

Is Thrombolytic Therapy Associated With Increased Mortality?

Meta-analysis of Randomized Controlled Trials

Ahmet Ergin, MD, PhD, MPH; Nesrin Ergin, MD

Background: Although thrombolytic therapy has shown substantial benefits in neural outcomes, concerns remain regarding the association between thrombolytic therapy and possible increased mortality.

Objective: To determine the mortality risk of certain thrombolytic agents that are a treatment option for acute ischemic stroke.

Data Sources, Extraction, and Synthesis: Studies were identified using MEDLINE, the Cochrane Central Register of Controlled Trials, and the reference lists of the articles selected. Randomized placebo-controlled trials of thrombolytic agents for the treatment of acute ischemic stroke patients were eligible. Study quality was evaluated using a previously validated scale. Data were extracted in duplicate by two independent investigators. All-cause mortality during follow-up was the main outcome. Random effects models were used to pool the individual effects of trials. Several preplanned sensitivity

and subgroup analyses were completed to explain the heterogeneity among trials. Odds ratios, absolute risk differences, and numbers needed to harm were calculated.

Results: Eleven placebo-controlled randomized trials of thrombolytic agents involving 3709 participants were included in the analysis. Thrombolytic therapy was associated with an insignificant increase in mortality (odds ratio, 1.07; 95% confidence interval, 0.8-1.39; $P = .3$). The treatment was associated with an absolute increased risk of mortality of 11 per 1000 persons (95% confidence interval, -24 to 48; $P = .3$), and the number needed to harm was 84 (the 95% confidence interval included 0).

Conclusion: These findings suggest that thrombolytic therapy does not significantly increase all-cause mortality.

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Author Affiliations:

Department of Epidemiology, Tulane University School of Public Health and Tropical Medicine (Dr A. Ergin), and Department of Neurology, Tulane University School of Medicine (Dr N. Ergin), New Orleans, La. Dr A. Ergin is now with the Department of Public Health, Pamukkale University School of Medicine, Denizli, Turkey. Dr N. Ergin is now with Özel Saglik Hospital, Denizli, Turkey.

SINCE THE NATIONAL INSTITUTE of Neurological Disorders and Stroke Recombinant Tissue Plasminogen Activator Stroke Study demonstrated substantial benefits in neurological outcomes at 3 and 12 months,^{1,2} thrombolytic therapy has become a subject of great interest in stroke medicine. However, neurologists' enthusiasm for the efficacy of thrombolytic agents is tempered by their concern about a rate of early symptomatic intracranial hemorrhage that is 3.5 times higher with this treatment and about possible increased overall mortality.^{3,4} Sample sizes of individual thrombolytic therapy trials have been insufficiently large to evaluate the rare mortality incidents associated with the treatment. With its increased power, meta-analysis has a greater ability than individual trials to evaluate the risk of mortality. A previous meta-analysis found significantly in-

creased death from all causes with thrombolysis.⁴ However, this meta-analysis pooled data from streptokinase trials. All major streptokinase trials were terminated early because of an unacceptable rate of major adverse effects as well as the inefficacy of streptokinase in acute stroke therapy.⁵⁻⁷ Furthermore, a meta-analysis of individual patient data from streptokinase trials did not indicate any beneficial effect of streptokinase in any subgroup.⁸ As a result, future use of streptokinase in acute ischemic stroke has become very unlikely.

The objectives of this study were to determine the all-cause mortality risk of certain thrombolytic agents for acute ischemic stroke that either are currently available or may become available in the future and to assist clinicians by providing a review focused on new information from recently published and ongoing studies.

METHODS

LITERATURE SEARCH

A database search of the English-language literature was conducted using MEDLINE and the Cochrane Central Register of Controlled Trials (1966–March 2003). A thorough manual review of reference lists from original research and review articles was performed. Abstract collections from pertinent conferences were sought as well. In addition, the National Institutes of Health Web sites, the National Stroke Association, and individual experts in the field of cerebrovascular diseases served as valuable resources.

STUDY SELECTION

Published manuscripts, abstracts, and interim reports were eligible for inclusion in this meta-analysis. Randomized controlled trials were included if they were pertinent to the research question, conducted with human subjects, and informative about all-cause mortality during follow-up. The population of interest was patients treated with thrombolytic therapy. Studies of thrombolytic agents vs another agent and studies with historical controls were excluded.

Fourteen potentially eligible studies were identified.^{1,9-21} Of these, 3 were excluded from analysis. The Emergency Management of Stroke Bridging Trial¹⁹ was not eligible because it compared intravenous and local intra-arterial recombinant tissue plasminogen activator (rt-PA) therapy with intravenous-only rt-PA therapy. The Standard Treatment With Alteplase to Reverse Stroke study²⁰ and the Canadian Activase for Stroke Effectiveness Study²¹ were not eligible because they did not have controls. Ancrod trials^{16,17} were included in the analysis because ancrod promotes the release of endogenous tissue plasminogen activator.^{22,23} Although thrombolysis is only one of several presumed mechanisms of ancrod's effect, a sensitivity analysis excluding the ancrod trials from this meta-analysis showed the robustness of the pooled estimate. Therefore, we decided to keep the ancrod trials in our pooled estimate and reported a separate pooled estimate without the ancrod trials. The commercial availability of ancrod in Europe and Canada since the 1970s was a contributing factor in the inclusion of the ancrod trials in this meta-analysis.

QUALITY ASSESSMENTS AND DATA EXTRACTION

Once studies were determined to be eligible for the meta-analysis, two investigators independently assessed study quality using a previously validated scale.²⁴ The scale mainly evaluates trials regarding their blinding, randomization, and statistical analysis. A standard form was used for data extraction for demographic and clinical characteristics of study participants, ancillary medication, dosing regimens, and nature and definition of outcome assessments. Published reports were the primary source of the data for this meta-analysis, and there was no attempt to obtain data directly from the primary investigators of the eligible studies.

STATISTICAL ANALYSIS

Both odds ratio (OR) and absolute risk difference were used to measure the relationship between thrombolytic therapy and all-cause mortality. Mortality rates for the treatment and placebo groups were recorded for each study using 2 × 2 tables. The ORs and absolute risk differences and their 95% confidence intervals (CIs) were calculated individually for each study.

Numbers needed to harm, the number of patients that would have to be treated to cause one additional adverse outcome, were also calculated if a significant treatment effect was observed (ie, if the 95% CI of the OR did not include 1).²⁵

The ORs from individual studies were transformed to their natural logarithm (ln[OR]) values before pooling. Pooled ln(OR) values were then calculated by assigning each a weight—the reciprocal of the variance of each study's ln(OR).²⁶ Homogeneity of the ln(OR) values across studies was tested using the DerSimonian and Laird Q test statistic, which sums the squared deviation of each individual ln(OR) from the pooled ln(OR) weighted by the reciprocal of its estimated variance.²⁷ Random effects models were used to pool the individual effects of trials. Effect measures were back-transformed and re-expressed as ORs. The pooled absolute risk difference was calculated by assigning each a weight—the reciprocal of the variance of each study's absolute risk difference. Two-tailed tests of statistical significance were used, with an α level of 0.05. Sensitivity analyses were performed to determine whether the pooled estimates were robust for different study and participant characteristics. Limited numbers of subgroup analyses were completed to explain the heterogeneity among the results of individual trials. The potential for publication bias was examined using a funnel plot, with sample size was plotted against log(OR).

RESULTS

Data from 11 trials with 3709 participants were analyzed. Participant and study design characteristics for these trials are presented in **Table 1**. With the exception of 3 studies,^{9,10,15} all had relatively large sample sizes. In 7 of the trials rt-PA was the thrombolytic agent used.^{1,9-14} Placebo was used as control in most of the trials, except the prourokinase trials,^{15,16} which used heparin as control. All but 2 of the prourokinase trials^{15,16} used an intravenous route for drug administration. Mean follow-up time was 5 months (range, 1-12 months).

Thrombolytic therapy was associated with an insignificant increase in mortality by the end of follow-up (OR, 1.07; 95% CI, 0.8-1.39; $P=.3$) (**Table 2**). The treatment was associated with an absolute increased risk of mortality of 11 per 1000 persons (95% CI, -24 to 48; $P=.3$), and the number needed to harm was 84 (the 95% CI included 0).

Thrombolytic therapy was associated with an insignificant increase in mortality during the first month of therapy (OR, 1.14; 95% CI, 0.75-1.73; $P=.6$) (**Table 3**). Additionally, treatment was associated with an insignificant increase in mortality when the ancrod trials were excluded (OR, 1.13; 95% CI, 0.77-1.68; $P=.2$). In contrast, for rt-PA trials that had treatment within 3 hours, treatment was associated with an insignificant decrease in mortality (OR, 0.98; 95% CI, 0.63-1.53; $P=.8$). When only trials that used rt-PA were included, treatment was associated with an insignificant increase in mortality (OR, 1.25; 95% CI, 0.87-1.78; $P=.1$) (**Figure**).

A plot of sample size vs OR showed no obvious pattern, suggesting no publication bias (data not shown).

COMMENT

This meta-analysis indicates that thrombolytic therapy does not significantly increase all-cause mortality at the

Table 1. Characteristics of Randomized Controlled Trials Included in the Meta-analysis

Source	Country of Origin	Treatment/ Placebo, No. of Participants	Type of Stroke	Blinding	Treatment Regimen			Follow-up, mo
					Medication Used	Timing of Treatment, h	Ancillary Medication	
Mori et al, 1992 ⁹	Japan	19/12	ICA / MCA (proven by angiogram)	D	rt-PA, approximately 40 or 60 mg (20 or 30 MIU)	6	Avoid for 24 h	1
Haley et al, 1993 ¹⁰	US	14/13	All (except severe)	Open	rt-PA, 0.85 mg/kg; 90 mg max	3	Avoid heparin IV for several hours	3
NINDS, 1995 ¹	US	312/312	All (except severe)	D	rt-PA, 0.9 mg/kg; 90 mg max	3	Avoid for 24 h	12
ECASS, 1995 ¹¹	Europe	313/307	Carotid territory	D	rt-PA, 1.1 mg/kg; 100 mg max	6	Avoid aspirin for 24 h; SC heparin allowed during first 24 h	3
ECASS II, 1998 ¹²	Europe/ Australia/ New Zealand	409/391	Carotid territory	D	rt-PA, 0.9 mg/kg; 90 mg max	6	Avoid aspirin for 24 h; SC heparin allowed during first 24 h	3
ATLANTIS A, 2000 ¹³	US	71/71	All (except severe)	D	rt-PA, 0.9 mg/kg; 90 mg max	6	Avoid for 24 h	3
ATLANTIS B, 1999 ¹⁴	US	307/306	All (except severe)	D	rt-PA, 0.9 mg/kg; 90 mg max	3-5	Avoid for 24 h	3
PROACT, 1998 ¹⁵	US	26/14	ICA / MCA	D	IA prourokinase, 6 mg	6	All heparin IV; avoid aspirin for 24 h	3
PROACT II, 1999 ¹⁶	US/Canada	121/59	ICA / MCA	Open	IA prourokinase, 9 mg	6	All heparin IV; avoid aspirin for 24 h	3
Ancrod Stroke Study, 1994 ¹⁷	US/Germany	64/68	All	D	Ancrod, 0.5 U/kg, dose titrated to target fibrinogen level of 70-100 mg/dL	6	28% of participants were taking aspirin at enrollment	12
STAT, 1999 ¹⁸	US/Canada	248/252	All	D	Ancrod, dose titrated to target fibrinogen level of 40-70 mg/dL	3	Avoid while receiving therapy	12

Abbreviations: ATLANTIS, Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke Trial; D, double blind; ECASS, European Cooperative Acute Stroke Study; ECASS II, Second European-Australasian Acute Stroke Study; IA, intra-arterial; ICA, internal carotid artery; IV, intravenously; max, maximum; MCA, middle cerebral artery; NINDS, National Institute of Neurological Disorders and Stroke rt-PA Stroke Study; PROACT, Prolyse in Acute Cerebral Thromboembolism Study; rt-PA, recombinant tissue plasminogen activator; SC, subcutaneous; STAT, Stroke Treatment With Ancrod Trial; US, United States.

end of the follow-up. These findings are consistent with the findings of several phase 4 trials in the United States and Germany. The Standard Treatment With Alteplase to Reverse Stroke Study,²⁰ which included 389 patients treated with intravenous rt-PA, had a 30-day mortality rate of 13%. In another study, 100 consecutive patients were treated with intravenous rt-PA, and the 90-day all-cause mortality rate was 10%.²⁸ These results are comparable with the results of the control arm of the National Institute of Neurological Disorders and Stroke rt-PA Stroke Study.

In addition to failing to demonstrate any significant excess mortality among treated stroke patients, we did not show any significant mortality risk associated with thrombolytic therapy in any subgroup (Table 3). However, the CIs of the estimates became bigger, indicating that more data may be needed to reach a definitive conclusion. For example, there was an insignificant increase in mortality when only rt-PA studies were included in the meta-analysis. However, we found an insignificant decrease in mortality for trials with thrombolytic therapy within 3 hours of acute stroke.

The Third International Stroke Trial²⁹ started patient recruitment in May 2000. This trial aims primarily to de-

termine whether a wider range of patients might benefit from rt-PA therapy, and it targets 6000 patients worldwide. There is a strong possibility that results from this big trial will shed light on the controversy about thrombolytic therapy and mortality in acute ischemic stroke. Additionally, the European Stroke Treatment With Ancrod Trial³⁰ results are still pending. In this trial of 1222 patients, ancrod was compared with placebo.

One major limitation of this meta-analysis is that we could not evaluate the effect of thrombolysis on cause-specific mortality, including mortality from intracranial hemorrhage. The reasons for this shortcoming were as follows:

1. It was difficult to determine the true causes of deaths in some trials because some patients died without a computed tomographic scan or postmortem examination. Thus, the true rate of mortality from intracranial hemorrhage may be different than that suggested by the data.

2. On the other hand, awareness among researchers of the association between early intracranial hemorrhage and thrombolysis may indicate an inflated number of deaths attributed to intracranial hemorrhage. For instance, review of published computed tomographic

Table 2. All-Cause Mortality Associated With Thrombolytic Therapy in Patients With Acute Ischemic Stroke

Source	No. of Events/ No. of Participants		OR (95% CI)*	ARD (95% CI), per 1000 Persons*	NNH (95% CI)†	P Value
	Treatment	Placebo				
Mori et al, 1992 ⁹	2/19	2/12	0.58 (0.07-4.85)	-61.4 (-313 to 190.6)6
Haley et al, 1993 ¹⁰	1/14	2/13	0.42 (0.02-5.32)	-82.4 (-320.5 to 155.6)5
NINDS, 1995 ¹	76/312	87/312	0.84 (0.59-1.19)	-35.3 (-104.0 to 33.6)2
ECASS, 1995 ¹¹	69/313	48/307	1.52 (1.01-2.29)	64.1 (2.8-125.4)	16 (8-360)	.04
ECASS II, 1998 ¹²	43/409	42/391	0.97 (0.62-1.53)	-2.3 (-45.0 to 40.4)9
ATLANTIS A, 2000 ¹³	16/71	5/71	4.2 (1.4-12.1)	160.0 (49-272)	6 (4-20)	.002
ATLANTIS B, 1999 ¹⁴	33/307	21/306	1.60 (0.87-2.92)	37.9 (-5.6 to 85.6)09
PROACT, 1999 ¹⁵	7/26	6/14	0.49 (0.12-1.92)	-159.3 (-469.6 to 15.9)3
PROACT II, 1999 ¹⁶	29/121	16/59	0.84 (0.41-1.72)	-31.5 (-168.1 to 105.1)6
Ancrod Stroke Study, 1994 ¹⁷	8/64	14/68	0.55 (0.21-1.42)	-80.9 (-206.6 to 44.8)20
STAT, 1999 ¹⁸	83/248	82/252	1.05 (0.72-1.52)	9.3 (-72.1 to 93.8)8
Overall	367/1904	325/1805	1.07 (0.8-1.39)	11 (-24 to 48)3

Abbreviations: ARD, absolute risk difference; ATLANTIS, Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke Trial; CI, confidence interval; ECASS, European Cooperative Acute Stroke Study; ECASS II, Second European-Australasian Acute Stroke Study; NINDS, National Institute of Neurological Disorders and Stroke Recombinant Tissue Plasminogen Activator Stroke Study; NNH, number needed to harm; OR, odds ratio; PROACT, Prolyse in Acute Cerebral Thromboembolism Study; STAT, Stroke Treatment With Ancrod Trial.

*The ORs and ARDs and their 95% CIs are from a random effects model.

†Values are given only when a significant treatment effect was observed.

Table 3. All-Cause Mortality Associated With Thrombolytic Therapy in Randomized Controlled Trials

	No. of Trials	OR (95% CI)	P Value
All trials during follow-up	11	1.07 (0.8 to 1.39)	.3
Mortality within 1 mo	9	1.14 (0.75 to 1.73)	.6
Ancrod trials excluded	9	1.13 (0.77 to 1.68)	.2
rt-PA therapy within first 3 h	4	0.98 (0.63 to 1.53)	.8

Abbreviations: CI, confidence interval; OR, odds ratio; rt-PA, recombinant tissue plasminogen activator.

scans suggested that, at least in some trials, symptomatic intracranial hemorrhage included patients with very large swollen infarcts with trivial amounts of hemorrhage within them.⁴ Therefore, overestimation of the risk of death from intracranial hemorrhage is a strong possibility.

3. Finally, a number of the studies did not report detailed numbers for causes of mortality but did mention the most frequent cause of mortality at the end of the follow-up. A meta-analysis of individual patient data re-evaluated by a group blinded to patient allocation may be a solution for this shortcoming.

There is always a possibility of publication bias in a meta-analysis. However, we conducted a comprehensive search with a systematic strategy to avoid bias. We also attempted to find unpublished trials, corresponding with experts in the field and searching abstracts from recent conferences. We believe we have identified most of the available research dealing with this issue. Another possible limitation of this study may be the question of whether the ancrod and/or prourokinase data should be included in the meta-analysis given the differences in the mechanism of action (ancrod) and the route of delivery and heparin use in controls (prouroki-

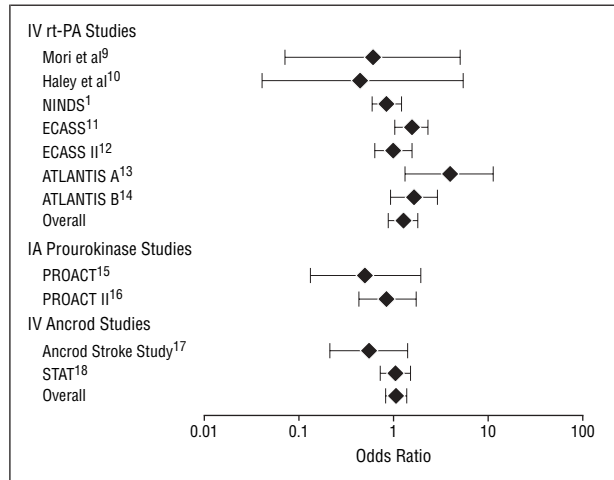


Figure. All-cause mortality at the end of the follow-up by medication. Error bars indicate 95% confidence intervals. IV indicates intravenous; rt-PA, recombinant tissue plasminogen activator; NINDS, National Institute of Neurological Disorders and Stroke rt-PA Stroke Study; ECASS, European Cooperative Acute Stroke Study; ECASS II, Second European-Australasian Acute Stroke Study; ATLANTIS A, Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke Trial, Part A; ATLANTIS B, ATLANTIS, Part B; IA, intra-arterial; PROACT, Prolyse in Acute Cerebral Thromboembolism Study; and STAT, Stroke Treatment With Ancrod Trial.

nase). To remove the effect of this limitation we calculated separate pooled estimates for different medication groups. This approach did not change the interpretation of our pooled estimate; however, it reduced the possibility of publication bias.

In conclusion, available data do not indicate significant excess mortality among patients treated with thrombolytic agents. This meta-analysis provides further evidence of a clear need for additional randomized trials of thrombolytic therapy. In combination with the results from a meta-analysis that used individual patient data from intravenous rt-PA studies and that showed that these pa-

tients had a higher probability than nontreated patients of recovering with little or no deficit,³¹ our results may imply that thrombolytic treatment should be seriously considered for acute ischemic stroke patients who have the right indications.

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Correspondence: Ahmet Ergin MD, PhD, MPH, Department of Public Health, Pamukkale University School of Medicine, Bursa Cad. No. 119, Kinikli, Denizli 20020, Turkey (aergin@pamukkale.edu.tr).

Author Contributions: Study concept and design: A. Ergin and N. Ergin. Acquisition of data: A. Ergin and N. Ergin. Analysis and interpretation of data: A. Ergin and N. Ergin. Drafting of the manuscript: A. Ergin and N. Ergin. Critical revision of the manuscript for important intellectual content: A. Ergin and N. Ergin. Statistical analysis: A. Ergin. Study supervision: N. Ergin.

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