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## Use of Thrombolytic Therapy in Patients With Acute Ischemic Stroke

This systematic review abstract is taken from Wardlaw JM, del Zoppo G, Yamaguchi T. Thrombolysis for acute ischaemic stroke (Cochrane Review). In: The Cochrane Library. Issue 2. Oxford, United Kingdom: Update Software; 2001.

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0196-0644/2002/\$35.00 + 0

47/1/122205

doi:10.1067/mem.2002.122205

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## Use of Thrombolytic Therapy in Patients With Acute Ischemic Stroke

[Lang ES. Use of thrombolytic therapy in patients with acute ischemic stroke. *Ann Emerg Med.* March 2002;39:296-298.]

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### TAKE HOME MESSAGE

In appropriately selected patients treated in centers that possess the necessary expertise, intravenous thrombolytic therapy reduces the risk of death or dependency. However, this treatment also increases the risk of early death because of intracranial hemorrhage (ICH). Recombinant tissue plasminogen activator (rtPA) administered within 3 hours of stroke onset seems to carry the greatest benefit and the lowest risk.

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### OBJECTIVE

To determine whether low molecular weight heparin is superior to heparin therapy for the treatment of patients with venous thromboembolism.

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### DATA SOURCES

The Cochrane Stroke Group maintains its own database of relevant studies in a "Specialized Register" that relies on electronic and hand searching. This register was searched in March 1999 for the purpose of selecting studies for this review. An additional search was conducted in EMBASE from 1980 to February 1997. The Stroke Group also contacted the principal investigators of trials conducted in the United States, Europe, China, and Japan, as well as drug manufacturers. The review was updated in July 1999.

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### STUDY SELECTION

Studies were included if they were randomized, controlled trials that compared the use of a thrombolytic agent

(urokinase [UK], recombinant pro-urokinase [rp-UK], streptokinase [SK], rtPA, or lumbrokinase) with placebo. Eligible studies recruited patients with presumed ischemic stroke who underwent computed tomography (CT) scanning to exclude hemorrhage before randomization.

#### DATA EXTRACTION

All 3 authors contributed to data collection with the tabulated results cross-checked and verified by the principal investigator of each study. The principal outcome measures were both early death (within 7 to 10 days) and all-cause mortality at the end of follow-up for each study (typically 3 months, range 1 to 6). Other outcomes included symptomatic or fatal ICH within 7 to 10 days and "poor functional outcome" as reflected in the combined outcome of death or dependency at the end of study follow-up. Dependency was defined as a modified Rankin score of 3 (moderate disability, requiring some help, but able to walk without assistance) to 6 (death). Results for these outcomes are expressed as an odds ratio (OR) with 95% confidence intervals (CIs). Subgroup analyses focused on variables related to stroke severity, thrombolytic agent used, time to treatment, and concomitant use of antithrombotic agents (aspirin and heparin).

#### MAIN RESULTS

There were 17 trials in the review, resulting in 5,216 included patients. Intravenous thrombolytic agents were used in 15 of the 17 trials; intra-arterial thrombolysis was used in the remaining 2. Eight of the trials used intravenous rtPA accounting for 56% of the data included in the review. Four trials examined SK, 3 used UK, and the 2 intra-arterial studies used rp-UK. In terms of study quality, 15 of the trials were conducted in a double-blind manner, and although only 10 studies conducted an intention-to-treat (ITT) analysis, the principal investigators provided the data necessary to include only ITT results in this review.

Pooling data from all trials, the risk of early death (7 to 10 days) was increased significantly as a result of thrombolytic administration (16.6% versus 9.8% [OR 1.85; 95% CI 1.48 to 2.32]). Similarly, thrombolysis was associated with an increase in fatal ICH (5.4% versus 1.0% [OR 4.15; 95% CI 2.96 to 5.84]). All cause mortality at the end of study follow-up was higher in the thrombolysis group (16% versus 19% [OR 1.31; 95% CI 1.13 to 1.52]). In absolute terms, this amounts to an increase of 36 deaths at the end of follow-up for every 1,000 patients treated with thrombolytics. Thrombolytic therapy reduced the risk of

the combined end point of death or dependency from 60% to 55% (OR 0.83; 95% CI 0.73 to 0.94) or 44 fewer patients dead or dependent for every 1,000 patients treated.

Concomitant use of antithrombotic drugs was associated with nonsignificant trends to increased mortality rates and no evidence of benefit. An analysis of stroke severity based on case fatality rates also failed to identify a subgroup of stroke patients who might derive particular benefit from thrombolysis. However, in terms of time to treatment and agent used, there appears to be a clinically and statistically significant advantage associated with early reperfusion therapy. Specifically, for patients treated with rtPA in less than 3 hours, the risk of death or dependency was reduced from 68% to 55% (OR 0.58; 95% CI 0.5 to 0.7) or 126 fewer patients dead or dependent for every 1,000 treated. The authors advise caution on the interpretation of this last result because it is heavily weighted by data from the National Institute of Neurological Disorders and Stroke (NINDS)<sup>1</sup> trial, in which differences in baseline characteristics between the intervention and control arms might have led to an inflated measure of benefit. There was no significant heterogeneity of treatment effect between trials for comparisons of early death and fatal ICH, as well as for the composite end point of dependency or death. There was, however, significant heterogeneity for the comparisons of death at the end of follow-up and the outcome of death or dependency when considering the 6 relevant rtPA studies alone.

#### CONCLUSIONS

When considering all thrombolytic agents together, their use in acute ischemic stroke increases the risk of death within the first week to 10 days after treatment, usually as a result of a fatal ICH. Although less pronounced, this increase in mortality is sustained beyond this initial treatment period. However, thrombolysis improves functional status in the survivors of acute stroke such that its use is associated with a longer-term reduction in the risk of the combined outcome of either death or dependency. These positive effects are seen most clearly in patients treated within 3 hours of symptom onset and in those who receive rtPA as the thrombolytic agent. Similarly, this particular subgroup of patients does not appear to be at increased risk of death beyond the 7- to 10-day window.

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COMMENTARY: CLINICAL IMPLICATION

The applicability of this evidence into routine clinical practice is controversial and raises unique challenges that may severely hamper the effectiveness of this intervention in many emergency departments. Presentations that mimic stroke, concerns regarding the availability and reliability of rapid CT scan interpretation, and the small proportion of stroke patients who meet eligibility criteria call into doubt whether the widespread use of thrombolysis can be advocated. Studies of the “real-life” effectiveness of rtPA have reached conflicting conclusions on the safety and efficacy of this intervention in clinical practice.<sup>2,3</sup>

This thorough and methodologically rigorous systematic review synthesizes all data currently available on the topic. In summary, the evidence presented here suggests that clinicians are justified in withholding thrombolytic therapy if they (or their patients) are uncomfortable with the definite risks or feel that the treatment environment is suboptimal. The same evidence also supports the administration of thrombolytic therapy in specialized centers that have identified the appropriate candidates.

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EVIDENCE-BASED MEDICINE TEACHING POINTS

**Intention-to-Treat.** ITT is the principle of attributing all patients to the group in which they were randomized, even if they did not receive some part or all of the intervention they were allocated to. Excluding patients who are “noncompliant” or who become too sick (or too well) to receive the intervention or analyzing them as if they were in the control group destroys the unbiased comparison provided by randomization. Noncompliant or excluded patients often have worse outcomes (or better) because of factors other than those related to the treatment itself.

1. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. *N Engl J Med.* 1995;333:1581-1587.
2. Albers GW, Bates VE, Clark WM, et al. Intravenous tissue-type plasminogen activator for treatment of acute stroke. The Standard Treatment with Alteplase to Reverse Stroke (STARS) Study. *JAMA.* 2000;283:1145-1150.
3. Katzan IL, Furlan AJ, Lloyd LE, et al. Use of tissue-type plasminogen activator for acute ischemic stroke: the Cleveland area experience. *JAMA.* 2000;283:1151-1158.