THE UNIVERSITY of TENNESSEE HEALTH SCIENCE CENTER

# Current tPA Label

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## Disclosures

Speaker's Bureau: Genentech, Inc.

## Outline

1. A brief history of tPA label
2. Adoption of tPA treatment, increasing use and safety
3. Challenging a priori chosen exclusions
4. Current (2015) tPA label

The New England
Journal of Medicine



Volume 333 DECEMBER 14, 1995 Number 24

**TISSUE PLASMINOGEN ACTIVATOR FOR ACUTE ISCHEMIC STROKE**

THE NATIONAL INSTITUTE OF NEUROLOGICAL DISORDERS AND STROKE rt-PA STROKE STUDY GROUP*

Modified Rankin Scale

| | 0–1 | 2–3 | 4–5 | Death |
|---|---|---|---|---|
| Placebo | 26 | 25 | 27 | 21 |
| t-PA | 39 | 21 | 23 | 17 |

Percentage of Patients

Number needed to treat to normal = 7

Number needed to treat to benefit = 3

## NINDS-rt-PA Stroke Study

**Inclusion / exclusion criteria essentially became the first label and guidelines**

PLA 96-0350 Genentech, Inc. Activase® for Acute Ischemic Stroke Summary Basis for Approval 8

3. Patient eligibility criteria

*Inclusion Criteria*

1) Age 18 or older
2) Clinical diagnosis of acute ischemic stroke with measurable neurologic deficit
3) Time of onset is <180 min of when treatment can begin,
4) The Clinical Center administering the specific treatment site has adequate balance of patients between strata (enrollment into 90-180 min stratum was permitted only if the number of patients in 90-180 min. stratum is not more than 2 greater than in the 0-90 stratum).

www.fda.gov/downloads/drugs/.../ucm080828.pdf

## NINDS-rt-PA Stroke Study

**Inclusion / exclusion criteria essentially became the first label and guidelines**

*Exclusion Criteria*

1) Only minor stroke or symptoms rapidly improving at time of infusion start
2) Evidence of hemorrhage on CT scan
   No other formal CT scan exclusion criteria.
3) Clinical presentation suggesting subarachnoid hemorrhage
4) Female & lactating or pregnant
5) Platelet count < 100,000, PT > 15, Heparin within 48 hrs & PTT > normal, or
   Patient on oral anticoagulants.
6) Major surgery or body trauma within 14 d prior; serious head trauma within 3 mo
7) Hx of GI or UT hemorrhage in prior 21 d.
8) Noncompressible arterial puncture within 7d; LP within 7 d
9) Systolic BP > 185 or diastolic > 110
10) Hx of stroke in prior 3 mo, prior ICH suggesting risk factor.
11) Serious medical illness that would interfere with trial
12) Glucose <50 or > 400
13) Clinical presentation consistent with MI or postMI pericarditis
14) Seizure at onset of stroke

There were no formal CT scan-based exclusion criteria other than the finding of hemorrhage.

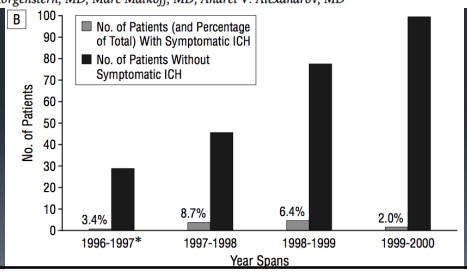
www.fda.gov/downloads/drugs/.../ucm080828.pdf

*Arch Neurol. 2001;58:2009-2013*

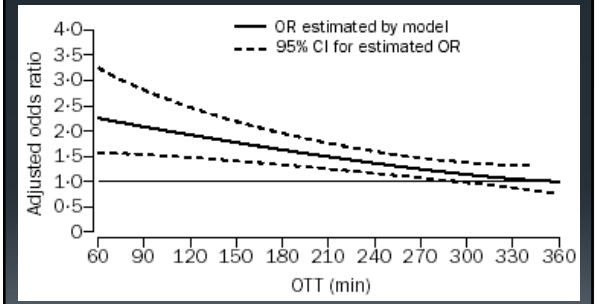
## Intravenous Tissue-Type Plasminogen Activator Therapy for Ischemic Stroke

*Houston Experience 1996 to 2000*

*James C. Grotta, MD; W. Scott Burgin, MD; Ashraf El-Mitwalli, MD; Megan Long; Morgan Campbell, MD; Lewis B. Morgenstern, MD; Marc Malkoff, MD; Andrei V. Alexandrov, MD*




## Reperfusion Rx: Faster is Better




ATLANTIS, ECASS, and NINDS-rt-PA Stroke Study. Lancet 2004;363:768-774.

## Inadvertent tPA: Is Safety Compromised?

- **"Time is Brain!" mantra prompts clinicians to make decisions with often limited past medical history and other patient information**
- **Many exclusions for iv tPA in the NINDS-rt-PA Stroke Study and ECASS were not data driven**
- **Clinicians started to re-think the exclusionary paradigm around iv tPA (Tong D. SMART criteria)**

Stroke 2012 Mar;43(3):625-6.

## Inadvertent tPA Administration

Determine safety of systemic thrombolysis in acute ischemic stroke patients with inadvertent violation of current tPA label inclusion/exclusion criteria compared to those deemed "on label" after all relevant history, imaging and laboratory data became available

## Subjects & Methods

Consecutive ischemic stroke patients treated with iv tPA at a single tertiary care center

NIHSS scores were obtained as standard of care by treating physicians

Label violation was determined by retrospective chart review

Symptomatic ICH was defined by NIHSS≥4 worsening

## Inadvertent tPA: Results

191 patients received iv tPA
- 150 (79%) at our center
- 41 (21%) phone-assisted "drip'n'ship"

Age 66±16 years
Women 45%
Median pre-tPA NIHSS score 12 (IQR 7-17)

Inadvertent tPA use was found in 35 (18%)

## Inadvertent tPA Label Violations

| Violation | n | % |
|---|---|---|
| Questionable onset time | 8 | 23% |
| Elevated coagulation profile | 7 | 20% |
| Stroke within past 3 months | 5 | 14% |
| BP >185/110 at time of bolus | 3 | 9% |
| Seizure at stroke onset | 3 | 9% |
| Platelet count < 100,000 | 3 | 9% |
| Stroke mimic | 2 | 6% |
| GI hemorrhage within 21 days | 1 | 3% |
| Major surgery within past 14 days | 1 | 3% |
| Hx of intracranial trauma/hemorrhage | 1 | 3% |
| Hx of clipped intracranial aneurysm | 1 | 3% |

## Potential Con-founders

15 (8%) patients with NIHSS<4 were treated for the presence of disabling deficit.

On-treatment BP protocol violations (at least 1 during the first 24 hrs) occurred in 77 (40%) of cases.

## Inadvertent tPA Safety/Outcome

A total of 2 patients (1%) had sICH:
- 1 on-label case with BP protocol violations
- 1 in a patient with unknown chronic subdural hematoma unapparent on pre-treatment scan

Median discharge NIHSS was 6 (IQR 2-13) and was lower than admission NIHSS scores (mean difference 2.6; 95% CI 1.3-4.0; p<.001)

Median discharge mRS 3 (IQR 2-4).

## Inadvertent tPA at Single CSC

**Our findings support selection of patients for intravenous tPA based on identifying patients with disabling deficits and brain imaging consistent with potential reversibility of ischemia.**

**The inadvertent tPA use with such an approach appears to be as safe as routine on-label use.**

Chaudhary A, et al.
European Stroke Conference 2012

## Current tPA Label

**FULL PRESCRIBING INFORMATION**

**1 INDICATIONS AND USAGE**

**1.1 Acute Ischemic Stroke**

Activase is indicated for the treatment of acute ischemic stroke.

Exclude intracranial hemorrhage as the primary cause of stroke signs and symptoms prior to initiation of treatment *[see Contraindications (4.1)]*. Initiate treatment as soon as possible but within 3 hours after symptom onset.

www.accessdata.fda.gov/drugsatfda_docs/label/2015/103172s5203lbl.pdf

## Current tPA Label

**4 CONTRAINDICATIONS**

**4.1 Acute Ischemic Stroke**

Do not administer Activase to treat acute ischemic stroke in the following situations in which the risk of bleeding is greater than the potential benefit *[see Warnings and Precautions (5.1)]*:

- Current intracranial hemorrhage
- Subarachnoid hemorrhage
- Active internal bleeding
- Recent (within 3 months) intracranial or intraspinal surgery or serious head trauma
- Presence of intracranial conditions that may increase the risk of bleeding (e.g., some neoplasms, arteriovenous malformations, or aneurysms)
- Bleeding diathesis
- Current severe uncontrolled hypertension.

www.accessdata.fda.gov/drugsatfda_docs/label/2015/103172s5203lbl.pdf