

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?

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See related editorial, p 675, and related article, p 639.

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CLINICAL SCENARIO

You have recently joined the ED staff at a 200-bed hospital located in a city with population of 175,000. The annual census of the ED is 44,000. Your ED group has been approached by the hospital administration and neurologists to help put together a plan for treating patients who have sustained acute ischemic strokes. They are particularly interested in recent, highly publicized studies on the use of thrombolytic agents. The hospital has full-time neurology coverage but does not have a dedicated stroke unit. Computed tomography (CT) scans may be obtained 24 hours a day. A radiologist is available in-house between the hours of 8 AM and 6 PM and is on-call after hours and on weekends and holidays. Discussions are under way to make possible off-hours interpretations of CT scans through telephonic transmission. The hospital serves as a base station for the local EMS service. The hospital library has computerized literature search and interlibrary loan capabilities. As your first assignment after joining the group, you volunteer to review the literature on thrombolysis in stroke and to report back on the feasibility of implementing a stroke-thrombolysis protocol from an emergency medicine standpoint.

In the remainder of this review we will lead the reader systematically through the process of formulating the question, searching for the best evidence, analyzing the evidence, and applying the evidence to practice. At the end of the review the scenario will be resolved in the form of possible "bottom-line" conclusions.

FORMULATING THE QUESTION

You recognize that success will depend on how clearly and precisely you can define the question. "Should our ED develop a protocol for thrombolysis in stroke?" encompasses many more specific questions. Such questions could involve issues of therapy ("Do thrombolytic agents work for stroke?"), diagnosis ("Can ischemic stroke be accurately diagnosed in the ED?"), harm ("Is thrombolysis too dangerous to be considered for my stroke patients?"), or even prognosis ("What is the long-term outlook with conventional therapy of stroke patients whom I would be likely to treat with thrombolytic agents?"). It is also clear that questions within any one of these categories could lead in different directions by being made more focused and specific. A diagnosis question could be restricted to the accuracy of head CT or could, more generally, ask whether a clinical prediction rule made up of any combination of clinical, laboratory, and imaging criteria has been developed to differentiate patients with ischemic stroke from those with hemorrhagic stroke.

One approach to a problem involving many different questions is to seek a general review in a peer-reviewed publication. General reviews are not, however, structured in a fashion that ensures that all the experimental evidence pertaining to each question has been considered or that a systematic and unbiased approach to appraising the validity and applicability of such evidence has been employed.¹ You therefore elect to focus on a question regarding the therapeutic efficacy of thrombolytic agents.

To define the question in a way that can be searched and answered, the patients, interventions and outcomes necessary to a study relevant to a particular practice setting must be considered.² Studies involving patients with an acute presentation of ischemic stroke enrolled during the emergency phase of their care are therefore preferable. To ensure that the results of the studies selected are applicable to routine hospital practice, you decide to include only studies in which the diagnosis of ischemic stroke was made by means of clinical evaluation and CT scan and to exclude studies involving angiography and other diagnostic modalities not readily available on an emergency basis before the initiation of thrombolysis. The findings of recent studies involving the use of streptokinase in ischemic stroke have been negative.^{3,4} A search limited to trials involving intravenously administered recombinant tissue plasminogen activator (rt-PA) is therefore most relevant. Finally, to ensure that the benefits of thrombolysis are important enough to stroke patients to warrant the risks of therapy, emphasis on studies using direct measures of long-term functional recovery as the principal outcome is appropriate.

The reformulated question is: "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?"

SEARCHING FOR THE BEST EVIDENCE

Once the question has been formulated, the search can be defined. Several factors shape your approach. Administration of agents known to cause intracranial hemorrhage could worsen the outcomes of patients with ischemic stroke. Unequivocal evidence is therefore necessary to justify a positive recommendation. The search is therefore limited to randomized controlled trials. Randomization of patients in a clinical study minimizes the risk of distortion of the results through bias and maximizes internal validity.⁵

It is important to determine whether a metaanalysis has been published on your question. Such an analysis would involve statistical pooling of data from individual trials and might make possible a definitive conclusion regarding efficacy lacking in any one study.⁶ Conventional Medline programs allow publication types to be specified. Metaanalysis must be specified for this type of review to be reliably found. The Cochrane Database of Systematic Reviews⁷ and the *ACP Journal Club*⁸ are also important sources. To minimize the chance of missing important studies, a broad, minimally restricted search strategy should be adopted, and the search should be extended back to 1980.

The Medline search from 1980 to 1996 yields 313 citations (Figure). A scan of the titles allows 302 titles unrelated to stroke to be eliminated. Medline also allows the abstracts of the remaining 11 citations to be scanned, resulting in the elimination of an additional 6 citations. The remaining five studies are randomized controlled trials of rt-PA for ischemic stroke.⁹⁻¹³ The total search time is less than 30 minutes.

The hospital library enables access to full texts of published studies through interlibrary loan. Review of the bibliographies of these studies, as well as those of several general reviews cited in them, yields one more individual randomized controlled trial¹⁴ and one systematic overview.¹⁵ The Cochrane Database reveals one systematic overview,¹⁶ last updated August 12, 1996. The two systematic overviews combine reviews of efficacy of all thrombolytic agents, including streptokinase, in ischemic stroke, and hence do not correspond to the question. They do, however, confirm the absence of other randomized trials of rt-PA in stroke.

Two of the six primary studies^{12,13} were preliminary to or otherwise included in the National Institute of Neurological Disorders and Stroke (NINDS) study,⁹ and two^{10,14} involved angiographic demonstration of carotid artery occlu-

sion before the initiation of thrombolytic therapy. Exclusion of these studies leaves the NINDS study⁹ and the European Cooperative Acute Stroke Study (ECASS).¹¹

ANALYZING THE EVIDENCE

To streamline the process of analyzing the NINDS and ECASS studies, you adopt the approach outlined in the User's Guide to articles on therapy.⁵ This involves a systematic appraisal of a study's validity, results, and applicability to practice.

It is useful to jot down the defining features of the two studies in the process of reading through the Methods and Results sections, again emphasizing patients, interventions, and outcomes (Table 1).

Plotting these characteristics of the studies facilitates recognition of important similarities and differences in the patient populations and protocols and sets the stage for the assessment of the applicability of the studies to a particular practice setting. In this case differences in rt-PA dose, protocols for blood pressure control, and inclusion criteria with respect to time from onset of symptoms are notable. The authors

of neither trial reported the number of stroke patients that were screened to generate the 600-odd study subjects. The fact that a single participating center enrolled, on average, two to five patients per year makes it likely that only a small fraction of stroke patients seen at the participating centers were eligible.

After surveying the two studies, their validity is assessed. The term "validity" is sometimes used in different ways, with resulting confusion. Internal validity pertains to the likelihood that factors inherent in the design of the two studies might have served to erroneously steer the results in one direction or the other. Such an influence is termed "bias"; it is the equivalent of giving one or more of the contestants in a competitive sports event some number of points before the game begins. The phrase "external validity" is frequently used to denote the likelihood that the results observed in a study will be achievable in a different, nonexperimental, setting. For the sake of clarity, the term "applicability" has been adopted in place of "external validity" in this review.

Following the User's Guides,⁵ the studies are surveyed for five key points of validity. This survey reveals both the NINDS and ECASS studies to be methodologically strong. The full protocol of the ECASS study was published in a European journal not included in Medline and not available in the National Library of Medicine collection.¹⁷ However, the description of the methods in the ECASS report indicates that the study design was carefully planned. Both the NINDS and ECASS studies were randomized and blinded in a fashion appropriate to a multicenter design. The intention-to-treat principle, followed in both trials, requires that all patients accepted for enrollment and randomly assigned to a study group be included in the final analysis of the

Table 1.
Details of the NINDS and ECASS studies.

	PATIENTS					
	Number	Age	Sex	NIHSS Centers		
		Mean (SD)	M/F (%)	Median	Number	Pts/Center/Yr
NINDS	624	67 (±12)	62/38	14	39	5
ECASS	620	68 (±12)	58/42	12	75	2.5
	Included			Excluded		
NINDS	0-3 hours from onset no hemorrhage by CT abnormal neuro exam			BP >185/110 improving symptoms anti-coagulated recent stroke		
ECASS	0-6 hours from onset no hemorrhage by CT minimum deficit			improving symptoms pre-existing deficit "early infarct" on CT		
	INTERVENTIONS					
	rt-PA	BP Protocol	Anti-coag/Anti-thromb			
NINDS	.9 mg/kg to 90 mg	Yes	No			
ECASS	1.1 mg/kg to 100 mg	No	No*			
	OUTCOMES					
	Barthel	Rankin	NIH Scale	Mortality		
NINDS	+	+	+	+		
ECASS	+	+	+	+		

*Salicylates administered at discretion of treating physicians.

Figure.
Principal search: Grateful Med-Medline (last updated July 31, 1997).

Strategy		
Stroke OR infarct (text) AND acute (text) AND explode: plasminogen OR plasminogen activators (MESH) restrict to randomized controlled trials (pt) OR metaanalysis (pt)		
Total citations found through Medline		313
Method of elimination	Reason	Number
Title screen	non-stroke	302
Abstract screen	non-stroke	3
	non-rt-PA	2
	commentary	1
	Total eliminated	308
Included from Medline search		5

results and that they be analyzed in the groups to which they were assigned. The elimination of selected groups of randomized patients from one or more study groups threatens the ability of the randomization procedure to eliminate unanticipated biases.

The study groups in both the NINDS and ECASS studies were well balanced with respect to factors that could influence outcome. Although more rt-PA patients in NINDS had been receiving maintenance aspirin therapy before their strokes, a statistical adjustment for a potential aspirin effect served to strengthen the observed results of the study.

With regard to cointerventions (therapeutic interventions other than those being studied), some potentially important questions are left unanswered in both study reports. Although ECASS gives data on aspirin use by participants before their enrollment, the number of patients in each group given salicylates during the trial was not reported. The NINDS trial involved a protocol for blood pressure control, but the authors did not report its details or how many patients in the different study groups actually received such intervention. If different numbers of patients in the two groups received antihypertensive agents, a bias could have been introduced into the results.

These questions notwithstanding, there is no direct indication in either trial that concomitant therapies significantly unbalanced the different study groups. From the standpoint of validity, both NINDS and ECASS rate "excellent" on a four-point categorical scale of "weak, fair, very good, excellent." It is therefore appropriate to proceed to review the magnitude and precision of the results.

The NINDS and ECASS trials present a complex array of data that a reader not accustomed to evaluating the results of research could find intimidating. Both used an array of scored outcome measures and both present the data in at least two different ways. You decide to concentrate on the combined results of all patients rather than on subgroups and to pay most attention to the outcome measure which most clearly reflects the priorities likely to be important to your patients. The overriding questions are, "If true, would the observed results be clinically important to my patients?" and, "How sure am I that the observed results are the true results?"

The authors of the two trials used a selection of scoring systems designed to measure neurologic deficit (National Institutes of Health Stroke Scale [NIHSS]), independence in activities of daily living (ADLs) (Barthel Index [BI]), and global outcome measures including the modified Rankin Scale (RS) and the Glasgow Outcome Scale. A published review of these outcome measures is relevant to the appraisal of the primary studies.¹⁸

Although measurements of neurologic deficit such as the NIHSS are highly reproducible, they tell little about the extent of a patient's actual disability. Functional scales such as the BI are more directly related to a patient's ability to function independently. However, a particular BI score may still correspond to a broad range of actual disabilities. On the modified RS, a score of 0 is assigned to patients with no residual deficits, 1 to those with deficits but no disability, 2 to patients with some disability but full independence, 3 to patients with some dependence who can walk unassisted, 4 to those who require assistance in bodily needs and walking, and 5 to those who require assistance in all ADLs and are bedridden.

Both NINDS and ECASS studies used the RS, and, although they reported them differently in their primary analysis, they provided data permitting direct comparison of their results. Furthermore, in both trials patients who died during the 90-day follow-up period were assigned the worst RS of 5. This is reasonable to the extent that most patients would feel that being bedridden and totally dependent on assistance in all ADLs would be as bad as having died. The RS is a functional neurologic-outcome system with moderate to good interobserver reliability.^{18,19} The NINDS investigators defined survivors with a modified RS of 1 or less as enjoying complete recovery. Such a patient may have deficits but no functional disability. You find this definition to be in accord with patients' values. In Tables 2 and 3 are presented the results of the two trials as measured with the RS in a form that allows direct comparisons of the results.

Accepting a RS score of 1 or less as a reasonable criterion for complete recovery, the two studies show an increase in likelihood of such a good outcome of 7% to 13%. If 100 eligible patients were treated with rt-PA, this result would mean that 7 to 13 more would recover fully than if rt-PA was withheld. For one extra patient to recover, 100/13 to 100/7—8 to 14 patients would have to be treated with rt-PA. The NINDS study showed a decreased percentage of patients in each RS score greater than 1, including death, among patients treated with rt-PA.

Both trials showed an increased incidence of secondary intracranial hemorrhage among patients receiving rt-PA. In NINDS both mortality and the percentage of patients in each RS score category above 1 consistently favored treatment with rt-PA. Hence no trade-off between mortality and disability was observed in NINDS.

An unusual feature of the ECASS study's approach to the data must be addressed. The investigators presented their results in two separate analyses. One followed the intention-to-treat (ITT) principle explained above. The other excluded from the final analysis almost 18% of the patients who had

been randomized. The investigators termed the latter approach the target population (TP) method. This modification had the effect of significantly narrowing the 95% confidence interval (CI) around the observed benefit enjoyed by the rt-PA patients as measured with the RS. This interval is the range of values that are also consistent with the observed data. In other words, the RS result by the ITT analysis was not statistically significant by conventional ($P < .05$) criteria.⁵ In the TP analysis, the entire CI is within the range of values that define treatment benefit. This is another way of saying that the results of the TP analysis were statistically significant.

Which analysis should one believe?

Violation of the ITT principle can be tantamount to changing the rules of a game after the clock has started and may threaten the effectiveness of the randomization. In the ECASS study, 66 of the 109 patients left out of the TP analysis were eliminated because of reinterpretation of their initial CT scans as having "early infarct" signs excludable under the study protocol. Despite blinding, patients receiving rt-PA were more likely to have their initial CT scans reinterpreted in this way than those receiving placebo. This feature of ECASS is remarkable, considering that the investigators had taken great pains to instruct the participating centers before the study began on how to interpret the baseline CT scans, and also in view of the fact that the scans were initially interpreted by staff neurologists and neuro-radiologists in those hospitals.

If only eligibility criteria were involved in the TP adjustment, the issue at hand might have more to do with questions of external applicability of the ECASS results to practice than with their internal validity. However, 43 patients, representing 7% of the patients randomized, were excluded from the TP analysis for other reasons. The TP analysis would be more convincing if only patients with reinterpreted CTs had been excluded and if some objective measure, such as an interobserver agreement assessment, of the reproducibility of the definitive CT readings had been provided.

Under the circumstances, and out of concern that rt-PA does more good than harm to patients with ischemic stroke, you elect to adhere to the ITT analysis of the ECASS study. Accepting this assessment, only one study, NINDS, showed unequivocal benefit to a 95% level of confidence.

Finally, 90-day mortality was different in NINDS and ECASS. NINDS showed a nonsignificant decrease in mortality in patients treated with rt-PA. ECASS reported an increase in mortality in the treatment group. This result was statistically significant in the ITT analysis and was reduced but not eliminated in the TP analysis. Although the ECASS investigators incorporated mortality into the RS, and although the different mortality results of the trials might or might not be statistically significant, there is cause for concern about a clinically important difference in the results of large studies with similar objectives. This difference points to potential problems pertaining to the application of these studies to a routine hospital practice setting.

APPLYING THE EVIDENCE

The two studies most relevant to the question that has been posed involved a substantial number of centers, resources, and preparation. Each reflected a high degree of methodologic rigor. Despite some unanswered questions, significant bias from known or unknown factors is unlikely; hence the benefits observed in the treatment groups in each study are most likely attributable to rt-PA. Each trial observed a clinically significant benefit in the rt-PA group in the most clinically relevant outcome measure. The fact that the benefit in the ECASS study is slightly equivocal notwithstanding, the evidence is such that there is little doubt that rt-PA can reduce disability or mortality when patients with acute ischemic stroke are accurately selected and treated in a setting comparable to those involved in the trials.

The question that remains is whether the benefits observed in the clinical research setting can be achieved in a

Table 2.

Ninety-day outcomes of the NINDS and ECASS trials, by dichotomized RS (% of patients scoring 1 or less on modified RS).

Study	rt-PA (%)	Placebo (%)	OR (95% CI)*	NNT (95% CI)
NINDS†	39	26	1.7 (1.1–2.6)	8(5–17)
ECASS ITT	36	29	1.15 (.98–1.35)	14 (7–NA)‡
ECASS TP	41	29	1.29 (1.09–1.54)	9 (5–29)

NNT, number of patients needed for treatment to avoid one bad outcome.
*For good outcome.

†Part 2 results, 0 to 180 minutes from onset.

‡See reference 26 for calculation guidelines.

Table 3.

Ninety-day outcomes of the NINDS and ECASS studies, by median score on modified RS.

Study	rt-PA	Placebo	P
NINDS	2–3*	3–4*	Not given
ECASS ITT	3	3	.41
ECASS TP	2	3	–.035

*Estimated from published table.

hospital practice under nonexperimental conditions. This category of concern is commonly defined as the issue of translating the efficacy observed in an experimental setting into effectiveness, the achievement of the benefit observed in studies in the less controlled setting of clinical practice.

Assessment of the applicability of a study requires that the clinician step beyond the framework of considerations of study design and combine the observed results with his or her knowledge of clinical practice and ability to accurately assess the individual patient. Such assessment involves, inescapably, value decisions, both of physician and patient. Furthermore, the evidence itself may be incomplete with respect to many relevant issues, requiring that the clinician make assumptions to complete the decision-making process. Because value judgments and assumptions may not be avoidable, integrity of the decision-making process can only fairly demand that they be made explicit and subject to scrutiny.

Beginning with the initial screening of the study designs, and extending through the review of methodology and results, you have accumulated a list of observations and questions pertaining to the applicability of the NINDS and ECASS studies. A checklist of applicability points includes the following factors.

Only a small percentage of stroke patients treated in the participating centers were eligible. An average enrollment of only two to five patients per participating hospital per year was achieved. Reflecting the effectiveness of patient selection, the NINDS investigators successfully limited patients classifiable as having sustained TIAs (symptoms spontaneously resolving within 24 hours of symptom onset) to less than 2% of the study population. Comparable data were not reported in the ECASS study.

Despite advance circulation to participating hospitals of a detailed instruction manual on the CT criteria for inclusion and exclusion of patients in the ECASS study, 11% of the initial scans, which were read by staff neurologists and neuroradiologists, were subsequently reinterpreted as having shown "early infarct signs." Exclusion of these patients in the TP analysis may have converted a negative study into a positive one. In the NINDS study, patients with early infarct signs were not excluded. The reported incidence of 2% to 6% of such patients was 50% or less of that observed in ECASS.

The protocol of the only study showing unequivocal benefit of rt-PA (NINDS), excluded patients with blood pressure greater than 185/110 mm Hg at the point of treatment or requiring intensive therapy to bring the blood pressure into this range and incorporated an algorithm for control of blood pressure within a predefined range. As noted above, bias could have been introduced if this algorithm had been fol-

lowed unequally between the two NINDS study groups. However, even in the absence of bias, blood pressure control might constitute a crucial adjunct to thrombolytic therapy, making it unwise to administer rt-PA to ischemic stroke patients without full knowledge of the protocol used. Neither of these aspects can be evaluated from the data included in the NINDS report.

NINDS and ECASS observed a net mortality difference between rt-PA and placebo groups in opposite directions, NINDS showing a consistent decrease in the treatment group, ECASS a consistent increase.

In neither study was a time-dependent benefit reported. Patients treated earlier were no more likely to benefit than those treated later in the allowed time period. Nor was it reported that any of the adverse outcomes were time dependent, even though the authors of one previous study reported such a correlation.²⁰

These items define issues of the applicability of the NINDS and ECASS results to a non-research hospital setting. Of particular concern are the issues of appropriate selection of patients and of the effects of cointerventions, including blood pressure control and critical care, that might be crucial for the benefits of rt-PA to be achieved.

The issue of selecting the appropriate patients to receive rt-PA for ischemic stroke encompasses issues pertaining to both clinical assessment of the patients themselves and to accurate interpretation of imaging studies. Both of these may in turn require intensive participation of specialty services for acceptable results to be achieved. The difficulties encountered with the reproducibility of CT interpretation in the ECASS study have been mentioned above. Although similar difficulties were not reported by the NINDS investigators, the NINDS protocol did not attempt to exclude patients with "early infarct signs," as did ECASS. However, a much lower incidence of such patients was encountered in NINDS. An interaction between the importance of "early infarct signs" on CT, rt-PA dose, and time to treatment is a possibility. In other words, if the lower rt-PA dose is used and used fast enough, it may not be as important to exclude the early-infarct patients, and the requirements for accuracy of CT reading may be significantly lower. However, current evidence does not allow a firm conclusion on this issue.

Clinical misidentification of patients as having ischemic stroke could lead to inappropriate administration of thrombolytic agents and obliterate the net benefits of the therapy. TIAs, as well as conditions entirely unrelated to cerebrovascular ischemia, must be carefully excluded. In one study conducted in conjunction with the NINDS trial, 19% patients given the diagnosis of ischemic stroke before CT were found to have noncerebrovascular causes for their symptoms, in-

cluding sepsis, seizure disorders, and toxic-metabolic syndromes.²¹ Can such patients be adequately excluded in the setting of a busy ED?

In addition to the potential importance of a blood pressure protocol as mentioned above, the overall intensity of care and monitoring in patients with acute ischemic stroke may play an important role in determining the safety of administration of rt-PA. Metaanalyses of stroke-unit trials have reported that disability and mortality in stroke patients are reduced by admission to stroke units as opposed to general neurology services.^{22,23} The presence or absence of a critical care unit and the close patient monitoring provided by such a unit might affect the outcome of patients equally, whether or not they receive thrombolytic agents. However, the absence of such care might have even greater consequences for the stroke patients undergoing an intervention that, by nature, requires intensive monitoring. If this were the case, the efficacy of rt-PA in the absence of this intensive level of care might be lessened, eliminated, or even reversed. Although the nature of the participating hospital settings is not characterized in the published reports of either NINDS or ECASS, the study protocols themselves may have served to enhance the level of care and monitoring afforded the trial enrollees beyond that customary in those settings under nonstudy conditions.

The increased mortality in the ECASS rt-PA group, in contrast to the decreased mortality observed in the NINDS rt-PA group, might have been caused by several factors, including the higher dose of rt-PA used in ECASS, the longer time to treatment in the ECASS study, the fact that aspirin was not uniformly withheld from ECASS patients during the 24 hours after admission, and the possibility of a higher TIA rate in ECASS or the absence of a BP protocol in ECASS. However, it may also have been caused by factors that have not occurred to you or may not even have been reported.

CLINICAL SUMMARY

Weighing all of these considerations and thinking carefully through the details of your practice setting, you find yourself faced with several questions that will have to be answered before you can recommend administration of rt-PA to patients presenting to your ED with an initial diagnosis of acute ischemic stroke. The answers to some of these questions may be found in published articles other than the primary trial reports. Some may require contact with the trial investigators themselves or with other individuals close to the research efforts. In still other cases, evidence may be lacking, forcing you to make assumptions based on your own or others' opinions.

Examples of all of these categories of question pertain to the question at hand. Studies conducted in preparation for the NINDS trial provide evidence that doses of rt-PA greater than .85 mg/kg, as used in ECASS, are likely to increase the incidence of intracranial hemorrhage without increasing efficacy.^{24,25} The details of the blood pressure protocol followed in NINDS could be obtained through personal contact with the investigators.

Questions for which the evidence is indirect or inconclusive include the appropriate time window for administration of rt-PA in the setting of acute ischemic stroke and the intensity of clinical monitoring and supervision, both diagnostic and therapeutic, required to maximize effectiveness. The former question can be provisionally resolved simply by adopting the 3-hour time window adhered to in NINDS. The issue of intensity of care will require clinical judgment and close collaboration with other involved services. Under the circumstances, you recommend that a multidisciplinary team, including representatives of the involved services, as well as nursing and administration, be assembled in your hospital to address the issues raised by your review. You recommend that the initial items on the agenda be obtaining the entirety of both the NINDS and ECASS protocols, resolving the issues of CT scan interpretation and addressing the issue of interdepartmental responsibility for rapid clinical assessment and appropriate monitoring of potentially eligible patients.

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Question	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? P Wyer, H Osborn. October 30, 1996. Update recommended July 31, 1998.
Clinical Summary	rt-PA reduced the risk of disability and mortality in selected patients with acute ischemic stroke when administered in a carefully controlled research setting. Whether the same benefit can be achieved in a less controlled setting may depend on the management of blood pressure, the intensity of diagnostic scrutiny of patients for inclusion, and the level of ongoing care.
Search Strategy	Medline by way of Grateful Med: "stroke OR infarct" (as text words) AND "acute" (as text word) AND "expose plasminogen OR expose plasminogen activators" (as MESH terms); limited to "randomized controlled trials OR metaanalysis" (as publication types) from years 1980-96.
Citations	1. Hacke W, Kaste M, Fieschi C, et al: ECASS. <i>JAMA</i> 1995;27:1017-1025. 2. The NINDS rt-PA Stroke Study Group: Tissue plasminogen activator for acute ischemic stroke. <i>N Engl J Med</i> 1995;333:1581-1587.
Study Characteristics	Population: Adults with clinically diagnosed ischemic stroke and negative CT findings 0 to 6 hours after onset of symptoms. Patients with improving symptoms excluded. Patients with "early infarct" signs on CT excluded from ECASS; blood-pressure control protocol followed as prerequisite to eligibility in NINDS only. Interventions: Intravenous rt-PA or placebo; .9 mg/kg to 90 mg (NINDS) or 1.1 mg/kg to 100 mg (ECASS). Outcomes: Modified RS score 90 days, BI 90 days, NIH stroke scale 90 days, both trials. Patients who died given worst score in both studies.

Critical review form for therapy.

Guide	Comments
Are the results valid?	
Was the assignment of patients to treatments randomized?	Yes: NINDS, blocked and stratified; ECASS, centralized
Were all patients who entered the trial properly accounted for and attributed at its conclusion?	Yes
Was follow-up complete?	Both trials: 98% to 99%
Were patients analyzed in the groups to which they had been randomized?	Both trials: ITT analysis
Were patients, health workers, and study personnel blinded to treatment?	NINDS: Yes; well-documented; ECASS: Protocol not available
Were the groups similar at the start of the trial?	Yes: imbalances in NINDS corrected for
Aside from experimental intervention, were the groups treated equally?	Unclear in both trials; no direct evidence of imbalance
Overall validity rating (weak-fair-good-excellent)=Excellent	
What were the results?	
How large was the treatment effect?	Relative risk of death or disability: .82 NINDS, .91 ECASS Number Needed to Treat 8 NINDS, 16 ECASS 95% CI around NNT: 5-7 NINDS; 7-∞ ECASS
How precise was the treatment effect?	
Will the results help me care for my patients?	
Can the results be applied to my patients' care?	Unclear; significant concern exists regarding the role of intensive care, blood-pressure control, and exclusion of patients with nonstroke syndromes
Were all clinically important outcomes considered?	Yes; at least four scoring systems were used, including direct measures of disability and mortality
Are the likely benefits worth the potential harms and costs?	Yes, provided experimental results can be reproduced in practice

Insights

[Editor's note: Insights in this issue address the current evidence-based emergency medicine (EBEM) installment regarding patients presenting with acute ischemic stroke. These comments are culled from the EBEM series peer reviewers, others who have informally reviewed the manuscript, and relevant sources, which are cited after each excerpt. In the future, Insights will feature comments not only regarding the current EBEM installment, but also comments from Annals readers on previously published installments. We invite Annals readers to become active in submitting contributions to this section. Contributions from individuals will be published anonymously, unless otherwise requested. The editors have taken the liberty of correcting obvious spelling and grammatical errors. Readers should send comments about the EBEM series to the Annals editorial office by fax to 972-580-0051 or e-mail to ebem@annalsem.org.]

One reviewer who was familiar with the NINDS study design offered: “One of the assumptions is that it is likely that many of the participating hospitals in the NINDS study qualified as stroke units or intensive care neurology services. This in fact was not the case. Two of the sites in the NINDS study (San Diego and Cincinnati) enrolled more than half the patients in the study. Both Cincinnati and San Diego enrolled most of their thrombolytic candidates in community hospitals and not in academic teaching centers. None of these hospitals had stroke units or intensive care neurology services. Additionally, many of the hospitals involved in the study that were teaching hospitals did not have defined neuro-intensive care or stroke units.

“Another assumption was that the NINDS investigators somehow successfully limited patients with transient ischemic attacks (TIAs) in the study to a small percentage. Statistically, 80% of TIAs last less than 15 minutes, which was probably the major reason a small number of TIAs were entered in the NINDS study.

“The authors also make some major decisions and assumptions based on the provisions for control of blood pressure in the NINDS study. The NINDS study specified that patients who required aggressive measures to control their blood pressure before treatment with thrombolytic agents should not receive thrombolytic agents. The NINDS study, however, did have a protocol for treatment of increased blood pressure after treatment with thrombolytic agents, suggesting the use of very standard antihypertensives such as labetalol, ACE inhibitors and nitroprusside if necessary. The main lesson from the NINDS study was that any patient with increased blood pressure requiring intensive measures to control it should not receive the therapy.”

Another reviewer commented: “You need to provide concise and accurate definitions of validity, including internal and external validity. The effect of bias should be explained in terms of its effect on internal validity—if the study is biased, the results will not reflect the true treatment effect, even for the population at the study centers. Differences among the populations included in the published studies and the population at the community hospital may result in a lack of external validity. An inability to achieve the same diagnostic accuracy at the community hospital as achieved in the NINDS study would also reduce the external validity.”

A co-investigator of the NINDS study informed the authors that: “Although some of the participating centers were community hospitals and did not have stroke units, the study protocol required that all patients enrolled in the trial be observed in an ICU setting for at least 24 hours. All study sites had organized stroke teams, generally made up of neurologists, who read the CTs and who oversaw the clinical evaluation of patients at the point of arrival in the ED.”

Published commentaries: The following excerpt is from the systematic overview on thrombolytic therapy in acute ischemic stroke published in the Cochrane Database and last updated August 12, 1996. Cochrane reviews follow the most rigorous existing protocol for systematic overviews and are considered the “Cadillac” of evidence-based medicine resources.

“The totality of the evidence on thrombolysis to treat acute ischaemic stroke is based on just over 3000 patients—a very small number compared with how common and heterogeneous acute ischaemic stroke is in the developed world. There is so far insufficient evidence from these trials to justify the use of thrombolysis to treat ischaemic stroke routinely. The centres which took part in all these trials were in general specially interested in, and familiar with, the investigation and management of acute stroke. To extrapolate the overview results to apply thrombolysis more widely in clinical practice could result in much greater hazard and negate any potential benefit. Much more information is needed on the influence of stroke severity and type, age of patient, time window, concomitant exposure to antithrombotic drugs, dose of thrombolytic drug, which thrombolytic drug, and CT scan appearances before thrombolytic drugs should be used outside randomized controlled trials.”¹⁶