Special Article

Neurology 1996;47:835–839

Practice Advisory:

Thrombolytic therapy for acute ischemic stroke—Summary Statement

Report of the Quality Standards Subcommittee of the American Academy of Neurology

An article was published in the New England Journal of Medicine in December 1995[1] describing modest benefit from a clinical trial using recombinant tissue plasminogen activator (rtPA) for acute ischemic stroke within the first three hours of onset. The use of thrombolytic agents increases the risk of intracranial hemorrhage that can be severe or fatal. An accompanying editorial,[2] struck a cautiously optimistic note. Considerable excitement ensued, especially among neurologists because no effective treatment for stroke had, as yet, been approved by the Food and Drug Administration (FDA). Subsequently, the FDA approved rtPA for use in stroke on June 18, 1996. The American Academy of Neurology (AAN) was inundated with calls and letters seeking information on whether this thrombolytic therapy should be used in patients with ischemic stroke and, if so, under what conditions. The queries were directed to the Quality Standards Subcommittee (QSS) of the AAN.

The QSS mission is to develop scientifically sound, clinically relevant practice parameters for the practice of neurology. A formal process has evolved for development of these papers. The AAN recognized the urgent need to develop a practice advisory pertaining to thrombolytic therapy for acute ischemic stroke. The Stroke Council of the American Heart Association (AHA) also recognized the need for such a guideline and appointed a panel of experts in thrombolytic therapy to prepare a statement on the use of such treatments in acute ischemic stroke. Since many of the panelists were also members of the AAN and the document produced by the AHA panel could be reviewed using the AAN process, this presented an opportunity for collaboration. Moreover, the AHA Stroke Council panel had already analyzed the background literature which facilitated development of this practice advisory. This AAN practice advisory is a summary based on a background paper developed by the AHA Stroke Council.[3]

Justification. Stroke afflicts about a half million Americans annually and leaves a significant proportion permanently disabled. Economic as well as medical justification exists not only because of the high hospital and rehabilitation costs for stroke patients, but also because many stroke patients permanently lose their economic productivity and must depend on their family and society for care. Many stroke patients need special facilities for long-term care and even those who return home often require costly home adaptations to accommodate impairments.

Any treatment that ameliorates the burden of stroke would be eagerly accepted and widely implemented by neurologists. However, it is important to temper eagerness since such treatments may also have adverse effects. In evaluating the use of thrombolytics for treatment of acute ischemic stroke, risks as well as benefits must be considered. Thrombolytic therapy for acute ischemic stroke was not approved by the Food and Drug Administration until June 18, 1996. Until that time, the package insert for some forms of thrombolytics sanctioned for use in acute myocardial infarction list the use of these drugs in stroke patients as contraindicated.

Methods. A panel selected by the AAN and working in conjunction with the AHA Stroke Council reviewed the relevant literature. The most important evidence underlying the use of intravenous streptokinase for acute ischemic stroke is found in three clinical trials (table 1). These trials are the Multicenter Acute Stroke Trial-Europe (MAST-E), Australian Streptokinase Trial (ASK), and the Multicenter Acute Stroke Trial-Italy (MAST-I). The recommendations underlying the use of intravenous rtPA for acute ischemic stroke were based on two other clinical trials: the European Cooperative Acute Stroke Study (ECASS) (both the intention-to-treat analysis and the ECASS-target population analysis as one trial) and the National Institute of Neurologic Dis-

See page 839 for Subcommittee members.

Approved by the AAN Practice Committee on May 17, 1996; approved by the AAN Executive Board on June 8, 1996.
Accepted July 1, 1996.

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Table 1 *Results of recent clinical trials of intravenous streptokinase in treatment of persons with acute ischemic stroke*[3]

Event	MAST-E (%)	ASK (%)	MAST-I (%)
Acute mortality			
Streptokinase	35*	NA	19
Control	18	NA	13
Streptokinase and aspirin	–	–	34‖
Aspirin	–	–	10
Symptomatic hemorrhage			
Streptokinase	18†	NA	6¶
Control	3	NA	0.6
Streptokinase and aspirin	–	–	10‖
Aspirin	–	–	2
Long-term mortality			
Streptokinase	45‡	44*	28
Control	35	22	29
Streptokinase and aspirin	–	–	44¶
Aspirin	–	–	20
Death and disability			
Streptokinase	NA	62§	62
Control	NA	43	68
Streptokinase and aspirin	–	–	63
Aspirin	–	–	61

* p value = 0.001.
† p value = <0.001.
‡ p value = 0.05.
§ p value = <0.005.
‖ p value = <0.001.
¶ p value = <0.01.

Mast-E = Multicentre Acute Stroke Trial-Europe; ASK = Australian Streptokinase Trial; Mast-I = Multicentre Acute Stroke Trial-Italy; NA = not available.

eases and Stroke (NINDS) clinical trial. These are summarized in table 2.

Recommendations. Substantial scientific evidence or expert consensus suggests the following:

A. Recommendations for initiating thrombolytic treatment.

1. Intravenous rtPA (0.9 mg/kg; maximum of 90 mg), with 10% of the dose given as a bolus, followed by an infusion lasting 60 minutes, is recommended treatment within three hours of onset of ischemic stroke. The benefit from the use of intravenous rtPA for acute ischemic stroke beyond three hours from onset of symptoms is not established. At this time, intravenous administration of rtPA for a person who has had a stroke >3 hours cannot be recommended. Intravenous rtPA is not recommended when the time of onset of stroke cannot be ascertained reliably; this includes persons whose strokes are recognized upon awakening.
2. Intravenous administration of streptokinase, outside the setting of a clinical investigation, is not indicated for the management of persons with ischemic stroke. Data on the efficacy or safety of any other intravenously administered thrombolytic drugs are not available to provide a recommendation.
3. Thrombolytic therapy is not recommended unless the diagnosis is established by a physician who has expertise in the diagnosis of stroke, and a CT of the brain is assessed by physicians who have expertise in reading this imaging study. If a CT demonstrates early changes of a recent major infarction, such as sulcal effacement, mass effect, edema, or possible hemorrhage, thrombolytic therapy should be avoided.
4. Thrombolytic therapy cannot be recommended for persons who had one of the following reasons for exclusion from the NINDS study, including:
   a. Current use of oral anticoagulants or a prothrombin time >15 seconds (INR > 1.7)
   b. Use of heparin in the previous 48 hours and a prolonged partial thromboplastin time
   c. A platelet count <100,000/mm^3
   d. Another stroke or any serious head injury in the previous 3 months
   e. Major surgery within the preceding 14 days
   f. Pre-treatment systolic blood pressure >185 mm Hg or diastolic blood pressure >110 mm Hg
   g. Neurological signs that are improving rapidly
   h. Isolated mild neurological deficits, such as ataxia alone, sensory loss alone, dysarthria alone, or minimal weakness
   i. Prior intracranial hemorrhage
   j. A blood glucose <50 mg/dl or >400 mg/dl
   k. Seizure at the onset of stroke
   l. Gastrointestinal or urinary bleeding within the preceding 21 days
   m. Recent myocardial infarction
5. Thrombolytic therapy should not be given unless the emergent ancillary care (Section D) and the facilities to handle bleeding complications are readily available.
6. Caution is advised before giving intravenous rtPA to persons with severe stroke (NIH Stroke Scale >22).[4]
7. Because the use of thrombolytic drugs carries the real risk of major bleeding, the risks of potential benefits of rtPA should be discussed whenever possible with the patient and family before treatment is initiated.

Table 2 Results of recent clinical trials of intravenous rtPA in treatment of persons with acute ischemic stroke[3]

	ECASS Intention-to-Treat (%)	ECASS Target Population (%)	NINDS (%)
30-day mortality			
rtPA	17.9	14.6	12.9
control	12.7	11.7	15.8
Symptomatic or parenchymal hemorrhage			
rtPA	19.8†	19.4†	6.4†
control	6.5	6.8	0.3
90-day mortality			
rtPA	22.4	19.4	17.4
control	15.8	14.8	20.6
90-day death and disability*			
rtPA	64.3	59.1‡	61†
control	70.7	70.8	74

* Disability as measured by Rankin Scale. In the NINDS Study, the Rankin Scale of 2 or greater (on a scale of 0 = normal to 6 = dead) was considered as disabled. In the ECASS Study, the Rankin Scale of 3 or greater was considered as disabled.
† p value = <0.001 (Mantel-Haenszel test).
‡ p value = 0.035 (Wilcoxon test).

ECASS = European Cooperative Acute Stroke Study; NINDS = National Institute of Neurological Disorders and Stroke Acute Stroke Study.

B. Management of bleeding complications. Before using thrombolytic therapy, the following should be considered. Thrombolytic therapy should not be used unless the treatment facility is staffed and equipped to handle bleeding complications. Bleeding is the most feared complication and can be fatal. Hemorrhagic events generally are divided into those that directly affect the central nervous system and those that involve other organs. The treatment of thrombolysis-related bleeding is guided by a) the location and size of the hematoma, b) the likelihood that the bleeding can be controlled mechanically, c) the risk of neurological worsening or death, d) the interval between administration of the drug and the onset of hemorrhage, and e) the thrombolytic drug used. Information necessary to guide recommendations about treatment of hemorrhagic complications of thrombolytic therapy is scarce.

If bleeding is suspected, blood should be drawn to measure the patient's hematocrit, hemoglobin, partial thromboplastin time, prothrombin time/INR, platelet count, and fibrinogen. Blood should be typed and cross-matched if transfusions are needed (at least 4 units of packed red blood cells, 4–6 units of cryoprecipitate or fresh frozen plasma, and 1 unit of single donor platelets).

1. Thrombolytic therapy should not be used unless facilities to handle bleeding complications are readily available.
2. Bleeding should be considered the likely cause of neurological worsening following use of a thrombolytic drug until a CT is available. The study should be obtained on an emergent basis whenever neurologic worsening follows administration of rtPA.
3. Any life-threatening hemorrhagic complication, including intracranial bleeding, should lead to the following sequential steps:
   a. Discontinue infusion of thrombolytic drug if still being given;
   b. Obtain blood samples for coagulation tests (see above);
   c. Obtain surgical consultation, as necessary.

C. Antithrombotic and antiplatelet aggregating drugs and the use of thrombolytic drugs.

1. Based on expert consensus, persons who have taken aspirin are eligible for treatment with rtPA if they meet all other criteria for therapy. Information about the safety of the use of rtPA in the management of acute ischemic stroke in persons who have taken ticlopidine or other antiplatelet agents does not permit any recommendation.
2. Persons who are taking warfarin or heparin or who have prolongation of baseline clotting factors should not be given rtPA for treatment of acute ischemic stroke.
3. Persons given intravenous rtPA should not receive aspirin, heparin, warfarin, ticlopidine, or other antithrombotic or antiplatelet aggregating drugs within 24 hours of treatment. Additional research on the usefulness of such adjunctive therapies is needed because they may

Table 3 Emergent management of arterial hypertension for persons receiving thrombolytic drugs for acute ischemic stroke method used by the NINDS study group[3]

1. Monitor arterial blood pressure during the first 24 hours *after starting treatment.*
   - Every 15 minutes for 2 hours after starting the infusion, then
   - Every 30 minutes for 6 hours, then
   - Every 60 minutes until 24 hours after starting treatment.
2. If systolic blood pressure is 180–230 mm Hg or if diastolic blood pressure is 105–120 mm Hg for two or more readings 5–10 minutes apart, the following is recommended.
   - Give intravenous labetalol 10 mg over 1 to 2 minutes. The dose may be repeated or doubled every 10 to 20 minutes up to a total dose of 150 mg.
   - Monitor blood pressure every 15 minutes during treatment and observe for development of hypotension.
3. If systolic blood pressure is greater than 230 mm Hg or if diastolic blood pressure is in the range of 121–140 mm Hg for two or more readings 5 to 10 minutes apart, the following is recommended.
   - Give intravenous labetalol 10 mg over 1 to 2 minutes. The dose may be repeated or doubled every 10 minutes up to a total dose of 150 mg.
   - Monitor blood pressure every 15 minutes during *use of labetalol* treatment and observe for development of hypotension.
   - If no satisfactory response, infuse sodium nitroprusside (0.5 to 10 mcg/kg/minute).*
   - Continue monitoring of blood pressure.
4. If the diastolic blood pressure is greater than 140 mm Hg for two or more readings 5 to 10 minutes apart, the following is recommended.
   - Infuse sodium nitroprusside (0.5 to 10 mcg/kg/minute).*
   - Monitor blood pressure every 15 minutes *during the infusion of sodium nitroprusside* and observe for development of hypotension.

* The use of continuous arterial monitoring is advised if sodium nitroprusside is used. The risk of bleeding secondary to arterial puncture should be weighed against the possibility of missing dramatic changes in pressure during the infusion.

affect time to lysis, degree of reperfusion, occurrence of reocclusion and/or clinical outcome.

D. **Ancillary management practices.** There are no data that define the precise risks and benefits of ancillary management practices. However, the investigators in the NINDS study paid considerable attention to ancillary care during the administration of rtPA and the ensuing 24 hours. Accordingly, the ancillary care used by this group is advised.
   1. Admission to a skilled care facility (intensive care unit or acute stroke care unit) which permits close observation, frequent neurological assessments, and cardiovascular monitoring.
   2. Careful management of arterial blood pressure is critical during the administration of rtPA and the ensuing 24 hours (table 3). An excessively high blood pressure might predispose the patient to bleeding, while an excessive lowering blood pressure may worsen ischemic symptoms.
   3. Central venous access and arterial punctures are restricted during the first 24 hours (table 3).
   4. Placement of an indwelling bladder catheter should be avoided during the period of drug infusion and for at least 30 minutes following the end of the infusion.
   5. Insertion of a nasogastric tube should be avoided if possible during the first 24 hours after treatment.

Use of thrombolytic therapy in management of stroke in infants and children. There are no data concerning the use of rtPA for the treatment of acute ischemic stroke in neonates, infants, or children. The recent trials did not enroll persons under the age of 18. Thrombolytic drugs have been given to children with other thromboembolic diseases, including arterial thrombosis, right atrial and caval thrombosis, pulmonary embolism, thrombosis of a Blalock-Taussig shunt, thrombosed dialysis shunts, and cerebral venous thrombosis. One study suggests that a dose 0.5 mg/kg should be used in children.[5]

The safety and efficacy of the use of rtPA in neonates, infants, and children with acute ischemic stroke requires further study. The risk of bleeding may be particularly high in neonates because plasminogen concentrations often are low, hemostatic and fibrinolytic mechanisms are not fully developed, and the cerebral vasculature is immature.

If rtPA is to be given to a pediatric patient for acute ischemic stroke, the same precautions as in adults should be followed. This medication should only be administered with caution and in a highly individualized manner to pediatric patients with acute ischemic stroke. Due to the potential high risk of hemorrhage, neonates and infants should be treated only in very exceptional circumstances.

Future research. Additional information is needed to assess current criteria for patient selection, method of administration, and the window of

Appendix *AHA Stroke Council levels of evidence and grading of recommendations for treatment of patients with acute ischemic stroke**

Level of Evidence	
Level I	Data from randomized trials with low false-positive (alpha) and low false-negative (beta) errors
Level II	Data from randomized trials with high false-positive (alpha) or high false-negative (beta) errors
Level III	Data from nonrandomized concurrent cohort studies
Level IV	Data from nonrandomized cohort studies using historical controls
Level V	Data from anecdotal case series
Strength of Recommendation	
Grade A	Supported by Level I evidence
Grade B	Supported by Level II evidence
Grade C	Supported by Levels III, IV, or V evidence

* Adapted from references 3 and 6.

time during which thrombolytic drugs are effective. Whether lacunar stroke and larger infarcts benefit equally with thrombolytic therapy, as now appears to be the case, must be reviewed as more experience is gained. Although stroke in the pediatric age group is uncommon, there are situations where thrombolytic therapy may be beneficial, but more data are needed before thrombolytic agents can be recommended in children.

Acknowledgments

The Quality Standards Subcommittee wishes to thank members of the American Heart Association Stroke Council Special Writing Group for their work in the preparation of the background paper for this practice advisory: Harold P. Adams, Jr., MD, Chair; Thomas G. Brott, MD; Anthony J. Furlan, MD; Camilo R. Gomez, MD; James Grotta, MD; Cathy M. Helgason, MD; Thomas Kwiatkowski, MD; Patrick D. Lyden, MD; John R. Marler, MD; James Torner, PhD; William Feinberg, MD; Marc Mayberg, MD; and William Thies, PhD.

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QSS thanks Milton Alter, MD, PhD, for his work as QSS facilitator of this project. QSS also would like to thank Patrick D. Lyden, MD, Thomas G. Brott, MD, and James C. Grotta, MD for their contribution.

Definitions

Class I: Evidence provided by one or more well-designed randomized controlled clinical trials, including overviews (meta-analyses) of such trials.

Class II: Evidence provided by well-designed observational studies with concurrent controls (e.g., case control and cohort studies).

Class III: Evidence provided by expert opinion, case series, case reports, and studies with historical controls.

Strength of Recommendations

Standards: Principles for patient management that reflect a high degree of clinical certainty (usually this requires Class I evidence that directly addresses the clinical question, or overwhelming Class II evidence when circumstances preclude randomized clinical trials).

Guidelines: Recommendations for patient management that reflect moderate clinical certainty (usually this requires Class II evidence or a strong consensus of Class III evidence).

Practice option/Advisory: Strategy for patient management for which the clinical utility is uncertain (inconclusive or conflicting evidence or opinion).

Note. This statement is provided as an educational service of the American Academy of Neurology. It is based on an assessment of current scientific and clinical information. It is not intended to include all possible proper methods of care for a particular neurologic problem or all legitimate criteria for choosing to use a specific procedure. Neither is it intended to exclude any reasonable alternative methodologies. The AAN recognizes that specific patient care decisions are the prerogative of the patient and the physician caring for the patient, based on all of the circumstances involved.

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Practice Advisory [RETIRED]: Thrombolytic therapy for acute ischemic stroke--Summary Statement

Neurology 1996;47;835-839
DOI 10.1212/WNL.47.3.835