

# Tissue plasminogen activator improved function at 6 and 12 months after ischemic stroke

Kwiatkowski TG, Libman RB, Frankel M, et al., for the National Institute of Neurological Disorders and Stroke Recombinant Tissue Plasminogen Activator Stroke Study Group. **Effects of tissue plasminogen activator for acute ischemic stroke at one year.** *N Engl J Med.* 1999 Jun 10;340:1781-7.

## QUESTION

What is the efficacy of intravenous recombinant tissue plasminogen activator (tPA) in patients with acute ischemic stroke?

## DESIGN

Randomized, blinded (patients, clinicians, and outcome assessors),\* placebo-controlled trial with follow-up at 6 and 12 months.

## SETTING

{8 U.S. clinical centers and affiliated hospitals.}†

## PATIENTS

{624 patients (mean age 76 y, 58% men, 65% white) who had an acute ischemic stroke and no evidence of intracranial hemorrhage. Exclusion criteria were uncontrolled hypertension, possible subarachnoid hemorrhage, recent hemorrhage or arterial puncture at a noncompressible site, seizure at stroke onset, recent use of anticoagulants or heparin, elevated partial thromboplastin time, prothrombin time > 15 seconds, platelet counts < 100 000/mm<sup>3</sup>, or glucose level < 2.7 mmol/L or > 22.2 mmol/L.}‡ Follow-up was 96%.

## INTERVENTION

Patients were stratified by clinical center and time to start of treatment (< 90 or 91

to 180 min) and allocated to alteplase (recombinant tPA), 0.9 mg/kg of body weight ( $n = 312$ ), or to placebo ( $n = 312$ ).

## MAIN OUTCOME MEASURES

A global statistic derived from scores on the Barthel Index, modified Rankin Scale, and Glasgow Outcome Scale (GOS). 6- and 12-month data were post hoc analyses.

## MAIN RESULTS

More patients in the tPA group had minimal or no disability (Barthel score 95 or 100, modified Rankin score 0 or 1, or GOS score 1) than did patients in the placebo group at 6 and 12 months (odds ratio for the global statistic for both periods 1.7, 95% CI 1.2 to 2.3). Each individual measure also showed less disability at both periods (12-mo data in Table

( $P \leq 0.006$  for all comparisons). The groups did not differ for all-cause mortality at 6 months (21% for tPA vs 23% for placebo,  $P = 0.3$ ) or 12 months (24% vs 28%,  $P = 0.3$ ).

## CONCLUSION

Tissue plasminogen activator improved the rate of minimal or no disability at 6 and 12 months in patients with ischemic stroke.

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\*See Glossary.

†*N Engl J Med.* 1995;333:1581-7.

## Patients with minimal or no disability at 12 months after stroke with tissue plasminogen activator (tPA) vs placebo‡

Scale	tPA	Placebo	RBI (95% CI)	NNT (CI)
Barthel Index Score $\geq 95$	50%	38%	29% (8 to 55)	9 (5 to 29)
Modified Rankin Scale score of 0 or 1	41%	28%	46% (17 to 83)	8 (5 to 19)
Glasgow Outcome Scale score of 1	43%	32%	33% (8 to 63)	10 (6 to 34)

‡Abbreviations defined in Glossary; RBI, NNT, and CI calculated from data in article.

## COMMENTARY

Kwiatkowski and colleagues extend information on the National Institute of Neurological Disorders and Stroke (NINDS) tPA trial, finding that the significant benefit in functional outcome at 3 months seen with alteplase in acute ischemic stroke is maintained to 12 months (1). However, this analysis is post hoc (6- and 12-mo follow-up were not prespecified outcomes), and other alteplase trials (2, 3) have not reported data beyond 3 months. Therefore, the findings remain provisional.

The routine use of thrombolysis in acute ischemic stroke is limited. First, alteplase is currently licensed only in North America and New Zealand. Second, alteplase can be used only within 3 hours of stroke onset if the NINDS protocol (1) is followed: Patients need to get to the hospital within 2.25 hours to allow time for clinical and computed tomography (CT) workup. If alteplase was shown to be effective when given later, for example, after 6 hours (as in the European Cooperative Acute Stroke Study [ECASS] trials [2, 3]), the incentive would be greater to set up emergency referral and hospital systems (including routine 24-hour CT scan availability) to facilitate its

delivery. Third, the existing alteplase trials have given mixed results—NINDS results were positive, but those of ECASS I and II (and the unpublished Alteplase Thrombolysis for Acute Noninterventive Therapy in Acute Stroke [ATLANTIS] studies) were neutral (1–4). The small study sizes may be the cause of this discrepancy. Finally, < 3000 patients have been included in stroke alteplase trials (in contrast to > 60 000 patients studied in thrombolysis trials in acute myocardial infarction). Because thrombolysis is not without substantial hazard, another, much larger trial is urgently required to determine whether, when, and to whom alteplase can be given (4).

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## References

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