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## AAEM Position Paper

### TISSUE PLASMINOGEN ACTIVATOR AND STROKE: REVIEW OF THE LITERATURE FOR THE CLINICIAN

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**Abstract—Background:** Alteplase (tPA) is a United States (US) Food and Drug Administration-approved treatment for acute ischemic stroke, though there are significant barriers to thrombolytic use, including Emergency Physicians' (EPs') concern for level of supporting evidence. **Study Objectives:** To review the medical literature on the topic of acute cerebrovascular accident (CVA) management and to offer EPs evidence-based recommendations for patients who present to the Emergency Department with an acute CVA. **Methods:** A MEDLINE literature search from 1990 to 2011 and limited to human studies written in English for articles with keywords of: CVA AND (thromboly\* OR alteplase). Guideline statements and non-systematic reviews were excluded. Studies targeting differences between specific populations (males vs. females) were excluded. Studies identified then underwent a structured review from which results could be evaluated. **Results:** There were 407 papers on thrombolytic use screened, and 15 appropriate articles were rigorously reviewed and recommendations given. **Conclusions:** tPA is an effective treatment for stroke when given in prepared stroke centers; EPs and hospitals treating stroke patients with tPA need to have the necessary resources in place and a specific plan for timely care of patients with acute stroke. © 2012 Published by Elsevier Inc.

**Keywords—stroke; CVA; cerebral vascular accident; TIA; tPA; alteplase; tissue plasminogen activator**

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#### INTRODUCTION

Alteplase, a tissue plasminogen activator (tPA) for acute ischemic stroke, has been controversial in the Emergency Medicine community, even though the therapy has been recommended by other bodies, such as the American Heart Association (1). Nearly half of those eligible for thrombolytic therapy receive the recommended treatment, amounting to 1–3% of all ischemic stroke patients in community settings (2). There are significant perceived barriers to thrombolytic use, including Emergency Physicians' (EPs') concern for level of supporting evidence (3). We acknowledge that the controversy continues; however, important additional randomized clinical trial and registry data from phase IV studies have been published since the 1995 National Institute of Neurological Disorders and Strokes trial and are of relevance to the practicing EP. This article seeks to review the medical literature on the topic of thrombolytics for ischemic stroke and to offer evidence-based recommendations to EPs for evaluation and treatment of patients who present with ischemic stroke. The clinical question being asked was: Is intravenous (i.v.) thrombolysis safe and effective for stroke? This work was done at the request of and published as a clinical practice statement by the American Academy of Emergency Medicine (AAEM) Clinical Guidelines Committee. Please see: [http://www.aaem.org/emtopics/tissue\\_plasminogen\\_activator.pdf](http://www.aaem.org/emtopics/tissue_plasminogen_activator.pdf).

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**Table 1. The Definitions of the Grades of Evidence of the Articles**

|         |  |
|---------|--|
| Grade A | Randomized clinical trials or meta-analyses (multiple clinical trials) or randomized clinical trials (smaller trials), <i>directly</i> addressing the review issue   |
| Grade B | Randomized clinical trials or meta-analyses (multiple clinical trials) or randomized clinical trials (smaller trials), <i>indirectly</i> addressing the review issue |
| Grade C | Prospective, controlled, non-randomized, cohort studies  |
| Grade D | Retrospective, non-randomized, cohort or case-control studies  |

## MATERIALS AND METHODS

This was a structured review of the literature on the topic of thrombolytics in stroke. A literature search of the National Library of Medicine's MEDLINE database's PubMed system was performed and limited to studies published from January 1990 to October 20, 2011 written in the English language. Keywords searched were: CVA AND (thromboly\* OR alteplase) and stroke AND (thromboly\* OR alteplase). After searching the articles found from these key word parameters, the reference sections were also reviewed for additional articles. Studies included for the final review were limited to randomized controlled trials, clinical trials, and prospective cohort studies and meta-analyses in human subjects. Case reports, case series, general review articles, and guideline statements were not included for the selection criteria for formal rigorous review. Studies targeting differences between specific populations (males vs. females) were excluded.

Two Emergency Medicine physicians independently conducted a structured review of identified thrombolytic studies, and each study was individually classified based on a Grade of Evidence Review. The level of the evidence was assigned a grade using the definitions as noted in Table 1, and were based on reference focus, specific research design, and methodology. Each of the selected articles was also subjected to detailed review and assigned a Quality Ranking based on a critical assessment with regards to quality of the design and methodology. This includes Design Consideration (e.g., focus, model structure, presence of controls) and Methodology Consid-

eration (actual methodology utilized). The definitions of the Quality Ranking scores are included in Table 2.

Independent review of the articles, as well as discussion and joint review by the authors, was undertaken to answer the clinical question. The references were sorted into three categories: supportive, neutral, and opposed. A table was constructed to assign the supportive references to the appropriate location using both the Grade of Evidence and the Quality of Evidence. Finally, recommendations were made based on the review of the literature and assigned a level of recommendation, which are defined in Table 3.

## RESULTS

The literature search provided 407 citations, including meta-analysis, high-quality clinical trials, and multicenter studies in core clinical journals. These abstracts were examined to assess relevance to study questions, and 18 manuscripts were selected based on their suspected relevance to the clinical question. One of these was identified in PubMed as a meta-analysis, but actually no meta-analysis was performed; two of these were subsequent updates of earlier Cochrane Reviews and were excluded. Fifteen total manuscripts were reviewed in detail (4–18). The same author performed a significant proportion of the reviews, and the articles are listed in Table 4. From these original articles, the reference sections were also reviewed, and no further novel articles were identified.

Table 5 includes the Grade of Evidence and the Quality of Evidence for each of the reviewed articles.

### Recommendation 1: *tPA is Safe and Effective for Acute Ischemic CVA*

*Level of recommendation: Class A.* The current human literature has found evidence of improved neurologic outcomes with use of tPA within 3 h that corroborates earlier studies. A significant reduction in disability was estimated, despite inclusion of trials enrolling most patients after 4.5 h. A positive effect was observed for secondary outcomes, such as achieving independence. Studies did demonstrate a correlation between protocol violations and increased mortality. Inclusion of high-risk patients, such as computed tomography (CT) scan evidence of

**Table 2. The Definitions of the Quality Ranking Scores of the Articles**

| Ranking        | Design Consideration Present | Methodology Consideration Present | Both Considerations Present |
|----------------|------------------------------|-----------------------------------|-----------------------------|
| Outstanding    | Appropriate                  | Appropriate                       | Yes, both present           |
| Good           | Appropriate                  | Appropriate                       | No, either present          |
| Adequate       | Adequate with possible bias  | Adequate                          | No, either present          |
| Poor           | Limited or biased            | Limited                           | No, either present          |
| Unsatisfactory | Questionable/none            | Questionable/none                 | No, either present          |

**Table 3. Definitions for Recommendations**

| Level of Recommendation                                    | Criteria for Level of Recommendation   | Mandatory Evidence   |
|--|--|--|
| Class A<br>(recommended with outstanding evidence)         | <ul style="list-style-type: none"> <li>• Acceptable</li> <li>• Safe</li> <li>• Useful</li> <li>• Established/definitive</li> </ul> | <ul style="list-style-type: none"> <li>• Level A/B grade</li> <li>• Outstanding quality</li> <li>• Robust</li> <li>• All positive</li> </ul>                                     |
| Class B<br>(acceptable and appropriate with good evidence) | <ul style="list-style-type: none"> <li>• Acceptable</li> <li>• Safe</li> <li>• Useful</li> <li>• Not yet definitive</li> </ul>     | <ul style="list-style-type: none"> <li>• Level A/B grade lacking</li> <li>• Adequate to good quality</li> <li>• Most evidence positive</li> <li>• No evidence of harm</li> </ul> |
| Class B 1  | <ul style="list-style-type: none"> <li>• Standard approach</li> </ul>  | <ul style="list-style-type: none"> <li>• Higher grades of evidence</li> <li>• Consistently positive</li> </ul>   |
| Class B 2  | <ul style="list-style-type: none"> <li>• Optional or alternative approach</li> </ul>   | <ul style="list-style-type: none"> <li>• Lower grades of evidence</li> <li>• Generally, but not consistently, positive</li> </ul>  |
| Class C<br>(not acceptable or not appropriate)             | <ul style="list-style-type: none"> <li>• Unacceptable</li> <li>• Unsafe</li> <li>• Not useful</li> </ul>                           | <ul style="list-style-type: none"> <li>• No positive evidence</li> <li>• Evidence of harm</li> </ul>   |
| Class indeterminate<br>(unknown)                           | <ul style="list-style-type: none"> <li>• Minimal to no evidence</li> </ul>   | <ul style="list-style-type: none"> <li>• Minimal to no evidence</li> </ul>   |

ischemic changes, seems to bias results toward finding no effect. Data from several post-marketing surveillance and other observational studies have established that the complication rate from this therapy is similar to what was observed in clinical trials (3–5). Additionally, the estimated rate of symptomatic intracranial hemorrhage (ICH) in post-marketing surveillance derived safety data was 5.2%, and no excess mortality was observed, which was similar to randomized controlled trial data.

#### Recommendation 2: *Early Thrombolytic Treatment of Stroke Improves Outcomes in Acute Ischemic Stroke*

*Level of recommendation: Class A.* Comparing tPA trials in which the time to treatment differs substantially, without adjustment for differences in baseline stroke severity, poses potential difficulties in generalization of results. Current summation of tPA literature for trials and meta-analysis demonstrates an overall improved outcome with early stroke treatment. Pooled analyses of randomized controlled stroke trials confirms benefit of i.v. thrombolysis for stroke and illustrates that time to treatment is a very important prognostic factor. Better results were noted in patients treated in < 90 min from onset of symptoms, though this may not be reflective of routine clinical practice. Benefit from tPA diminishes as time elapses during the first 3 h after onset of the stroke symptoms.

#### Recommendation 3: *Tissue Plasminogen Activator 3 to 4.5 Hours After Acute Ischemic Stroke Improves Outcome Without Increasing Morbidity*

*Level of recommendation: Class A.* Data from the recent European Cooperative Acute Stroke Study (ECASS) III trial demonstrates a significantly improved chance of a good outcome in patients treated up to 4.5 h after the onset of symptoms. Although differences exist between the

treatment and placebo groups for important prognostic variables (severity and history of prior stroke), the investigators performed adjustments to account for these baseline differences and continued to observe a persistent, significant clinical effect (6). The lower mean National Institutes of Health Stroke Scale and prevalence of prior stroke in the treatment group were not intentional but occurred by random chance. Further discussion is needed before widespread incorporation of the findings of ECASS III into broad clinical practice, although one important implication of this work is relevant to all EPs now: it is unlikely that a therapy that has demonstrated efficacy between 3 and 4.5 h would not be efficacious between 0 and 3 h.

ECASS III was a randomized, double-blind, controlled clinical trial of 800 patients with acute stroke treated with tPA or placebo between 3 and 4.5 h after symptom onset. The results of this trial were published in September of 2008. ECASS III shows an absolute benefit of 7% in good neurological outcomes at 3 months in patients treated with tPA. This is almost the same effect size that was predicted by the pooled analysis of the prior five smaller randomized, controlled trials, none of which were individually powered to detect that size effect (2). As in the previous ECASS trials, they excluded the highest-risk patients (e.g., elderly, extremely severe strokes, massive early ischemic signs on initial CT).

The symptomatic ICH rate was similar to that observed in prior trials, although the definition used by the ECASS III investigators (which more closely examined whether the ICH was the likely cause of the deterioration) yielded a rate of 2.4%. Mortality at 90 days was similar between treatment and placebo groups in ECASS III (7.7% and 8.4%, respectively), and lower than the older tPA stroke trials in which mortality was around 20% in treatment and placebo groups.

**Table 4. Details of the Reviewed Articles**

| List #<br>(Ref. #) | Article Information  | Grade | Quality  | Design, Size                              |
|--------------------|--|-------|----------|---|
| 1 (4)              | Hacke W, Donnan G, Fieschi C, et al. Association of outcome with early stroke treatment: pooled analysis of ATLANTIS, ECASS, and NINDS rt-PA stroke trials. <i>Lancet</i> 2004;363:768–74.   | A     | Good     | Meta-analysis<br>(Composite n = 2775)     |
| 2 (5)              | Graham GD. Tissue plasminogen activator for acute ischemic stroke in clinical practice: a meta-analysis of safety data. <i>Stroke</i> 2003;34:2847–50.   | B     | Adequate | Meta-analysis<br>(Composite n = 2639)     |
| 3 (6)              | Lansberg MG, Bluhmki E, Thijs VN. Efficacy and safety of tissue plasminogen activator 3 to 4.5 hours after acute ischemic stroke: a meta-analysis. <i>Stroke</i> 2009;40:2438–41.  | A     | Good     | Meta-analysis<br>(Composite n = 1622)     |
| 4 (7)              | Wahlgren N, Ahmed N, Dávalos A, et al. Thrombolysis with alteplase for acute ischaemic stroke in the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST): an observational study. <i>Lancet</i> 2007;369:275–82.  | D     | Adequate | Registry/Prospective Cohort<br>(n = 6483) |
| 5 (8)              | Mielke O, Wardlaw J, Liu M. Thrombolysis (different doses, routes of administration and agents) for acute ischaemic stroke. <i>Cochrane Database Syst Rev</i> 2004;(4):CD000514.   | B     | Adequate | Meta analysis<br>(Composite n = 1641)     |
| 6 (9)              | Wardlaw JM, Zoppo G, Yamaguchi T, Berge E. Thrombolysis for acute ischaemic stroke. <i>Cochrane Database Syst Rev</i> 2003;(3):CD000213.   | A     | Adequate | Meta analysis<br>(Composite n = 5727)     |
| 7 (10)             | Wardlaw JM, Sandercock PA, Berge E. Thrombolytic therapy with recombinant tissue plasminogen activator for acute ischemic stroke: where do we go from here? A cumulative meta-analysis. <i>Stroke</i> 2003;34:1437–42.   | A     | Adequate | Meta analysis<br>(Composite n = 5210)     |
| 8 (11)             | Wardlaw JM, Warlow CP, Counsell C. Systematic review of evidence on thrombolytic therapy for acute ischaemic stroke. <i>Lancet</i> 1997;350:607–14.  | A     | Adequate | Meta analysis<br>(Composite n = 3435)     |
| 9 (12)             | Hacke W, Kaste M, Bluhmki E, et al; ECASS Investigators. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. <i>N Engl J Med</i> 2008;359:1317–29.   | A     | Good     | Prospective Cohort<br>(n = 821)           |
| 10 (13)            | Clark WM, Wissman S, Albers GW, Jhamandas JH, Madden KP, Hamilton S. Recombinant tissue-type plasminogen activator (Alteplase) for ischemic stroke 3 to 5 hours after symptom onset. The ATLANTIS Study: a randomized controlled trial. Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke. <i>JAMA</i> 1999;282:2019–26. | A     | Good     | Prospective Controlled Trial<br>(n = 613) |
| 11 (14)            | Hacke W, Kaste M, Fieschi C, et al. Randomised double-blind placebo-controlled trial of thrombolytic therapy with intravenous alteplase in acute ischaemic stroke (ECASS II). Second European-Australasian Acute Stroke Study Investigators. <i>Lancet</i> 1998;352:1245–51.   | A     | Adequate | Prospective Controlled Trial<br>(n = 800) |
| 12 (15)            | Tissue plasminogen activator for acute ischemic stroke. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. <i>N Engl J Med</i> 1995;333:1581–7.   | A     | Good     | Prospective Controlled Trial<br>(n = 623) |
| 13 (16)            | Hacke W, Kaste M, Fieschi C, et al. Intravenous thrombolysis with recombinant tissue plasminogen activator for acute hemispheric stroke. The European Cooperative Acute Stroke Study (ECASS). <i>JAMA</i> 1995;274:1017–25.  | A     | Adequate | Prospective Controlled Trial<br>(n = 620) |
| 14 (17)            | Cronin CA. Intravenous tissue plasminogen activator for stroke: a review of the ECASS III results in relation to prior clinical trials. <i>J Emerg Med</i> 2010;38:99–105.   | A     | Adequate | Meta analysis<br>(Composite n = 2733)     |
| 15 (18)            | Bhatnagar P, Sinha D, Parker RA, et al. Intravenous thrombolysis in acute ischaemic stroke: a systemic review and meta-analysis to aid decision making in patients over 80 years of age. <i>J Neurol Neurosurg Psychiatry</i> 2011;82:712–7.   | A     | Adequate | Meta analysis<br>(Composite n = 3556)     |

## DISCUSSION

The primary goal in conducting this literature search was to identify optimal management for a patient who presents with an ischemic cerebrovascular accident (CVA). Stroke is the fourth leading cause of death and a leading cause of adult disability in the United States and an important public health problem worldwide (19). The Emer-

gency Department is often the focal point of decision-making and treatment initiation for acute ischemic stroke.

Additional trial and post-marketing surveillance data have accumulated since tPA was approved by the Food and Drug Administration (FDA) in 1996. The data were reviewed and synthesized as a clinical practice advisory for the AAEM. The key findings of this review show that i.v. thrombolysis can be an effective treatment for

**Table 5. Quality and Grade of the Supportive Evidence**

| Quality/Grade  | Supportive Evidence (Article # Referenced) |     |   |   |   |   |
|----------------|--|-----|---|---|---|---|
|                | A  | B   | C | D | E | F |
| Outstanding    |  |     |   |   |   |   |
| Good           | 1,3,9,10,12                                |     |   |   |   |   |
| Adequate       | 6,7,8,11,13,14,15                          | 2,5 |   | 4 |   |   |
| Poor           |  |     |   |   |   |   |
| Unsatisfactory |  |     |   |   |   |   |

stroke when delivered under the right circumstances up to 4.5 h from symptom onset.

EPs play a critical role in this process and often must discuss the benefits and risks of the therapy directly with patients and families; this is especially true in centers without organized acute stroke teams, structured plans for managing these patients, or substantial involvement from Neurology. A pooled analysis of the three major thrombolytic trials utilizing alteplase at the established dosing confirmed benefit within 3 h and suggested that benefit might exist up to 4.5 h (2). It is hoped that a recently completed National Institutes of Health-funded cluster randomized trial will soon provide high-quality, prospective data regarding use in community practice (20).

#### *Resources for Developing Local Protocols and Consent Scripts or Templates*

We would urge clinicians to examine and become familiar with these tools *before* considering using them as an adjunct to the standard consent process. Ideally, these tools would assist the clinician in developing a standardized consent process for their institution. Clinicians should consider discussing and documenting reasons for not offering treatment in both potentially eligible and non-eligible patients.

1. The Outcome Wheel: a potential tool for shared decision-making in ischemic stroke thrombolysis—<http://www.sem-bc.com/cvatoolkit/>—provides a visual tool that estimates likelihood of being disability free, disabled, or dead when treated or not treated with i.v. tPA and prompts for exclusions. Requires Microsoft Excel (Microsoft Corporation, Redmond, WA).
2. Stroke thrombolytic predictive instrument—<https://research.tufts-nemc.org/asat/>—provides estimates of likelihood of good outcome with and without treatment based on age, glucose, blood pressure, and severity.
3. tPA for Stroke—Potential Benefit, Risk and Alternatives—<http://www.aaem.org/education/tpaedtool-AAEM.pdf>—handout developed by AAEM.
4. Activase patient information—[http://www.activase.com/media/Activase\\_PatientBroch.pdf](http://www.activase.com/media/Activase_PatientBroch.pdf)—handout

developed by the manufacturer, Genentech (South San Francisco, CA). As such, the brochure is regulated and examined by the FDA for accuracy.

As noted above, the literature review for this clinical guideline focused on studies that involved rigorous methodologies to evaluate tPA in humans. We did not include specific case reports or case series reporting utilization of tPA. We also did not include animal studies, which are often more limited in scope and have questionable applicability to clinical human findings.

## CONCLUSIONS

These results represent supportive if not confirmatory trial data on the use of thrombolysis in acute ischemic stroke that many colleagues have been requesting for years to settle disagreements about the adequacy of the supporting data for this rather persistent and often contentious clinical question. Alteplase has demonstrated benefit in academic centers and organized stroke centers, but the benefit is not established at other types of hospitals. Additionally, all hospitals should have a protocol or plan in place (i.e., stroke team) for the care of suspected acute stroke patients. Individual EPs have been faulted for utilizing or withholding thrombolytics when a bad outcome has occurred. The institution of a structured stroke plan incorporating all the stroke resources available at a hospital helps to minimize exposure to this type of retrospective criticism. EPs working in sites without an institutional plan for stroke care are in a suboptimal situation, and the discussion regarding use of thrombolytics for acute stroke does not pertain to these settings. EPs should work with their hospitals to ensure that the proper systems are in place to evaluate and treat stroke patients and deliver treatment when appropriate.

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