two studies have shown that patients with stroke mimics were frequently misdiagnosed with strokes.^{13,17} Administration of tPA to such patients would carry all of the bleeding risks without any of the potential benefits. A separate study assessing clinicians' ability to interpret CT scans showed an alarming rate of misread CTs, with emergency physicians identifying only 73% of hemorrhages.¹⁴ Only 52% of radiologists in this study were able to identify all cases of hemorrhage on five cranial CT scans. Post-marketing registries and regional databases have yielded conflicting results regarding the effectiveness of this therapy in clinical practice, making it difficult to determine the true impact of widespread implementation of thrombolytic protocols.^{15,18}

Conclusion

It is the position of the American Academy of Emergency Medicine that objective evidence regarding the efficacy, safety, and applicability of tPA for acute ischemic stroke is insufficient to warrant its classification as standard of care. Until additional evidence clarifies such controversies, physicians are advised to use their discretion when considering its use. Given the cited absence of definitive evidence, AEM believes it is inappropriate to claim that either use or non-use of intravenous thrombolytic therapy constitutes a standard of care issue in the treatment of stroke.

References

1. The National Institute of Neurological Disorders and Stroke t-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. N Engl J Med 1995;333:1581-1587.
2. Guidelines 2000 for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Part 7: The era of reperfusion: section 2: acute stroke. The American Heart Association in collaboration with the International Liaison Committee on Resuscitation. Circulation 2000;102(8):1204-1216.
3. Kothari RJ, Hacke W, Brott T, et al. Cardiopulmonary resuscitation and emergency cardiovascular care. Stroke. Am J Emerg Med 2001; 37(4):5137-144.
4. Marler JR, Tilley BC, Lu M, et al. Early stroke treatment associated with better outcome: The NINDS t-PA stroke study. Neurology 2000;55:1649-1655.

Link to AEM Position Statement

tPA for Stroke – Potential Benefit, Risk and Alternatives

Definitions

tPA stands for tissue Plasminogen Activator, a strong "clot dissolving" medicine.

Stroke occurs when an area of the brain is deprived of oxygen and nutrients because of a blocked blood vessel. Many sudden blockages are due to a blood clot, and can result in loss of function in the affected area of the brain. Common signs and symptoms of stroke include abrupt onset of one-sided weakness/numbness, and difficulty with vision, speaking, thinking or coordination. The National Institute of Health Stroke Scale (NIHSS) is a standardized way to measure the severity of a stroke on a 0-42 point scale (normal to worst).

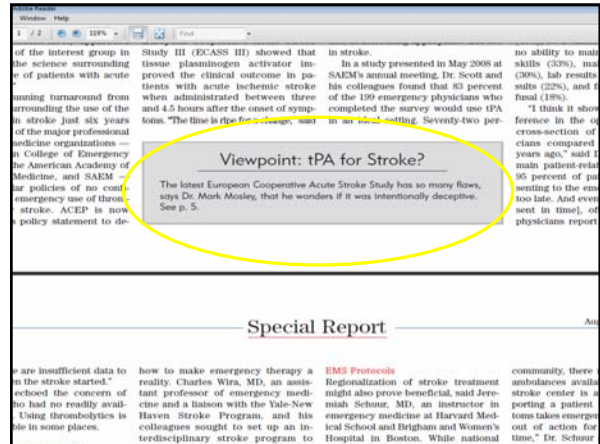
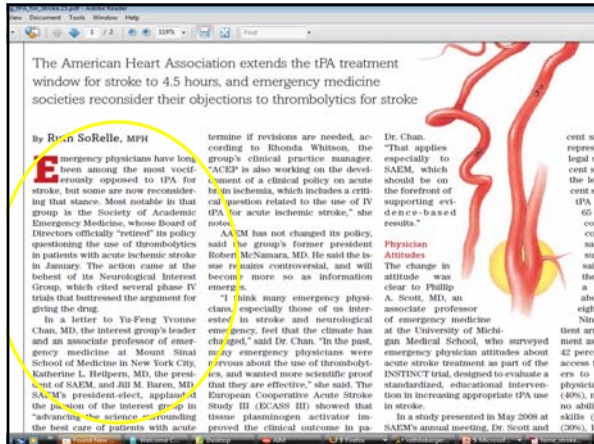
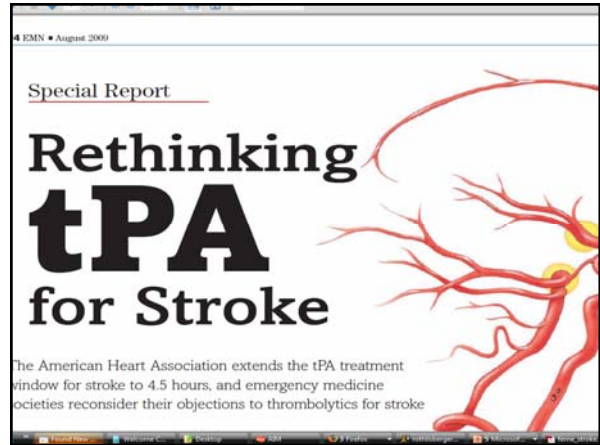
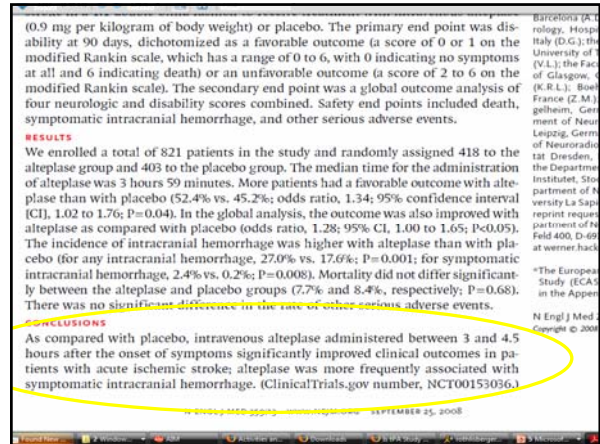
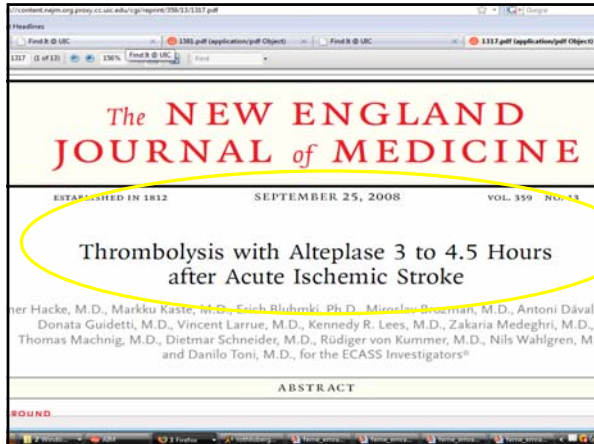
Stroke mimic is a term used for medical problems that can present in a manner similar to stroke and not the result of a blocked blood vessel. Causes include aftereffects of seizures and migraine headaches, among others. Stroke mimics may be initially misinterpreted as a stroke.^{1,2}



tPA 3-4.5 Hour Data

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Viewpoint  **Is tPA Study Intentionally Deceptive?**

By Mark Mosley, MD

The European Cooperative Acute Stroke Study III (ECASS III) looked at approximately 400 patients in an IV tPA arm who received the drug between three and four-and-a-half hours after ischemic stroke onset. (N Engl J Med 2008;359:1317-1327.) The investigators measured clinical outcomes at 30 and 90 days using the modified Rankin Scale, and found significantly improved clinical outcomes in the IV tPA group. They acknowledged that IV tPA caused more "symptomatic intracranial hemorrhage," but this did not result in a difference in mortality.

If all you read is the abstract, it sounds good, even radical because it attempts to create a new standard of how to treat ischemic strokes that qualify. Unfortunately, its conclusions are problematic if not deceptive.

The placebo and IV tPA groups were not equivalent. The most important prognostic indicator for ischemic stroke is the baseline NIH score. This was statistically worse in the placebo group. The other statistically different variable in the placebo group was "previous history of stroke." I wonder if people with worse strokes who have more previously damaged brain might have worse outcomes at 30 and 90 days?

The symptomatic ICH is deceptively "redlined." In the ECASS III study, the patients had relatively mild strokes that were not high risk for bleeding, and yet there was bleeding in the brain in one of four patients. The operative word in other studies and in this one is "symptomatic" intracranial hemorrhage. By the NINDS criteria for symptomatic intracranial hemorrhage, the ECASS III patients had a symptomatic head bleed rate of one in every 12 patients (7.9%). ECASS I, ECASS II, and now ECASS III are all consistent in that the IV tPA arm causes twice the amount of "symptomatic" intracranial hemorrhage as placebo in patients at lower risk for bleeding.



Dr. Mark Mosley

Continued on next page

AHA/ASA Science Advisory

Expansion of the Time Window for Treatment of Acute Ischemic Stroke With Intravenous Tissue Plasminogen Activator

A Science Advisory From the American Heart Association/American Stroke Association

Gregory J. del Zoppo, MD, MS, FAHA, Chair; Jeffrey L. Saver, MD, FAHA; Edward C. Jauch, MD, MS, FAHA; Harold P. Adams, Jr, MD, FAHA; on behalf of the American Heart Association Stroke Council

Current guidelines for the management of patients with acute ischemic stroke published by the American Heart Association Stroke Council include specific recommendations for the administration of intravenous recombinant tissue plasminogen activator (tPA).¹ Despite its effectiveness in improving neurological outcomes, the majority of patients with acute ischemic stroke are not treated with tPA, largely because they arrive after the currently approved 3-hour time window for administration of the medication. One of the potential approaches to increase treatment opportunities has been to expand the time window for treatment to 4.5 hours (95% CI 1.4% to 2.0%; Figure 3 in Wahlgren et al²). The frequency of symptomatic intracranial hemorrhage per the Cochrane/National Institute of Neurological Disorders and Stroke (NINDS) definition at 24 hours after tPA was 6.7% (95% CI 6.7% to 7.9%). By comparison, this frequency was slightly less than 8.6% in data taken from a pool of randomized controlled trials (Figure 2 in Wahlgren et al²). For efficacy, the frequency of scores of 0, 1, and 2 on the combined Rankin scale at 90 days was 54.8% (95% CI 53.5% to 56.1%) among tPA patients, which was comparable to the

del Zoppo et al Treatment of Acute Ischemic Stroke With Intravenous tPA 2947

The primary efficacy outcome in the ECASS-3 trial was the modified Rankin Scale score of 0 to 1 at 90 days, which was significantly greater with tPA (OR 1.41, 95% CI 1.01 to 1.97; P=0.04). The point estimate seen in ECASS-3 (OR for 1.28, 95% CI 1.00 to 1.65) was less than that seen in the ECASS-2 trial (OR for 1.28, 95% CI 1.00 to 1.65) and was similar to that in the results of subjects enrolled in the previous trials of tPA (OR 1.41, 95% CI 1.01 to 1.97).¹ These findings limit conclusions about these observations as assessed as a modified Barthel Index score ≥ 95 , a National Institutes of Health Stroke Scale score of 0 or 1, and a Glasgow Coma Scale score ≥ 13 at 90 days. ECASS-3 mortality in the 2 treatment groups was similar, although it was nominally higher with placebo.⁵

These findings represent an important advance in the treatment of acute ischemic stroke. The results, which are consistent with those of previous trials,^{1,2,4,7} provide evidence that intravenous tPA can be given safely to patients who are within the 3- to 4.5-hour time window for treatment with tPA. Although a longer time window for treatment with tPA has been tested previously,⁸ delays in evaluation and initiation of therapy should be avoided, because the opportunity for improvement is greater with earlier treatment.


tPA should be administered to eligible patients who can be treated in the time period of 3 to 4.5 hours after stroke (Class I Recommendation, Level of Evidence B). The eligibility criteria for treatment in this time period are similar to those for persons treated at earlier time periods, with any one of the following additional exclusion criteria: Patients older than 80 years, those taking oral anticoagulants with an international normalized ratio ≤ 1.7 , those with a baseline National Institutes of Health Stroke Scale score ≥ 25 , or those with both a history of stroke and diabetes. Therefore, for the 3-to-4.5-hour window, all patients receiving an oral anticoagulant are excluded regardless of their international normalized ratio. The relative utility of tPA in this time window compared with other methods of thrombus dissolution or removal has not been established. The efficacy of intravenous treatment with tPA within 3 to 4.5 hours after stroke in patients with these exclusion criteria is not well established (Class IIb Recommendation, Level of Evidence C) and requires further study.

Ancillary care for patients receiving tPA at 3 to 4.5 hours after ischemic stroke should be similar to that included in the

tPA Use Facts

- tPA has been shown to be effective
- tPA can be used clinically with success in the care of stroke patients
- Patients and society expect tPA use
- Clinicians remain divided Re: tPA use
- The ASA has now forced our hands
- We must lead efforts Re: use of tPA in the 3-4.5 hour window


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This Educational Session

- This introduction and perspective
- E Bradshaw Bunney, MD: The 3-4.5 hour window tPA data
- Panel discussion:
 - What do we think?
 - What should we do in our systems?
 - What are the best clinical options?

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Panel Discussion

- Yu-Feng Yvonne Chan, MD
 - Mt Sinai, NY, NY
 - SAEM Neuro Interest Group
- E Bradshaw Bunney, MD
 - Univ Illinois, Chicago, IL
 - FERNE
 - Residency Director
 - Get with the Guidelines

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Panel Discussion

- Jonathan Edlow, MD
 - Beth Israel Hospital, Boston, MA
 - FERNE
 - Neurological Emergencies
- Richard Shih, MD
 - Morristown Memorial Hospital, NJ
 - Residency Director
 - MEMC V Scientific Chair

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Clinical Questions

- Is the 3-4.5 hour window data adequately supportive of the ASA recommendation Re: tPA use?
- Will it be possible for clinicians to replicate the ECASS 3 outcomes?

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Systems Questions

- What must be done in our institutions in order to implement the ASA recommendations?
- What are some unique approaches to the use of tPA in the 3 -4.5 hour window?
- How should we continue to educate in order to optimize stroke patient care and EM clinical practice?

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Unanswered Questions

- Up to 3 hours: tPA first, then interventional radiology techniques
- In the 3 -4.5 hour window, what is the best approach?
- Has anything changed significantly?
- Where do we go from here?

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Conclusions

- Important disease state
- Patients and clinicians care about the use of tPA in optimizing outcomes
- This is an evolving process
- FERNE continues to educate
- Clinicians continue to clarify practice
- Systems continue to adapt to needs

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Questions?

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