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INTRAVENOUS RECOMBINANT TISSUE PLASMINOGEN ACTIVATOR AND ISCHEMIC STROKE: FOCUSED UPDATE OF 2010 CLINICAL PRACTICE ADVISORY FROM THE AMERICAN ACADEMY OF EMERGENCY MEDICINE

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□ **Abstract—Background: Stroke treatment is a continuum that begins with the rapid identification of symptoms and treatment with transition to successful rehabilitation. Therapies for acute ischemic stroke (AIS) may vary based on anatomic location, interval from symptom onset, and coexisting health conditions. Successful therapy requires a seamless systematic approach with coordination from prehospital environment through acute management at medical facilities to disposition and long-term care of the patient. The emergency physician must balance the benefits and risks of alteplase recombinant tissue plasminogen activator (rtPA) for AIS management. Objective: We review the recent medical literature on the topic of AIS and assess intravenous rtPA for the following questions: 1) is there any applicable, new, high-quality evidence that the benefits of intravenous rtPA are justified in light of the harms associated with it, and 2) if so, does the evidence clarify which patients, if any, are most likely to benefit from the treatment. Methods: A MEDLINE literature search from January 2010 to October 2016 and limited to human studies written in English for articles with keywords of cerebrovascular accident and (thromboly* OR alteplase). Guideline statements and nonsystematic 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: Three hundred twenty-two papers on thrombolytic use were screened and nine appropriate articles were rigorously reviewed and recommendations given. Conclusions: No new studies published between 2010 and 2016 meaningfully reduced uncertainty regarding our understanding of the benefits and harms of intravenous rtPA for AIS. Discussions regarding benefit and harm should occur for patients, and risk prediction scores may facilitate the conversation. Published by Elsevier Inc.**

□ **Keywords—AIS; alteplase; cerebrovascular accident; CVA; rtPA; stroke; tissue plasminogen activator**

INTRODUCTION

In 2010, the American Academy of Emergency Medicine (AAEM) issued a clinical practice advisory reviewing the available evidence for recombinant tissue plasminogen activator (rtPA) in patients with acute ischemic stroke (AIS). The objective of this focused review is to assess the impact of new evidence regarding intravenous (IV) rtPA in AIS that has emerged since 2010. While a previous AAEM clinical practice committee statement

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summarized the evidence available at the time with specific recommendations, many emergency physicians (EPs) continue to have concerns regarding rtPA use for AIS. The major summary findings of the 2010 statement were as follows:

1. rtPA is an effective treatment for stroke when given in academic medical centers and prepared stroke centers.
2. EPs should have necessary resources (i.e., a stroke team) to optimally care for patients with a suspected stroke.
3. Hospitals should formulate a plan for timely care of patient with suspected AIS.

This current update addresses two primary questions for the clinician: 1) are there any applicable, new, high-quality evidence that the benefits of rtPA are justified in light of the harms associated with it and, if so, 2) does the evidence clarify which patients, if any, are most likely to benefit from the treatment? This review focuses on IV rtPA. Other interventions, including intra-arterial and mechanical thrombus extraction devices, are excluded from this review. Please see AAEM consensus statements regarding these topics for more information.

Stroke remains a significant contributor to the burden of disease in the United States. Annually, almost 800,000 people in the United States have suffered a stroke, with 610,000 of these as initial disease presentation and 185,000 as recurrent strokes (1). Almost three quarters of strokes occur in people >65 years of age, and for every decade over 55 years of age, the risk of experiencing a stroke is more than doubled (2,3). Stroke is the fifth leading cause of mortality and remains a leading cause of serious long-term disability for adults (1,2). One in 20 deaths are attributable to stroke, killing >130,000 Americans each year (3). Approximately 3% of men and 2% of women reported that they were disabled because of a stroke (4). The economic burden of stroke is currently over $72 billion in annual costs, with total direct medical stroke-related costs projected to triple by 2030 (5,6).

By 2030, an additional 3.4 million U.S. adults are projected to experience a stroke, a 20.5% overall increase in prevalence from 2012 (6). The aging population is expected to contribute to overall stroke mortality prevalence among the population ≥65 years of age (6).

Stroke treatment is a continuum that begins with the rapid identification of symptoms and treatment with transition to successful rehabilitation. Therapies for AIS may vary based on anatomic location, interval from symptom onset, and coexisting health conditions. EPs must balance the benefits and risks of rtPA for AIS management. Numerous trials have demonstrated benefit in reducing disability after AIS. However, a major risk of rtPA treatment in AIS is symptomatic intracerebral hemorrhage (sICH), which occurs more often among treated patients than placebo (7). This risk coupled with other factors provide significant challenges for EPs when considering rtPA for AIS. Eligible patients are often not treated because of mild stroke symptoms or clinical improvement, perceived protocol exclusions, emergency department referral delay, and significant comorbidity (8–10).

MATERIALS AND METHODS

This was a structured review of the literature using the MEDLINE database on the topic of thrombolytics in stroke from January 2010 to October 2016. The search for articles was limited to human studies written in English with keywords of CVA and (thromboly* OR alteplase). Guideline statements, nonsystematic reviews, case reports, and case series were excluded. Studies targeting differences between specific populations (males vs. females) were also excluded. Studies included for the final review were limited to randomized controlled trials, clinical trials, and prospective cohort studies and meta-analyses in human subjects. The literature search was independently conducted by three EPs who reached consensus on articles to include in the update. The results of the search were categorized in two tiers based on research design presented in the manuscript.

An independent standardized structured review was performed initially. Each study was individually classified based on a grade according to the Clinical Practice Committee's Evidence Review process for evaluating the manuscript's quality. Assignment of individual study grades were based on definitions noted in Table 1 and show the level of evidence. Reference focus, specific research design, and methodology were individual components of the assessment. A quality ranking for the selected articles comprised design considerations

Table 1. Definitions of the Grades of Evidence

Grade	Definition
A	Randomized clinical trials or meta-analyses (multiple clinical trials) or randomized clinical trials (smaller trials), directly addressing the review issue
B	Randomized clinical trials or meta-analyses (multiple clinical trials) or randomized clinical trials (smaller trials), indirectly addressing the review issue
C	Prospective, controlled, nonrandomized, cohort studies
D	Retrospective, nonrandomized, cohort or case-control studies