

# WAPRACTICE *Matters*

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## ACUTE STROKE TREATMENT

- *Stroke is the nation's third leading cause of death, and the leading cause of serious, long-term disability.*
- *There are about 13,500 strokes each year in VA.*
- *Stroke and related diseases consume 5% of VHA resources.*
- *Certain veteran populations such as POWs and those with PTSD, have an increased risk of stroke.*
- *85% of strokes are ischemic, resulting from insufficient blood flow to the brain; 15% are hemorrhagic, resulting from bleeding into the brain.*
- *Stroke can be viewed as a "brain attack". Time is brain. Fast treatment helps stop tissue damage, save brain function, and reduce patient dependency.*
- *Antiplatelet drugs and some thrombolytics show new promise in reducing death and disability from stroke.*
- *Treatments must be chosen carefully because they have important trade-offs in benefits and harms.*
- *VA sponsored research has led to important advances in stroke prevention and recovery.*

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MANAGEMENT DECISION  
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## TREATMENT GOALS

**B**rain damage after an ischemic stroke occurs quickly and progressively over a period of hours. A rapid CT scan or MRI is necessary to determine if a patient is a candidate for thrombolytic therapy, which must be given within 3 hours of symptom onset.

The goals of treatment are to improve survival and reduce disability, which occurs in as many as 50% of stroke patients. Paralysis and loss of vision or speech are most common.

Treatment decisions are based on many factors, including:

- cause, location and extent of brain injury;
- availability of CT scan equipment; and
- availability of appropriate medications within a tight time frame.

## THERAPIES

### Thrombolytic Therapy

**I**ntravenous thrombolytic therapy appears to improve outcomes when administered to carefully selected patients within 3 hours of symptom onset, based on evidence from about 3,000 patients.

When given immediately, there is no increased mortality overall but the risk of intracranial hemorrhage increases about five-fold. rt-PA is currently the only agent licensed by the FDA for the treatment of acute ischemic stroke.

*Given per 1,000 patients. Most data relevant to 3-hour timing are from single large trial evaluating rt-PA.*

#### **Thrombolytic agent given regardless of timing**

- **Benefit:** No benefit for survival or reduced disability
- **Harm:** Results in an increase of about 30 deaths and about 68 more intracranial hemorrhages.

#### **Thrombolytic agent given within 3 hours**

- **Benefit:** Prevents about 50 deaths at 3-6 months and results in about 160 fewer dead or disabled patients at 3-6 months.
- **Harm:** Causes about 58 more intracranial hemorrhages at 14 days.

### Anti-Platelet Therapy

**T**hree trials involving more than 40,000 adults with acute ischemic stroke show aspirin is modestly more effective than placebo in preventing most adverse outcomes. Researchers gave doses of 160 to

300 mg as soon as possible after stroke, usually within 48 hours.

In 1,000 patients, evidence showed that aspirin prevented about 5 deaths and 11 strokes within the first month, and at six months, resulted in about 13 fewer instances of death or disability. On the downside, aspirin is blamed for causing two hemorrhagic strokes in 1,000 patients.

### Anti-coagulant Therapy

**T**he recent International Stroke Trial indicates subcutaneous heparin given in doses of 5,000 to 12,000 units twice daily *does not prevent* death or dependency from stroke at 6 months. It is associated with a modest decrease in recurrent ischemic strokes at 14 days which is offset by a similar increase in hemorrhagic strokes.

Meta-analysis of 15 trials show anticoagulation therapy with either heparin or warfarin *does prevent* deep venous thrombosis, a major complication of stroke, in about a third of patients treated.

### Acute Stroke Units

**T**welve trials show that stroke patients managed in a specialized, multidisciplinary stroke unit are more likely to be alive and living at home a year later than those managed in general medical wards. Length of hospital stay has not been increased by such units.

### Insufficient Evidence

**S**ystematic reviews of over 50 clinical stroke trials testing the treatments listed below concluded that current evidence is insufficient to recommend routine use of:

- hemodilution
- corticosteroids
- fibrinogen-depleting agents
- prostacyclins
- theophylline, caffeine and analogues
- glycerol
- gangliosides

It is unclear whether high blood pressure should, or should not, be altered medically during the acute phase of stroke. But a large thrombolytic trial with positive outcomes controlled blood pressure to <185/105 mmHg.

## EXPERT OPINION

### Thrombolytic Therapy

By the end of 1996 several large well designed trials of thrombolysis for stroke have been completed (1,2). Although some observers have characterized the results as contradictory, and some meta-analyses have inappropriately combined disparate trials, if one carefully looks at the several trials, a pattern emerges that is useful to the treating physician. Clinical trials established that intravenous rt-PA is safe and highly effective for acute stroke victims, if therapy is initiated within 3 hours of stroke onset. A large European trial showed that rt-PA given in the first 6 hours after stroke was effective, but only if certain "high risk" patients were excluded. Meanwhile, 3 large multi-center trials indicated that streptokinase was associated with higher risk and poor outcomes, as was predicated by the animal studies. To lump all of these trials into one meta-analysis is not only inappropriate, but scientifically unjustifiable.

There is a hope that subgroups who are at particular risk of harm or benefit can be identified. Retrospective analyses using formal regression methods have been done to identify such subgroups. Unfortunately there are no subgroups that clearly demonstrate increased risk or benefit from rt-PA for acute stroke. Therefore, the standard guidelines contained in the package insert and published by the American Heart Association and the American Academy of Neurology (3,4) should be used to guide therapy. There is no special subgroup from whom therapy should be withheld.

Stroke code teams have been established in VA Medical Centers. At the San Diego VAMC, door-to-needle times under 45 minutes can be accomplished. Given the burden that stroke causes our patients and health care system, I believe that it is imperative that VA Medical Centers establish stroke treatment teams. No additional equipment or staff are needed. All that is required is a willingness to examine pre-conceived notions and to change nihilistic attitudes. The benefits, measured in disability and dollars saved, are potentially enormous.

Future trials must address a number of remaining questions. What is the latest safe time point to treat stroke? Can an agent other than rt-PA be used safely? Should heparin or aspirin or warfarin be used within the first 24 hours after stroke; currently NINDS

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## RECOMMENDATIONS

- Early aspirin therapy is recommended for patients who don't receive treatment with rt-PA.
- Intravenous rt-PA given within 3 hours of symptom onset should be considered for patients who: do not have bleeding contraindications, have blood pressure < 185/110 mmHg, have had stroke diagnosed by an experienced physician, and have had a CT ruling out hemorrhagic stroke.
- In patients on rt-PA, avoid any antiplatelet or anti-coagulant agents for first 24 hours.
- Thrombolytic therapy should not be used unless facilities to handle bleeding complications exist.
- To prevent deep venous thrombo-embolism, low dose heparin (5,000 units subcutaneously twice daily) may be given concomitantly with aspirin. Alternatively, intermittent pneumatic compression, which is proven beneficial in neurosurgical patients, may be considered.
- Local institutions should aim for routine provision of specialized multidisciplinary care for patients with acute stroke. Initial care should be coordinated by a team consisting of an emergency medical person, a radiologist and a neurologist.

### Acknowledgments

This Acute Stroke Treatment issue of *Practice Matters* was prepared by the VA San Antonio Cochrane Center staff, Karen Stamm, Elaine Chiquette, PharmD and Cindy Mulrow, MD using the Cochrane Library of Systematic Reviews 1997 Issue 3, the Stroke Council of the American Heart Association, and the scientific publications cited in the evidence table. Other major contributors were: Lawrence M. Brass, MD, Chief, Neurology Service, VAMC West Haven, John Booss, MD, Director of Neurology, John R. Feussner, MD, Chief Research and Development Officer, Patrick Lyden, MD, Staff Physician, VAMC San Diego.

## EXPERT OPINION

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guidelines prohibit the use of such drugs. What are the risk factors that seem to predispose patients to hemorrhage? What is the pathophysiology of hemorrhage and can it be prevented? While studies are underway to address these questions, acute stroke therapy with rt-PA should be implemented.

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# PRACTICE *Matters*

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## Evidence Chart for Acute Stroke Treatments

## MAJOR THROMBOLYTIC TRIALS

<i>Study</i>	<i>Participants</i>	<i>Interventions</i>	<i>Outcomes</i>
ASK JAMA. 1996; 276:96 1-966	N= 340 Cortical and lacunar ischemic stroke  Excluded subjects with SBP>200 mmHg or DBP>120mmHg	<b>Streptokinase</b> (SK) 1.5 MU within 4 hrs of symptom onset with aspirin (ASA) 100 mg qd. No other anticoagulants allowed in first 48 hrs. Trial terminated prematurely due to excess mortality in streptokinase group	<b>Intracranial Hemorrhage</b> 13% vs 2.4% (SK vs Placebo) <b>Mortality@3mo.</b> 36% vs. 21% (SK vs Placebo) <b>Death &amp; disability@3mo.</b> 48% vs 45% (SK vs Placebo)
MAST E N Engl J Med 1996; 335:145-50	N=310 Subjects with symptoms of large acute ischemic stroke in the middle cerebral artery territory. Excluded subjects with SBP>220 and DBP>110	<b>Streptokinase</b> 1.5MU within 6 hrs of symptom onset Heparin ±ASA allowed in first 24 hrs and later at MD discretion Trial terminated prematurely due to excess cerebral hemorrhages and mortality in the streptokinase group	<b>Intracranial Hemorrhage</b> 21% vs. 3% (SK vs Placebo) <b>Mortality @6mo.</b> 47% vs 38% (SK vs Placebo) <b>Death &amp; disability@6mo</b> 79% vs 82% (SK vs Placebo)
MAST I Lancet 1995; 346: 1509-14	N=622 All acute ischemic stroke (cortical, lacunar and posterior circulation) Factorial study design: streptokinase alone, aspirin 300mg alone, both or neither	<b>Streptokinase</b> 1.5 MU within 6 hrs  Trial suspended because of slow randomization rate.	<b>Intracranial Hemorrhage</b> P ASA SK SK+ASA 0.6 % 2% 6% 10% <b>Mortality @6mo.</b> P ASA SK SK+ASA 29% 20% 28% 44% <b>Death &amp; disability@6mo.</b> P ASA SK SK+ASA 68% 61% 62% 63%
ECASS JAMA. 1995; 274: 1017-1025	N=620 Acute ischemic hemispheric stroke with moderate to severe neurological deficits Excluded subjects with DBP>110 and SBP>200	<b>rt-PA</b> 1.1 mg/kg MAX: 100mg or placebo within 6 hrs  No anticoagulants or ASA allowed in first 24 hours except heparin SQ	<b>Intracranial Hemorrhage</b> 19.8% vs. 6.5% (rt-PA vs Placebo) <b>Mortality @3mo.</b> 22% vs 16% (rt-PA vs Placebo) <b>Death &amp; disability@3mo.</b> 63% vs 72% (rt-PA vs Placebo)
NINDS N Engl J Med 1995; 333: 1581-7	N=624 Ischemic stroke in either the carotid or vertebrobasilar circulation with neurological deficit measurable on NIH Stroke Scale	<b>rt-PA</b> 0.9 mg/kg MAX:90 mg or placebo within 3 hrs  No antithrombotic agents allowed for the first 24 hrs	<b>Intracranial Hemorrhage</b> 6.4% vs. 0.6% (rt-PA vs Placebo) <b>Mortality @3mo.</b> 17% vs 21% (rt-PA vs Placebo) <b>Death &amp; disability@3mo.</b> 57% vs 73% (rt-PA vs Placebo)

\*All patients had pre-entry CT scans to exclude cerebral hemorrhage. Delivery of drug was intravenous.

## MAJOR ASPIRIN TRIALS

<i>Study</i>	<i>Participants</i>	<i>Interventions</i>	<i>Outcomes</i>
IST Lancet 1997; 349: 1569-81	N= 19435 Acute stroke irrespective of severity	ASA 300mg Heparin SQ (5000U or 12500U) Alone, in combination or neither  First dose immediately, then daily x 14 days	<b>Death from all causes @14 days</b> 9.0% vs 9.4% (ASA vs no ASA) <b>Death or disability @6mo.</b> 62.2% vs 63.5% (ASA vs no ASA) <b>Hemorrhagic stroke</b> 0.5 vs 0.3% (ASA vs no ASA)
CAST Lancet 1997; 349: 1641-49	N=21106 Suspected acute ischemic stroke	ASA 160mg/d within 48 hrs, continue x 4 wks	<b>Death from all causes @4 weeks</b> 3.3% vs 3.9% (ASA vs placebo) <b>Death or disability @4 weeks</b> 30.5% vs 31.6% (ASA vs placebo) <b>Hemorrhagic stroke</b> 1.1% vs 0.9% (ASA vs placebo)
MAST I Lancet 1995; 346: 1509-14	N=622 All acute ischemic stroke (cortical, lacunar and posterior circulation)	ASA 300mg qd x 10 days  Factorial study design: streptokinase alone, aspirin 300mg alone, both or neither.	<b>Death from all causes @6mo.</b> 20% vs 29% (ASA vs placebo) <b>Death &amp; disability @6mo.</b> 61% vs 68% <b>Hemorrhagic stroke</b> 2% vs 0.6% (ASA vs placebo)



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