Clinical Policy: Use of Intravenous tPA for the Management of Acute Ischemic Stroke in the Emergency Department

This clinical policy is the result of a collaborative project of the American College of Emergency Physicians and the American Academy of Neurology.

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ABSTRACT

This policy was developed by a joint writing panel of the American College of Emergency Physicians and the American Academy of Neurology. The panel reviewed the literature to derive evidence-based recommendations to help clinicians answer the following critical questions:

(1) Is intravenous tissue plasminogen activator (tPA) safe and effective for acute ischemic stroke patients if given within 3 hours of symptom onset? (2) Is intravenous tPA safe and effective for acute ischemic stroke patients treated between 3 to 4.5 hours after symptom onset? Evidence was graded and recommendations were given based on the strength of the available data in the medical literature.

INTRODUCTION

It is estimated that there are 795,000 new strokes in the United States each year.[1] Stroke is the third leading cause of death in the United States, causing 1 of every 17 deaths in 2005.[1]

In 1996, the Food and Drug Administration (FDA) approved intravenous (IV) tissue plasminogen activator (tPA) as

a treatment for acute ischemic stroke. Since then, the use of IV tPA for stroke has been one of the most contentious medical treatments.

METHODOLOGY

A joint development panel was appointed by the American College of Emergency Physicians (ACEP) and the American Academy of Neurology (AAN) to produce a clinical evidence–based guideline on the use of tPA for acute ischemic stroke.

This clinical policy was created after careful review and critical analysis of the medical literature. Multiple searches of MEDLINE and the Cochrane Database for articles published between January 1999 and May 2011 were performed using a combination of key words, including "cerebrovascular accident," "tissue plasminogen activator," "tPA," "thrombolytic therapy," "stroke," "intracerebral hemorrhage," "subarachnoid hemorrhage," "emergency department," "emergency service," "emergency room," "therapy in emergency department," and "treatment in emergency department." The searches were limited to the English language and human studies. Additional articles were reviewed from the bibliographies of studies cited. Panel members supplied articles from their own knowledge and files, and more recent articles identified during the process were also included.

The reasons for developing ACEP's clinical policies and the approaches used in their development have been enumerated.[2] Expert review comments were received from emergency physicians, neurologists, and individual members of the American Academy of Family Physicians, American College of Physicians, Emergency Nurses Association, American Stroke Association, National Stroke Association, Neurocritical Care Society, and the Society for Academic Emergency Medicine. Their responses were used to further refine and enhance this policy; however, their responses do not imply endorsement of this clinical policy. Comments were also received from internal ACEP and AAN committees and workgroups. ACEP clinical policies are scheduled for revision every 3 years; however, interim reviews are conducted when technology or the practice environment changes significantly. ACEP and AAN are the funding source for this clinical policy.

The searches resulted in 1,140 articles, of which 303 were selected for additional review and grading. All articles used in the formulation of this clinical policy were independently graded by at least 2 panel members for strength of evidence and classified by the panel members into 3 classes of evidence on the basis of the design of the study, with design 1 representing the strongest evidence and design 3 representing the weakest evidence for therapeutic, diagnostic, and prognostic clinical reports, respectively (Appendix A). Articles were then graded on 6 dimensions thought to be most relevant to the development of a clinical guideline: blinded versus nonblinded outcome assessment, allocation, direct or indirect outcome measures, biases (eg, selection, detection, transfer), external validity (ie, generalizability), and sufficient sample size. Articles received a final grade (Class I, II, III) on the basis of a predetermined formula taking into account design and quality of study (Appendix B). Articles with fatal flaws were given an "X" grade and not used in formulating recommendations in this policy. Evidence grading was done with respect to the specific data being extracted and the specific critical question being reviewed. Thus, the level of evidence for any one study may vary according to the question, and it is possible for a single article to receive different levels of grading as different critical questions are answered. Question-specific level of evidence grading may be found in the Evidentiary Table included at the end of this policy.

Clinical findings and strength of recommendations regarding patient management were then made according to the following criteria:

Level A recommendations. Generally accepted principles for patient management that reflect a high degree of clinical certainty (ie, based on strength of evidence Class I or overwhelming evidence from strength of evidence Class II studies that directly address all of the issues).

Level B recommendations. Recommendations for patient management that may identify a particular strategy or range of management strategies that reflect moderate clinical certainty (ie, based on strength of evidence Class II studies that directly address the issue, decision analysis that directly addresses the issue, or strong consensus of strength of evidence Class III studies).

Level C recommendations. Other strategies for patient management that are based on Class III studies, or in the absence of any adequate, published literature, based on panel consensus.

There are certain circumstances in which the recommendations stemming from a body of evidence should not be rated as highly as the individual studies on which they are based. Factors such as heterogeneity of results, uncertainty about effect magnitude and consequences, and publication bias, among others, might lead to such a downgrading of recommendations.

When possible, clinically oriented statistics (eg, likelihood ratios, number needed to treat) will be presented to help the reader better understand how the results can be applied to the individual patient. For further definition of these statistical concepts, see Appendix C.

This policy is not intended to be a complete manual on the evaluation and management of adult patients with acute ischemic stroke but rather a focused examination of critical issues that have particular relevance to the current practice of emergency medicine. It is the goal of this panel to provide an evidence-based recommendation when the medical literature provides enough quality information to answer a critical question. When the medical literature does not contain enough quality information to answer a critical question, the members of the panel believe that it is equally important to alert physicians to this fact. Recommendations offered in this policy are not intended to represent the only diagnostic and management options that the physician should consider. ACEP

and AAN clearly recognize the importance of the individual physician's judgment. Rather, this guideline defines for the physician those strategies for which medical literature exists to provide support for answers to the critical questions addressed in this policy.

Scope of Application. This guideline is intended for physicians working in hospital-based emergency departments (EDs).

Inclusion Criteria. This guideline is intended for adult patients presenting to the ED with acute ischemic stroke.

Exclusion Criteria. This guideline is not intended to be applied to children younger than 18 years.

CRITICAL QUESTIONS

1. **Is IV tPA safe and effective for acute ischemic stroke patients if given within 3 hours of symptom onset?**
2. **Is IV tPA safe and effective for acute ischemic stroke patients treated between 3 to 4.5 hours after symptom onset?**

Patient Management Recommendations

Level A recommendations. In order to improve functional outcomes, IV tPA should be offered to acute ischemic stroke patients who meet National Institute of Neurological Disorders and Stroke (NINDS) inclusion/exclusion criteria and can be treated within 3 hours after symptom onset.*

Level B recommendations. In order to improve functional outcomes, IV tPA should be considered in acute ischemic stroke patients who meet European Cooperative Acute Stroke Study (ECASS) III inclusion/exclusion criteria and can be treated between 3 to 4.5 hours after symptom onset.*

*The effectiveness of tPA has been less well established in institutions without the systems in place to safely administer the medication.

Note: Within any time window, once the decision is made to administer IV tPA, the patient should be treated as rapidly as possible. As of this writing, tPA for acute ischemic stroke in the 3- to 4.5-hour window is not FDA approved.

Level C recommendations. None specified.

Most ischemic strokes in adults are caused by thrombotic or embolic occlusions of an artery. With tPA, inactive plasminogen is converted into the active form plasmin, which promotes thrombolysis by cleaving fibrin. In 1995, the NINDS tPA Stroke Study Group published a 2-part randomized controlled trial showing that human recombinant tPA improved outcomes after ischemic stroke.[3] This publication led to FDA approval in 1996. Reaction to the availability of tPA for acute ischemic stroke has ranged from skepticism[4] to unbridled enthusiasm.[5]

The Class I NINDS tPA study was divided into 2 parts.[3] Each part was performed in a unique, independently enrolled population of patients with acute ischemic stroke but with different prespecified primary outcomes. In both parts, acute ischemic stroke patients presenting within 3 hours of symptom onset were randomized 1:1 to placebo versus IV treatment with 0.9 mg/kg of the human recombinant tPA alteplase, with 10% of the total dose administered as a bolus and the remaining 90% infused over 60 minutes (maximum dose 90 mg). Randomization was stratified by clinical center and by time from the onset of stroke to treatment (0 to 90 minutes and 91 to 180 minutes). The prespecified primary outcome of NINDS part I (n=291) was early clinical improvement, defined as complete resolution of the stroke symptoms or an improvement in the National Institutes of Health Stroke Scale (NIHSS) (Figure 1) score by 4 or more points at 24 hours. There was no difference in early clinical improvement in the tPA group compared with the placebo group (relative risk 1.2; 95% confidence interval [CI] 0.9 to 1.6; P=.21). The prespecified primary outcome of NINDS part II (n=333) was a favorable outcome at 3 months, determined using 4 assessment scales: the Barthel Index (Figure 2), modified Rankin Scale (Table 1), Glasgow Outcome Scale (Table 2), and NIHSS (Figure 1). To test the primary hypothesis, a global endpoint was derived from the individual scales with the use of scale-specific cut points. The odds ratio (OR) for a favorable outcome in the tPA group, defined as minimal or no disability at 90 days, was 1.7 (95% CI 1.2 to 2.6; P=.008). A favorable outcome for the tPA group was observed on each of the 4 assessment scales (P=.02 to .03), with absolute percentage differences between tPA and placebo ranging from 11% to 13%. For example, a modified Rankin Scale score outcome of 0 or 1, indicating no residual disabling stroke symptoms, was achieved in 39% of tPA-treated patients versus 26% of placebo-treated patients. There was a 12% absolute increase in the number of patients with minimal or no disability in the tPA group, defined by the global statistic. This corresponds to a number needed to treat of 8.3, meaning that 8.3 patients would need to be treated for 1 additional patient to achieve a favorable outcome with essentially no stroke-related disability. A subsequent reanalysis of the trial data suggested that the number needed to treat to produce a 1-point shift in the Rankin Scale, including from states of severe disability to more moderate disability, may be as low as 3.[6]

Combined analysis of parts I and II of the NINDS study showed a consistent effect of IV tPA on favorable outcome at 90 days.[3] This beneficial effect was observed in both the 0- to 90-minute and the 91- to 180- minute time strata. Mortality was similar in both groups (17% for tPA versus 21% for placebo; P=.30). There was, however, an increase in symptomatic intracerebral hemorrhage in the tPA-treated group during the first 36 hours (6% versus 0.6% in the placebo group; P<.001). Many of these tPA-related hemorrhages were fatal (45%). Therefore, the improved 90-day outcomes in the tPA group (without an increased overall mortality) occurred despite the excess mortality in patients who had symptomatic intracerebral hemorrhage.

National Institutes of Health Stroke Scale.

Level of consciousness 1a–1c:
1a. Alertness
0=alert and responsive
1=arousable to minor stimulation
2=arousable only to painful stimulation
3=reflex responses or unarousable

1b. Orientation: Ask the patient his or her age and the month; answers must be exact.
0=Both correct
1=One correct (or dysarthria, intubated, foreign language)
2=Neither correct

1c. Commands: Ask the patient to open/close eyes and to grip/release the nonparetic hand (or other 1-step command). Grip and release nonparetic
0=Both correct (OK if impaired by weakness)
1=One correct
2=Neither correct

2. Best Gaze: Only horizontal eye movements are checked by voluntary movement or reflective movement (Doll's eyes, not by calorics).
0=Normal
1=Partial gaze palsy
2=Forced eye deviation or total paresis that cannot be overcome by Doll's eyes

3. Visual Field: Test using confrontation (or visual threat if necessary).
0=No visual loss
1=Partial hemianopia, quadrantanopia, extinction
2=Complete hemianopia
3=Bilateral hemianopia or blindness (including cortical blindness)

4. Facial Palsy: If stuporous, check symmetry of grimace to pain.
0=Normal
1=Minor paralysis, flat nasolabial fold or asymmetric smile
2=Partial paralysis (lower face)
3=Complete paralysis (upper and lower face)

5. Motor Arm: arms outstretched 90 degrees (patient sitting) or 45 degrees (patient supine) for 10 seconds. Encourage patient for best effort. Assess both sides.
0=No drift x 10 seconds
1=Drift but does not hit bed
2=Some antigravity effort but cannot sustain
3=No antigravity effort, but even minimal movement counts
4=No movement at all
X=Unable to assess because of amputation, fusion, fracture, etc

6. Motor Leg: Raise leg to 30 degrees and hold for 5 seconds; test both sides.
0=No drift x 5 seconds
1=Drift but does not hit bed
2=Some antigravity effort but cannot sustain
3=No antigravity effort, but even minimal movement counts
4=No movement at all
X=Unable to assess because of amputation, fusion, fracture, etc
Left or Right

7. Limb Ataxia: Check finger to nose and heel to shin (only scoring + if out of proportion to weakness).
0=No ataxia (or aphasic, hemiplegic)
1=Ataxia in 1 limb
2=Ataxia in 2 limbs
X=Unable to assess because of amputation, fusion, fracture, etc
Left or Right

8. Sensory: Use safety pin.
Check grimace or withdrawal if stuporous. Score only stroke-related losses.
0=Normal
1=Mild to moderate unilateral loss but patient aware of touch (or aphasic, confused)
2=Total loss, patient unaware of touch, coma, bilateral loss

9. Best Language: Describe cookie jar picture, name objects, and read sentences (these standard items can be found on the Web and at the American Heart Association Web site).
0=Normal
1=Mild to moderate aphasia (partly comprehensible)
2=Severe aphasia (almost no information exchanged)
3=Mute, global aphasia, coma.

10. Dysarthria: Read list of words.
0=Normal
1=Mild to moderate, slurred but intelligible
2=Severe, unintelligible or mute
X=Intubation or mechanical barrier

11. Extinction/Inattention: Simultaneously touch patient on both hands, show fingers in both visual fields, ask whether patient recognizes own left hand.
0=Normal, none detected (visual loss alone)
1=Neglects or extinguishes to double simultaneous stimulation in any modality
(visual, auditory, sensory, special or body parts)
2=Profound neglect in more than 1 modality, does not recognize own left hand

The NIHSS is an 11-part scale that measures the neurologic examination in a codified manner. The scale ranges from 0 to 42. A score of less than 5 indicates a small stroke, and greater than 20 indicates a large stroke. Physicians can learn to perform the NIHSS on a training module on the Internet. Standard pictures (eg, the cookie jar picture) and lists of words can also be downloaded from the Internet.

Figure 1. National Institutes of Health Stroke Scale.

Barthel Index.*

Activity

Feeding
0=unable
5=needs help cutting, spreading butter, etc or requires modified diet
10=independent

Bathing
0=dependent
5=independent (or in shower)

Grooming
0=needs help with personal care
5=independent face/hair/teeth/shaving (implements provided)

Dressing
0=dependent
5=needs help but can do about half unaided
10=independent (including buttons, zips, laces, etc)

Bowels
0=incontinent (or needs to be given enemas)
5=occasional accident
10=continent

Bladder
0=incontinent, or catheterized and unable to manage alone
5=occasional accident
10=continent

Toilet Use
0=dependent
5=needs some help, but can do something alone
10=independent (on and off, dressing, wiping)

Transfers (bed to chair and back)
0=unable, no sitting balance
5=major help (1 or 2 people, physical), can sit
10=minor help (verbal or physical)
15=independent

Mobility (on level surfaces)
0=immobile or <50 yards
5=wheelchair independent, including corners, >50 yards
10=walks with help of 1 person (verbal or physical) >50 yards
15=independent (but may use any aid; for example, stick) >50 yards

Stairs
0=unable
5=needs help (verbal, physical, carrying aid)
10=independent

TOTAL (0-100):

*Mahoney FI, Barthel D. Functional evaluation: the Barthel Index. *Maryland State Med J.* 1965;14:56-61. Used with permission.

The Barthel ADL Index: Guidelines

1. The index should be used as a record of what a patient does, not as a record of what a patient could do.
2. The main aim is to establish degree of independence from any help, physical or verbal, however minor and for whatever reason.
3. The need for supervision renders the patient not independent.
4. A patient's performance should be established using the best available evidence. Asking the patient, friends/relatives, and nurses are the usual sources, but direct observation and common sense are also important. However, direct testing is not needed.
5. Usually the patient's performance over the preceding 24 to 48 hours is important, but occasionally longer periods will be relevant.
6. Middle categories imply that the patient supplies over 50 percent of the effort.
7. Use of aids to be independent is allowed.

The Barthel Index measures a person's ability to function in terms of the activities of daily living and mobility. It consists of 10 items, and scores range from 0 to 100. The higher the score, the more independent a patient is.

Figure 2. Barthel Index.

Secondary subgroup analyses of the combined NINDS part I and part II studies failed to find evidence of a different effect of tPA according to age, sex, stroke severity, and stroke type.[7]

In 1995 and 1996, several other large randomized trials of thrombolytic agents in acute ischemic stroke were published, including the Australian Streptokinase trial,[8] Multicenter Acute Stroke Trial–Italy,[9] Multicenter Acute Stroke Trial–Europe,[10] and ECASS I.[11] All of these studies failed to demonstrate a benefit of thrombolysis for stroke, and some were halted early because of excessive mortality in the treatment arm.[9,10] All of these studies were different from the NINDS study in that they used different thrombolytic agents (streptokinase),[8-10] different time periods for treatment (up to 6 hours), higher

Table 1. Modified Rankin Scale.* (Used with permission).

Score	Description
0	No symptoms
1	No significant disability despite symptoms; able to carry out all usual duties and activities
2	Slight disability; unable to carry out all previous activities but able to look after own affairs without assistance
3	Moderate disability; requiring some help but able to walk without assistance
4	Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance
5	Severe disability; bedridden, incontinent, and requiring constant nursing care and attention
6	Dead

Rankin J. Cerebral vascular accidents in patients over the age of 60. II. Prognosis. *Scott Med J*. 1957;2:200−215. © Copyright 1957 Royal Society of Medicine Press, UK.
*The modified Rankin Scale is a 6-point clinical outcome scale that measures a patient's function and independence. A lower score indicates a better outcome.

Table 2. Glasgow Outcome Score.* (Used with permission).

5	Good Recovery	Resumption of normal life despite minor deficits.
4	Moderate Disability	Disabled but independent. Can work in sheltered setting.
3	Severe Disability	Conscious but disabled. Dependent for daily support.
2	Persistent vegetative	Minimal responsiveness
1	Death	

Jennett B, Bond M. Assessment of outcome after severe brain damage. *Lancet*. 1975;1:480-484. © Copyright 1975, with permission from Elsevier.
*The Glasgow Outcome Score is another simple measure of functional outcome.

doses of tPA (1.1 mg/kg),[11] or allowed other concomitant antithrombotics (aspirin).[9]

Other randomized trials of IV tPA, using the same dose but with longer time periods, generated mixed outcomes. The Class I ECASS II tested tPA (0.9 mg/kg) versus placebo in acute ischemic stroke of less than 6 hours' duration.[12] The primary endpoint was the proportion of patients with a favorable outcome on the modified Rankin Scale, defined as a score of 0 or 1. There was no difference in this outcome between tPA-treated and placebo controls in the overall cohort (40% versus 37%; $P=.28$) and in patients treated within 3 hours (42% versus 38%; $P=.63$), although less than 20% of patients were treated within that time period. Parenchymal hemorrhage on posttreatment computed tomography (CT) was observed in 12% of tPA and 3% of placebo patients ($P<.001$). The 90-day mortality rate was equal (11%) for both the tPA and placebo groups ($P=.99$).

The Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke (ATLANTIS) trial also tested IV tPA (0.9 mg/kg) versus placebo in patients with stroke symptoms of fewer than 6 hours' duration.[13] The trial was stopped prematurely after enrolling 142 patients because of increased symptomatic intracerebral hemorrhage in patients enrolled 5 to 6 hours after stroke symptom onset. The trial protocol was modified and a new trial, enrolling patients 0 to 5 hours after stroke onset, was begun (ATLANTIS Part B). In ATLANTIS Part B, 613 patients were randomized 1:1 to 0.9 mg/kg tPA or placebo.[14] After 31 patients were enrolled, the time window was changed to 3 to 5 hours after symptom onset because of FDA approval for IV tPA in 1996. The primary outcome was the proportion of patients with an excellent recovery, defined as an NIHSS score of 0 or 1 at 90 days. There was no difference in the primary outcome between tPA-treated patients and placebo controls (34% versus 32%; $P=.65$). In the tPA-treated group, there was a higher rate of symptomatic intracerebral hemorrhage (7% versus 1%; $P<.001$) and a trend toward higher mortality (11% versus 6.9%; $P=.09$).[14] The mean time to treatment in this study was 4 hours 28 minutes. Among the 61 patients randomized within 3 hours, of whom 23 were randomized to tPA and 38 were randomized to placebo, more tPA-treated patients achieved the primary outcome (61% of tPA versus 26% of placebo; $P=.01$) and had symptomatic intracerebral hemorrhage (13% of tPA versus 0% of placebo; $P=.05$).[15]

The NINDS part II study is therefore unique in showing a benefit in the preselected primary outcome for 0.9 mg/kg tPA for patients with ischemic stroke of less than 3 hours' duration.[3] The reproducibility of the finding is supported by the reanalysis of the NINDS study, which found that 90-day outcomes were again significantly improved, without a difference in mortality rates.[16] Furthermore, a Class II patient-level meta-analysis that includes data from the NINDS, ECASS, ATLANTIS, and Echoplanar Imaging Thrombolytic Evaluation Trial (EPITHET) studies of patients treated within 3 hours also supports the efficacy of tPA.[17] The increased number of patients in this meta-analysis provided a more precise estimate of the potential effect of treatment, and the calculated 95% CIs suggested that tPA's benefit diminished over time but remained significant up to 4.5 hours after onset of symptoms.[17]

Two independent groups have reanalyzed the NINDS trial data. First, an independent committee was commissioned by the NINDS to verify the validity of the NINDS trial results and to address the concern that an imbalance in stroke severity at baseline may have confounded the analysis of the relationship between IV tPA and the likelihood of a good outcome.[16] Although the median baseline NIHSS score was not different in the tPA and placebo groups ($P=.10$), there were more patients in the 91- to 180-minute stratum with baseline NIHSS 0 to 5 who were randomized to tPA rather than placebo (29 patients to tPA versus 7 patients to placebo). The committee found that the relationship between tPA use and good outcome remained robust (OR 2.1; 95% CI 1.5 to 2.9) after adjustment for baseline NIHSS and other factors related to stroke outcome, using data from NINDS part I and part II.[16] Second, an independent author group reanalyzed the data with graphic analysis but without statistical testing.[18] They concluded that tPA had only a small effect on the change in NIHSS score between baseline and day 90. The NIHSS change was not a

primary outcome of the NINDS part II trial, however, and the authors did not dispute that tPA had a statistically significant effect on the primary trial outcome.

Data have been accumulating addressing the use of IV tPA within 3 to 4.5 hours after onset of symptoms. As noted above, the Class II meta-analysis of studies using 0.9 mg/kg of tPA confirmed a benefit for tPA within 3 hours of onset of symptoms and suggested that the benefit remained significant up to 4.5 hours from symptom onset.[17] The benefit of 0.9 mg/kg tPA between 3 to 4.5 hours after symptom onset was directly tested in the Class I ECASS III randomized controlled trial.[19] The trial used the same dosing regimen and inclusion/exclusion criteria as the NINDS protocol (Figure 3), with additional exclusions: age greater than 80 years, baseline NIHSS score greater than 25, any oral anticoagulant use (regardless of the international normalized ratio), and the combination of a previous stroke and diabetes mellitus. In addition, in contrast to the NINDS protocol, patients were permitted to receive parenteral anticoagulants for prophylaxis of deep venous thrombosis within the first 24 hours after treatment with tPA. The frequency of the primary efficacy outcome in ECASS III (defined as modified Rankin Scale score 0 to 1 at 90 days after treatment) was significantly greater with tPA (291/418; 52.4%) than placebo (182/403; 45.2%) (OR 1.34; 95% CI 1.02 to 1.76; risk ratio 1.16; 95% CI 1.01 to 1.34; P=.04). Mortality rates were equivalent (7.7% for tPA-treated patients versus 8.4% for placebo-treated patients). Symptomatic intracranial hemorrhage, as defined by the criteria used in the NINDS study, was reported in 33 subjects treated with t-PA (7.9%) and in 14 subjects given placebo (3.5%) (OR 2.38; 95% CI 1.25 to 4.52; P=.006). The hemorrhage rates were slightly higher for both placebo and tPA-treated patients compared with that in the NINDS study, which may be attributable to the early use of parenteral deep venous thrombosis prophylaxis allowed in this study. The benefit in ECASS III was more modest than that observed in the NINDS trials, and the number needed to treat to achieve 1 excellent outcome was 14 in this study. This is consistent with the tPA meta-analysis within this timeframe and reinforces the concept that earlier time to treatment has a large impact on likelihood of good outcome within any defined timeframe. Therefore, although the time window for tPA treatment may have been lengthened based on the ECASS III results, the aggregate data strongly suggest that patient outcomes will be optimized by the earliest possible administration of tPA after a safe and thorough clinical and brain imaging evaluation. The notion that there is "plenty of time" to evaluate patients and administer tPA could lead to delays that reduce the effectiveness of the drug.[20]

The substantial increased rate of symptomatic intracerebral hemorrhage among tPA-treated patients has tempered enthusiasm for the rapid adoption of tPA as routine care, in part because of the concern that treatment may be less safe in routine clinical practice than in the highly monitored setting of a clinical trial. As a result, regulatory agencies in the United States, Canada, and the European Union mandated phase IV studies to determine whether outcomes in clinical practice matched those achieved in the trials. Single-center (or in 1 case, single system[21]) studies from early adopters suggested cause for concern, with major protocol violations occurring in 9% to 67% of treated patients.[21-26] Most violations were related to time criteria, blood pressure monitoring and control, or provision of antithrombotics or anticoagulants within 24 hours of tPA administration. Some studies found that protocol violations were associated with a higher rate of symptomatic intracerebral hemorrhage[22] and mortality.[24]

The first large postmarketing multicenter study, mandated by the FDA, was the Class III Standard Treatment with Alteplase to Reverse Stroke (STARS) study.[27] Most of the participating centers had previously enrolled patients in clinical trials of tPA for stroke. The administration of tPA followed the NINDS protocol.[3] Outcomes were similar to those in the tPA arm of the NINDS trial (see Evidentiary Table). Two larger registries from Canada and Europe found that tPA administered in clinical practice had rates of symptomatic intracerebral hemorrhage of 4% to 5% and rates of disability and mortality similar to that observed in the NINDS trial.[28,29] The Class II Canadian Alteplase for Stroke Effectiveness Study (CASES)[28] tracked outcomes of 1,135 tPA-treated patients, which the authors estimated to represent 84% of all treated patients in Canada during the study period. Using multivariable-adjusted predictive modeling, the authors found no difference between the observed rate of a good outcome and the expected rate based on a model derived from the NINDS data set. The Class II Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST) tracked outcomes of 6,442 tPA-treated patients from 285 centers in Europe.[29] The proportion with good outcome was 38.9%, and symptomatic intracerebral hemorrhage, defined according to criteria used in ECASS II,[12] was 4.6%.

There are fewer data on the use of tPA in clinical practice in the 3- to 4.5-hour time period. The Class III Safe Implementation of Treatments in Stroke–International Stroke Thrombolysis Registry (SITS-ISTR) 3- to 4.5- hour study was a post hoc assessment of data acquired between December 2002 and February 2010 from an ongoing international registry.[30] This study reported outcomes in 2,317 patients treated with tPA between 3 to 4.5 hours after onset. Most patients were treated after publication of the ECASS III trial in October 2008. There were 44.5% with good outcome (modified Rankin Scale score 0 or 1), whereas 7.4% had symptomatic intracranial hemorrhage by the NINDS trial definition and 12.0% died by 3 months. Compared with the ECASS III tPA-treated arm, the proportion with good outcome was somewhat lower and the proportion with mortality was somewhat higher, probably because patients in the SITS-ISTR registry had higher initial stroke severity and more medical comorbidities than the patients enrolled in the ECASS III trial.

NINDS and ECASS III inclusion and exclusion criteria for intravenous tPA for acute ischemic stroke.

NINDS Criteria[3]
Inclusion:
Acute ischemic stroke with clearly defined time of onset (who could be treated <3 hours of symptom onset)
Measurable deficit on the NIH stroke scale
Baseline brain CT scan that showed no evidence of hemorrhage.

Exclusion:*
Another stroke or serious head injury within the preceding 3 months
Major surgery within prior 14 days
History of intracranial hemorrhage
Systolic BP >185 mm Hg or diastolic BP >100 mm Hg
Rapidly improving or minor symptoms
Symptoms suggestive of subarachnoid hemorrhage
Gastrointestinal or genitourinary hemorrhage within the previous 21 days
Arterial puncture at a noncompressible site within the previous 7 days
Seizure at onset of stroke
Use of anticoagulation:
patients receiving heparin within the 48 hours preceding the onset of stroke who have an elevated PTT,
patients with a PT >15 seconds (or INR >1.6),
patients with a platelet count <100,000
Glucose level of <50 mg/dL or >400 mg/dL.

ECASS III Criteria[19]
Inclusion:
Acute ischemic stroke with a clearly defined time of onset (who could be treated between 3-4.5 hours from symptom onset)
Age 18-80 years
Stroke symptoms present for at least 30 minutes without significant improvement prior to treatment.
Baseline brain imaging that showed no evidence of hemorrhage.

Exclusion:*
Same as NINDS plus the following additional criteria:
Age >80 years
Severe stroke (NIHSS >25) or by appropriate imaging techniques (defined as >1/3 of the middle cerebral artery territory)
Combination of previous stroke and diabetes mellitus
Any oral anticoagulant use (regardless of INR or PT).

***Exclusions (or cautions) to tPA use that were not specifically mentioned in either study but are generally used**:
Myocardial infarction within previous 3 months (AHA 2007 guidelines)
Pregnancy and early postpartum period
Known bleeding diathesis, recent pericarditis, recent lumbar puncture (Brain Attack Coalition http://www.stroke-site.org/guidelines/tpa_guidelines.html, accessed March 1, 2012).

AHA, American Heart Association; *BP*, blood pressure; *CT*, computed tomography; *ECASS*, European Cooperative Acute Stroke Study; *INR*, International Normalized Ratio; *NIH*, National Institutes of Health; *NIHSS*, National Institutes of Health stroke scale; *NINDS*, National Institute of Neurological Disorders and Stroke; *PT*, prothrombin time; *PTT*, partial thromboplastin time; *tPA*, tissue plasminogen activator.

Figure 3. NINDS and ECASS III inclusion and exclusion criteria for intravenous tPA for acute ischemic stroke.

Putting the Evidence Into Clinical Context

Safe and effective administration of tPA relies on a hospital having a system in place for treating stroke patients. Patients must undergo rapid and accurate diagnosis of acute ischemic stroke, including rapid access to laboratory test results, brain imaging, and accurate image interpretation. Protocols must be in place for drug administration, close clinical monitoring, active blood pressure management, and treatment of

hemorrhagic complications (systemic or intracerebral) if they occur. If a given hospital is unable to provide this infrastructure, protocols should be in place for transferring patients to a facility that can. Whatever a hospital's approach is, an ongoing quality assurance program ought to be in place. Physician expertise and written protocols are therefore hypothesized to be important for use of tPA[31] but may be in short supply in smaller centers without an abundance of stroke specialists. The CASES and SITS-MOST studies, which included a broad selection of academic and community hospitals, showed results similar to those observed in the NINDS trial. Additionally, both studies failed to find a difference in outcomes in patients treated at more experienced centers, defined by tPA case volume, compared with less experienced centers. The SITS-MOST findings must be treated with some caution, however, because all centers were required to have a neurologist or other physician with "considerable experience in stroke care."[29] Adequate physician acute stroke care expertise has not been rigorously defined in the literature, based on either credential or degree of experience, or studied in clinical trials. The definition should not be restricted to neurologists and should include emergency physicians or other physicians with expertise and experience in stroke care, according to recommendations from the Brain Attack Coalition[31] and the Canadian Stroke Consortium.[32]

For centers without on-site acute stroke specialists, telestroke technology offers a means to obtain remote consultation about the administration of IV tPA. In a study by Fisher,[33] the formation of "telestroke" networks allowed inexperienced centers to obtain expert medical and radiologic consultation by remote video linkage. Accumulating data show that this model of stroke care produces results similar to those obtained by on-site consultation with stroke experts.[34-36] A Class III study from a network of hospitals in Bavaria, Germany, found that 115 patients treated with tPA at remote sites using telestroke had similar inhospital rates of symptomatic hemorrhage (7.8%) and mortality (3.5%) compared with locally treated patients at the academic stroke centers.[37] A randomized controlled trial showed that more accurate decisions are made when video consultation, rather than telephone consultation, is used.[38] The American Heart Association published recommendations on the use of telemedicine for acute stroke care.[39]

There has been clinical concern about treatment of patient groups who would meet NINDS criteria but have a poor prognosis for good outcome, irrespective of tPA use, including those with advanced age, severe clinical deficits, and CT hypodensity in a large portion of the middle cerebral artery territory or hemisphere. The SITS-MOST and SITS-ISTR treatment protocol excluded patients older than 80 years, with NIHSS score greater than or equal to 25, or with "severe stroke" on CT.[29,30] The Canadian guidelines list CT evidence of infarction involving more than one third of the middle cerebral artery territory as an exclusion criterion.[32] The American Heart Association/American Stroke Association guidelines include that CT does not show a "hypodensity greater than one third of the cerebral hemisphere" and a "caution" for the presence of major deficits,[40] and the American College of Chest Physicians guidelines recommend against treatment when clearly identifiable hypodensity is present in greater than one third of the middle cerebral artery territory while not disallowing treatment in the presence of early ischemic changes such as subtle loss of gray-white differentiation or sulcal effacement without hypodensity.[41] Patients with these characteristics have been excluded, underrepresented, or not reported on in the major observational studies; therefore, data on outcomes in these patient subgroups in clinical practice are lacking.

The exception is advanced age, for which several studies report generally worse outcomes compared with younger subjects but no increased risk of symptomatic intracerebral hemorrhage.[42-44] This is not a surprising finding, given that age is a well-established risk factor for poor outcome regardless of intervention. Although it is appropriate to exercise caution when considering treatment for these subgroups with poor prognosis, a post hoc analysis of the 1995 NINDS trial failed to show evidence of a differential effect of tPA according to patient subgroups, including those with advanced age, severe clinical deficits, and more extensive CT changes.[45]

Addendum

After this document was completed, the International Stroke Trial 3 (IST-3) was electronically published in *Lancet*.[46] IST-3 was designed to evaluate the effects of tPA on patients with ischemic stroke up to 6 hours from symptom onset in whom benefit was deemed to be uncertain (the vast majority of whom had contraindications to tPA defined by NINDS criteria in the 0- to 3-hour window or ECASS-3 criteria in the 3- to 4.5-hour window). IST-3 looked at a different cohort of patients than those on which this policy focuses. The published trial data were carefully reviewed by the writing panel, and it was determined that the study's methodology was such that the findings did not affect the recommendations made in this practice guideline.

Disclosures

Dr. Edlow serves on the Executive Committee of the Foundation for Education and Research in Neurologic Emergencies, coedited the textbook of *Neurological Emergencies* for Oxford University Press, and serves on the editorial board of the *Journal of Internal and Emergency Medicine* and the *International Journal of Emergency Medicine*. He also reviews medical malpractice cases for both plaintiff and defense.

Dr. Smith served on a scientific advisory board for Genentech in 2010, received speaker honoraria from the Canadian Conference on Dementia, serves as an assistant editor for *Stroke*, has served on speakers' bureaus for QuantiaMD and BMJ Best Practice, is on the Data and Safety Monitoring Board for the MR Witness trial funded by the National Institutes of

Health (NIH)/NINDS, and receives research support from the NIH/ NINDS, Canadian Institutes for Health Research, Canadian Stroke Network, the Alberta Heritage Fund for Medical Research, and the Heart and Stroke Foundation of Canada.

Dr. Stead is editor-in-chief of the *International Journal of Emergency Medicine*.

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Dr. Messé receives publishing royalties from Up-To-Date, formerly served on the speakers' bureau for Boehringer Ingelheim (ended 4/2011), and receives research support from Gore, the NIH (NIDDK, U01-DK060990, Endpoint Adjudication Committee), National Heart, Lung, and Blood Institute (NHLBI) (1R01HL084375-01A2, subinvestigator, neurologic assessments), NINDS (U01NS40406-04, local principal investigator), and NIH (HHSN268200800003C, backup medical monitor).

Dr. Jagoda serves on the executive board for the Brain Attack Coalition and for the Foundation for Education and Research in Neurologic Emergencies, serves on the advisory board for the Brain Trauma Foundation, and is a consultant for Banyan Biomarkers, Cyvek, Pfizer, and GORE. He is also editor-in-chief of *Emergency Medicine Practice* and serves on the editorial boards for *Pediatric Emergency Medicine Practice*, *Emergency Medicine Practice Guidelines*, *EM Critical Care*, *Annals of Emergency Medicine*, *ACEP News*, and *Australasian Journal of Emergency Medicine*.

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Evidentiary Table.

Study	Year	Design	Intervention(s)/Test(s)/Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
NINDS rt-tPA Stroke Study Group[3]	1995	Randomized, double-blind, placebo-controlled trial; N=291 for part I, N=333 for part II	IV tPA 0.9 mg/kg	Primary endpoints: Part I: NIHSS decrease ≥4 or resolution of symptoms by 24 h; Part II: global outcome measure (combination of mRS, Barthel, NIHSS, Glasgow Outcome Scale) at 90 days	Part I: no difference between tPA and placebo group (46.5% vs 38.8%, *P*=.21); Part II: OR for good global outcome 1.7 (1.2-2.6, *P*=.008); OR similar when parts I and II analyzed together (*P*<.01 for time strata 0-90 and 90-180)	Analysis of part I data confirmed finding of part II, that tPA confers an increased odds of good outcome, essentially meaning no stroke-related disability at 90 days (OR 2.1, 95% CI 1.3-3.2, *P*=.001); combining parts I and II, the rate of SICH was 6.3% in tPA vs 0.6% in placebo (*P*<.001), and mortality was 17.3% in tPA vs 20.5% in placebo (*P*=.30)	I
Hacke et al[12]	1998	Randomized, double-blind trial; N=800	IV tPA 0.9 mg/kg	mRS ≤1 at 90 days	mRS ≤1 in 40.3% of treatment group vs 36.6% placebo (*P*=.28); SICH 8.8% tPA vs 3.4% placebo; mortality 10.6% (both groups)	Multicenter trial that did not show benefit; analysis of patients treated from 0-3 h also did not show benefit but the numbers were low (158/800 patients); overall mortality was lower in ECASS II (10.6%) compared with NINDS (17% in the tPA group) and the good outcomes in the ECASS II placebo group (36.6%) were close to the tPA outcomes in NINDS (39%)	I

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Clark et al[14]	1999	Randomized double-blind trial of tPA 3- to 5-h window; N=613	IV tPA 0.9 mg/kg	NIHSS ≤1 at 90 days; SICH; mortality at 90 days	Excellent outcome in 32% (placebo) vs 34% (tPA) *P*=.65; SICH 1.1% (placebo) vs 7.0% (tPA) *P*<.001, and 90-day mortality 6.9% (placebo) vs 11% (tPA) *P*=.09	Multicenter trial that did not show benefit of tPA in the 3- to 5-h time window; the mean time to treatment was 4 h 28 min	I
Albers et al[15]	2002	Randomized, double-blind, placebo-controlled trial	IV tPA 0.9 mg/kg	NIHSS ≤1 at 90 days; SICH; mortality at 90 days	NIHSS ≤1 14/23 tPA vs 10/38 placebo (*P*=.01); SICH 3/23 tPA vs 0/38 placebo (*P*=.05); mortality 4/23 tPA vs 2/38 placebo (*P*=.12)	Post hoc analysis of ATLANTIS B patients treated within 3 h of symptom onset	I
Lees et al[17]	2010	Meta-analysis of patients from previous randomized controlled trials of IV tPA	Patient specific data from 8 randomized controlled trials of patients treated with IV tPA (parts I and II of NINDS, ATLANTIS A and B, ECASS I, II, and III, and the EPITHET trial)	mRS ≤1 at 90 days	N=3,760; OR for good outcome with tPA was 2.55 at 0-90 min (95% CI 1.44-4.52), 1.64 at 91-180 min (95% CI 1.12-2.40), and 1.32 at 181-270 min (95% CI 1.04-1.66)	Meta-analysis with some heterogeneity in the various studies in terms of tPA dose and primary outcome variables; some of the analyzed studies were industry supported	II

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Hoffman and Schriger[18]	2009	Randomized controlled trial; reanalysis of 1995 NINDS study data	IV tPA 0.9 mg/kg	Graphic display of 90-day NIHSS and change in NIHSS from day 0 to day 90	Authors concluded, based on qualitative visual review of graphs, that tPA has little effect on 90-day NIHSS or change in NIHSS from baseline to day 90	This graphic reanalysis is an alternate means of viewing the trial data, and according to the authors it "empowers readers to reach their own conclusions about the trial's meaning"; limitations: disability outcomes were not graphed and statistical testing was not done	II
Hacke et al[19]	2008	Randomized placebo-controlled clinical trial	0.9 mg/kg IV tPA vs placebo in patients onset to treatment 3-4.5 h	SICH; mRS (0-1); mortality	N=821; drug vs placebo: SICH was 2.4% vs 0.2% (*P*=.008); 52.4% vs 45.2% for mRS 0,1, OR 1.4 (*P*=.04); mortality was 7.7% vs 8.4% (not significant)	Industry supported; note use of 4 additional exclusion criteria compared with previous trials: 1) age >80 y; 2) NIHSS score >25; 3) any oral anticoagulant use; 4) diabetes plus previous stroke	I
Wang et al[21]	2000	Retrospective cohort study; N=57	IV tPA 0.9 mg/kg	mRS ≤1 at discharge; SICH; inhospital mortality	mRS ≤1 47.4%; SICH 5.3%; mortality 8.8%	Study of 5 rural hospitals (single system) giving tPA locally after telemedicine video consultation with a single academic referral center	III

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Lopez-Yunez et al[22]	2001	Retrospective cohort study; N=50	IV tPA 0.9 mg/kg	SICH	SICH 22% for all (3/8 patients with protocol violations, 2/42 patients without protocol violations)	Chart review of 50 patients treated at 10 Indianapolis hospitals July 1996 to February 1998; 8 of 50 patients had protocol violations; the SICH rate was significantly higher in those with violations compared with those without violations; in the latter group, the rate of SICH was similar to the rate in the NINDS trial	III
Katzan et al[23]	2000	Retrospective cohort study; N=70	IV tPA 0.9 mg/kg	SICH; inhospital mortality	SICH 15.7%; mortality 15.7%	Single-center study; showed deviation from guidelines was common (35/70) but not related to SICH	III
Bravata et al[24]	2002	Retrospective cohort study; N=63	IV tPA 0.9 mg/kg	Inhospital mortality; SICH	SICH 6.3%; mortality 25.4%	Single center; comparison with 1995 NINDS trial data, without adjustment for confounding, showed higher mortality in the case series (P=.01); high mortality (31.0%) in those with major protocol violations	III

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Szoeke et al[25]	2003	Retrospective cohort study; N=30	IV tPA 0.9 mg/kg	mRS ≤1 at 90 days; SICH; mortality at 90 days	mRS ≤1 36.7%; SICH 6.7%; mortality 10.0%	Single-center study	III
Bray et al[26]	2006	Cohort study, unclear whether prospective or retrospective; N=72	IV tPA 0.9 mg/kg	mRS ≤1 at 90 days; SICH; mortality at 90 days	mRS ≤1 37.5%; SICH 1.4%; mortality 9.7%	Single-center study	III
Albers et al[27]	2000	Prospective cohort study; N=382 for analyses of outcome, 389 for analyses of SICH	IV tPA 0.9 mg/kg	mRS ≤1 at 30 days; SICH; mortality at 30 days	mRS ≤1 34.6%; SICH 3.3%; mortality 13.4%	FDA-mandated multicenter observational study, involving sites previously participating in randomized trials of thrombolysis	III
Hill and Buchan[28]	2005	Prospective cohort study; N=1,135	IV tPA 0.9 mg/kg	mRS ≤1 at 90 days; SICH; mortality at 90 days	mRS ≤1 31.8%; SICH 4.6%; mortality 22.3%	Phase IV study mandated by Canadian regulatory authorities; comparison with 1995 NINDS trial, with adjustment for confounding, showed no statistical difference in chance of good outcome (P=.15)	II

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Wahlgren et al[29]	2007	Prospective cohort study; N=6,136 for analysis of mRS; N=6,442 for analysis of SICH; N=6,218 for analysis of mortality	IV tPA 0.9 mg/kg	mRS ≤1 at 90 days; SICH; mortality at 90 days	mRS ≤1 38.9%; SICH 4.6%; mortality 10.0%	Phase IV study mandated by European regulatory authorities, involved 285 centers in 14 countries; centers were required to have acute stroke protocol and stroke expert team	II
Ahmed et al[30]	2010	Post hoc analysis of international observational stroke registry	IV tPA 0.9 mg/kg	90-day mRS ≤1; SICH (NINDS definition), 90-day mortality	mRS ≤1 in 793/1,784 (44.5%); SICH in 52/2,317 (2.2%, SITS-MOST definition); mortality in 218/1,817 (12.0%)	Higher probability of poor outcome and mortality in this registry than in the ECASS III trial, probably related to higher stroke severity and more medical comorbidities in patients treated in the registry	III
Audebert et al[37]	2006	Prospective cohort study; N=115	IV tPA 0.9 mg/kg	SICH; inhospital mortality	SICH 7.8%; mortality 3.5%	Cohort consisted of consecutive cases treated at 12 regional hospitals with the help of video consultation ("telestroke")	III
Meyer et al[38]	2008	Randomized controlled trial	Remote consultation by video link vs by telephone only	Correct tPA decision, as adjudicated by blinded central committee	Correct decision in 108/111 (98%) in video group vs 91/111 (82%) in telephone-only group (*P*=.0009)	Study shows that telestroke tPA decisions are more accurate using a video link compared with telephone only	II

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/ Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Engelter et al[43]	2005	Cohort study, unclear whether prospective or retrospective; N=325	IV tPA 0.9 mg/kg	mRS ≤1 at 90 days; SICH; mortality at 90 days	mRS ≤1 36.3%; SICH 8.6%; mortality 14.5%	Multicenter stroke registry from 5 university and 4 community hospitals in Switzerland; also found no significant difference in SICH between ≥80-y-old and <80-y-old patients (13% vs 8%, *P*=.36)	III

ATLANTIS, Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke; *CI*, confidence interval; *ECASS*, European Cooperative Acute Stroke Study; *EPITHET*, Echoplanar Imaging Thrombolysis Evaluation Trial; *FDA*, Food and Drug Administration; *h*, hour; *IV*, intravenous; *mg/kg*, milligrams per kilogram; *min*, minute; *mRS*, modified Rankin scale; *NIHSS*, National Institutes of Health stroke scale; *NINDS*, National Institute of Neurological Disorders and Stroke; *OR*, odds ratio; *SICH*, symptomatic intracerebral hemorrhage; *SITS-MOST*, Safe Implementation of Thrombolysis in Stroke-Monitoring Study; *tPA*, tissue plasminogen activator; *vs*, versus; *y*, year.

Appendix A. Literature classification schema.*

Design/Class	Therapy†	Diagnosis‡	Prognosis§
1	Randomized, controlled trial or meta-analysis of randomized trials	Prospective cohort using a criterion standard or meta-analysis of prospective studies	Population prospective cohort or meta-analysis of prospective studies
2	Nonrandomized trial	Retrospective observational	Retrospective cohort Case control
3	Case series Case report Other (eg, consensus, review)	Case series Case report Other (eg, consensus, review)	Case series Case report Other (eg, consensus, review)

*Some designs (eg, surveys) will not fit this schema and should be assessed individually.
†Objective is to measure therapeutic efficacy comparing interventions.
‡Objective is to determine the sensitivity and specificity of diagnostic tests.
§Objective is to predict outcome including mortality and morbidity.

Appendix B. Approach to downgrading strength of evidence.

	Design/Class		
Downgrading	**1**	**2**	**3**
None	I	II	III
1 level	II	III	X
2 levels	III	X	X
Fatally flawed	X	X	X

Appendix C. Likelihood ratios and number needed to treat.*

LR (+)	LR (−)	
1.0	1.0	Useless
1-5	0.5-1	Rarely of value, only minimally changes pretest probability
10	0.1	Worthwhile test, may be diagnostic if the result is concordant with pretest probability
20	0.05	Strong test, usually diagnostic
100	0.01	Very accurate test, almost always diagnostic even in the setting of low or high pretest probability

LR, likelihood ratio.
*Number needed to treat (NNT): the number of patients who need to be treated to achieve 1 additional good outcome; NNT=1/absolute risk reductionx100, where absolute risk reduction is the risk difference between 2 event rates (ie, experimental and control groups).