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THROMBOLYTIC THERAPY FOR ACUTE ISCHEMIC STROKE BEYOND THREE HOURS

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Abstract

Background—Ischemic cerebrovascular accidents remain a leading cause of morbidity and mortality. Thrombolytic therapy for acute ischemic stroke within 3 h of symptom onset of highly select patients has been advocated by some groups since 1995, but trials have yielded inconsistent outcomes. One recent trial demonstrated significant improvement when the therapeutic window was extended to 4.5 h.

Clinical Question—Does the intravenous systemic administration of tPA within 4.5 h to select patients with acute ischemic stroke improve functional outcomes?

Evidence Review—All randomized controlled trials enrolling patients within 4.5 h were identified, in addition to a meta-analysis of these trial data.

Results—The National Institute of Neurological Disorders and Stroke (NINDS) and European Cooperative Acute Stroke Study III (ECASS III) clinical trials demonstrated significantly improved outcomes at 3 months, with increased rates of intracranial hemorrhage, whereas ECASS II and the Acute Noninterventional Therapy in Ischemic Stroke (ATLANTIS) study showed increased hemorrhagic complications without improving outcomes. Meta-analysis of trial data from all ECASS trials, NINDS, and ATLANTIS suggest that thrombolysis within 4.5 h improves functional outcomes.

Conclusion—Ischemic stroke tPA treatment within 4.5 h seems to improve functional outcomes and increases symptomatic intracranial hemorrhage rates without significantly increasing mortality.

Keywords

EBM; randomized controlled trial; stroke; thrombolysis; meta-analysis

CASE

A 68-year-old right-handed woman arrives from home with expressive aphasia and right-sided weakness beginning 2.5 h prior. The triage nurse astutely initiates the “stroke pager” as the emotional patient and her husband are wheeled back to their room. The neurologist arrives in the room at the same time as the emergency physician, quickly communicating with both the patient and her husband to complete the National Institute of Neurological Disorders and Stroke (NINDS) stroke checklist. As laboratory tests are sent and the patient transported across the hall for her emergent cranial computed tomography (CT) scan, the nervous new neurologist and emergency medicine (EM) team confirm that no thrombolysis exclusion criteria have yet been identified.

Laboratory tests and CT imaging are available within 45 min, pushing your patient across the 3-h no-thrombolysis threshold as Neurology and EM concurrently decide to administer tissue plasminogen activator (tPA). Shortly thereafter, your patient leaves the Emergency Department (ED) for the Neuro-intensive care unit without any clinical improvement or deterioration.

CLINICAL QUESTION

Does the intravenous systemic administration of tPA within 4.5 h to select patients with acute ischemic stroke improve functional outcomes?

CONTEXT

In 1995, the NINDS study group published the landmark paper demonstrating that alteplase (0.9 mg per kilogram body weight) within 3 h of symptom onset significantly improved functionally independent outcomes at 3 months in highly select acute ischemic stroke patients (Table 1) (1). Based upon this single trial, the Food and Drug Administration approved intravenous tPA for treatment of such patients in 1996 and the American Heart Association upgraded their recommendations for this therapy to Level I (definitely recommended) in 2000 (2). The European Medicines Agency similarly granted approval of alteplase in 2002 with two caveats. First, they requested a study demonstrating that alteplase could be safe and effective in non-research-based clinical practice—the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST) (3). Second, they requested a randomized trial extending the thrombolysis window beyond 3 h: the European Cooperative Acute Stroke Study III (ECASS III) (4).

The elevation of tPA to a Level I recommendation based upon a single trial generated significant controversy within EM (5–13). Previous and subsequent clinical and pragmatic real-world trials failed to reproduce the NINDS recovery benefits, and all demonstrated significantly increased risks for symptomatic intracranial hemorrhage (14–16). One community-based trial in Cleveland demonstrated alarmingly high rates of protocol violations, with intracranial hemorrhage complication rates exceeding those reported by NINDS, although re-analysis of the stroke outcomes at the same center with more rigid protocol adherence demonstrated complication rates comparable to NINDS (17,18).

The heterogeneous opinions within EM and between Neurology and EM clouded the standard of care for the few patients presenting within 3 h, opening a malpractice quagmire (19,20). Emergency physicians can be litigated for whatever decision they make regarding stroke thrombolysis, but one review of 33 cases found that 88% resulted from failure to treat with tPA (21,22). Previous re-analysis of the NINDS data has confirmed an overall benefit with thrombolysis, but one recent graphical re-analysis suggested that the benefit between

the tPA and placebo arms was less substantial than originally reported, with final outcomes highly dependent upon initial stroke severity (23–26). A recent Cochrane systematic review suggested an overall benefit for thrombolytic therapy within 3 h of symptom onset despite an increase in deaths (noted at 7 to 10 days and at final follow-up) and symptomatic intracranial hemorrhages (27). To explain these diverging interpretations of the data, some have questioned the scientific merit and competing financial influences surrounding acute stroke thrombolysis research and guideline development (6,8).

Stroke remains the leading cause of disability and the third leading cause of death in the United States. From 1999 to 2004, thrombolysis was used in 1.12% of ischemic stroke hospitalizations, and 69.5% of hospitals treating such patients did not employ thrombolysis (28). One barrier to widespread implementation of acute stroke thrombolysis is the 3-h treatment window coupled with delayed patient presentations (29,30). However, phase II imaging studies suggest that the reperfusion benefits of alteplase extend beyond this window (31,32). Thus, clinical equipoise exists with biological plausibility for a clinically important role for thrombolysis beyond 3 h. Nonetheless, although multicenter investigators have reported successful application of NINDS protocol thrombolysis in the absence of a dedicated stroke team or research milieu, neuro-emergency therapeutic nihilism remains a pervasive issue (3,5,7,33).

EVIDENCE SEARCH

Well-versed on the landmark NINDS trial, you conduct a three-part PubMed search. First, using the clinical queries therapy narrow/specific tab you search “ischemic stroke,” yielding 1608 citations. Second, you conduct an unfiltered search for “thrombolysis” (12,909 citations). Third, you combine PubMed search one and two together, yielding 111 citations that include all of the research reviewed below *except* the NINDS trial, of which you were already aware.

EVIDENCE REVIEW

NINDS

Tissue plasminogen activator for acute ischemic stroke. *New England Journal of Medicine*, 1995 (1)

Population: Patients were recruited from 37 university-affiliated hospitals with 24-h access to third- or fourth-generation CT scanners. Subjects were eligible if they had an ischemic stroke with a clearly defined onset < 180 min before tPA administration if they had a measurable and sustained deficit on the National Institutes of Health Stroke Scale (NIHSS) with no evidence of intracranial hemorrhage.

Study design: Subjects without exclusion criteria were randomized via permuted block design stratified by center and time-to-start of treatment (0–90 min or 91–180 min) to receive placebo or alteplase 0.9 mg/kg body weight (max 90 mg) with 10% as bolus and 90% as infusion over 60 min. No anticoagulants or antiplatelet agents were given for 24 h after treatment. The first part of the study looked at 24-h symptom improvement as measured by the NIHSS. The second part of the study assessed 3-month functional recovery. Genentech (South San Francisco, CA) supplied and distributed both the alteplase and the placebo, and monitored the clinical sites.

Primary outcome: The functional outcome at 3 months was assessed using four instruments: Barthel Index, modified Rankin Scale (mRS), Glasgow Outcome Scale, and the NIHSS (34–37). Low scores on the Barthel Index represent significant functional deficit (range 0–100). On the other hand, low scores on the mRS (range 0–5), Glasgow Outcome

Scale (range 1–5), and NIHSS (range 0–42) represent a good functional outcome. Outcomes were “determined at 24 h and 3 months by certified examiners who had not performed the baseline examination and had not been present during the initial treatment.” Patients who died before 3-month assessment were given the worst possible score for all outcomes. In surviving patients with missing data, results after 3 months were used, or if that were absent, results after 7 days closest to 3 months were used. Adverse events monitored included intracranial hemorrhage, serious systemic bleeding, death, and new stroke. Repeat CT scans were required at 24 h and 7–10 days after stroke onset. All CT results were made available to treating clinicians, but later CT scans were reviewed by a neuroradiologist at the CT reading center, blinded to clinical information.

Exclusion criteria: The extensive exclusion criteria are listed in Table 1.

Main Results: Over 3.5 years, 624 patients were randomized to tPA or placebo. After 24 h, 2% of the placebo group had complete resolution, suggesting a low prevalence of transient ischemic attacks among the population. Among 144 subjects in part 1 of the study, assessing 24-h outcomes failed to demonstrate a significant difference between tPA and placebo: outcome improved in 47% vs. 39%, respectively. However, when part 1 and part 2 subjects were combined, the subset treated within 90 min of symptom onset had a statistically significant ≥ 4 -point NIHSS improvement within 24 h (55% tPA vs. 42% placebo, number needed to treat [NNT] = 8).

Three-month outcomes consistently favored the tPA subset, with 12% absolute increase in favorable outcomes (minimal or no disability) equating to a NNT of 8. The inclusion of variables that differed at baseline (age, weight, aspirin use) magnified the tPA benefit (odds ratio [OR] 2.0; 95% confidence interval [CI] 1.3–3.1 vs. OR 1.7 in the unadjusted analysis). The proportion of patients with minimal or no deficit at 3 months was not accompanied by an increase in severe disability or mortality. At 3 months, 17% of the tPA patients had died, compared with 21% of the placebo group, which was not significant.

When parts 1 and 2 were combined, symptomatic intracranial hemorrhage (ICH) rates within the first 36 h were much more likely in the tPA group, occurring in 20/312 (6.4%) subjects vs. 2/312 (0.6%) placebo patients. Half of these early bleeds were fatal, and at 3 months, 17/28 (61%) of symptomatic ICH patients had died. ICH was more likely with greater stroke severity (median NIHSS among ICH patients 20, vs. non-ICH subset median NIHSS 14).

ECASS I

Intravenous thrombolysis with recombinant tissue plasminogen activator for acute hemispheric stroke: the European Cooperative Acute Stroke Study (ECASS). *JAMA*, 1995 (14)

Population: Patients were recruited from 75 hospitals in 14 European countries between late 1992 and early 1994. Subjects between 18 and 80 years of age were eligible if presented with moderate to high-grade hemispheric stroke as defined by the Scandinavian Stroke Scale (SSS) (38). This included paresis, sensory disturbance, dysarthria, or non-fluent aphasia and occasional hemianopia. Patients had to present within 6 h of onset of symptoms and have no or only minor early infarct signs on initial CT scan.

Study design: Subjects without exclusion criteria were randomized following a central randomization code to receive alteplase (tPA) 1.1 mg/kg body weight (max 100 mg) with 10% bolus followed by a 60-min infusion of the remaining dose or placebo. Intravenous

heparin, oral anticoagulants, hemorrhage control agents, and brain protective substances were not allowed within the first 24 h.

Primary outcome: The primary outcome was the difference between treatment group and placebo group using the Barthel Index and mRS at 3 months post-treatment. The differences between the two groups in the SSS at 3 months were also quantified. Mortality rates at 30 days were also part of the analysis. Other secondary parameters were assessed. These included: the SSS at 120 min, 8 h, 24 h, 7 days, and 30 days; duration of in-hospital stay, and the NIHSS at days 1 and 90. Safety was determined by overall mortality, frequency of hemorrhagic events, death related to hemorrhage, space-occupying infarction, and other serious adverse events in both treatment groups. Repeat CT scans were done at 24 h and between days 6 and 8 after stroke onset. They were reviewed for early infarct signs, hemorrhagic events, infarct size, and occurrences of space-occupying infarction. The reviewers were blinded to the treatment assignment.

Exclusion criteria: The extensive exclusion criteria are listed in Table 2.

Main results: There were 620 patients included in the target population (TP), with 313 patients in the alteplase group and 307 randomized to the placebo group. There were 109 patients (17.4%) excluded from the TP due to protocol violations. Most of these violations ($n = 66$) were in the alteplase group and were due to extended early infarct signs. This resulted in 264 patients in the placebo group and 247 in the alteplase group. There were no significant differences in the baseline SSS between the two treatment groups. Both TP and intention to treat (ITT) populations were analyzed.

There was no difference between tPA and placebo in the primary endpoints of Barthel Index scores in both ITT and TP analysis. The mRS was not significantly different either in the ITT analysis. However, TP analysis of mRS favored treatment with tPA (median score 2 for treatment vs. 3 for placebo group, $p = 0.035$). Mortality at 30 days was not different (17.9% tPA vs. 12.7% placebo).

Some secondary outcomes favored the treatment group. However, early ICH, fatal cerebral edema, and early mortality were more common in patients treated with tPA than placebo. Overall mortality at 90 days was also higher in the treated patients (22.4% tPA vs. 15.8% placebo).

ECASS II

Randomised double-blind placebo-controlled trial of thrombolytic therapy with intravenous alteplase in acute ischaemic stroke (ECASS II). *Lancet*, 1998 (15)

Population: Patients were recruited from 108 centers in 14 European countries, Australia, and New Zealand. Eligible subjects were aged 18–80 years with a clinical diagnosis of moderate to severe ischemic stroke, with no or minimal CT evidence of cerebral infarction who could be treated *within 6 h* of symptom onset.

Study design: Randomization occurred by a computer-generated procedure in blocks of four, with investigators blinded to allocation arm except in emergencies. Subjects in the treatment arm received alteplase 0.9 mg/kg intravenously (IV) with 10% over 1–2 min and the remainder over the next 60 min (max dose 90 mg). Control subjects received placebo. Subcutaneous heparin was allowed during the first 24 h, but not IV heparin, oral anticoagulants, antiplatelet agents, volume expanders, or potential neuro-protective agents. A standard protocol not detailed in the article was used to control blood pressure. Before and

during the trial, courses were run to improve the quality of CT scanning and interpretation. CT brain imaging was obtained at baseline, 22–36 h post-enrollment, and at Day 7. Adverse events monitored included symptomatic intracerebral hemorrhage and mortality at 30 and 90 days.

Primary outcome: The primary endpoint was the proportion of subjects with a favorable outcome (mRS 0 or 1) at 90 days post-treatment. Secondary outcomes included NIHSS and Barthel Index at 90 days, quality of life at 90 days, and hospital length-of-stay.

Exclusion criteria: The extensive exclusion criteria are listed in Table 3.

Main results: Over 15 months, 800 subjects were randomized to tPA or placebo with 72 protocol violations (34 tPA and 38 placebo). Although the trend consistently favored thrombolysis, there was no significant difference in the proportion of subjects with a mRS of 0 or 1 at 3 months: 40.3% tPA vs. 36.6% placebo. Post hoc analysis of those with mRS 0, 1, or 2 did favor tPA, with NNT 12 ($p = 0.024$). No other secondary outcomes demonstrated any differences between tPA and placebo. When analyzed by treatment within 3 h (19.8% of the subjects), no significant differences were noted (favorable mRS 42% tPA vs. 38% placebo). Overall, the 3-month mortality rate was 10.6%, with no differences noted between the tPA (10.5%) and placebo (10.7%) groups. Parenchymal hemorrhage of any kind was fourfold higher in the tPA group (11.8% vs. 3.1%), and large space-occupying ICH rates were 10-fold higher (8.1% vs. 0.8%), but hemorrhagic conversion of the strokes did not differ (19.6% tPA vs. 24.3% placebo). Symptomatic ICH occurred in 8.8% of tPA group compared with 3.4% of the placebo-group patients. No increases in other bleeding complications were noted in the tPA group.

ATLANTIS

Recombinant tissue-type plasminogen activator (alteplase) for ischemic stroke 3 to 5 hours after symptom onset: the ATLANTIS study: a randomized controlled trial. *JAMA*, 1999 (16)

Population: Patients aged 18 through 79 years presenting with a clinical diagnosis of ischemic stroke with the ability to administer study medication within 3–5 h after symptom onset and a measurable neurological deficit were enrolled from 140 North American community and university-affiliated sites over a 4.5-year period. Patients taking antiplatelet agents were allowed, as were those taking Coumadin (Bristol-Myers Squibb, New York, NY) if the international normalized ratio was normal.

Study design: This was a randomized, double-blinded placebo-controlled clinical trial. After randomization, subjects received either placebo or tPA 0.9 mg/kg (90 mg max dose) with 10% bolus over 1–2 min and the remainder over 60 min. After tPA or placebo administration, antiplatelet agents, heparin, and Coumadin were prohibited for 24 h. Nitropaste for blood pressure control was acceptable, but not aggressive blood pressure management (nitroprusside). Cranial CT scans to exclude intracranial ICH were obtained before randomization. Copies of all CT scans were sent to a central neuroradiologist blinded to the patient's treatment group. Cranial CT was also performed at 18–30 h and 23–37 days.

Primary outcome: The primary outcome was 3-month NIHSS of 0 or 1 (no disability). The trial had 80% power if the proportion of the placebo arm with NIHSS 0 or 1 was 35%, and the tPA arm was 44% if 968 patients were randomized. The trial was stopped prematurely based upon interim safety board analysis because “treatment was unlikely to prove beneficial.” Secondary outcome measures included NIHSS at 120 min, 24 h, and days 7, 30, and 90. In addition, Barthel Index, mRS, and Glasgow Outcome Scale were obtained at days

30 and 90, with excellent functional recovery on these scales as secondary outcomes. Safety parameters included overall mortality, asymptomatic ICH, symptomatic ICH, fatal ICH, and other serious adverse events in both treatment groups.

Exclusion criteria: The extensive exclusion criteria are listed in Table 4.

Main results: This study enrolled 613 patients, including 31 who received tPA or placebo within 3 h of symptom onset before the protocol was modified. A total of 32 protocol violations were reported (8 treated < 3 h and 24 treated > 5 h), and 3 subjects did not receive any study medication, leaving 547 who received tPA or placebo between 3 and 5 h. No benefit was noted for excellent recovery (NIHSS 0 or 1) at 3 months: 34% tPA vs. 32% placebo. No differences were noted for any of the secondary outcomes either. No global treatment effect was noted when adjusting for baseline differences between the tPA and placebo arm for diabetes and atrial fibrillation. No treatment effect was noted on early recovery rates, with mean NIHSS at 2 h 9.8 in the placebo set and 10.0 in the tPA set. When stratified by time-to-drug for the primary outcome, no beneficial effect was observed. Between 3 and 4 h (n = 111), the primary outcome was observed in 31% placebo and 34% tPA, and between 4 and 5 h (n = 436), 33% placebo and 34% tPA. Treatment with tPA significantly increased the rate of symptomatic (7% tPA vs. 1.1% placebo) and fatal (3% tPA vs. 0% placebo, NNH = 33) ICH, and there was a non-significant trend toward higher 3-month mortality (11% tPA vs. 6.9% placebo).

ECASS III

Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. *New England Journal of Medicine*, 2008 (4)

Population: Patients between 18 and 80 years of age were recruited from 130 sites in 19 European countries if they presented with clinically suspected acute ischemic stroke without pre-randomization ICH or major cerebral infarction (> 1/3 of middle cerebral artery territory) via CT or magnetic resonance imaging (MRI) if they could receive the study drug within 3–4.5 h after symptom onset.

Study design: Over 4.5 years, eligible subjects were randomized via an interactive voice system into blocks of four. The initial protocol had enrolled only subjects presenting within 3 to 4 h, but was expanded by 0.5 h at 2 years after 228 patients had been enrolled. Patients, clinicians, outcome assessors, and data safety board members were blinded to subject allocation arm. During the first 24 h, concomitant therapy with IV heparin, oral anticoagulants, aspirin, or volume expanders after study drug administration was prohibited. Clinical assessment occurred at 1, 2, and 24 h, as well as days 7, 30, and 90. CT or MRI was obtained before treatment and at 22–36 h post-treatment.

Primary outcome: The primary outcome was 90-day mRS favorable outcome (score of 0 or 1) vs. an unfavorable outcome (mRS 2–6). The secondary outcome was a 90-day global outcome measure including mRS 0 or 1 and Barthel Index ≥ 95 , and NIHSS 0 or 1 and a score of 1 on the Glasgow Outcome Scale. In the case of missing data among patients known to be alive, the worst possible outcome score was assigned. Initial analyses were performed without adjustment for confounding variables, but a post hoc stratified analysis for mRS was performed, adjusting for the two most strongly prognostic baseline variables (initial NIHSS and time to start of treatment). Safety endpoints included 90-day mortality, any ICH, symptomatic ICH, symptomatic cerebral edema, and “other serious adverse events.” The chairs of the Safety Outcome Adjudication Committee and the steering committee (who remained unaware of the treatment assignments) together adjudicated whether each death or score change indicating neurological deterioration was likely to have

been due to ICH, other brain injury or disease, or neither of these causes. The authors also reported symptomatic ICH stratified by treatment arm using the ECASS II, SITS-MOST, and NINDS definitions to permit comparison of adverse event rates across studies.

Exclusion criteria: The extensive exclusion criteria are listed in Table 5.

Main results: The study randomly assigned 821 patients, including 10% within 3–3.5 h, 46.8% within 3.5–4 h, and 39.2% within 4–4.5 h. Alteplase was administered a median of 3 h, 59 min after symptom onset. The placebo group had a statistically significant higher mean NIHSS (11.6 placebo vs. 10.7 tPA) and history of prior stroke (14.1% placebo vs. 7.7% tPA). A favorable outcome (mRS 0 or 1) was noted among 52.4% tPA group vs. 45.2% of the placebo group (NNT 14; 95% CI 7–255). In adjusting for initial NIHSS and prior stroke history, tPA remained associated with a favorable outcome (OR 1.42; 95% CI 1.02–1.98). Alteplase also improved secondary outcome measures (global OR 1.28, 95% CI 1.0–1.65, $p < 0.05$). Three-month mortality rates did not differ between tPA (7.7%) and placebo (8.4%). All symptomatic ICH occurred within 36 h of treatment and was significantly more likely with tPA (27% vs. 17.6%, NNH 47 with 95% CI 39–161). Symptomatic ICH rates were more likely with tPA when using the ECASS II (5.3% vs. 2.2%), SITS-MOST (1.9% vs. 0.2%), or NINDS (7.9% vs. 3.5%) definitions.

Meta-analysis (Lansberg 2009)

Efficacy and safety of tissue plasminogen activator 3 to 4.5 hours after acute ischemic stroke: a meta-analysis. Stroke, 2009 (39)

Population: Acute ischemic stroke patients treated with tPA in the 3 to 4.5-h time window.

Study design: Meta-analysis of randomized controlled trials ($n > 100$) of patients treated with tPA for acute ischemic stroke between 3 and 4.5 h. A PubMed search and authors' knowledge of the literature resulted in four studies included: ECASS I ($n = 234$), ECASS II ($n = 265$), ECASS III ($n = 821$), and ATLANTIS ($n = 302$).

Primary outcome: Three primary outcomes were defined, including 1) good global outcome measure (global odds ratio test based on three individual outcome scales at 90 days: mRS 0–1, NIHSS 0–1, and Barthel Index ≥ 95); 2) good functional outcome (mRS 0–1) at 90 days; and 3) 90-day mortality. If these outcomes were not reported in the original trials, meta-analysis authors contacted individual trial sponsors to request additional data. All analyses were based on the ITT populations.

Exclusion criteria: Observational research and trials of fewer than 100 subjects were not evaluated in this meta-analysis.

Main results: Thrombolysis treatment with tPA between 3 and 4.5 h resulted in a more favorable global outcome measure compared with placebo (OR 1.31, $p = 0.002$). This was also true of a more favorable mRS (0–1) (OR 1.31, $P = 0.008$), with a NNT of 15 (Table 6). There was no difference in mortality at 90 days (OR 1.04, $p = 0.83$).

CONCLUSION

NINDS demonstrated that tPA administered within 3 h of symptom onset to highly select patients significantly reduces functional deficit at 3 months (NNT = 8). These benefits are associated with a significantly increased risk of symptomatic ICH within 36 h (6% vs. 0%; NNH = 18), but no overall increase (or decrease) in 3-month mortality. ECASS I demonstrated improvement in some outcomes, but increased early ICH rates and 90-day

mortality. ECASS II demonstrated that tPA within 6 h of symptom onset yielded a non-significant trend toward improved outcomes while significantly increasing the risk of ICH within 7 days. ATLANTIS demonstrated no difference for primary or secondary outcomes, but tPA within 3–5 h significantly increased ICH rates, so the trial was stopped early.

ECASS III demonstrated that tPA administered 3–4.5 h after symptom onset for ischemic stroke in select patients (Table 3) in a research environment is associated with a clinically significant improvement in the proportion of patients with functionally independent favorable outcomes (NNT = 14) without increasing mortality or symptomatic ICH rates (NNH = 47). Reanalysis of the ECASS III data using each gradation of mRS as an outcome suggests that the benefit-to-harm ratio may be even more profound for those treated within 4.5 h (NNT 6, NNH 37.5) (40). Additionally, the Safe Implementation of Thrombolysis in Stroke International Stroke Register (SITS-ISTR), real-world community-based settings, has safely implemented 4.5-h stroke protocols, replicating ECASS III results (41). Clinical equipoise still exists for stroke patients presenting with minimal or rapidly improving symptoms (42–44).

There is less disagreement that earlier thrombolysis improves outcomes relative to delayed thrombolysis (45). The likelihood of help vs. harm decreases from 18 to 6 when comparing those who present within 1.5 h vs. 3–4.5 h (46). Therefore, patients who can be treated within 3 h should not have their treatment delayed (47). Lacking other effective interventions for acute ischemic stroke, the NNT, NNH, and limitations of these studies should be discussed with patients in collectively deciding upon the best option for an individual. A decision wheel based upon one reanalysis of the NINDS data can be downloaded to assist these discussions (23,48). In addition, the American Academy of Emergency Medicine has a teaching tool to facilitate informed consent (<http://www.aaem.org/education/tpaedtool-AAEM.pdf>) (49). Optimally, as suggested in the Cochrane review, future studies will be expeditiously conducted to clarify which patients are most likely to benefit from thrombolysis and in which settings (27). In fact, the International Stroke Trial III is currently investigating the role of thrombolysis up to 6 h after symptom onset, including those over age 80 years and patients with early ischemic changes on CT (50,51). However, the sum of ECASS III, the meta-analysis including all prior randomized controlled trials, and SITs-ISTR currently represents the best evidence by which to acutely treat (otherwise untreatable) ischemic strokes, and ought to be discussed with patients and families in conjunction with a local neurological protocol to provide the best possible care to every patient.

COMMENTARY

Stroke is a devastating disease, and few effective treatments exist. Fewer still are available for acute treatment. As this critical appraisal has concluded, thrombolysis for appropriate patients should not be delayed. This conclusive position, however, has not been achieved without controversy. Some of the controversy has resulted from issues related to the scientific process, such as balance in allocation of research subjects and heterogeneity of results. Other parts of this story are probably linked to barriers referenced in the Knowledge Translation paradigm (52). The flow of evidence to optimal patient outcomes can leak or be disrupted at several key stages. These obstacles involve physicians, health care teams, health care environments, and patients, and can delay uptake and application of new knowledge. The tPA in acute ischemic stroke pathway likely has encountered, and continues to encounter, leaks at every potential barrier. Utilization of tPA for ischemic stroke requires a team commitment and effort and is not an ED intervention alone. Integration and support is required from the hospital, consulting or treating neurologists, and inpatient physicians to achieve the results seen in clinical trials. The Joint Commission process for accrediting

Primary Stroke Centers takes this teamwork into account. Clinical trials can also be difficult to interpret and apply to practice. The data provided are usually not in black and white, but shades of grey. Additional data and trials that occur subsequent to the initial result, such as ECASS, ECASS II, ECASS III, ATLANTIS, SITS-MOST, and SITS-ISTR, can better inform us in our clinical decision-making (Figure 1). Acute ischemic stroke treatment is a case study in the Knowledge Translation process. The landmark NINDS trial was conducted with positive, but sometimes controversial, results. Shades of grey may remain, but the answer to this question is more black and white today.

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ARTICLE SUMMARY

1. Why is this topic important?

Controversial therapy (tPA) for a devastating and common disease (ischemic stroke).

2. What is the clinical question?

Does the intravenous systemic administration of tPA within 4.5 h to select patients with acute ischemic stroke improve functional outcomes?

Search Strategy: PubMed clinical queries, category: therapy, and scope: narrow and wide; keywords: ischemic stroke, thrombolysis

Citations Appraised:

- Tissue plasminogen activator for acute ischemic stroke. *New England Journal of Medicine*, 1995 (1).
- Intravenous thrombolysis with recombinant tissue plasminogen activator for acute hemispheric stroke: the European Cooperative Acute Stroke Study (ECASS). *JAMA*, 1995 (14).
- Randomised double-blind placebo-controlled trial of thrombolytic therapy with intravenous alteplase in acute ischaemic stroke (ECASS II). *Lancet*, 1998 (15).
- Recombinant tissue-type plasminogen activator (alteplase) for ischemic stroke 3 to 5 hours after symptom onset: the ATLANTIS study: a randomized controlled trial. *JAMA*, 1999 (16).
- Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. *New England Journal of Medicine*, 2008 (4).
- Efficacy and safety of tissue plasminogen activator 3 to 4.5 hours after acute ischemic stroke: a meta-analysis. *Stroke*, 2009 (39).

3. Are the results valid?

Yes – four randomized controlled trials with a subsequent meta-analysis for recommending current therapy. Potential harm risk must be included in clinical decision-making for every patient.

4. What are the results?

Ischemic stroke patients who can be treated within 3 h should not have their treatment delayed. Patients between 3 and 4.5 h may experience significant clinical benefit as well.

Can I apply the results to my practice?

Yes.

Risk of Benefit

The chance of a positive outcome occurring to a patient secondary to an intervention chosen by a clinician. The number needed to treat (NNT) is a practically useful statistic to describe risk of benefit.

Risk of Harm

The chance of an adverse outcome occurring to a patient secondary to an intervention chosen by a clinician. The number needed to harm (NNH) is a practically useful statistic to describe risk of harm.

Risk-Benefit Ratio

The direct comparison of the negative and positive outcome risks of an intervention. In clinical decision-making, physicians should use the best evidence available to counsel patients regarding therapeutic choices. In research, the investigator must assure that the amount of benefit clearly outweighs the amount of risk. In research and clinical settings, therapy should be recommended only if there is favorable risk-benefit ratio.

Outcome Measures – Functional

Hypothesis-driven clinical research studies should have primary endpoints or outcomes that are measurable. Classical statistics holds that as the chance of finding at least one comparison that is statistically significant due to chance increases with the number of comparisons made, a primary outcome or endpoint should drive research design and implementation. Functional outcome measures should accurately and reliably measure changes in disability as the functional consequence of impairment. Problems with these measures include variation with individual patient performance, for example, good days and bad days, and subjectivity bias on the part of the evaluator. Commonly used instruments in stroke research and rehabilitation include the National Institutes of Health Stroke Scale, Barthel Index, Functional Independence Measure (FIM), the Modified Rankin Handicap Scale, Glasgow Coma Scale (GCS), Scandinavian Stroke Scale, and the Western Aphasia Battery.

PubMed Clinical Queries Search – Narrow Scope

This preset strategy leads to a specific or narrow search. The overall sensitivity/specificity cited by PubMed is 54%/99%. For Clinical Prediction Guides, the exact search field strategy used is: (validation[tiab] OR validate[tiab]).

PubMed Search – Wide Scope

This preset strategy leads to a sensitive or broad search. The overall sensitivity/specificity cited by PubMed is 96%/79%. For Clinical Prediction Guides, the exact search field strategy used is: (predict*[tiab] OR predictive value of tests[mh] OR scor*[tiab] OR observ*[tiab] OR observer variation[mh]).

Confidence Interval (CI)

The CI is an indicator of the precision of a study result or estimate. It is a range between two values within which it is probable that the true value lies for the whole population of patients from which the study patients were selected. With a 95% CI, the true value can be expected to be within that interval with 95% confidence.

Figure 1.
Evidence-based medicine teaching points.

Table 1**NINDS Exclusion Criteria**

Stroke or serious head trauma within the preceding 3 months
Major surgery within 14 days; history of intracranial hemorrhage
Systolic blood pressure above 185 mm Hg or diastolic blood pressure above 110 mm Hg
Rapidly improving or minor symptoms
Symptoms suggestive of SAH
GI or urinary tract hemorrhage within 21 days
Arterial puncture at a non-compressible site within 7 days
Seizure at time of stroke
Anticoagulants or heparin within 48 h with elevated PTT
PT > 15 s
Platelets < 100 K
50 mg/dL > glucose > 400 mg/dL
If aggressive treatment is required to maintain the blood pressure within pre-specified limits

NINDS = National Institute of Neurological Disorders and Stroke; SAH = subarachnoid hemorrhage; GI = gastrointestinal; PTT = partial thromboplastin time; PT= prothrombin time.

Table 2**ECASS I Exclusion Criteria**

Severe hemispheric stroke syndrome
Mild neurologic deficit defined as SSS > 50
Patient is already improving
Patient does not meet the 6-h time window
Pre-existing disabling neurologic disease
Concomitant medical conditions such as esophageal varices, gastroduodenal ulcer, colitis, aortic aneurysm
Recent trauma, operation or punctures (within 3 months)
Computed tomography (CT) scan documented intracranial or intracerebral hemorrhage
Major early infarct signs on CT scans such as diffuse swelling of affected hemisphere, parenchymal hypodensity, or effacement of cerebral sulci in more than 33% of the MCA territory

ECASS = European Cooperative Acute Stroke Study; SSS = Scandinavian Stroke Scale; MCA= middle cerebral artery.

Table 3**ECASS II Exclusion Criteria**

Age < 18 or > 80 years
Intracerebral hemorrhage
> 1/3 middle cerebral artery distribution hypoattenuation on CT
SAH
Unknown symptom onset time
Coma or stupor
Hemiplegia with fixed eye deviation
Minor stroke symptoms [*] or rapid symptom improvement before t-PA
SBP > 185 mm Hg or DBP > 110 mm Hg
Traumatic brain injury within 14 days
CNS surgery within 3 months
GI or urinary tract hemorrhage
IV or SQ heparin
Hereditary or acquired bleeding diathesis
Lactation or pregnancy
Contraception
50 mg/dL > glucose > 400 mg/dL
Participation in another drug trial within 3 months

ECASS = European Cooperative Acute Stroke Study; CT = computed tomography; SAH = subarachnoid hemorrhage; tPA = tissue plasminogen activator; SBP = systolic blood pressure; DBP = diastolic blood pressure; CNS = central nervous system; GI = gastrointestinal; IV = intravenous; SQ = subcutaneous.

* Scandinavian Stroke Scale > 50.

Table 4**ATLANTIS Exclusion Criteria**

Coma, severe obtundation, fixed eye deviation, or complete hemiplegia
Patient has only minor stroke symptoms (i.e., < 4 points on the National Institutes of Health Stroke Scale and normal speech and visual fields) or major symptoms that are rapidly improving by the time of randomization
History of stroke within the previous 6 weeks
Known active seizure disorder or a first seizure within the 6 h immediately before administration of study drug
Previous known intracranial hemorrhage, neoplasm, subarachnoid hemorrhage, arteriovenous malformation, or aneurysm
Clinical presentation suggestive of subarachnoid hemorrhage, even if initial computed tomographic scan is normal
Hypertension, defined as systolic blood pressure > 185 mm Hg or diastolic blood pressure > 110 mm Hg on repeated measures before study entry or requiring aggressive (e.g., intravenous antihypertensive) treatment to reduce blood pressure to within these limits
Presumed septic embolus
Presumed pericarditis or presence of either ventricular thrombus or aneurysm related to recent acute myocardial infarction
Recent (within 30 days) surgery or biopsy of a parenchymal organ
Recent (within 30 days) trauma with internal injuries or ulcerative wounds
Recent (within 90 days) head trauma
Any active or recent (within 30 days) hemorrhage
Known hereditary or acquired hemorrhagic diathesis, e.g., activated partial thromboplastin time or prothrombin time greater than normal; unsupported coagulation factor deficiency; or oral anticoagulant therapy with prothrombin time greater than normal
Pregnancy, lactation, or parturition within the previous 30 days
Baseline laboratory values: glucose, < 50 mg/dL (2.8 mmol/L) or > 400 mg/dL (22.2 mmol/L); platelet count < 100,000/ μ L; hematocrit measurement < .25
Other serious, advanced, or terminal illness
Any other condition that the investigator feels would pose a significant hazard to the patient if recombinant tissue-type plasminogen activator therapy were initiated
Current participation in another research drug treatment protocol

ATLANTIS = Acute Noninterventional Therapy in Ischemic Stroke study.

Table 5**ECASS III Exclusion Criteria**

Intracranial hemorrhage
Time of symptom onset unknown
Symptoms rapidly improving or only minor before start of infusion
Severe stroke as assessed clinically (e.g., NIHSS score > 25) or by appropriate imaging techniques [*]
Seizure at the onset of stroke
Stroke or serious head trauma within the previous 3 months
Combination of previous stroke and diabetes mellitus
Administration of heparin within the 48 h preceding the onset of stroke, with an activated partial-thromboplastin time at presentation exceeding the upper limit of the normal range
Platelet count of < 100,000 per cubic millimeter
Systolic blood pressure > 185 mm Hg or diastolic blood pressure > 110 mm Hg, or aggressive treatment (intravenous medication) necessary to reduce blood pressure to these limits
Blood glucose < 50 mg per deciliter or > 400 mg per deciliter
Symptoms suggestive of subarachnoid hemorrhage, even if CT scan was normal
Oral anticoagulant treatment
Major surgery or severe trauma within the previous 3 months
Other major disorders associated with an increased risk of bleeding

ECASS = European Cooperative Acute Stroke Study.

^{*} A severe stroke as assessed by imaging was defined as a stroke involving more than one-third of the middle cerebral artery territory. NIHSS denotes National Institutes of Health Stroke Scale, in which total scores range from 0 to 42, with higher values reflecting more severe cerebral infarcts.

Table 6

NNT and NNH for Acute Ischemic Stroke tPA Trials Treated Within 3- to 4.5-Hour Window

	tPA	Placebo	NNT	95% CI
ECASS I	42/114	35/120	13	NNTH 26 to NNTB 5
ECASS II	52/131	40/134	11	NNTH 67 to NNTB 5
ATLANTIS	50/145	56/157	N/A	NNTH 10 to NNTB 10
ECASS III	219/418	182/403	14	NNTB 204 to NNTB 8
Total	363/808	313/814	16	NNTB 62 to NNTB 9

* Modified Rankin Scale of 0 or 1 at 3 months.

NNT = number needed to treat; NNH = number needed to harm; tPA = tissue plasminogen activator; NNT = number needed to treat; CI = confidence interval; NNTH = number needed to treat for harm; NNTB = number needed to treat for benefit; ECASS = European Cooperative Acute Stroke Study; ATLANTIS = Acute Noninterventional Therapy in Ischemic Stroke study.