Thrombolysis in Acute Ischemic Stroke

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Editors' Note: *This month we continue the new feature—STEPped Care: An Evidence-Based Approach to Drug Therapy. These articles are designed to provide concise answers to the drug therapy questions that family physicians encounter in their daily practice. The format of the feature will follow the mnemonic STEP: safety (an analysis of adverse effects that patients and providers care about), tolerability (pooled drop-out rates from large clinical trials), effectiveness (how well the drugs work and in what patient population[s]), and price (costs of drug, but also cost-effectiveness of therapy).[1] Hence, the name STEPped Care.*

Since the informatics pioneers at McMaster University introduced evidence-based medicine,[2] Slawson and Shaughnessy[3,4] have brought it to mainstream family medicine education and practice. This feature is designed to further the mission of searching for the truth in medical practice. Authors will provide information in a structured format that allows the readers to get to the meat of a therapeutic issue in a way that can help physicians (and patients) make informed decisions. The articles will discourage the use of disease-oriented evidence (DOE) to make treatment decisions. Examples of DOEs include blood pressure lowering, decreases in hemoglobin A_{1c}, and so on. We will include studies that provide POEMs—patient-oriented evidence that matters (myocardial infarctions, pain, strokes, mortality, etc)—with the goal of offering patients the most practical, appropriate, and scientifically substantiated therapies. Number needed to treat to observe benefit in a single patient will also be included as a way of defining advantages in terms that are relatively easy to understand.[5,6]

At times this effort will be frustrating. Even as vast as the biomedical literature is, it does not always support what clinicians do. We will avoid making conclusions that are not supported by POEMs. Nevertheless, POEMs should be incorporated into clinical practice. The rest is up to the reader. Blending POEMs with rational thought, clinical experience, and importantly, patient preferences can be the essence of the art of medicine.

We hope you will find these articles useful and easy to read. Your comments and suggestions are welcome. You may contact the editors through the editorial office of JABFP or on the Internet (http://clinic.isu.edu/drugsteps/intro.html). We hope the articles provide you with useful information that can be applied in everyday practice, and we look forward to your feedback.

Rex W. Force, PharmD, *STEPped Care Feature Editor*
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Stroke is the third leading cause of death in the United States. Although the mortality rate from stroke has decreased during the past 50 years, this trend may be ending.[1] The reasons for the change in stroke mortality are unclear, and many factors, including the aging of the population, might be involved. Medications improving both quality of life and survival after an acute ischemic stroke are urgently needed.

Thrombolysis was first tested as a treatment for acute ischemic stroke almost 40 years ago. Only 14 randomized, placebo-controlled trials for a total of 3500 patients with acute ischemic stroke have been published.[2] One study, the National Institute of Neurological Disorders and Stroke (NINDS) trial, showed a statistically significant decrease in poor functional outcome with the use of recombinant tissue plasminogen activator (rt-PA) when given within 3 hours of the onset of acute ischemic stroke.[3] Based on this study, the Food and Drug Administration approved the use of rt-PA for acute

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Table 1. Bleeding Complications and Mortality in the European Cooperative Acute Stroke Study (ECASS) and the National Institute of Neurological Disorders and Stroke (NINDS) Trial, and Number Needed to Harm (NNH).

Trial	rt-PA Dosage	Bleeding Complication and Mortality	Treatment Group No. (%)	Placebo Group No. (%)	NNH
ECASS[10]	1.1 mg/kg (10% as bolus)	Total hemorrhagic events	134/313 (42.8)	113/307 (36.7)	NS
		Parenchymal hematoma	62/313 (19.8)*	20/307 (6.5)	8
		Total mortality	69/313 (22.0)†	48/307 (15.6)	16
NINDS[3‡]	0.9 mg/kg (10% as bolus)	Symptomatic intracranial hemorrhage§	20/312 (6.4)*	2/312 (0.6)	17
		Asymptomatic intracranial hemorrhage§	14/312 (4.5)	9/312 (2.9)	NS
		Total mortality	54/312 (17.0)	64/312 (21.0)	NS

NNH – number of patients who, if they received rt-PA, would lead to 1 additional patient being harmed compared with those receiving placebo.
*$P < 0.001$ versus placebo.
†$P = 0.04$.
‡All patients, parts 1 and 2.
§Within 36 hours of treatment.

ischemic stroke. Both the American Heart Association and the American Academy of Neurology have now issued practice guidelines recommending the use of rt-PA.[4,5] Controversy continues, however, because the evidence supporting its safe use in routine medical practice is limited.

Methods

A MEDLINE search from January 1966 through November 1997 was performed using the search terms "thrombolytic," "stroke," "mortality," "disability," and "randomized controlled trials." Additional studies were found by examining the references cited in trials involving thrombolysis. Studies were selected if they enrolled at least 100 patients, used computed tomographic (CT) scans to exclude patients with intracerebral hemorrhage, and included patient-oriented evidence that matters (POEMs), such as mortality or disability, as primary outcomes. Older trials using urokinase were excluded, because patients were enrolled up to 30 days after onset of symptoms.[6] The Australian Streptokinase (ASK) trial, the Multicenter Acute Stroke Trial-Europe (MAST-E), and the Multicenter Acute Stroke Trial-Italy (MAST-I) were not included because they were stopped early as a result of an increased mortality rate among streptokinase-treated patients. No data support the use of streptokinase in the treatment of acute ischemic stroke.[7-9] As a result, only the NINDS and the European Cooperative Acute Stroke Study (ECASS), which used rt-PA, are discussed in this review.[3,10]

This review will use the STEP approach: *s*afety (an analysis of hemorrhagic complications), *t*olerability (pooled drop-out rates from the trials), *e*ffectiveness (how well rt-PA works in patients with acute ischemic stroke and in what patient populations), and *p*rice (costs of the drug; cost effectiveness of the therapy) to review the role of rt-PA in the treatment of acute ischemic stroke.

Safety and Tolerability

Safety and tolerability outcomes that are relevant to thrombolytic therapy in acute ischemic stroke are fatal and nonfatal intracranial hemorrhage death, and other adverse events. The incidence of hemorrhage that occurred in NINDS and ECASS is summarized in Table 1. For every 8 patients assigned to rt-PA in the ECASS trial, 1 additional patient would develop a parenchymal hematoma (as compared with placebo). Parenchymal hematoma is usually responsible for clinical deterioration. For every 17 patients assigned to rt-PA in the NINDS trial, 1 additional patient would develop a symptomatic intracranial hemorrhage (as compared with placebo).

Other adverse events were mentioned in the ECASS trial. No difference was found in the occurrence of serious adverse events other than intracranial hemorrhage. Events reported included cardiac arrest, cardiac failure, intracranial hypertension, atrial fibrillation, myocardial infarction, pulmonary embolism, somnolence, pneumonia, respiratory insufficiency, renal failure, and cere-

Table 2. Instruments Used to Measure Outcome in the European Cooperative Acute Stroke Study (ECASS) and the National Institute of Neurological Disorders and Stroke (NINDS) Trial.

Instrument[11]	What It Measures	Point Range	Examples of Ratings
Barthel Index (BI)	Ability to perform activities of daily living (ie, eating, bathing, walking, using the toilet)	0 - 100	No disability = 100
Scandinavian Stroke Scale	Neurologic deficit	0 - 58	Mild neurologic deficit > 50 No deficit = 58
Modified Rankin Scale (RS)	Global clinical impression, overall function assessment	0 - 5	No symptoms (total recovery) = 0 Severe disability = 5
Glasgow Outcome Scale	Global assessment of function	1 - 5	Good recovery = 1 Moderate disability = 2 Severe disability = 3 Vegetative state = 4 Death = 5
National Institutes of Health Stroke Scale (NIHSS)	Serial measure of neurologic deficit	0 - 42	No deficit = 0 Mild facial paralysis = 1 Complete right hemiplegia with aphasia, gaze deviation, visual-field deficit, dysarthria, and sensory loss = 25
Wald test	Global test statistic, simultaneously tests for effect in four outcomes measures (BI, RS, NIHSS, and Glasgow Outcome Scale)		

brovascular disorder.[10] No other adverse events were mentioned in the NINDS trial, although outcome data were missing on 5 patients.[3]

Effectiveness

Improved functional status and decreased mortality are the primary efficacy outcomes on trials of thrombolytic therapy in acute ischemic stroke. ECASS and NINDS differed in their study design, including dosages of rt-PA, exclusion criteria, concomitant treatments, evaluation instruments, and time from the onset of the stroke to the receipt of the rt-PA. Table 2 describes the instruments used to assess outcomes in these studies.[11]

Table 3. Number Needed to Treat for rt-PA Versus Placebo.

Instrument	Number Needed to Treat*	
	ECASS (90 days)	NINDS, Part 2 (90 days)
Barthel Index	NS	8
Modified Rankin Scale	NS	8
Scandinavian Stroke Scale	NS	NR
National Institutes of Health Stroke Scale	NR	9
Glasgow Outcome Scale	NR	8

*Number of patients who need to receive treatment to prevent a single adverse outcome.
ECASS - European Cooperative Acute Stroke Study. NINDS - National Institute of Neurological Disorders and Stroke.
NS - not statistically significant.
NR - not reported.

European Cooperative Acute Stroke Study (ECASS)

ECASS enrolled 620 patients who were randomized to treatment with rt-PA (1.1 mg/kg) or placebo within 6 hours after the onset of symptoms.[10] The median time from stroke onset to treatment was 4.3 hours. A bolus of 10 percent of the total dose was given during the first 1 to 2 minutes, followed by a 60-minute infusion of the remaining dose. ECASS excluded concomitant use of heparin and anticoagulants, but permitted aspirin.[10] Functional and clinical outcomes were defined by changes in the Barthel Index (activities of daily living) and the modified Rankin Scale (global functional assessment) at 90 days. Mortality and neurologic deficit were measured at 30 days with the Scandinavian Stroke Scale.[11] The following summarizes the results from the intention-to-treat analysis of the data (Table 3).

The rt-PA and placebo groups were similar in the change in ability to perform activities of daily living ($P = 0.99$). There was no difference between the rt-PA and placebo groups functionally ($P = 0.41$) or neurologically ($P = 0.54$) at 90 days. The mortality rate was significantly higher in the rt-PA

Table 4. Contraindications to the Use of rt-PA in Acute Ischemic Stroke.

CT scan reveals intracranial hemorrhage
Initiation of treatment more than 3 hours after onset of symptoms
Previous intracranial hemorrhage
Previous stroke or serious head trauma within 3 months
Rapidly improving or minor symptoms
Symptoms suggestive of subarachnoid hemorrhage
Major surgery within 14 days
Urinary or gastrointestinal hemorrhage within 21 days
Arterial puncture at noncompressible site within 7 days
Seizure at stroke onset
Elevated partial thromboplastin time (PTT)
Elevated prothrombin time > 15 seconds
Platelet count < 100,000/L
Use of oral anticoagulants or heparin within 48 hours with elevated PTT
Serum glucose < 50 mg/dL or > 400 mg/dL
Systolic blood pressure > 185 mmHg or diastolic blood pressure > 110 mmHg at time of treatment or aggressive treatment to reduce blood pressure needed to reach specified limits

group at 90 days (22.4 versus 15.8 percent for placebo, $P = 0.04$). There were significantly more hemorrhage-related deaths in the rt-PA group (6.3 percent) versus the placebo group (2.4 percent), $P = 0.02$. Functional outcome data for those with a hemorrhagic event versus those without were not presented.

In evaluating ECASS, important considerations are the analyses of the data and the interpretation of CT findings.[12,13] The intention-to-treat analyses of ECASS did not show a benefit with rt-PA compared with placebo for the primary endpoints of the Barthel Index and modified Rankin Scale at 90 days. Exclusion of the 109 patients who were considered to have a protocol violation resulted in a target population that, when analyzed again, showed a significant benefit with rt-PA as measured by the Rankin Scale. In the intention-to-treat analysis, ECASS reported a statistically significant increase in mortality with rt-PA that was subsequently reduced in the target population analysis. Most of the protocol violations were due to CT exclusions, with 66 patients removed from the target population because reinterpretation of their CT scans showed the presence of "early infarct signs."[12]

The data reported in ECASS from the target population might not be as reflective of the patients that physicians commonly see as were the data from the intention-to-treat population. The critical issue for practice is whether the second analysis essentially turned a negative study into a positive one. In addition, and perhaps most important, is the issue that the radiologists involved in ECASS had been specifically trained in the protocol, and yet a large percentage of patients were excluded in the target population analysis because of initial misreading of CT scans. How well would an experienced radiologist at a community hospital do, where reinterpretation of the CT scan before administration of the drug might not be possible? These issues raise serious concerns about the use of this study for recommendations about rt-PA in routine medical practice.

National Institute of Neurological Disorders and Stroke (NINDS) trial

The NINDS trial was divided into two parts. Each was essentially an independent study, but the same protocol was followed in both parts.[3] In both studies patients were randomized to receive either intravenous rt-PA (0.9 mg/kg) or placebo within 3 hours of the onset of symptoms. Ten percent of the dose was given as a bolus, with the rest of the dose given as an 1-hour infusion. The NINDS trial restricted the use of any anticoagulant, antiplatelet, or heparin therapy for 24 hours.[3] The exclusions for this trial are listed in Table 4.

The first part of the trial examined the resolution of neurologic deficits within 24 hours of the onset of symptoms (n = 291). The second part evaluated clinical outcomes at 3 months (n = 333), using the Wald test, which combines results from four scales: Barthel Index, modified Rankin Scale, Glasgow Outcome Scale, and the National Institute of Health Stroke Scale. A favorable outcome was defined based on specific values for each of the four indexes, reflecting minimal or no disability, such as mild facial droop or slight arm drift.

Improvement in neurologic status at 24 hours was not different between the rt-PA and placebo groups ($P = 0.21$). The odds ratio for a favorable outcome with rt-PA at 90 days, determined by the Wald test, was 1.7 (95 percent confidence interval [CI], 1.2-2.6). Patients who received rt-PA were 30 percent more likely to have minimal or no disability at 3 months ($P = 0.026$). Mortality rates were 17 percent and 21 percent in the rt-PA and placebo groups, respectively ($P = 0.30$). Sixty-one

Table 5. Drug STEPS Quick Read.

Safety and **T**olerability	ECASS[10]—more patients who received rt-PA died versus placebo ($p = 0.04$). Significantly more parenchymal hematomas occurred in rt-PA group versus placebo (19.4% versus 6.8%, $P < 0.001$)
	NINDS[3]—rt-PA was associated with significantly higher number of symptomatic intracranial hemorrhage compared with placebo (6.4% versus 0.6%, $P < 0.001$).
Effectiveness	NINDS[3]—rt-PA did not result in decrease in mortality from acute ischemic stroke, but functional outcome was shown to improve.
	ECASS[10]—rt-PA increased mortality and did not improve functional outcome.
Price	One dose of rt-PA costs $2750; however, in the context of total cost of ischemic strokes, this cost is small.
Summary	If patients are admitted within 3 hours of symptom onset, NINDS exclusion criteria are not present, and CT scanning has ruled out intracranial hemorrhage, patients can have better functional status after stroke. Few patients who receive rt-PA are likely to meet these conditions.

percent of the patients with symptomatic hemorrhage had died at 3 months. Table 3 summarizes these results with number-needed-to-treat data. Functional outcome data comparing patients with intracranial hemorrhage versus those without were not presented. Current recommendations for the use of rt-PA have been based on the strengths of this study.

Implications for Practice

For the practicing physician, the most important question remains, Can the benefits reported in NINDS be safely achieved in the hospital to which I admit my patients with acute ischemic stroke? In general, if rt-PA is to be used safely based on the NINDS, three specific components of care in the form of a stroke team should be present.[14] First, a physician with appropriate expertise to diagnose the stroke must be available. Although attention has been focused on whether a given hospital has an organized stroke unit or neurologic intensive care unit, many of the institutions involved with NINDS had neither.[15] The second factor is the 24-hour availability of a facility to provide CT scanning. As mentioned previously, 11 percent of scans in ECASS were later reinterpreted to have "early infarct signs" suggesting hemorrhagic transformation. The third basic consideration is that the facility have the capability to manage intracranial hemorrhage and other complications of thrombolytic therapy.

Do any patient-related factors predict either a good or bad (ie, intracranial hemorrhage or lack of benefit) outcome with rt-PA? Using information from the NINDS trial, two subsequent analyses failed to discover factors that would be clinically useful in predicting these outcomes consistently.[16,17] Patients who were at higher risk for an adverse event were just as likely to receive benefits from treatment. For example, older patients with higher baseline National Institutes of Health Stroke Scale (NIHSS) scores were more likely to have a poor outcome, regardless of treatment. These patients, however, also benefited from treatment, as did patients with moderate deficits at baseline. Although the second analysis found that a severe neurologic deficit and brain edema (or mass effect) on CT scan at baseline were associated with a higher risk of intracranial hemorrhage, these variables predicted its occurrence only 57 percent of the time. Patients with these characteristics who received rt-PA were also more likely to have a favorable outcome than patients in the placebo group with these characteristics.

Another potential confounding variable is the use of aspirin in acute ischemic stroke. Aspirin is the current standard of care based on the International Stroke Treatment (IST)[18] and the Chinese Acute Stroke Treatment (CAST)[19] trials. Aspirin was shown to decrease slightly the combined endpoints of death and recurrent stroke without increasing hemorrhagic infarctions. Because ECASS and NINDS did not use aspirin to any appreciable extent, and IST and CAST did not use rt-PA, it is difficult to sort out the treatment effects of these medications in 1998.

How do physicians resolve the conflict between the differing results of ECASS and NINDS? The answer to this question is not known; however, one might postulate that more patients who received rt-PA died in ECASS because of the greater dose of rt-PA (1.1 mg/kg versus 0.9 mg/kg in NINDS), longer time to treatment (6 hours versus 3 hours), or differences in CT technology between Europe and the United States.

Perhaps the most important consideration, however, is the recognition that most stroke patients will not be eligible for rt-PA either because they will have had symptoms for longer than 3 hours (or upon arising in the morning) or they will

have an exclusion according to the NINDS criteria (Table 4). Each hospital participating in NINDS enrolled on average only 2 to 5 patients per year.

If the appropriate conditions are met, intravenous rt-PA in a dosage of 0.9 mg/kg (up to a maximum of 90 mg) has been shown to have potential benefits. The rt-PA should be given with 10 percent of the dose administered as a bolus followed by a 60-minute infusion within 3 hours of the onset of symptoms. In summarizing the safety and effectiveness of rt-PA, patients must seek help early, their condition must be carefully evaluated, they should receive a CT scan to rule out hemorrhage, and they should receive the drug within a 3-hour period.

Price

In the context of the total costs associated with treatment in the intensive care unit and subsequent rehabilitation, rt-PA costs ($2750) are negligible. While several cost-effectiveness and quality-of-life models have been published on the use of thrombolytic therapy in acute myocardial infarction, similar information on the use of rt-PA for acute ischemic stroke is not currently available. Improvements in the functional status of stroke survivors should benefit the person's quality of life and potentially decrease nursing home costs; however, data specifically with rt-PA have not been published. Similarly, several studies have shown that patients at risk for a stroke consider a severe stroke with disabling hemiplegia, confusion, or global aphasia to be equal to or worse than death.[20] If rt-PA can be used safely and effectively to improve functional status, one intuitively suspects that quality of life should be improved.

Summary

The administration of rt-PA to patients with acute ischemic stroke can result in improved functional outcomes. The safe and effective use of rt-PA in routine medical practice requires that patients seek help early, have a well-defined onset of their symptoms, be carefully examined for contraindications to rt-PA, receive a CT scan and interpretation to exclude hemorrhage, and receive the drug within a 3-hour period (Table 5).

Intravenous rt-PA is given in a dosage of 0.9mg/kg (up to a maximum of 90 mg) with 10 percent of the dose administered as a bolus followed by a 60-minute infusion within 3 hours of the onset of symptoms. If these conditions cannot be achieved, the drug should not be administered. Although most patients will not meet the criteria of the NINDS trial, rt-PA is an important advance in the treatment of acute ischemic stroke.

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