

Evidence-Based Emergency Medicine: Updates, Feedback, and Links

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Editors' note: The goal of the Evidence-Based Emergency Medicine (EBEM) series is to teach the process of translating research into clinical practice. In this issue, we introduce a new component of the series titled "Updates, Feedback, and Links." Because biomedical research is constantly and rapidly changing, we will provide "Updates" to previously addressed clinical questions. And because there is more than one way to skin a cat (if you will forgive the expression), we hope to provide a forum for "Feedback" regarding evidence-based medicine (EBM) as applied to the specialty of emergency medicine. Our objective in the feedback segments is to engage you, the reader, in the issues and dilemmas that arise from a systematic attempt to integrate evidence into clinical decisionmaking. We welcome comments, suggestions, and criticisms by E-mail or post from readers and users of the EBEM series. These comments and questions may address specific EBEM installments, EBM in general, and the application of EBM skills in clinical practice. In responding to such queries, we will draw on the expanding range of individuals and expertise currently surrounding the EBEM feature, including a team of librarians who regularly review the search strategies of EBEM installments. Finally, in the section called "Links," we may recommend paper-based resources and Web sites that may be used to facilitate the translation of research into clinical practice.

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EBEM Series Editors

Please send feedback—comments, questions, and recommendations to Peter C Wyer, MD, at the *Annals* Editorial Office or electronically to pwyer@worldnet.att.net.

UPDATE: RECOMBINANT TISSUE PLASMINOGEN
ACTIVATOR IN ACUTE ISCHEMIC STROKE*

[Wyer PC: Update: Recombinant tissue plasminogen activator in acute ischemic stroke. *Ann Emerg Med* November 1999;34:658-659.]

An update of the MEDLINE search on Internet Grateful Med between January 1, 1997, and January 28, 1999, using the search strategy and selection criteria previously described,¹ found 1 randomized controlled trial,² 1 meta-analysis,³ 4 secondary analyses⁴⁻⁷ of the ECASS (European Cooperative Acute Stroke Study) I trial,⁸ and 2 secondary analyses^{9,10} of the National Institute of Neurological Disorders and Stroke (NINDS) trial¹¹ that were not considered in the original evidence-based emergency medicine (EBEM) review. Of these, one³ is a summary of a systematic overview published by the Cochrane Library.^{1,12}

ECASS II² is the one new randomized controlled trial of intravenous recombinant tissue plasminogen activator (rtPA) in acute ischemic stroke to appear since the NINDS study. The expanded ECASS study effort encompassed 108 centers in 14 European countries, Australia, and New Zealand. ECASS II was an attempt to reproduce the results of the NINDS trial in this practice setting. There were several modifications of the ECASS I protocol to conform to the NINDS protocol. These included lowering the dose of intravenous rtPA from 1.1 to 0.9 mg/kg, adding a blood pressure control protocol, and prohibiting the use of aspirin during the first 24 hours after presentation. In addition, outcome measures were analyzed in the dichotomized form used in the NINDS study. Finally, whereas ECASS I excluded patients with hypodensity (brain swelling) on the initial computed tomographic (CT) scan only if one entire brain hemisphere were involved, ECASS II excluded patients with greater than 33% of involvement of the affected side. This had the effect of making the population studied in ECASS II more similar to that of NINDS, in which fewer than 5% of patients had edema or mass effect on initial CT scan.

As with ECASS I and in contrast to NINDS, ECASS II included patients up to 6 hours after onset of symptoms. The authors report that 800 patients were included in ECASS II out of 814 patients "considered." This amounts to 1 patient every 2 months per participating center. It

would seem, therefore, that only a very small percentage of all patients presenting with acute ischemic stroke were eligible for ECASS II. This is in line with the highly selected nature of the patient populations involved in the ECASS I and in the NINDS trials. ECASS II is the largest randomized trial to date on the efficacy of intravenous rtPA for patients with acute ischemic stroke.

The methodologic quality of ECASS II was very high, as judged by the criteria elaborated in the previous review.¹ The controversial "target population" approach to analysis of results, used in ECASS I, was dropped, and the results of ECASS II were presented with rigid adherence to the "intention-to-treat" principle. The importance of this was discussed in the original EBEM review of this topic.¹ Complete (100%) follow-up for the study period was achieved.

Despite rigorous methods and equalization of the protocol with that of NINDS, the ECASS II investigators failed to detect a statistically significant benefit in the dichotomized outcome measure of the modified Rankin Score (mRS) used in NINDS. In the mRS, a score of 2 or greater, used in NINDS, corresponds to a patient outcome of "death or disability." The NINDS investigators observed a clinically and statistically significant benefit of rtPA therapy for this outcome.¹ The ECASS II investigators suggest that the failure to demonstrate a statistically significant benefit of rtPA therapy in this study resulted from the lower severity of baseline deficits in the ECASS II study population compared with the NINDS trial. The median National Institutes of Health Stroke Scale (NIHSS) score in NINDS was 14, compared with 11 in ECASS II and 13 in ECASS I. The NIHSS score is based on clinical assessment of neurologic deficits. The highest possible NIHSS score, 42, reflects the greatest possible deficit in a living patient. The clinical significance of the difference in median NIHSS score of 3 points observed between ECASS II and NINDS is borderline. Pilot studies done in connection with the NINDS trial identified a change in NIHSS score of 4 or greater as defining clinical significance.^{1,3} A retrospective analysis of ECASS II data found a statistically significant benefit ($P=.024$) of rtPA when the dichotomization of the mRS was reset at a score of 3 or greater.² Such a score reflects death or dependence in the activities of daily living. This might be considered by many, or even by most, ischemic stroke patients to be a persuasive reason to take rtPA. However, the failure of ECASS II to reproduce the results of the NINDS trial with respect to the most clinically unambiguous, prospectively defined, outcome measure (mRS <1), despite a larger patient sample and a virtually identi-

*This article is an update to: Wyer PC, Osborn HH: Recombinant tissue plasminogen activator: In my community hospital ED, will early administration of rt-PA to patients with the initial diagnosis of acute ischemic stroke reduce mortality and disability? *Ann Emerg Med* 1997;30:629-638.

cal study protocol, casts as much darkness as light on the question of the true potential benefit of this therapy and what must be done to achieve it. It is imperative that major clinical research continue to be directed toward clarification of the question of which patients with ischemic stroke are likely to experience a net benefit from thrombolytic therapy and of what cointerventions are required to realize that benefit. The evidence to date clearly justifies further inquiry. In the meantime, clinicians are best advised to approach the issue of use of this therapy with some caution.

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Updated Critically Appraised Topic (CAT): Recombinant Tissue Plasminogen Activator in Acute Ischemia Stroke

Question	Will early administration of rtPA to patients in my ED with the initial diagnosis of acute ischemic stroke reduce mortality and disability?
Reviewed by	Wyer PC, Osborn HH
Date	October 30, 1996
Update	Wyer PC
Date	January 28, 1999
Clinical bottom line	Recombinant tissue plasminogen has reduced the risk of disability, dependence, or mortality in selected patients with acute ischemic stroke when administered in several carefully controlled research settings. ECASS II failed to reproduce the statistically significant benefit observed in NINDS as measured by the prospectively defined dichotomized mRS corresponding to presence or absence of death or disability, despite a rigidly controlled research protocol designed to be identical to that of NINDS. Whether the benefit of rtPA for reducing death or disability in patients with acute ischemic stroke can be achieved in a non-research setting remains unclear. Benefit of rtPA may depend on the intensity of diagnostic scrutiny of patients for inclusion, including precise reading of the initial CT scan, or on the nature of cointerventions such as the level of ongoing care. A time sensitivity of treatment efficacy within the first 6 hours of onset of symptoms has not been demonstrated in published studies.
Search strategy	MEDLINE via Internet Grateful Med: "stroke" OR "infarct" (as text words) AND "acute" (as text word) AND "explode Plasminogen" OR "explode Plasminogen activators" (as MeSH terms); limited to "randomized controlled trials" OR "meta-analysis" (as publication types) from years 1980 to 1996, updated through January 28, 1999.
Citations (randomized controlled trials)	<ol style="list-style-type: none"> 1. Tissue plasminogen activator for acute ischemic stroke. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. <i>N Engl J Med</i> 1995;333:1581-1587. 2. Hacke W, Kaste M, Fieschi C, et al: Intravenous thrombolysis with recombinant tissue plasminogen activator for acute hemispheric stroke—The European Cooperative Acute Stroke Study (ECASS). <i>JAMA</i> 1995;274:1017-1025. 3. Hacke W, Kaste M, Fieschi C, et al: Randomised double-blind placebo-controlled trial of thrombolytic therapy with intravenous alteplase in acute ischaemic stroke (ECASS II). Second European-Australasian Acute Stroke Study Investigators. <i>Lancet</i> 1998;352:1245-1251. 4. For the full review and update on this topic by the authors of this CAT, see <i>Ann Emerg Med</i> 1997;30:629-638.
Study characteristics	<p>Population Adults with clinically diagnosed ischemic stroke and CT-negative for hemorrhage 0 to 6 hours from onset of symptoms. Patients with improving symptoms excluded. Patients with "early infarct" signs on CT scan excluded from ECASS I and II; blood pressure control protocol followed as prerequisite to eligibility in NINDS and ECASS II.</p> <p>Interventions Intravenous rtPA or placebo; 0.9 mg/kg to 90 mg (NINDS, ECASS II) or 1.1 mg/kg to 100 mg (ECASS I).</p> <p>Outcomes mRS 90 days, BI 90 days, National Institutes of Health Stroke Scale 90 days. Dichotomized Rankin and BI in NINDS and ECASS II. Patients who died assigned worst score in all studies.</p>
Methodologic quality	Uniformly high in ECASS II. Cointerventions not specifically documented between the study groups.
Results	MRS >1=death or disability

	NINDS	ECASS I*	ECASS II
NNT (95% CI)	7 (5, 12)	14 (7, 396)	28 (NS)
RR (95% CI) of death or disability	0.78 (0.68, 0.88)	0.89 (0.78, 1.00)	0.94 (0.84, 1.05)

NNT=The number of patients who would have to take the treatment to prevent one case of death or disability in a patient otherwise destined for same.

RR=The risk of death or disability among patients who received rtPA divided by the risk of death or disability among patients who received placebo.

*Revised data from *Stroke* 1998;29:2073-2075.

FEEDBACK: WALK OR DIE!

[Cordell WH: Feedback: Walk or die! *Ann Emerg Med* November 1999;34:661.]

Comment

We used one of the *Annals* EBEM installments on rtPA in acute ischemic stroke¹ as the basis of one of our Evidence-Based Journal Clubs. After reviewing the evidence, the majority of participants had severe reservations about using thrombolytic agents in patients. Although they recognized the therapeutic benefits, they were greatly concerned with the risk of brain hemorrhage. However, when the question was phrased, “Would you want rtPA if you had an ischemic stroke with aphasia or hemiplegia?”, most said “yes.” In other words, it appears they had qualms about using it on patients, but fewer qualms about having it used on themselves. One physician commented, “For me, personally, the choice is ‘Walk or die!’”

William H Cordell, MD

1. Wyer PC, Osborn HH: Recombinant tissue plasminogen activator: In my community hospital ED, will early administration of rt-PA to patients with the initial diagnosis of acute ischemic stroke reduce mortality and disability? *Ann Emerg Med* 1997;30:629-638.

In response

[Wyer PC: Feedback: Walk or die! [in response]. *Ann Emerg Med* November 1999;34:661-662.]

It is fascinating to see that physicians can come to diametrically contrasting conclusions about a therapy while thinking of themselves as doctors from those reached while thinking of themselves as potential patients! “Walk or die” reflects the value system that many but not all patients might hold. Would the individual patient be willing to sacrifice life itself to avoid major disability? Have the authors of the studies provided the data to allow the clinician and patient to weigh the possible tradeoffs between outcomes?

The modified Rankin Score (mRS), used in all 3 trials,¹⁻³ is the outcome measure that best applies to this question. The Rankin Score is a measure of functional outcome. It is important to recognize that the Rankin Score does not take into account the effect of an ischemic stroke on cognitive function of the survivor. It is possible that thrombolytic therapy might preserve his or her ability to walk, but that she or he might not retain a coherent ability to determine a rational destina-

tion or purpose. The mRS scoring system is detailed in Table 1.

The authors of the published studies of efficacy of rtPA in ischemic stroke assigned patients who died to either a mRS of 5² or created a higher category 6 for this designation.^{1,3,4} They also reported death as an independent outcome measure.

As seen in Table 1, an mRS of 4 or more means that the stroke survivor is unable to walk unassisted. In other words, the physician who said “walk or die” is asserting that his or her personal bottom line for taking rtPA in the context of stroke is that it not increase the probability of survival at the expense of an increased risk of having an mRS of 4 or 5. One can assume that she or he would be even happier if the therapy also increased the likelihood of a full recovery or of recovery with less severe deficits.

The concept of tradeoffs between different outcomes is well established in the medical literature and is central to patient-oriented decision analysis. For example, a standard outcome measure in such analyses, the “quality-adjusted life year” (QUALY), is a measure of how many years of disabled life a patient would be willing to sacrifice per completely functional year of life gained.⁵

To assess all possible outcomes relevant to a patient-value orientation, from a physical function standpoint, would require that the proportion of patients in both treatment and placebo groups who fall into each mRS category be reported, with mortality reported as an additional category. However, the authors of only 1 of the 3 major trials of rtPA versus placebo for ischemic stroke reported the data in this fashion.³ On the other hand, the published reports of all of the trials do allow the reader to determine the percentage of patients in the treatment and placebo groups who survived with a score of 4 or 5 and also the mortality rates within treatment and control

Table 1.
 Modified Rankin scoring system.

mRS	Outcome
0	No deficits and full recovery
1	Some deficits on neurologic examination, no disability
2	Some disability but full independence
3	Some dependence but able to walk unassisted
4	Needs assistance walking
5	Needs assistance in all activities of daily living
D	Death (scored as 5 or 6 in the rtPA stroke trials)

groups. Table 2 recategorizes original data from the 3 primary trials of intravenous rtPA in ischemic stroke with respect to the mRS scores relevant to the “walk or die” bottom line.

As shown in Table 2, patient outcomes in NINDS² were enhanced in all mRS categories. Mortality and inability to walk were both reduced, and full recovery was increased by treatment with rtPA. Such a result, if true, would be in accord with almost all patient values. In ECASS II,³ mortality was identical between the 2 groups, and a small decrease in the inability to walk without assistance was observed in the rtPA group. This result is also compatible with most patients’ values. In other words, in neither of these studies is there a need to consider tradeoffs between outcomes.

In contrast to the results of NINDS and ECASS II, the results of ECASS I¹ are consistent with a tradeoff between mortality and an inability to walk without assistance. The percentage of patients able to walk unassisted was identical in both placebo and rtPA groups. rtPA increased mortality for the remainder of patients at the same time that the inability to walk unassisted (mRS of 4 or 5) was reduced.

By recategorizing the data in this fashion, we are able to address the tradeoff expressed by the physician who said, “For me, personally, the choice is ‘Walk or die!’” Before these results are embraced by the advocate of the “walk or die” value ethic, however, he or she might be advised some caution. The original investigators of the 3 studies did not analyze the outcomes as presented in Table 2 and

did not consider them in their experimental hypotheses. The statistical significance of the patterns and trends illustrated in Table 2 is therefore unclear.

Incorporation of patients’ value systems with evidence from clinical research is the crux of practicing in an evidence-based fashion. Therapies almost always involve tradeoffs between harms and benefits, and the evidence from research must always be integrated with patients’ rights, values and preferences. Thank you for offering the opportunity to explore this with a very pertinent example.

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Table 2.

Recategorization of original data from the 3 major trials of rtPA for patients with ischemic stroke. The percentage of patients in the placebo versus the rtPA groups falling within mRS intervals.

Trial Group	mRS 0-3* (%)	mRS 4-5† (%)	Mortality (%)
ECASS I‡			
Placebo	64	21	16
rtPA	63	15	22
ECASS II§			
Placebo	65	25	10
rtPA	69	21	10
NINDS			
Placebo	51	27	21
rtPA	60	23	17

*An mRS of 0 to 3 reflects a range of outcomes extending from complete recovery without detectable deficits to some disability with preservation of the ability to walk unassisted.

†An mRS of 4 or 5 indicates the inability to walk unassisted.

‡Data from reference 1.

§Data from reference 3.

||Data from reference 2.

LINKS: EVIDENCE-BASED MEDICINE INTERNET SITES

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