

Giving tPA

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- tPA: studies for efficacy and safety
- Mechanism of action
- Criteria
- Protocol/procedures

overview

- About 700,000 strokes annually.
Approximately 6000 veterans.
- Small percentage eligible for thrombolysis,
but benefit has been shown
- Uncommon use = delays
- Ideal targets for time for getting patients
from the door to treatment.
- Therapeutic nihilism- patients/some
practitioners believe that nothing can be
done for acute stroke.

Acute stroke treatment

- Every member of medical staff vital in recognition and implementation
- Step by step process
- Tissue Plasminogen Activator (tPA) is the only FDA approved medication for treatment of acute stroke. Considered standard of care.

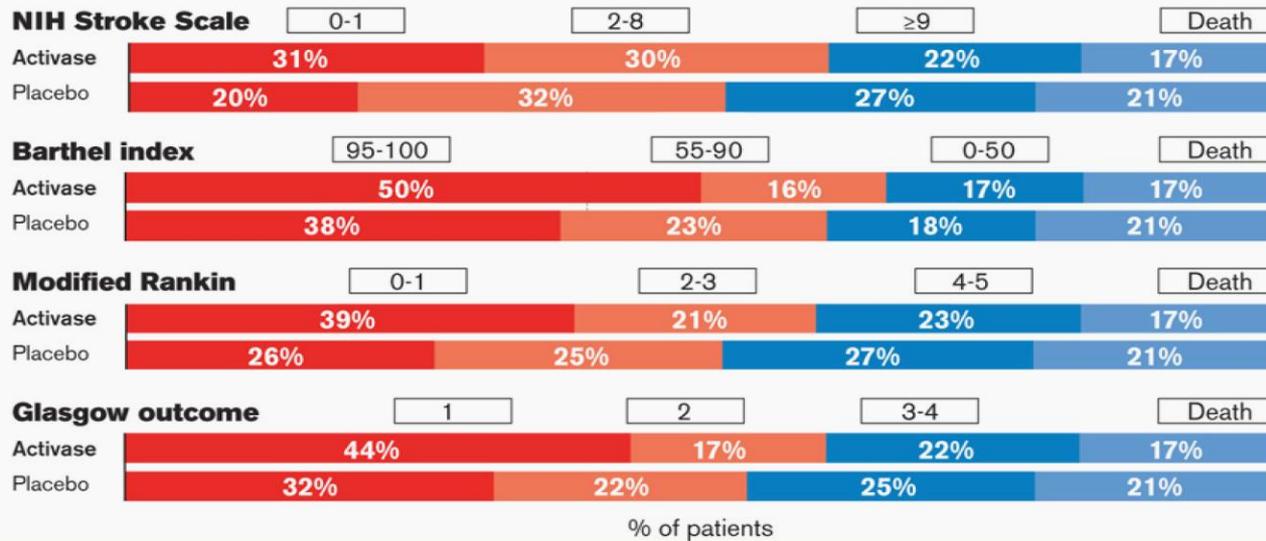
The first step

- fibrin-specific thrombolytic agent that activates plasminogen to form plasmin, a protease that cleaves fibrin.
- Efficacy in several trials following initial study
- Safety in community hospitals similar to trial centers. Hemorrhage rates of 6%
- Inclusion and exclusion criteria

tPA

More patients recover with minimal or no disability with Activase® (t-PA)

NINDS results at 3 months*



■ Minimal or no disability ■ Moderate disability ■ Severe disability ■ Death

*Values do not total 100% because of rounding.

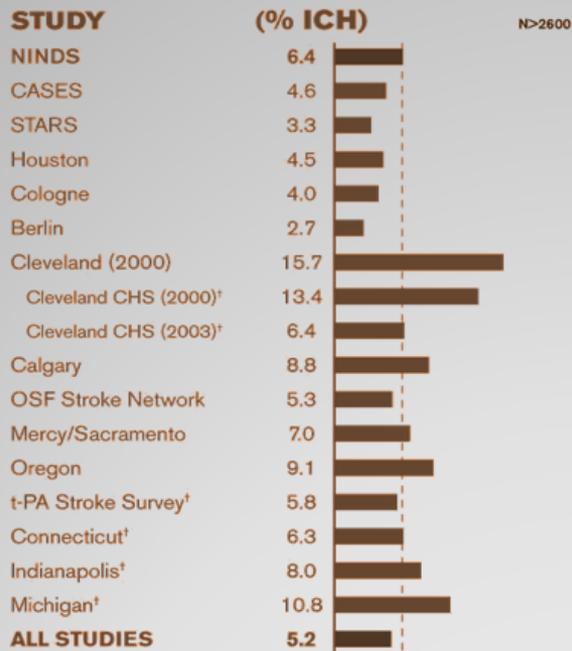
NIH = National Institutes of Health.

Scores of ≤ 1 on the NIHSS, 95 to 100 on the Barthel index, ≤ 1 on the modified Rankin scale, and 1 on the Glasgow outcome scale were considered to indicate a favorable outcome.

Reference: NINDS rt-PA Stroke Study Group. *N Engl J Med.* 1995;333:1581-1587.

Numerous studies demonstrate safety

Symptomatic ICH in clinical practice*

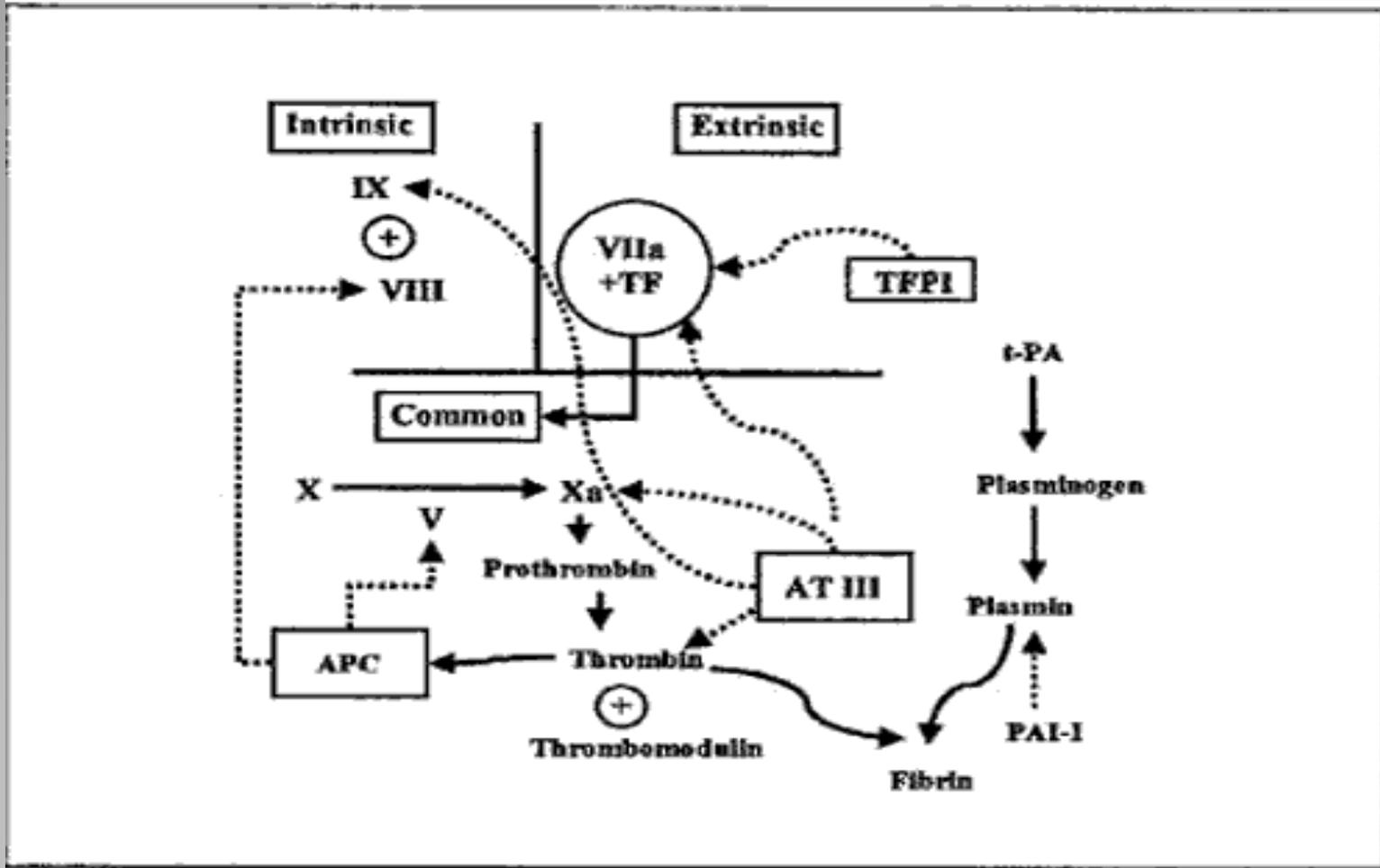


Cleveland (2000) study evaluated 29 area hospitals. Cleveland Clinic Health System (CHS) studies later evaluated a subset of 9 hospitals. The Cleveland CHS results were not factored into the overall 5.2% rate of ICH in "All Studies."

*Symptomatic intracranial hemorrhage (ICH) percentages are for bleeding within the first 36 hours or the closest reported time point.

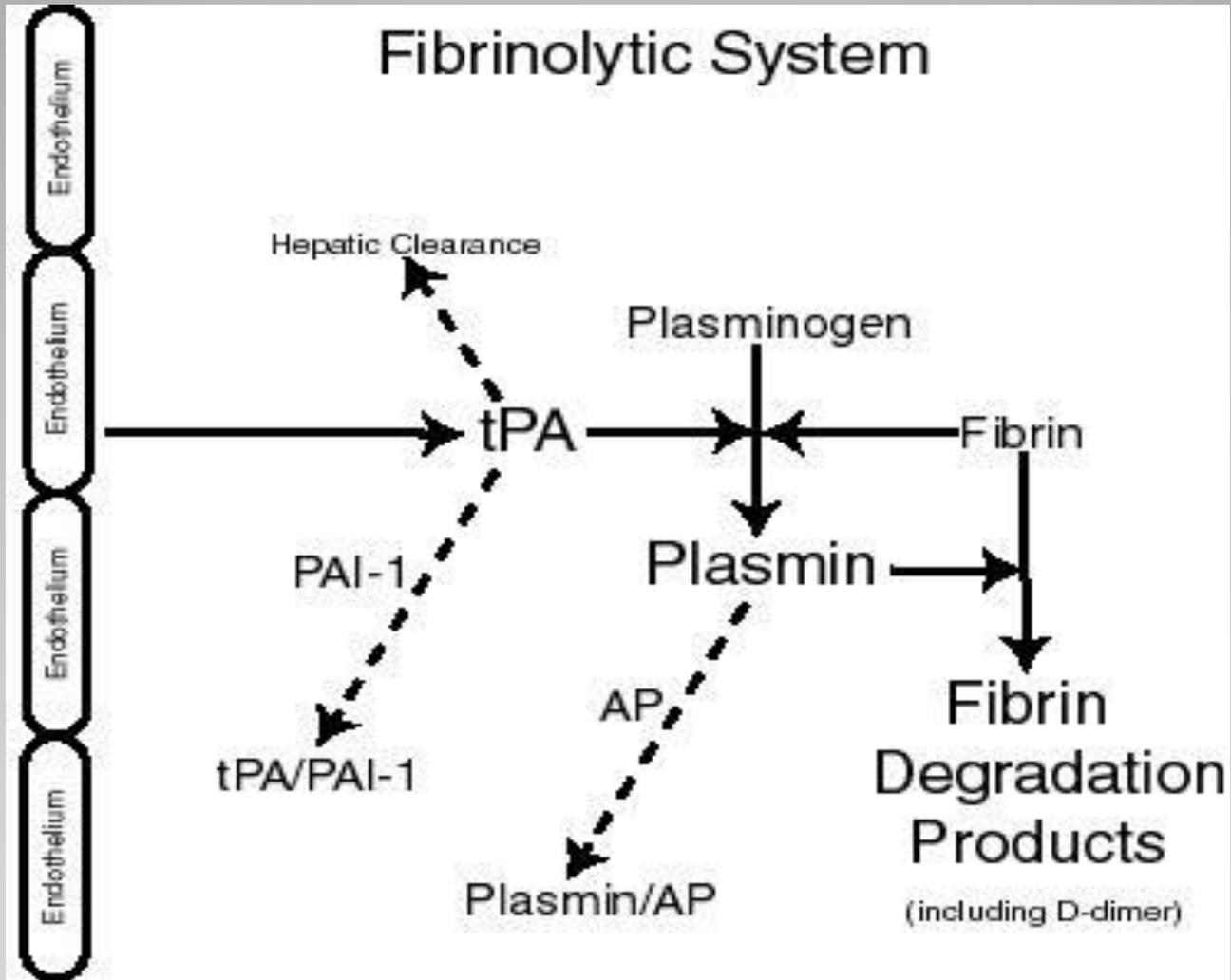
[†]Indicates retrospective study; all others were prospective.

Reference: Adapted from Graham. *Stroke*. 2003;34:2847-2850; and Katzan et al. *Stroke*. 2003;34:799-800.



Mechanism of action

Fibrinolytic System



- Age ≥ 18 years
- Clinical diagnosis of ischemic **stroke** causing a measurable neurologic deficit
- Time of symptom onset well established to be < 180 minutes before treatment would begin

Inclusion criteria for tPA

- ECASS 3. randomized tPA vs. placebo in stroke patients presenting 3-4.5 hrs.
- 52.4% of tPA patients had a favorable outcome (mRS 0 or 1) vs. 45.2%.
- Exclude: age over 80yrs; NIHSS >25; anticoagulants; Hx of stroke and diabetes.
- Not yet FDA approved.

3 to 4.5 hour window

- 1.** Evidence of intracranial hemorrhage on noncontrast head CT
- 2.** Only minor or rapidly improving stroke symptoms
- 3.** High clinical suspicion of subarachnoid hemorrhage even with normal CT
- 4.** Active internal bleeding (e.g., gastrointestinal bleed or urinary bleeding within last 21 days)

Exclusion criteria

5. Known bleeding diathesis, including but not limited to: Platelet count 100,000/mm. Patient has received heparin within 48 hours and had an elevated activated partial thromboplastin time (greater than upper limit of normal for laboratory). Recent use of anticoagulant (e.g., warfarin sodium) and elevated prothrombin time >15 seconds
6. Within 3 months of intracranial surgery, serious head trauma, or previous **stroke**

Exclusion criteria

7. Within 14 days of major surgery or serious trauma
8. Recent arterial puncture at noncompressible site
9. Lumbar puncture within 7 days
10. History of intracranial hemorrhage, arteriovenous malformation, or aneurysm
11. Witnessed seizure at **stroke** onset
12. Recent acute myocardial infarction
13. On repeated measurements, systolic pressure <185 mm Hg or diastolic pressure <110 mm Hg at time of treatment, requiring aggressive treatment to reduce blood pressure to within these limits
14. Use of dabigatran.

Exclusion criteria

- Door to physician-10 min
- Door to CT completion-25 min
- Door to CT reading-45 min
- Door to treatment-60 min
- Access to neurologic expertise-15 min
- Access to neurosurgical expertise-2 hr

Target time frames

- notification- prior to arrival or not
- Triage nurse- suspect stroke



Immediate Physician Notification

ED procedures

ABC
History

```
graph TD; A[ABC History] --- B[Vital sign monitoring  
Pulse ox  
IV access]; A --- C[Cardiac monitoring  
Neurologic monitoring  
Neurology consult  
CALL PHARMACY]; A --- D[Labs  
Head CT  
EKG and CXR];
```

Vital sign monitoring
Pulse ox
IV access

Cardiac monitoring
Neurologic monitoring
Neurology consult
CALL PHARMACY

Labs
Head CT
EKG and CXR

- Rapid blood glucose level. Accucheck
- CBC
- Coagulation profile
- BMP
- These results may be sent to Neuro ICU team that accepts the patient.

Labs

Noncontrast CT brain scans differentiate hemorrhagic from ischemic infarcts

wedge-shaped cortical infarct



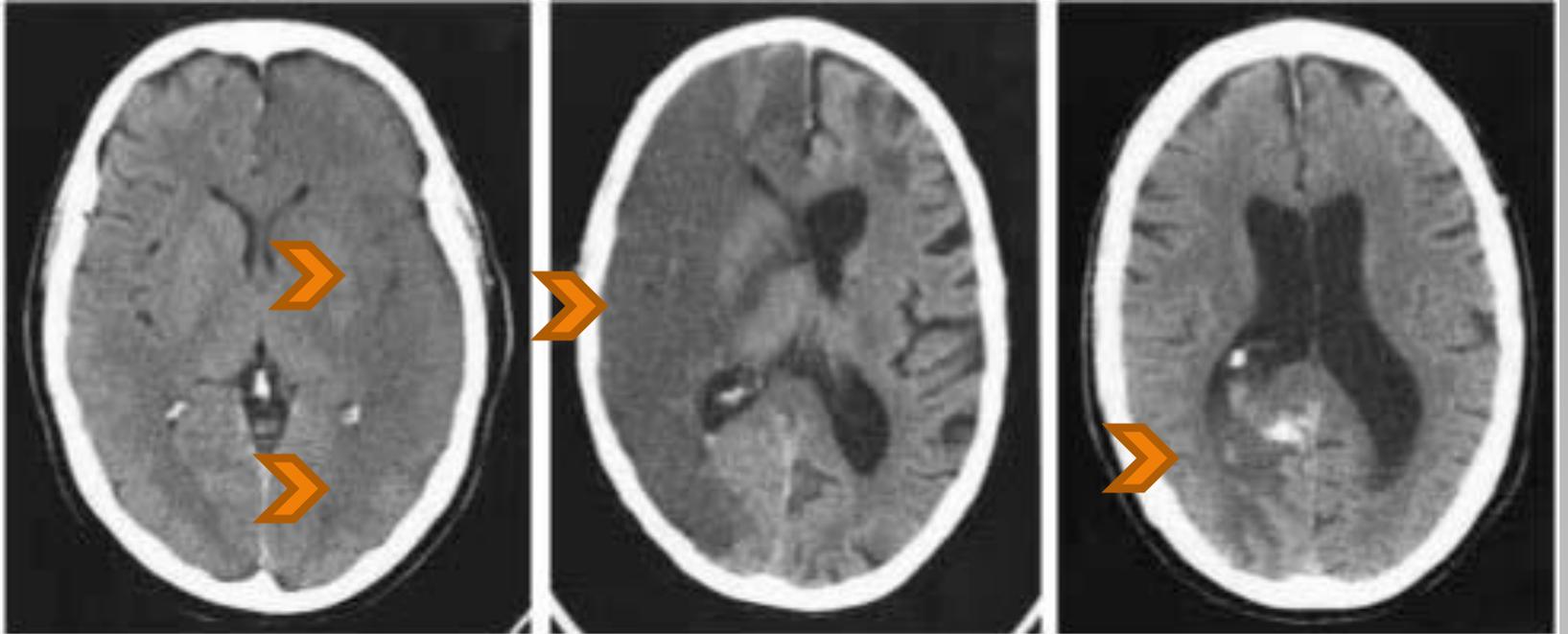
intracranial hemorrhage



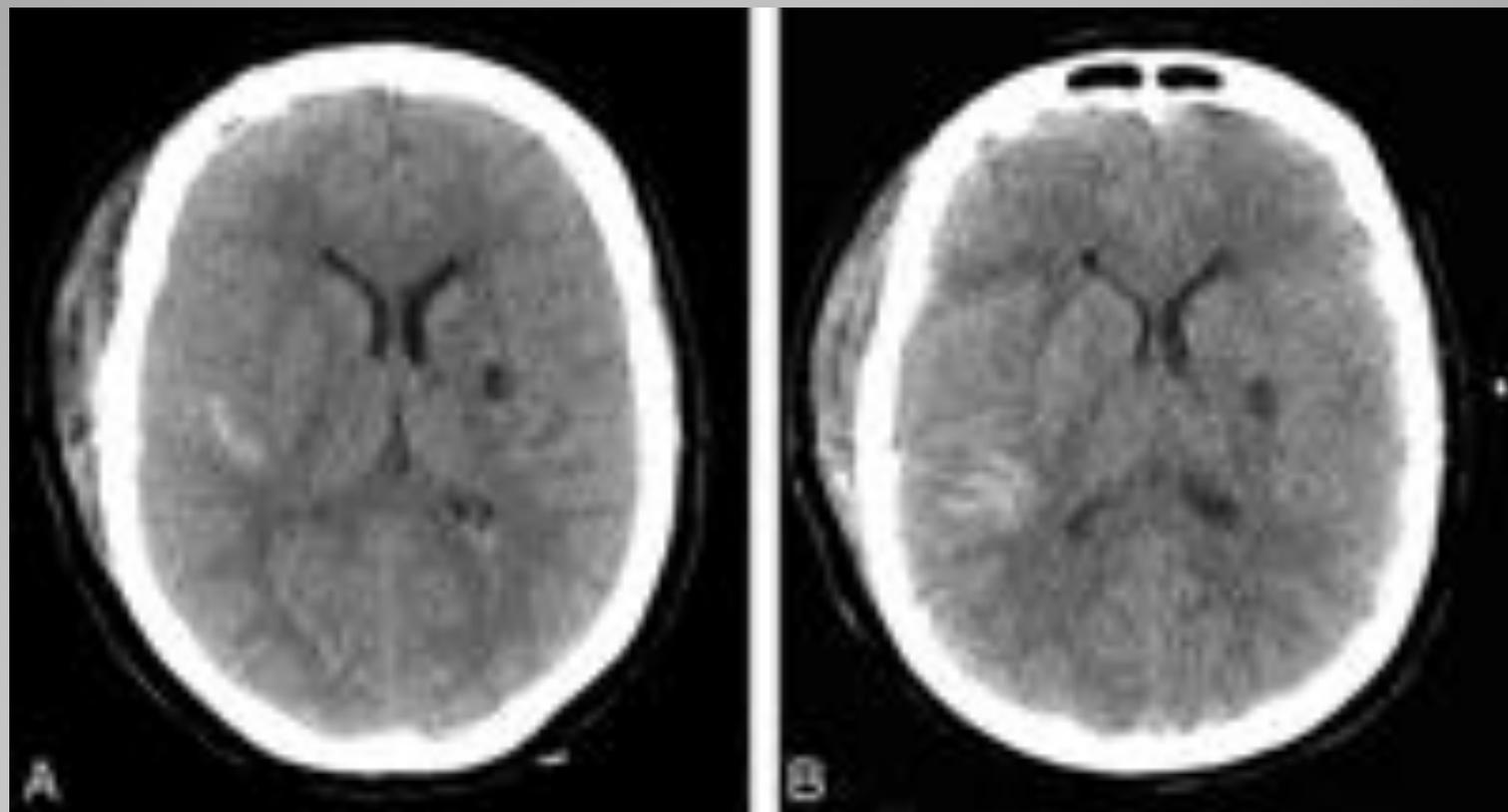
mass effect and shift of ventricles



Courtesy of Genentech, Inc.



> 1/3 hypodensity on CT



Chronic lacunar infarction

CT

Findings

Recommendations

None	Treat
Subtle < 1/3 MCA	Treat
Subtle > 1/3 MCA	Probably treat
Hypodensity < 1/3 MCA	Probably treat
Hypodensity > 1/3 MCA	Don't treat

rt-PA Treatment Based on CT Findings

- risks of potential benefits of rtPA should be discussed whenever possible with the patient and family. iMed formal consent to be signed in VA system.
- Don't give to severe stroke (NIH Stroke Scale >22).
- BP > 185/110mmHg : Lower with IV labetalol 10mg x 2 doses. If not sustained, don't give tPA

Give or not give tPA

- Intravenous rtPA (0.9 mg/kg; maximum of 90 mg), with 10% of the dose given as a bolus over 1 minute, followed by an infusion lasting 60 minutes
- Pharmacy to reconstitute. Don't wait for all investigations
- Tables



Dose

- While infusing:
 - Monitor for BP elevations and treat with IV labetalol or IV hydralazine (10mg) if above 180/105.
 - Monitor for clinical deterioration. If it occurs, then stop the IV infusion. CT head
 - Monitor for bleeding anywhere.
 - No catheters/ feeding tubes once infusion starts.

What next

- Transfer to hospital with Neurosurgery ICU.
- Contact transferring ED and Neurology resident. Neurointensive attending on call, if applicable.
- Disk of CT scan to be made and sent. Official read if time permits.
- VA ED arranges ambulance for transfer.

What next

- Education to staff.
- Protocols/templates. IRM. Stroke QUERI toolkit.
- Established transfer agreements as needed.

Key elements

TPA DOSING CHART FOR ACUTE ISCHEMIC STROKE [USING 100 MG TPA / 100ML] = 1 MG PER 1 ML

WEIGHT IN LBS	WEIGHT IN KG	DOSE TO REMOVE FROM VIAL & DISCARD [1 MG = 1 ML]	BOLUS DOSE [1 MG = 1 ML]	INFUSION DOSE IN ML / HR TO RUN OVER 1 HR]		WEIGHT IN LBS	WEIGHT IN KG	DOSE TO REMOVE FROM VIAL & DISCARD [1 MG = 1 ML]	BOLUS DOSE [1 MG = 1 ML]	INFUSION DOSE IN ML / HR TO RUN OVER 1 HR]
90	40.9	63	3.7	33		156	70.9	36	6.4	57
92	41.8	62	3.8	34		158	71.8	35	6.5	58
94	42.7	61	3.8	35		160	72.7	35	6.5	59
96	43.6	61	3.9	35		162	73.6	34	6.6	60
98	44.6	60	4	36		164	74.6	33	6.7	60
100	45.5	59	4.1	37		166	75.5	32	6.8	61
102	46.4	58	4.2	38		168	76.4	31	6.9	62
104	47.3	57	4.3	38		170	77.3	30	7	63
106	48.2	56	4.4	39		172	78.2	30	7	63
108	49.1	56	4.4	40		174	79.1	29	7.1	64
110	50	55	4.5	41		176	80	28	7.2	65
112	50.9	54	4.6	41		178	80.9	27	7.3	66
114	51.8	53	4.7	42		180	81.8	26	7.4	66
116	52.7	53	4.7	43		182	82.7	26	7.4	67
118	53.6	52	4.8	43		184	83.6	25	7.5	68
120	54.6	51	4.9	44		186	84.6	24	7.6	69
122	55.5	50	5	45		188	85.5	23	7.7	69
124	56.4	49	5.1	46		190	86.4	22	7.8	70
126	57.3	48	5.2	46		192	87.3	21	7.9	71
128	58.2	48	5.2	47		194	88.2	21	7.9	72
130	59.1	47	5.3	48		196	89.1	20	8	72
132	60	46	5.4	49		198	90	19	8.1	73
134	60.9	45	5.5	49		200	90.9	18	8.2	74
136	61.8	44	5.6	50		202	91.8	17	8.3	74
138	62.7	44	5.6	51		204	92.7	17	8.3	75
140	63.6	43	5.7	52		206	93.6	16	8.4	76
142	64.6	42	5.8	52		208	94.6	15	8.5	77
144	65.5	41	5.9	53		210	95.5	14	8.6	77
146	66.4	40	6	54		212	96.4	13	8.7	78
148	67.3	39	6.1	55		214	97.3	12	8.8	79
150	68.2	39	6.1	55		216	98.2	11	8.8	80
152	69.1	38	6.2	56		218	99.1	11	8.9	80
154	70	37	6.3	57		220 OR >	100 OR >	10	9	81

Jesse Brown VA Medical Center
Chicago, IL

Management of Acute Ischemic Stroke using tissue plasminogen activator (tPA)

Purpose:

To provide a protocol to assist physicians in using tissue plasminogen activator (tPA) for acute ischemic stroke.

Procedure:

All patients with symptoms or signs of an acute ischemic stroke identified by the Triage nurse should immediately be brought to the treatment room regardless of the severity of the deficit.

Family members may accompany the patient to the treatment room in order to obtain an accurate history. The patient or the family member is to be made aware of the benefits and risks of treatment.

Please see the brain attack/stroke guideline for further procedure.

Inclusion and Exclusion Criteria for tPA:

Inclusion Criteria:

- Age of 18 years or more
- Clinical diagnosis of ischemic stroke causing a measurable neurologic deficit <22 on the NIH stroke scale
- Clearly defined time of onset of less than 3 hours before treatment would begin

Exclusion Criteria:

- Minor or rapidly improving symptoms
- Other stroke or serious head trauma within the past 3 months
- Seizure at onset
- Subarachnoid Hemorrhage (SAH) or suspected SAH
- Any history of Intracranial Hemorrhage (ICH)
- Major surgery within the last 14 days
- Sustained systolic blood pressure > 185 mmHg and diastolic blood pressure >110 mmHg despite aggressive treatment.
- Gastrointestinal or urinary tract hemorrhage within the past 21 days
- Arterial puncture at a noncompressible site within 7 days
- Received heparin within 48 hours and has an elevated PTT > 15 seconds
- On oral anticoagulants with an INR >1.7
- Platelet count $<100,000$ mL

- Serum glucose <50 mg/dL or >400 mg/dL (or <3 or >22 mmol/L)
- Myocardial infarction in the prior 6 weeks
- Suspected septic embolism
- Infective endocarditis
- Hemorrhagic eye disorder

CT scan exclusion criteria:

- CT evidence of cerebral hemorrhage or subarachnoid hemorrhage
- CT evidence of ischemic stroke involving more than 1/3 of middle cerebral artery territory

Patient or Delegate Education:

The following benefits/risks of tPA treatment will be reviewed with the patient or delegate by a physician.

According to the 1995 study by the National Institute of Neurological Disorders and Stroke Study Group, in properly selected patients who received tPA within 3 hours of an ischemic stroke:

- A 30% increase in complete or almost complete recovery was seen at 3 months compared to those who did not receive tPA
- A worsening of strokes due to intracranial hemorrhage was seen in 6.4% of patients who received tPA compared to 0.6% of patients who did not receive tPA.

The patient or delegate will sign a consent form authorizing treatment with tPA.

Responsibilities:

Emergency Room Physicians:

Any Emergency Room Physician may initiate the process for treatment with tPA.

Neurologist:

A Neurologist, in conjunction with the Emergency Room Physician, will decide whether the patient is eligible for tPA based on the selection criteria and discussion with the patient or delegate.

Pharmacy:

Pharmacy will reconstitute the proper dose of tPA. The dose is 0.9 mg/kg, with a maximum of 90 mg. If the exact weight of the patient is not known, then at least two of the staff should make the best estimate.

The University of Illinois at Chicago's Neurology resident on-call and the Neurointensive attending on-call will be contacted to initiate transfer of the patient after tPA has been given.

The Emergency Room should contact ambulance services to expedite transfer of the patient to the University of Illinois at Chicago.

Treatment and Monitoring:

The dose of tPA is 0.9mg/kg, with a maximum of 90mg. It is given as an initial bolus of 10% of the total dose. The remaining dose is infused over one hour. For example, if the patient weighs 160 lbs, this is converted to 72.7 kg. The total dose of tPA is 65.4mg. 6.5mg, or 10% of the total dose, is given as a bolus. The remaining 58.9mg is infused over one hour.

Monitor the blood pressure every 15 minutes for the first 2 hours.

Monitor neurologic function for deterioration every 15 minutes.

Keep the patient NPO.

Placement of bladder catheters or feeding tubes should be delayed for 24 hours.

Monitor for bleeding from the mucous membranes, intravenous sites, urine, stool or elsewhere.

Intracranial hemorrhage is suspected if the following occurs:

- Neurologic deterioration
- New headache
- Acute hypertension
- Nausea
- Vomiting

If intracranial hemorrhage is suspected:

- Immediately discontinue tPA infusion
- Obtain immediate CT scan
- Draw PT, aPTT, platelet count, and fibrinogen
- Prepare to give 6-8 U of cryoprecipitate or 6-8 U of platelets
- Alert Neurosurgery

Once the infusion of tPA is finished, the patient can be transferred to University of Illinois at Chicago.