



# Fibrinolysis in Acute Ischemic Stroke--*Redux*: A Skeptical Perspective

“...still a man hears what he wants to hear  
and disregards the rest...”

‘The Boxer’ Paul Simon and Art Garfunkel, 1969

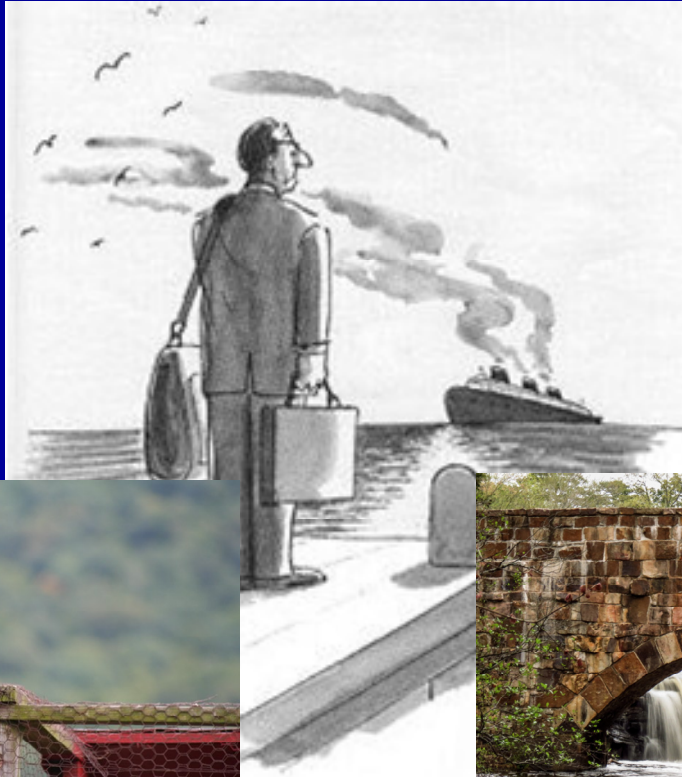


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# FIBRINOLYSIS IN ACUTE ISCHEMIC STROKE

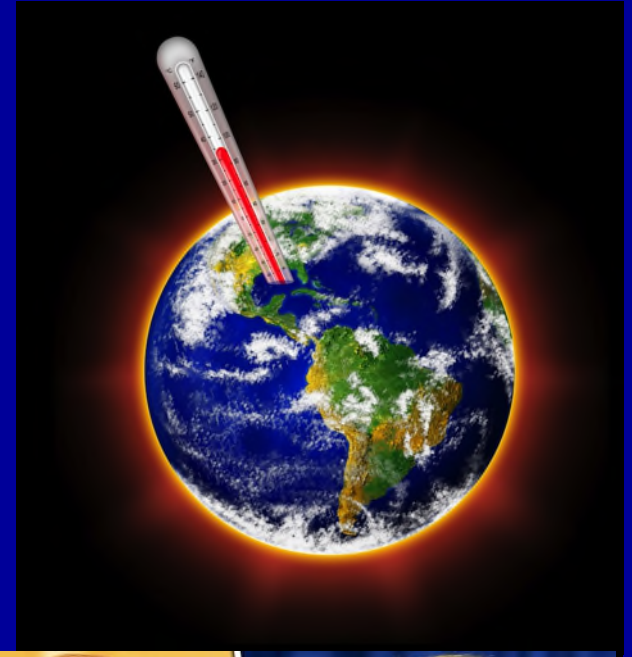
## "...Don't Go There..."





# FIBRINOLYSIS IN ACUTE ISCHEMIC STROKE

## Debate Topics With More Clarity



# FIBRINOLYSIS IN ACUTE ISCHEMIC STROKE

## BLUF Summary

- There is a subset of AIS patients who will benefit from tPA thrombolysis
- We cannot, with any degree of accuracy, identify those stroke patients who will benefit





# FIBRINOLYSIS IN ACUTE ISCHEMIC STROKE

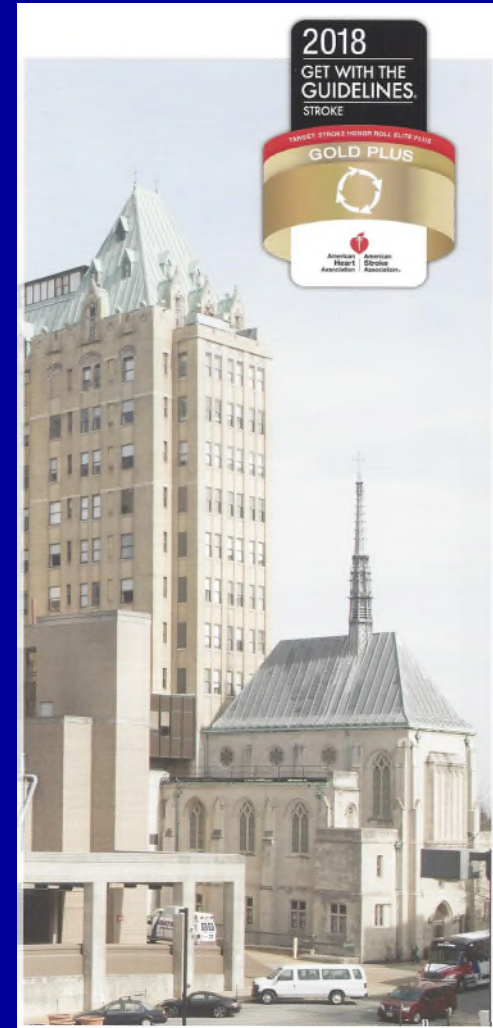
## Sharp Controversy



- No area where more tension and angst
- Believers v. nonbelievers
- Issues of Big Pharma sponsorship
- Mostly universal patient funding
- Disease mongering
- Reaction ranging from sharp skepticism to unbridled enthusiasm
- Ambiguous objective data
- Fundamental question:
  - Is restoring blood flow to the brain in an area of reduced blood flow a good thing?
  - Mixed bag (risk v. benefit)
    - Sketchy efficacy and effectiveness results
    - Swelling, bleeding, death
- Brickbats vs. lively discussion

# FIBRINOLYSIS IN ACUTE ISCHEMIC STROKE

## MidAmerica Stroke Network





# FIBRINOLYSIS IN ACUTE ISCHEMIC STROKE

## MidAmerica Stroke Network

### The MidAmerica Stroke Network: 2018 Highlights

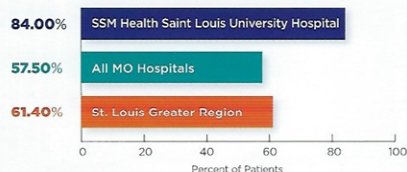
As the headquarters for the MASN, SSM Health Saint Louis University Hospital continued to see positive outcomes in treating the most serious of stroke cases in 2018. The hospital's stroke care measures were ranked higher than both the national and state averages, in terms of timeliness and effectiveness.

#### Key Stroke Core Measure Comparisons

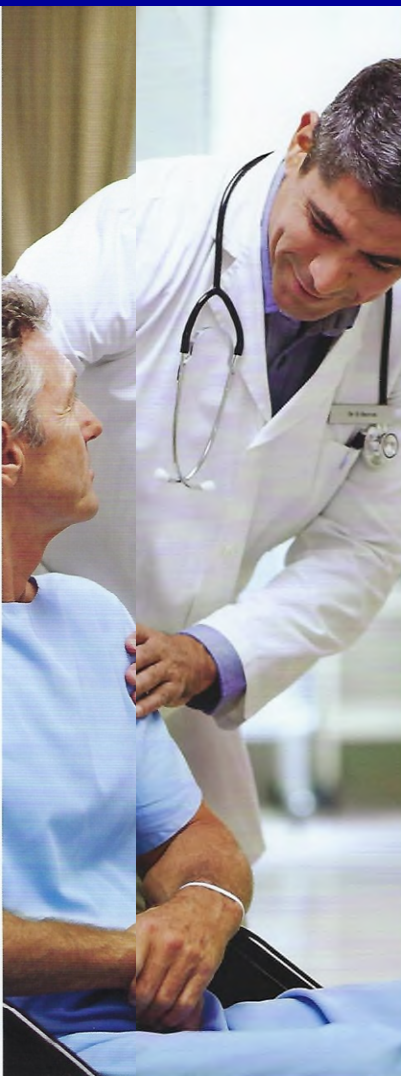
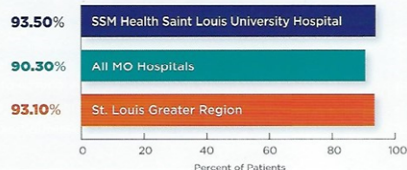
Time-to-IV Thrombolytic Therapy within 60 minutes (% of Patients)



Time-to-IV Thrombolytic Therapy within 45 minutes (% of Patients)



Door-to-IV, Arrive within 2 hours, Treat within 3 hours (% of Patients)



#### Key Highlights

The following are some of the key highlights from 2018, as it pertains to stroke patients at SLU Hospital:

Treated a total of  
**805**  
stroke cases –  
inpatient and outpatient.

More than  
**76%**  
of stroke patients received  
tPA within 45 minutes of  
arriving at  
SSM Health SLU Hospital's  
emergency department.  
That's compared to the  
state average of  
only 46.2%.

Nearly  
**92%**  
of stroke patients were  
treated with tPA within  
60 minutes of arriving at  
the hospital, which is  
10% more than the state  
average of 82%.

Median door-to-needle  
(DTN) time on coded  
stroke patients:  
**31 minutes.**

tPA administrations that  
coded as stroke:  
**50.**

tPA Administrations that  
met GWTG criteria for  
DTN <60 min: 44 total  
(administrations complete  
**96%**  
of the time – exclusion  
criteria includes intubation  
and BP control prior to tPA).

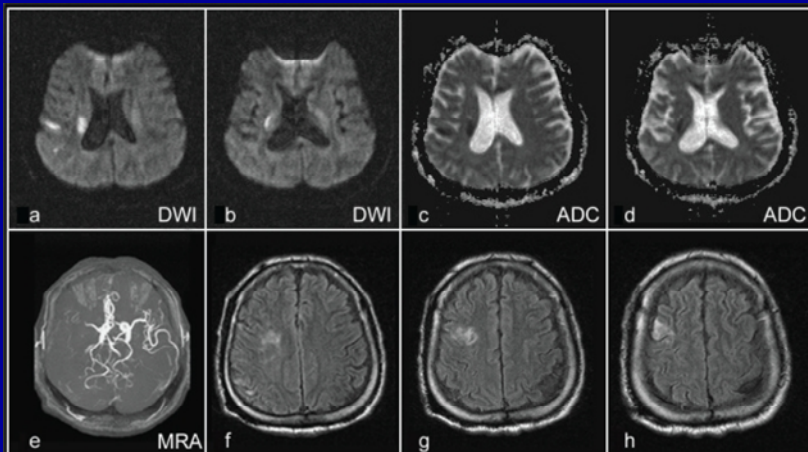
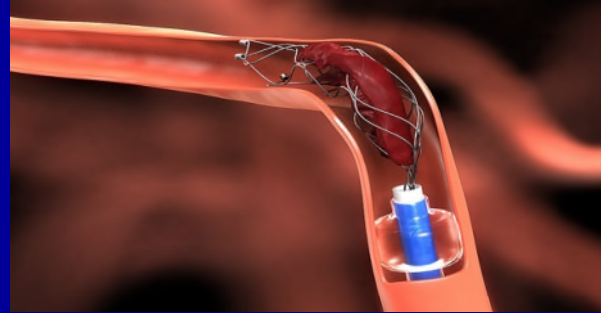
tPA Administrations that  
met GWTG criteria for  
DTN <45 min: 50 total  
(administrations complete  
**84%**  
of the time – GWTG does  
not exclude patients in  
this population).

tPA Administrations arrive  
by 2 hours, treat by 3 hours:  
**94%**  
of patients.

# FIBRINOLYSIS IN ACUTE ISCHEMIC STROKE

## Interventional Endovascular Clot Retrieval

- Endovascular appears to be working (all other trials stopped – unethical)
- Diffusion-weighted imaging up to 24 hours
- 10-13% eligible candidates most lack LVO; < 2% treated, denominator screened unknown





# FIBRINOLYSIS IN ACUTE ISCHEMIC STROKE

## Heterogenous Anecdotes



# FIBRINOLYSIS IN ACUTE ISCHEMIC STROKE

## Is Stroke a Health Problem in US?



- 800,000/year (600K new)
- 3<sup>rd</sup> (5<sup>th</sup>) leading cause of death
- One death every 3 min
- Leading cause of serious, long term disability
- 5M survivors with substantial morbidity
  - 18% unable to return to work
  - 4% requiring total custodial care



# FIBRINOLYSIS IN ACUTE ISCHEMIC STROKE

## Stroke Recovery



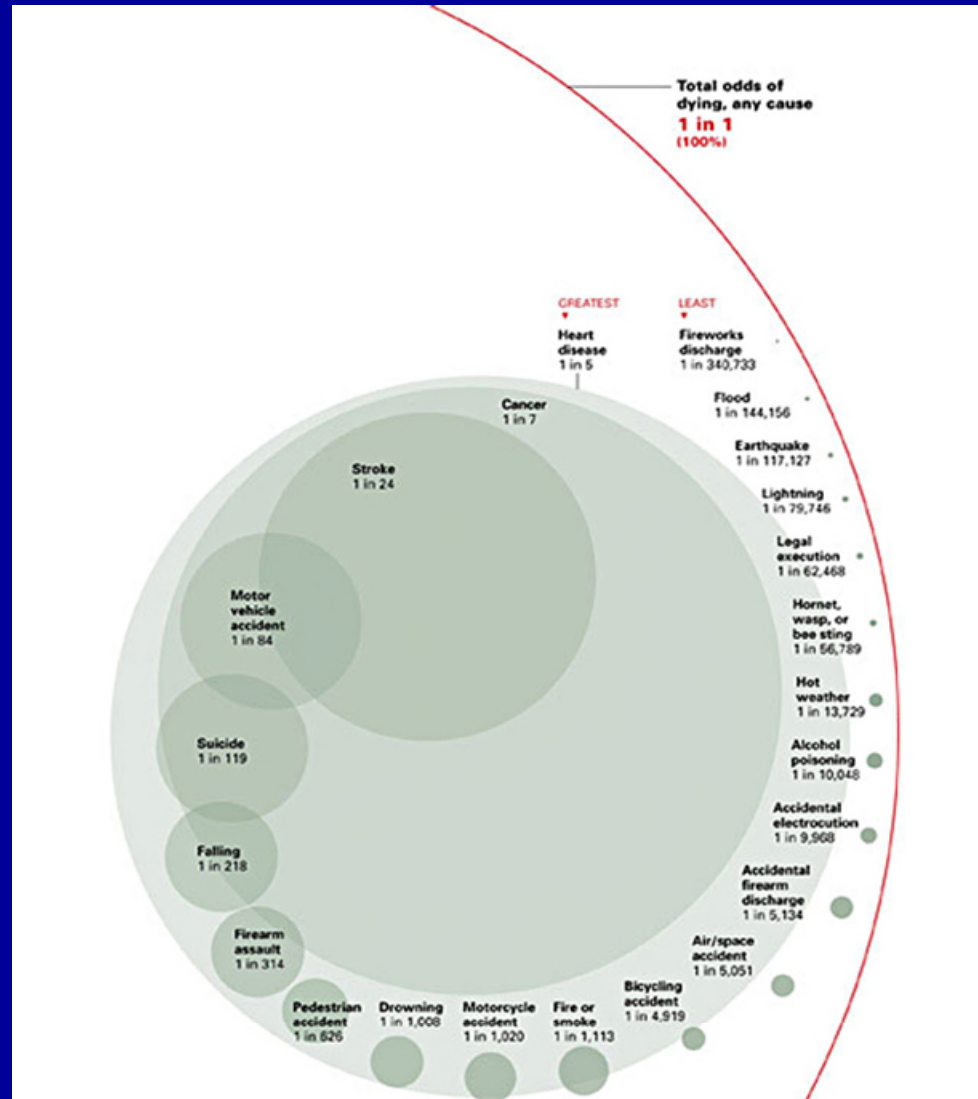
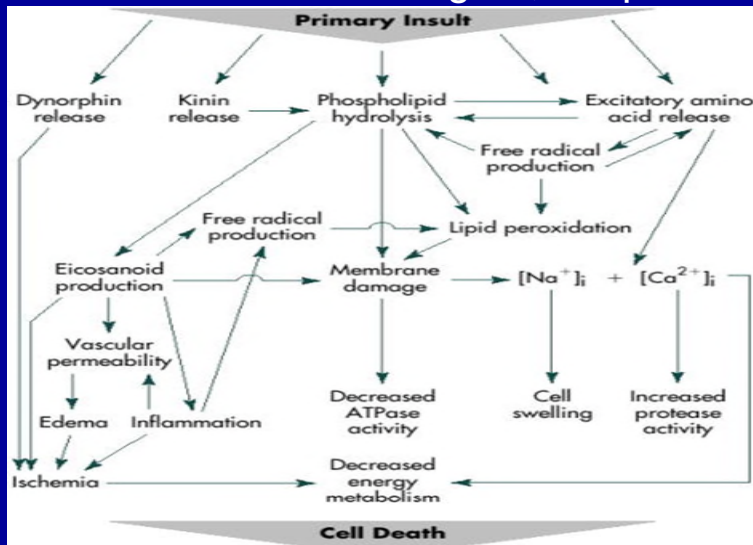
- 10% of stroke survivors recover completely
- 25% recover with minor neurologic impairments
- 40% recover with moderate to severe impairments requiring special care
- 10% require care in a skilled care or other long term care facility
- 15% die shortly following stroke (< 30d)
  - [www.stroke.org](http://www.stroke.org), National Stroke Association

# FIBRINOLYSIS IN ACUTE ISCHEMIC STROKE

## Cause of Death

### National Center for Health Care Statistics

- Stroke:
  - 800K annually (600K first-time)
  - 30-day mortality 15-20%
  - 3<sup>rd</sup> leading cause of death (1:17)
  - \$70B (\$180B by 2030)
- Search for stroke “Holy Grail/Magic Bullet” 1970s-80s
  - Neuroprotective agents, glutamate antagonists, anti-inflammatory agents, ion channel antagonists, CCBs, antioxidants, NMDA receptor antagonists, anticoagulants, ancrod, PEG-SOD, cooling helmets, steroids, free-radical scavengers, antiplatelets





# FIRBINOLYSIS IN ACUTE ISCHEMIC STROKE

## Landmark Paper

### The New England Journal of Medicine

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Volume 333

DECEMBER 14, 1995

Number 24

#### TISSUE PLASMINOGEN ACTIVATOR FOR ACUTE ISCHEMIC STROKE

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

**Abstract Background.** Thrombolytic therapy for acute ischemic stroke has been approached cautiously because there were high rates of intracerebral hemorrhage in early clinical trials. We performed a randomized, dou-

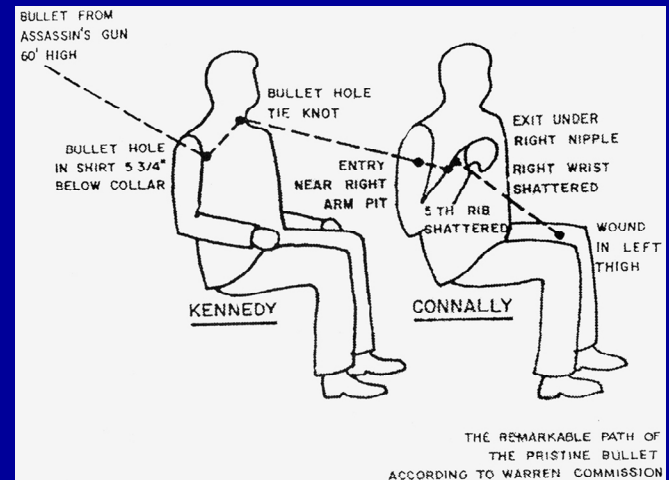
the percentages of patients with neurologic improvement at 24 hours, although a benefit was observed for the t-PA group at three months for all four outcome measures. In part 2, the long-term clinical benefit of t-PA predicted by



The NEW ENGLAND  
JOURNAL of MEDICINE

# FIBRINOLYSIS IN ACUTE ISCHEMIC STROKE

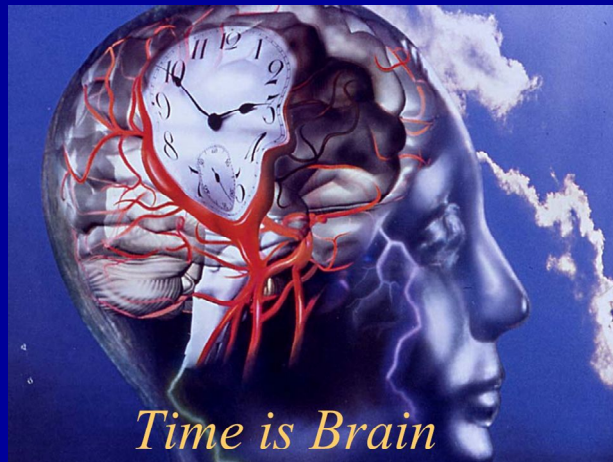
## Found: Holy Grail/Magic Bullet!!!





# FIBRINOLYSIS IN ACUTE ISCHEMIC STROKE

## Time is Brain?



- Neurologist Camilo Gomez coined:
  - “...time is brain...”
    - J Stroke Cerebrovasc Dis 1993;2(1)1
  - Borrowed from “...time is muscle...”
  - Promoted by AHA to support tPA for AMI in a 3-hr window
- NINDS proved that time was *not* brain
  - No statistical difference seen between IV tPA (0-3 hrs) and placebo measured first 24hrs
  - 12% difference mRS (0-1) at 90 days

# FIBRINOLYSIS IN ACUTE ISCHEMIC STROKE

## Brain Attack



- Bill Barsan (Univ Mich)/Brian Gibler (Univ Cinci), circa 1995
- Gleaned impact of this major disease process
- Univ Nebraska Stroke Team/ACEP volunteer Brain Attack Coalition
- 1 pt/16 months (35,000 annual visit Level I Trauma Center)

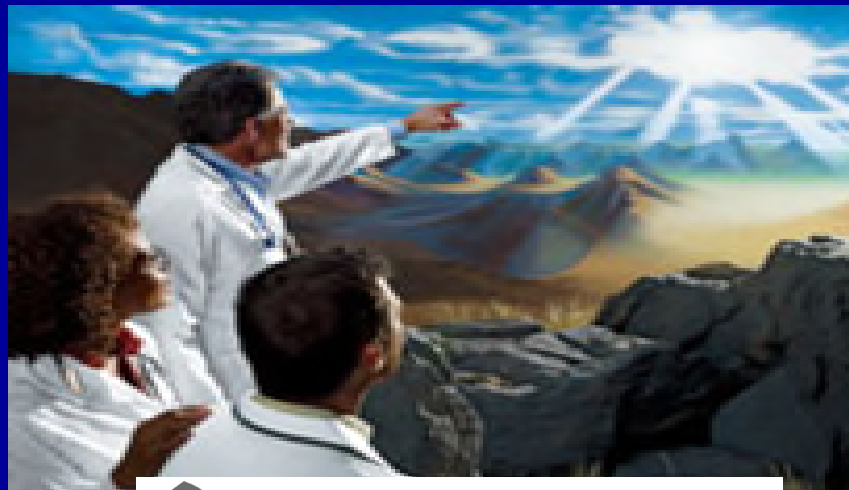




# FIBRINOLYSIS IN ACUTE ISCHEMIC STROKE

## Things That We Think We Know That Work That Don't or Produce Harm

- Medical Truths 1960s:
  - Lead is safe
  - Cigarettes don't cause disease
  - Homosexuality is a mental illness
- Physiological reasoning:
  - Pathway;  
neurohormonal  
mechanism
  - e.g., corticosteroids
  - But it doesn't work



# FIBRINOLYSIS IN ACUTE ISCHEMIC STROKE

## Things That We Think We Know That Work That Don't or Produce Harm (...almost)

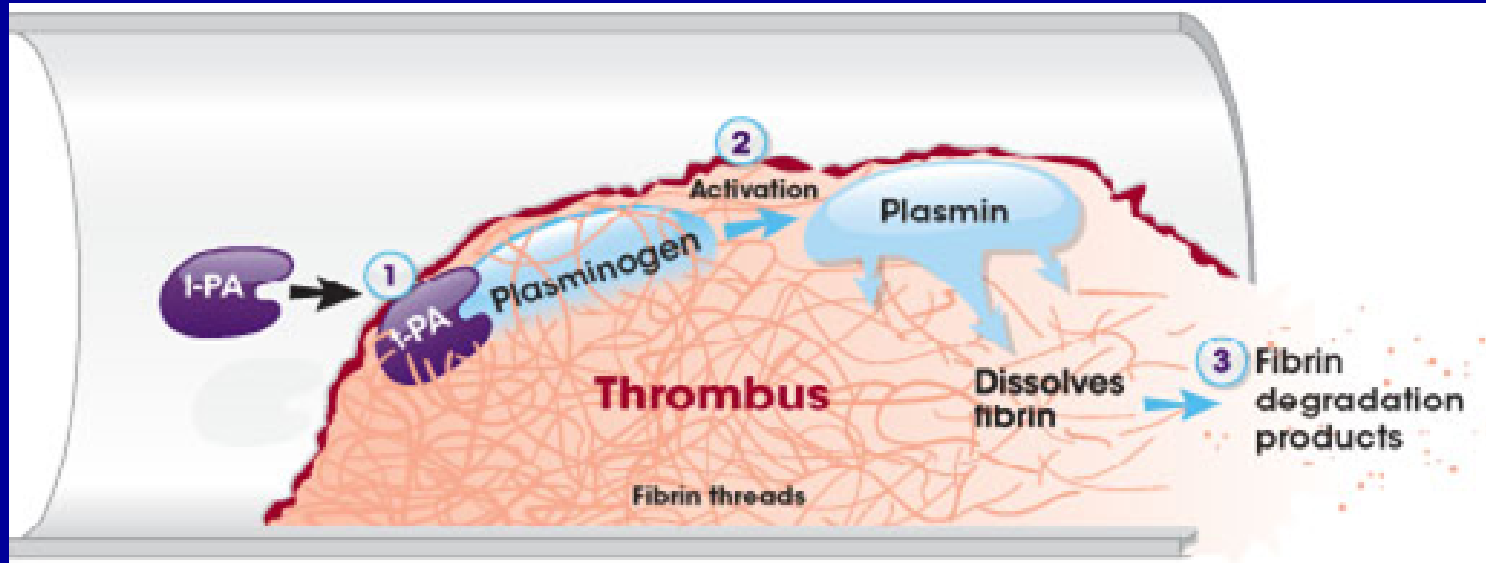
- Lipid lowering drugs
- CPR/ACLS
- Natrecor (nesiritide)
- Colonoscopy
- Mammography
- Tight control of glc in Type II DM
- PSA for prostate cancer
- Prostate cancer surgery
- Injectable NSAIDs
- Glycoprotein inhibitors
- Steroids in blunt spinal cord injury
- Pap smears
- Physical exams
- Lumbar spine surgery
- Coronary Artery Bypass Grafting
- Percutaneous Coronary Intervention
- Antibiotics for throat infections
- Antibiotics for otitis media
- Antibiotics for acute bronchitis
- Biphasic defibrillators
- Electronic fetal monitoring
- Rapid Response Teams
- Off-label Epogen
- Many adjuvant cancer treatments
- Most lab tests (surrogate markers)
- Cox-2 inhibitors
- Xigris (Drotrecogin alpha; recombinant protein C)
- HRT in postmenopausal women
- Tonsillectomy





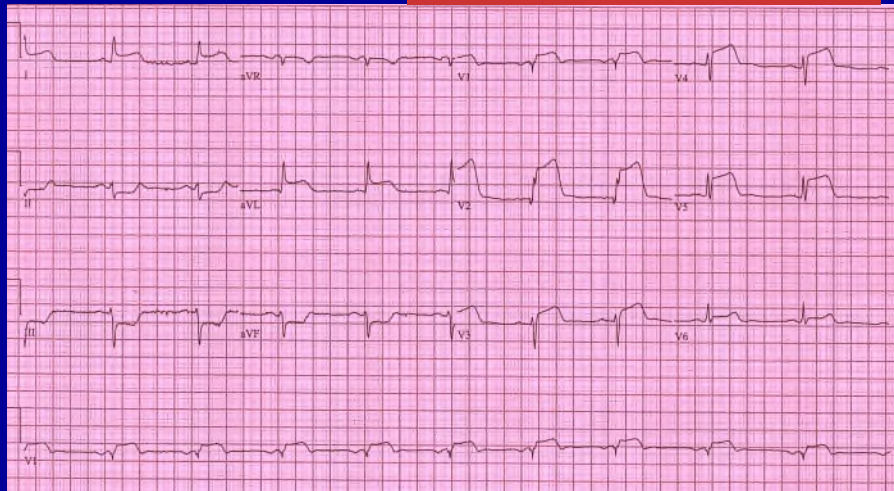
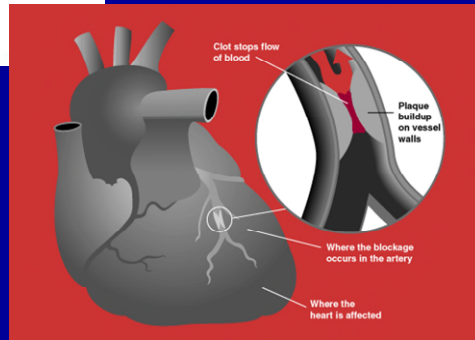
# FIBRINOLYSIS IN ACUTE ISCHEMIC STROKE

## tPA (Alteplase): Mechanism of Action



# FIBRINOLYSIS IN ACUTE ISCHEMIC STROKE

## Fibrinolysis in STEMI



- Unambiguous presentation
- Gold standard surrogate marker
- Inclusion/exclusion criteria
- Successful treatment signaled by resolution of symptoms, ECG S-T segments, and transient reperfusion arrhythmia (AIVR)
- Included heparin chaser
- Abort an MI "...everybody knows that..."
- Mortality benefit? 2%



# FIBRINOLYSIS IN ACUTE ISCHEMIC STROKE

## Published Literature Studies

- Efficacy studies:
  - RCTs in hands of experts
  - Academic Centers
  - Well-controlled conditions, inclusions, exclusions
  - Research Coordinators
  - Statisticians
  - Funding
- Effectiveness studies:
  - Observational studies in hands of the public
  - Protocol violations





# FIBRINOLYSIS IN ACUTE ISCHEMIC STROKE

## 13 Randomized Controlled Efficacy Trials

- **National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group.** *Tissue plasminogen activator for acute ischemic stroke (I and II).* *N Engl J Med.* 1995;333:1581-1587
- Donnan GA, Davis SM, Chambers BR, et al. Streptokinase for acute ischemic stroke with relationship to time of administration: Australian Streptokinase (ASK) Trial Study Group. *JAMA.* 1996; 276:961-966.
- Multicentre Acute Stroke Trial–Italy (MAST-I) Group. Randomised controlled trial of streptokinase, aspirin, and combination of both in treatment of acute ischaemic stroke. *Lancet.* 1995;346:1509-1514.
- The Multicenter Acute Stroke Trial–Europe Study Group. Thrombolytic therapy with streptokinase in acute ischemic stroke. *N Engl J Med.* 1996;335:145-150.
- Hacke W, Kaste M, Fieschi C, et al. Intravenous thrombolysis with recombinant tissue plasminogen activator for acute hemispheric stroke. The European Cooperative Acute Stroke Study (ECASS). *JAMA.* 1995;274:1017-1025.
- Hacke W, Kaste M, Fieschi C, et al. Randomised double-blind placebo-controlled trial of thrombolytic therapy with intravenous alteplase in acute ischaemic stroke (ECASS II). Second European-Australasian Acute Stroke Study Investigators. *Lancet.* 1998;352:1245.
- Clark WM, Albers GW, Madden KP, et al. Thrombolytic Therapy in Acute Ischemic Stroke Study Investigators. The rtPA (alteplase) 0-to 6-hour acute stroke trial, part A (A0276g): results of a double-blind, placebo-controlled, multicenter study. *Stroke.* 2000;31:811-816.
- Clark WM, Wissman S, Albers GW, et al. Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke Study Investigators. Recombinant tissue-type plasminogen activator (alteplase) for ischemic stroke 3 to 5 hours after symptom onset. The ATLANTIS Study: a randomized controlled trial. *JAMA.* 1999;282:2019-2026.
- Albers GW, Clark WM, Madden KP, et al. ATLANTIS trial: results for patients treated within 3 hours of stroke onset. *Stroke.* 2002; 33:493-496.
- **Hacke W, Kaste M, Bluhmki E, et al. ECASS Investigators.** *Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke (ECASS III).* *N Engl J Med.* 2008;359:1317-1329.

# FIBRINOLYSIS IN ACUTE ISCHEMIC STROKE

## Randomized Controlled Efficacy Trials

TRIAL	JOURNAL	TIME TO RX	PRIMARY BENEFIT	HARM
MAST – Italy (n=622)	Lancet 1995	< 6 hrs	None	Increased Early Death
ECASS – I (n=620)	JAMA 1995	< 6 hrs	None	Benefit Not Outweighed by Risk
NINDS – I (n=291)	NEJM 1995	< 3 hrs	None	No difference
MAST – Eu (n=310)	NEJM 1996	< 6 hrs	None	Stopped Early Due to Harm
ASK (n=340)	JAMA 1996	<4 hrs	None	Stopped early due to harm
ECASS – II (n = 800)	Lancet 1998	< 6 hrs	None	No difference
ATLANTIS – B (n=613)	JAMA 1999	3-4 hrs	None	Stopped early due to harm
ATLANTIS – A (n=142)	Stroke 2000	< 6 hrs	None	Stopped early due to harm
DIAS – 2 (n=193)	Lancet 2009	3-9 hrs	None	No difference
IST – 3 (n=3035)	Lancet 2012	< 6 hrs	None	No difference
NINDS – II (n=333)	NEJM 1995	< 3 hrs	12% absolute benefit mRS at 90d	Increased ICH
ECCAS – III (n=821)	NEJM 2008	(3-4.5 hrs)	7% absolute benefit OR=1.34 (95% 1.02-1.76)	Increased ICH

# FIBRINOLYSIS IN ACUTE ISCHEMIC STROKE

## Randomized Controlled Efficacy Trials

### *The* NEW ENGLAND JOURNAL *of* MEDICINE

#### Thrombolysis with Alteplase 3 to 4.5 Hours after Acute Ischemic Stroke

***Hacke W, Kaste M, Bluhmki E, et al. ECASS Investigators. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke (ECASS III). N Engl J Med. 2008;359:1317-1329.***

- ECASS I and II: both negative
- Manufacturer supported, double-blinded RCT, all authors with extensive ties to industry
- 90-days favorable outcome, Alteplase vs placebo
- 7% absolute benefit (1:14), different metric than 3-4% NINDS
- ICH 27% for Alteplase vs 17.6% for placebo
- Not FDA approved
- 3-4.5hrs captures 10X number of patients to treat



# FIBRINOLYSIS IN ACUTE ISCHEMIC STROKE

## Randomized Controlled Efficacy Trials

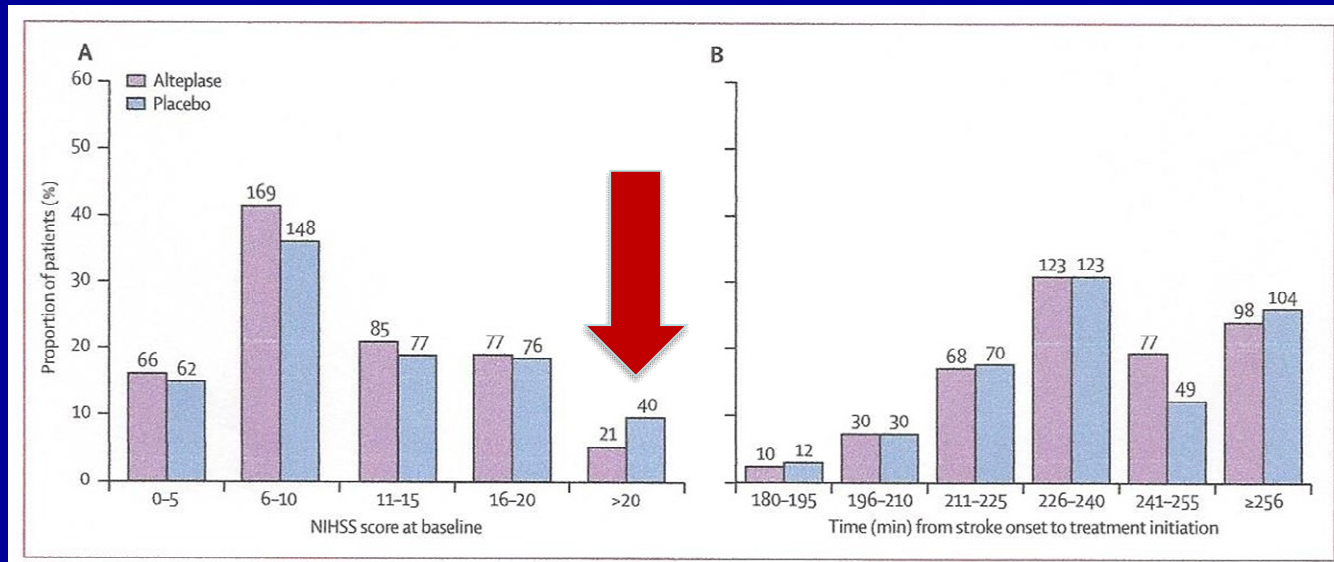
Stroke treatment with alteplase given 3·0–4·5 h after onset of acute ischaemic stroke (ECASS III): additional outcomes and subgroup analysis of a randomised controlled trial

Erich Bluhmki, Ángel Chamorro, Antoni Dávalos, Thomas Machnig, Christophe Sauce, Nils Wahlgren, Joanna Wardlaw, Werner Hacke

### Summary

**Background** In the European Cooperative Acute Stroke Study III (ECASS III), alteplase administered 3·0–4·5 h after the onset of stroke symptoms resulted in a significant benefit in the primary endpoint (modified Rankin scale [mRS])

**Findings** 418 patients were assigned to alteplase and 403 to placebo. Although not significant in every case, all additional endpoints showed at least a clear trend in favour of alteplase. Alteplase was effective in various subgroups, including older patients (<65 years: odds ratio 1·61, 95% CI 1·05–2·48; ≥65 years: 1·15, 0·80–1·64;  $p=0·230$ ) and the effectiveness



# The New England Journal of Medicine

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Volume 333

DECEMBER 14, 1995

Number 24

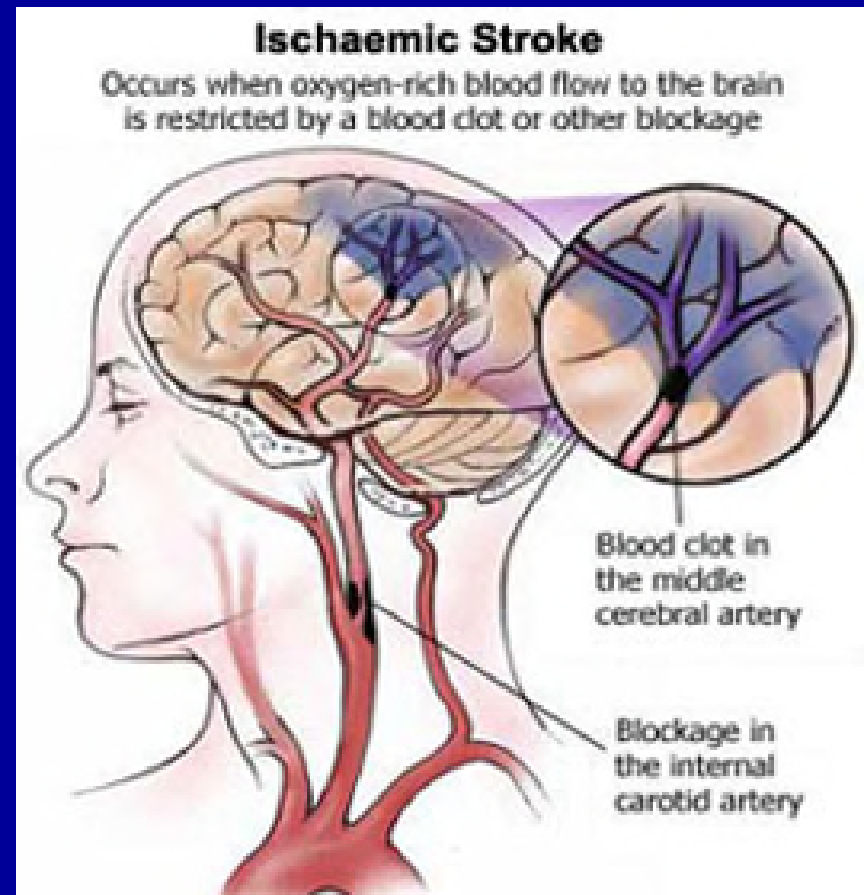
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**Abstract Background.** Thrombolytic therapy for acute ischemic stroke has been approached cautiously because of the high rates of intracerebral hemorrhage.

the percentages of patients with neurologic improvement at 24 hours, although a benefit was observed for the t-PA group at three months for all four outcome measures.

- Stroke: 800K/yr, 15-20% 30-day mortality
- 13 randomized controlled trials
- 1 positive study:
  - NINDS Trial, N Engl J Med, 1995 Dec; 333(24): 1581-1587
  - Functional improvement at 90 days only (no mortality benefit)
- We only want to believe the one study that shows it works
- 90-day reduction in bad outcome:
  - 30% (relative reduction)
  - 12% (absolute reduction), 88% no benefit (NNT 1:8-9)
  - tPA ICH vs placebo 6.4% vs 0.6%; (NNH 1:18)
  - NNT to benefit vs NNT to harm



# FIRINOLYSIS IN ACUTE ISCHEMIC STROKE

## Effectiveness Studies

- Cleveland 2000 (JAMA)
- 29 community hospitals
- 3948 stroke admits, 70 (1.8%) tPA
- 50% protocol violators
- ICH 22%
- Mortality 5.1% vs 15.7% w/ tPA





# FIRINOLYSIS IN ACUTE ISCHEMIC STROKE

## Effectiveness Studies

- Thrombolysis for acute ischemic stroke
- Canadian Alteplase for Stroke Effectiveness Study (CASES) Investigators
- CASES 2005 (CMAJ)
- Prospective observational, n=1135
- 14% protocol violators
- 16% lost to follow-up
- 32% < 2 mRS
- 37% < 2 mRS “adjusted”
- 5% symptomatic ICH
- 22% mortality at 90d
- “...tPA is safe and effective...”



# FIRINOLYSIS IN ACUTE ISCHEMIC STROKE

## Effectiveness Studies

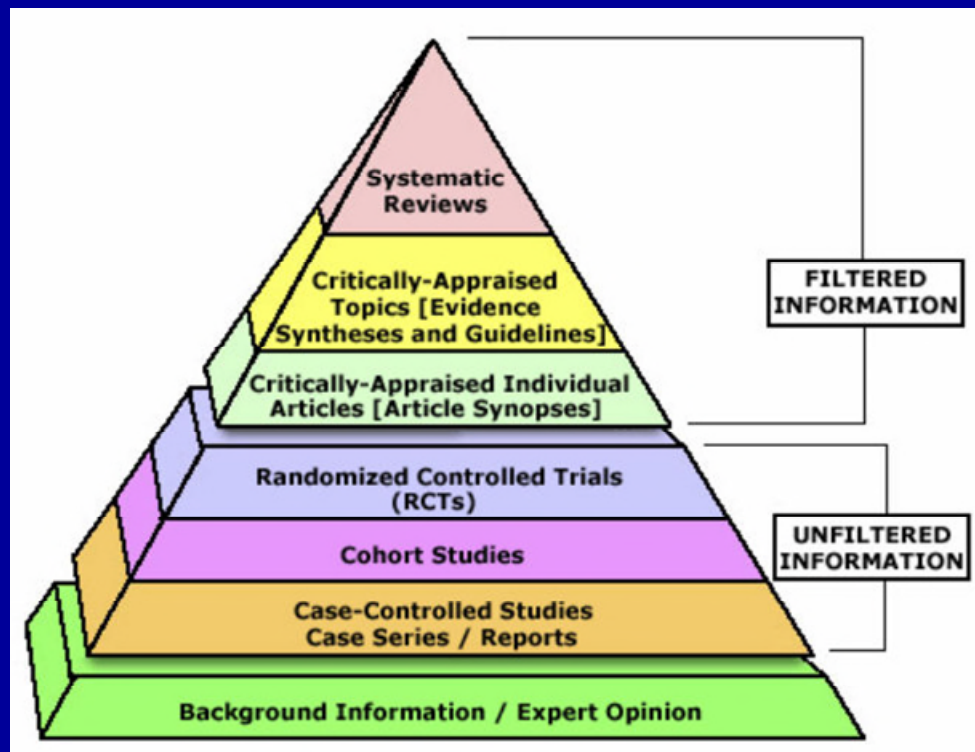


- SITS:MOST (2007) Lancet
  - Prospective observational, n=6483, 483 centers
  - 7% ICH at 7 days
  - 11% mortality at 90d
  - “...tPA is safe and effective...:
  - Excluded protocol violations
  - Outcome data missing from > 15%

# FIBRINOLYSIS IN ACUTE ISCHEMIC STROKE

## Cochrane Collaboration

- JM Wardlaw, et al, 2009:
- “...the available data do not provide sufficient evidence to determine the magnitude of treatment effect, the duration of the therapeutic time window, the optimum agent, dose or route of administration...”



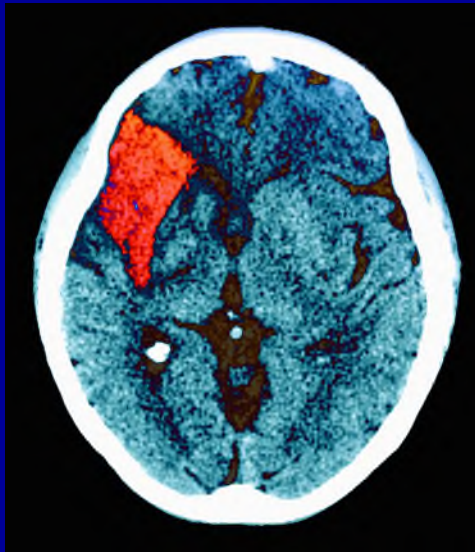


# FIBRINOLYSIS IN ACUTE ISCHEMIC STROKE

*For Many Strokes, There's an Effective Treatment.  
Why Aren't Some Doctors Offering It?*



- For The NY Times, Gina Kolata, March 26, 2018
- It was one of those findings that would change medicine, Dr. Christopher Lewandowski thought
- For years, doctors had tried — and failed — to find a treatment that would preserve the brains of stroke patients
- The task was beginning to seem hopeless: Once a clot blocked a blood vessel supplying the brain, its cells quickly began to die
- Patients and families could only pray the damage would not be too extensive



**The New York Times**

# FIBRINOLYSIS IN ACUTE ISCHEMIC STROKE

*For Many Strokes, There's an Effective Treatment.  
Why Aren't Some Doctors Offering It?*

- But then a large federal clinical trial proved that a so-called clot-buster drug, tissue plasminogen activator (tPA) could prevent brain injury after a stroke, by opening up the blocked vessel. Dr. Lewandowski, an emergency medicine physician at Henry Ford Health System in Detroit and the trial's principal investigator, was ecstatic.
- *“We felt the data was so strong we didn't have to explain it” in the published report, he said.*
- He was wrong.



# FIBRINOLYSIS IN ACUTE ISCHEMIC STROKE

## Reanalysis of NINDS Data

NEUROLOGY/ORIGINAL RESEARCH

### A Graphic Reanalysis of the NINDS Trial

Jerome R. Hoffman, MD, MA  
David L. Schrager, MD, MPH

From the Department of Emergency Medicine, University of California School of Medicine, Los Angeles, CA.

**Study objective:** Reports of clinical trials typically present only a fraction of the available data, at times hampering interpretation of their meaning. The initial report of the National Institute of Neurologic Diseases and Stroke (NINDS) trials of tissue plasminogen activator in acute ischemic stroke is an example of this phenomenon.

**Methods:** We used the original data from the NINDS trials to create graphs showing the effect of treatment on neurologic function in all 624 individual patients in the trial. Our goal was to show detailed graphics of the 90-day outcomes, stratified on relevant confounders and effect modifiers.

**Results:** Final outcomes were highly dependent on stroke severity. In many graphs, the small difference between groups favored tissue plasminogen activator, particularly when baseline NIHSS score was between roughly 5 and 22. These differences diminish or disappear when 90-day change in NIHSS is graphed. Our graphs fail to support the time-is-brain hypothesis.

**Conclusion:** Our graphical method of presenting the NINDS trial results provides more detail than was conveyed in the original report and empowers readers to reach their own conclusions about the trial's meaning. Outcomes for placebo and treatment limbs are sufficiently similar that larger trials, conducted under the same conditions as the NINDS trial, are needed to determine which patients benefit from this therapy. [Ann Emerg Med. 2009; 54:329-336.]

*Annals of Emergency Medicine*  
*An International Journal*



# FIBRINOLYSIS IN ACUTE ISCHEMIC STROKE

## Reanalysis of NINDS Data

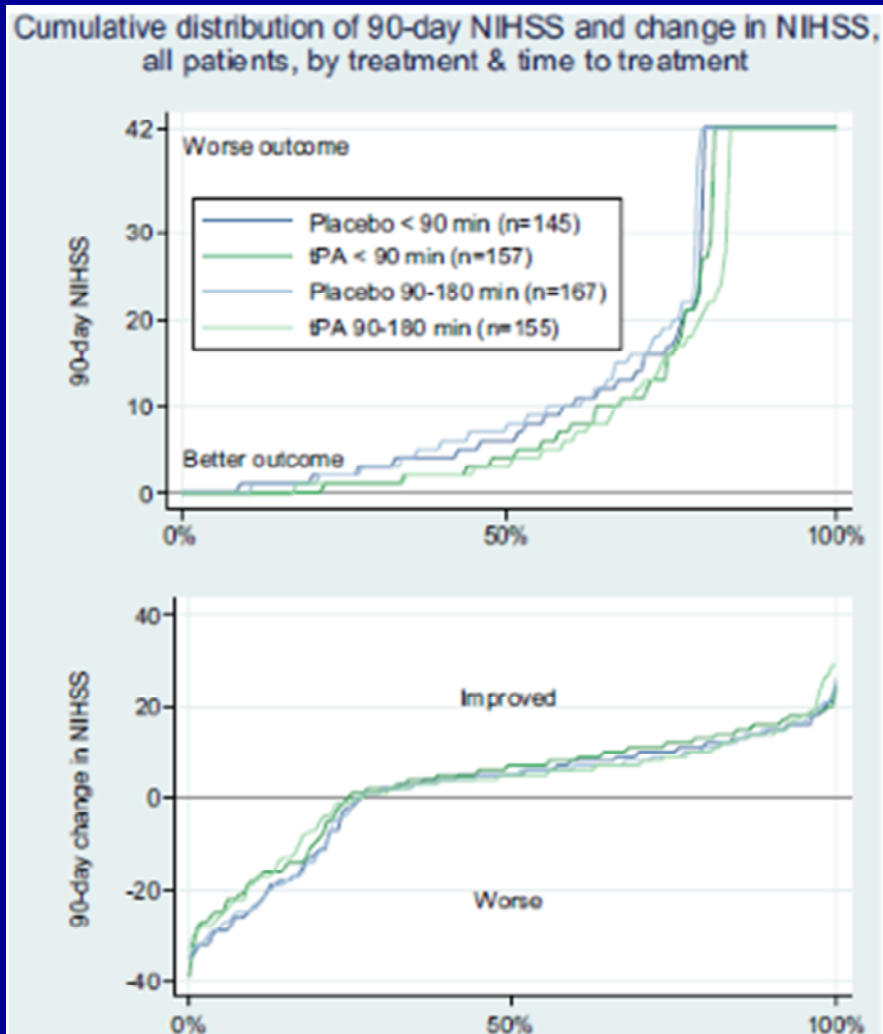
- **Study objective:** Reports of *clinical trials typically present only a fraction of the available data*, hampering interpretation. Initial report of NINDS trial is an example of this phenomenon.
- **Methods:** Original data from NINDS of 624 patients. Goal to show detailed graphics of 90-day outcomes, stratified on relevant confounders and effect modifiers.
- **Results:** *Final outcomes were highly dependent on stroke severity.* The small difference between groups favored fibrinolysis, particularly when baseline NIHSS score was between roughly 5 and 22. Differences diminish or disappear when 90-day change in NIHSS is graphed. **Graphs fail to support the time-is-brain hypothesis.**
- **Conclusion:** *Graphical method provides more detail than conveyed in the original report* and empowers readers to reach their own conclusions about the trial's meaning. **Outcomes for placebo and treatment limbs are sufficiently similar** that larger trials, conducted under the same conditions as the NINDS trial, are needed to determine which patients benefit from this therapy.

Ann Emerg Med. 2009; 54:329-336

Annals of Emergency Medicine  
*An International Journal*

# FIBRINOLYSIS IN ACUTE ISCHEMIC STROKE

## NINDS Redux



- NIHSS single greatest determinate of 90-day NINDS score
- Those who live can expect moderate improvement from baseline NIHSS score
- Graphs not identical, but differences quite small
- By chance, tPA group randomized to milder strokes, lower NIHSS scores with a preponderance in 0-90 min group

# FIBRINOLYSIS IN ACUTE ISCHEMIC STROKE

## NINDS Redux

Percentage of patients (N = 320) in the 91 to 180-minute subgroups with a specific baseline National Institutes of Health Stroke Scale (NIHSS) score\*

<b>Baseline NIHSS score</b>	<b>tPA-treated patients, % (n = 153)</b>	<b>Patients given placebo, % (n = 167)</b>
0-5	19.0	4.2
6-10	24.2	27.5
11-15	17.0	21.0
16-20	21.6	19.8
>20	18.3	27.5
tPA = tissue plasminogen activator		

More patients treated with alteplase than those treated with placebo had mild strokes at baseline in the 91-180 minute group, while those with the worst strokes were more likely to be in the placebo group. Mean scores overall were also lower at baseline for patients given alteplase

<b>Baseline NIHSS scores</b>	<b>Alteplase (%)</b>	<b>Placebo (%)</b>
0-5	19.0	4.2
>20	18.3	27.5

Marler JR, et al. Early stroke treatment associated with better outcome: the NINDS rt-PA stroke study. Neurology 2000; 55:1649.



# Position Statement: tPA for Stroke

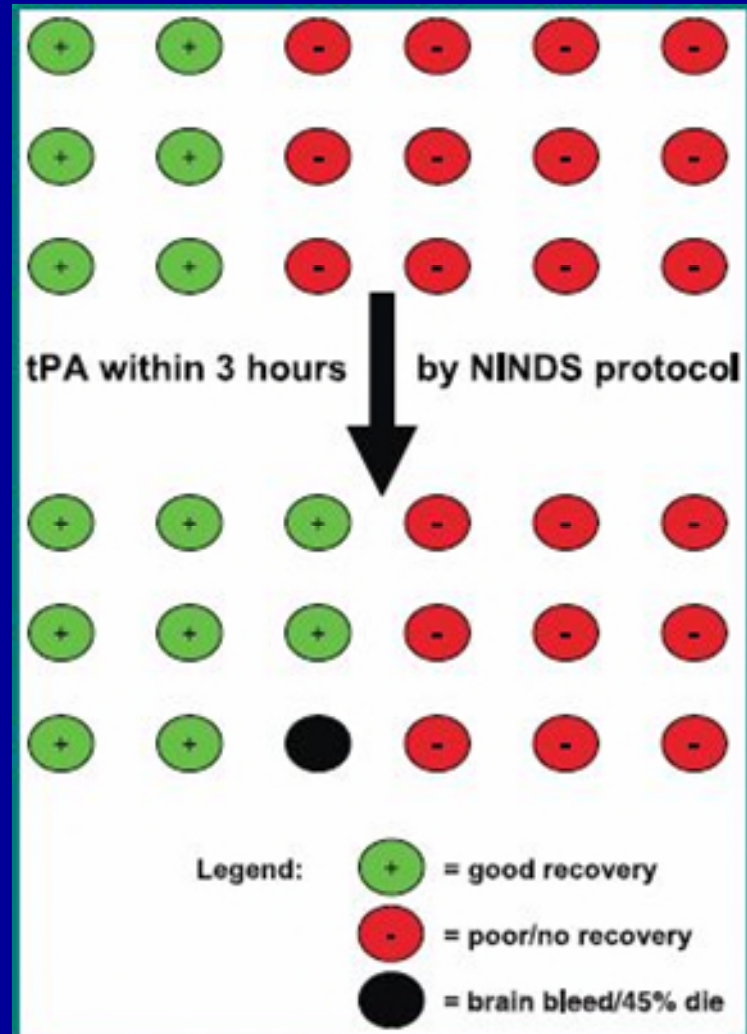
## Potential Benefit, Risk and Alternatives

### American Academy of Emergency Medicine



NNT = 8-9

NNH = 18



# FIBRINOLYSIS IN ACUTE ISCHEMIC STROKE

## Modified Rankin Scale (mRS)

- ***0 = No symptoms at all***
- ***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, able to look after own affairs without assistance**
- **3 = Moderate disability, needs some help but can walk without assistance**
- **4 = Moderately severe disability, unable to walk without assistance, unable to attend to own bodily needs without assistance**
- **5 = Severe disability, bedridden, incontinent, requiring constant nursing care**
- **6 = Dead**

# FIBRINOLYSIS IN ACUTE ISCHEMIC STROKE

## Bias





# FIBRINOLYSIS IN ACUTE ISCHEMIC STROKE

## Bias

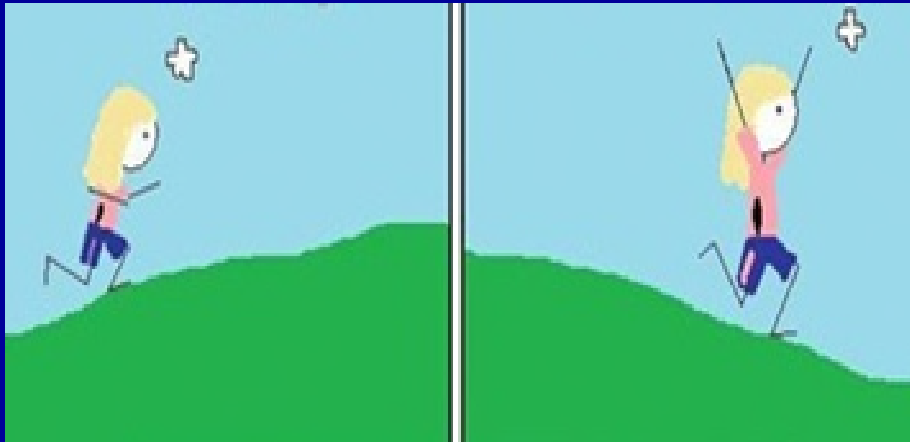


# FIBRINOLYSIS IN ACUTE ISCHEMIC STROKE

## Bias



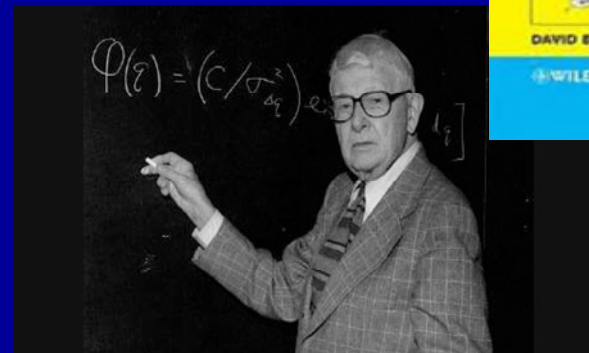
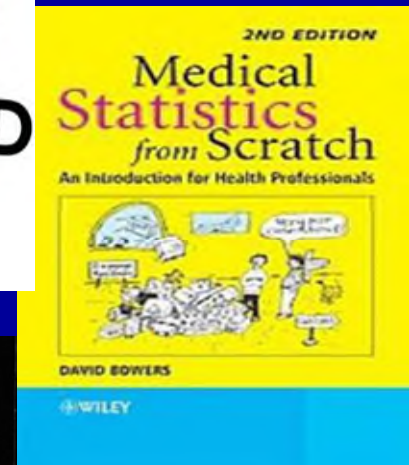
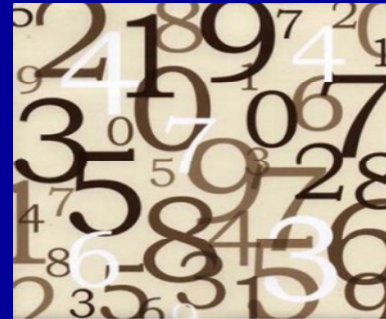
- Bias:
  - Prejudgment, prejudice, preconceived notions
- Clinical epidemiology, bias:
  - “...the nonrandomized introduction of error into the results of the study...”
- Study of foot speed in two groups:
  - Uphill
  - Downhill



# FIBRINOLYSIS IN ACUTE ISCHEMIC STROKE

## Randomized Controlled Trials

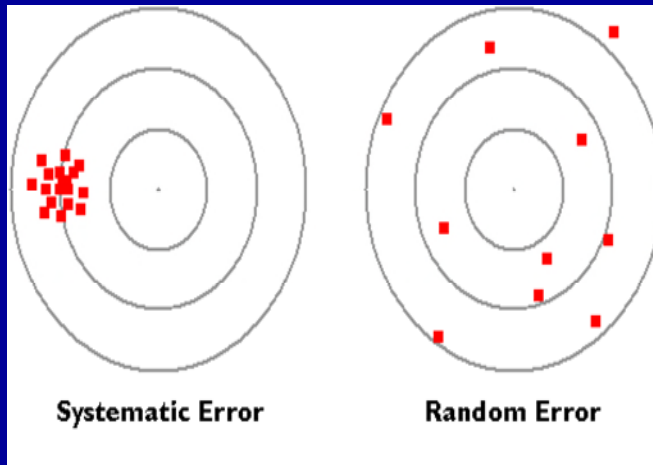
- Bias – introduction of nonrandomized error
- Chance
- Studied 1,000 patients, where the bad outcome is 10%
- Same medicine:
  - Drug A and Drug B
- Give same drug to two groups, compare medicine against itself
- Measure 10 outcomes
- 99% chance one outcome would not only be statistically better than itself, but at least twice as good as itself
- 5% chance one outcome will show one drug or the other 10 times better than itself
- 5% ( $p \leq 0.05$ ) is “significant”
  - RA Fisher (1925) , Edinburgh
  - 2-SD  $<X>$





# FIBRINOLYSIS IN ACUTE ISCHEMIC STROKE

## Bias



- Introduced bias for two reasons:
  - 1) Biased, cheating
  - 2) Experimental errors introduced, can't get everything right – age, sex, medications, genes, underlying medical issues, compliance, follow-up, etc.
- Researcher can't control all variables
- Chemistry, a test tube, reagents under controlled conditions, everything same except one thing being examined
- In medicine, can't control everything
- Control running uphill or downhill, too many uncontrolled variables
- Can't ensure everybody is same age, same weight, same genetics – many variables can affect the outcome
- Some bias in even the best studies
- Researcher's job to minimize bias



# FIBRINOLYSIS IN ACUTE ISCHEMIC STROKE

## Capture/Treat Most Acute Stroke Patients

- Lengthen treatment windows 9hrs
- Wake-up stroke (8-28%, 1:7)
- Minor stroke
- Rapidly improving stroke
- Pregnancy
- DOAC/coumadin
- Mobile CT/Stroke Units
- Age > 90 years
  - Poor QoL
  - Dementia



# FIRBINOLYSIS IN ACUTE ISCHEMIC STROKE

## 4.5 – 9hrs

- Thrombolysis guided by perfusion imaging up to 9 hours after onset of stroke. N Engl J Med 2019 May 9; 380:1795.
- Image-guided intravenous alteplase for stroke – Shattering a time window. N Engl J Med 2019 May 9; 380:1965.
- Extending Thrombolysis to 4.5-9 hrs and wake-up stroke using perfusion imaging. Lancet 2019 May 32019; [e-pub].
- Late thrombolysis for stroke works, but how do we do it? Lancet 2019 May 21; [e-pub].
- MRI-guided thrombolysis for stroke with unknown time of onset. N Engl J Med 2018 May 16; [e-pub].
- MRI-guided intravenous alteplase for stroke – Still stuck in time. N Engl J Med 2018 May 16; [e-pub].



# FIRBINOLYSIS IN ACUTE ISCHEMIC STROKE

## Wake-Up Stroke

### *The* NEW ENGLAND JOURNAL *of* MEDICINE

ESTABLISHED IN 1812

AUGUST 16, 2018

VOL. 379 NO. 7

## MRI-Guided Thrombolysis for Stroke with Unknown Time of Onset

G. Thomalla, C.Z. Simonsen, F. Boutitie, G. Andersen, Y. Berthezene, B. Cheng, B. Cheripelli, T.-H. Cho, F. Fazekas, J. Fiehler, I. Ford, I. Galinovic, S. Gellissen, A. Golsari, J. Gregori, M. Günther, J. Guibernau, K.G. Häusler, M. Hennerici, A. Kemmling, J. Marstrand, B. Modrau, L. Neeb, N. Perez de la Ossa, J. Puig, P. Ringleb, P. Roy, E. Scheel, W. Schonewille, J. Serena, S. Sunaert, K. Villringer, A. Wouters, V. Thijs, M. Ebinger, M. Endres, J.B. Fiebach, R. Lemmens, K.W. Muir, N. Nighoghossian, S. Pedraza, and C. Gerloff, for the WAKE-UP Investigators\*

### ABSTRACT

#### BACKGROUND

Under current guidelines, intravenous thrombolysis is used to treat acute stroke only if it can be ascertained that the time since the onset of symptoms was less than 4.5 hours. We sought to determine whether patients with stroke with an unknown time of onset and features suggesting recent cerebral infarction on magnetic resonance imaging (MRI) would benefit from thrombolysis with the use of intravenous alteplase.

#### METHODS

In a multicenter trial, we randomly assigned patients who had an unknown time

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Thomalla at Klinik und Poliklinik für Neurologie, Universitätsklinikum Hamburg-Eppendorf, Martinistrasse 52, D-20246 Hamburg, Germany, or at [thomalla@uke.de](mailto:thomalla@uke.de); or to Dr. Gerloff at [gerloff@uke.de](mailto:gerloff@uke.de).



# FIRBINOLYSIS IN ACUTE ISCHEMIC STROKE

## Wake-Up Stroke

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G. Thomalla, C.Z. Simonsen, F. Boutitie, G. Andersen, Y. Berthezene, B. Cheng, B. Cheripelli, T.-H. Cho, F. Fazekas,

#### RESULTS

The trial was stopped early owing to cessation of funding after the enrollment of 503 of an anticipated 800 patients. Of these patients, 254 were randomly assigned to receive alteplase and 249 to receive placebo. A favorable outcome at 90 days was reported in 131 of 246 patients (53.3%) in the alteplase group and in 102 of 244 pa-

#### RESULTS

##### CHARACTERISTICS OF THE PATIENTS

The steering committee stopped enrollment on June 30, 2017, on the basis of the anticipated cessation of funding from the European Union.

sis for the treatment of stroke.<sup>21</sup> The trial was stopped early because of a discontinuation of funding and enrolled fewer patients than planned. This factor limits the interpretation of the safety results because the observed trend toward a higher rate of death in the alteplase group may have become significant with a larger sample size.

# FIBRINOLYSIS IN ACUTE ISCHEMIC STROKE

## EXTEND Trial: 9 Hrs LKW

- The EXTEND trial: neurological deficits decreased with thrombolysis up to 9 hours after stroke onset, The Lancet, [e-pub] May 21, 2019
- Patients presenting between 4.5 and 9 hours after stroke onset with viable brain tissue who received thrombolytic therapy had better neurological outcomes compared to those receiving placebo (**35.4 vs 29.5%; 6%**)
- Symptomatic intracranial hemorrhage occurred in a higher number of patients in the thrombolysis group compared to placebo group (**6% vs 1%**)
- Evidence Rating Level: 1 (Excellent)



# FIBRINOLYSIS IN ACUTE ISCHEMIC STROKE

## Nondisabling/Minor Stroke

### PRISMS Trial: ASA vs tPA

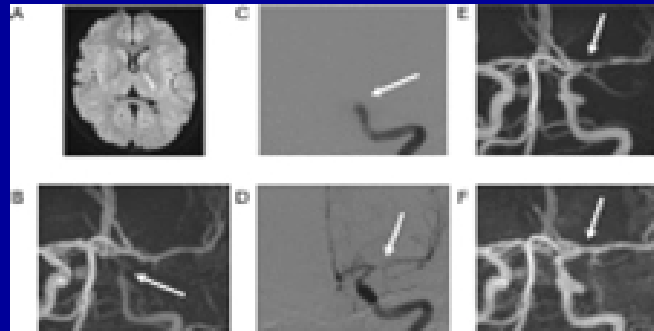
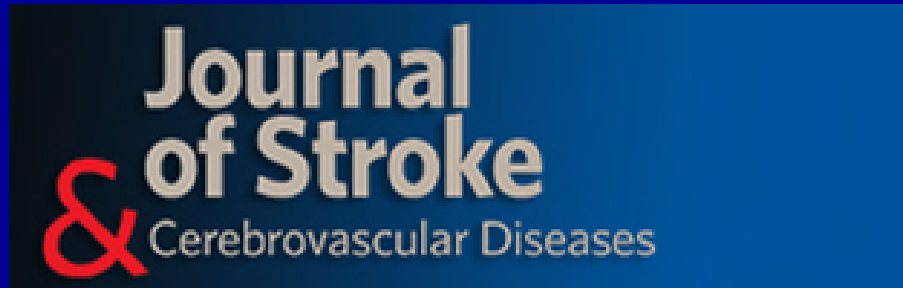
Effect Of Alteplase vs Aspirin On Functional Outcome For Patients With Acute Ischemic Stroke And Minor Nondisabling Neurologic Deficits: The PRISMS Randomized Clinical Trial Khatri, P., et al, JAMA 320(2):156, July 10, 2018

- Guidelines vague low NIHSS scores (0-5)
- 20-30% significant disability at 90 days
- **Alteplase vs ASA with mild stroke (NIHSS 0-5)**
- **“Not clearly disabling” by treating physician**
- RCT IV alteplase or 325 mg aspirin or placebos
- Primary outcome mRS 0-1 at 90 days (minimal disability)
- ***Terminated early, slow enrollment, sponsoring drug company withdrew***
- Enrolled 313 patients over 2.5 years, mean NIHSS score was 2
- **78.2% alteplase good neurologic outcome vs 81.5% of ASA group (NS)**
- **Five in alteplase (3.3%) symptomatic ICH within 36 hrs (0 in ASA group)**
- Serious adverse events in 26% alteplase group vs 13% in aspirin group
- ***Due to under-powering and stopping early*** – Bayesian analysis demonstrated < 25% chance alteplase could offer any benefit and less than 2% chance of benefit of at least 6% (1:16).



# FIBRINOLYSIS IN ACUTE ISCHEMIC STROKE

## Pregnancy



- Uneventful Pregnancy and Delivery, After Thrombolysis Plus Thrombectomy for Acute Ischemic Stroke: Case Study and Literature Review
  - Department of Neurology, Japanese Red Cross Musashino Hospital, Musashino, Tokyo, Japan
  - Journal of Stroke and Cerebrovascular Diseases, Vol. 28, No. 1 (January), 2019: pp 70-75



# FIBRINOLYSIS IN ACUTE ISCHEMIC STROKE

## Pregnancy

### PHARMACOTHERAPY

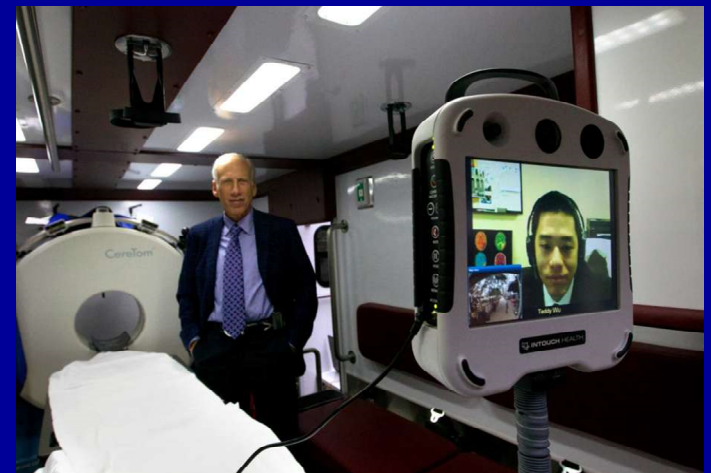
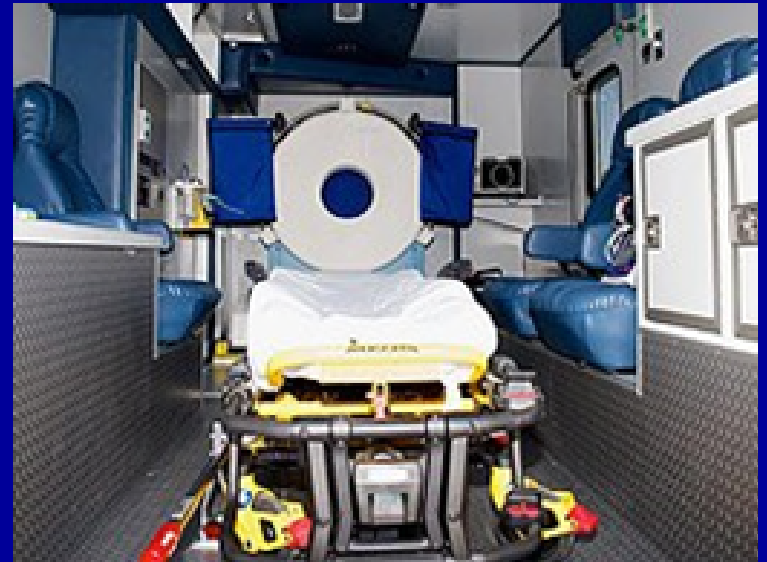
accp  
American College of  
Clinical Pharmacy

- **Alteplase Therapy for Acute Ischemic Stroke in Pregnancy: Two Case Reports and a Systematic Review of the Literature**
- [Klayton M. Ryman](#) [Wilson D. Pace](#) [Shawn Smith](#) [Gabriel V. Fontaine](#) *Pharmacotherapy*, 2019 Jul, 39: 767-774.



# FIRBINOLYSIS IN ACUTE ISCHEMIC STROKE

## Mobile CT/Stroke Unit



# FIBRINOLYSIS IN ACUTE ISCHEMIC STROKE

## Stroke Mimics

- Stroke mimics:
  - Complex migraine
  - Conversion disorder
  - Seizure
  - Metabolic disorder
  - Guillain-Barre, other neuro
  - TIA
- AIS mimic most commonly treated with IV tPA?
  - International Stroke Thrombolysis Register 2003-2017 found 429 mimics
  - Functional (31%), migraine (18%) and seizure (14%)
  - Eur J Neurol. 2019;26:1091



# FIBRINOLYSIS IN ACUTE ISCHEMIC STROKE

## Stroke Mimics

### Neurologic

Todd's paralysis

(persistent neurologic signs post seizure)

Complicated migraine

Non-convulsive status epilepticus

Neuropathies:

Bell's palsy

Radial nerve palsy

Spinal cord disorders

### Metabolic

Hypoglycemia

Hyperglycemia

Hyponatremia

Hypernatremia

Hepatic encephalopathy

### Infectious

Meningitis

Encephalitis

Brain abscess

Cerebral malaria

Rocky Mountain

Spotted Fever

### Neoplastic

Tumor

### Traumatic

Subdural hematoma

Epidural hematoma

### Toxic

Drug overdose

Botulism

Paralytic shellfish poisoning

### Vascular

Thoracic dissection

Vertebral artery dissection

Carotid artery dissection

Cerebral vasculitis

### Other

Heat stroke

Sickle cell crisis—  
cerebral crisis

- Stroke Mimics: An Important Source of Bias in Acute Ischemic Stroke Research
  - J Stroke Cerebrovasc Dis Sep 2019;28:2475
- Hard to distinguish from AIS treated with alteplase
- Inclusion of mimics leads to artificial inflation of favorable outcome
- Strict normal post-thrombolysis DWI-MRI-based definition of ischemic stroke indicate:
  - Prevalence of negative post-thrombolysis DWI 21 – 28% treated with alteplase



# FIBRINOLYSIS IN ACUTE ISCHEMIC STROKE

## Malpractice Allegation Threat

- 60K patients treated with IV tPA 2003-2012
  - Saver, *JAMA* 2013;309(23):2480-88
  - National Stroke Registry (Get With the Guidelines-Stroke Program)
- 789 stroke cases litigated 1999-2010
  - 40 involving tPA
  - 20 involving EPs
    - 10 without Neurologist

### Stroke Litigation and tPA 1999-2010\*

<u>CLAIM:</u>	<u>CASES:</u>	<u>VEDICT IN FAVOR OF:</u>
Failure to treat with tPA	28	Defendant: 19 Plaintiff: 7
Complications of tPA	2	Defendant: 1 Plaintiff: 1
Failure to diagnose	10	Defendant: 6 Plaintiff: 4
Total Claims	40	Defendant: 26 Plaintiff: 12

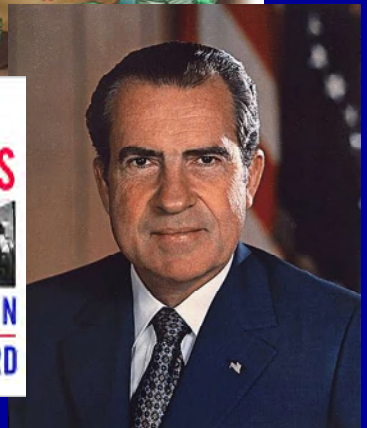
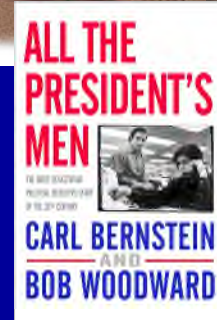
\*Stroke Res Treatment 2013:562564



# FIBRINOLYSIS IN ACUTE ISCHEMIC STROKE

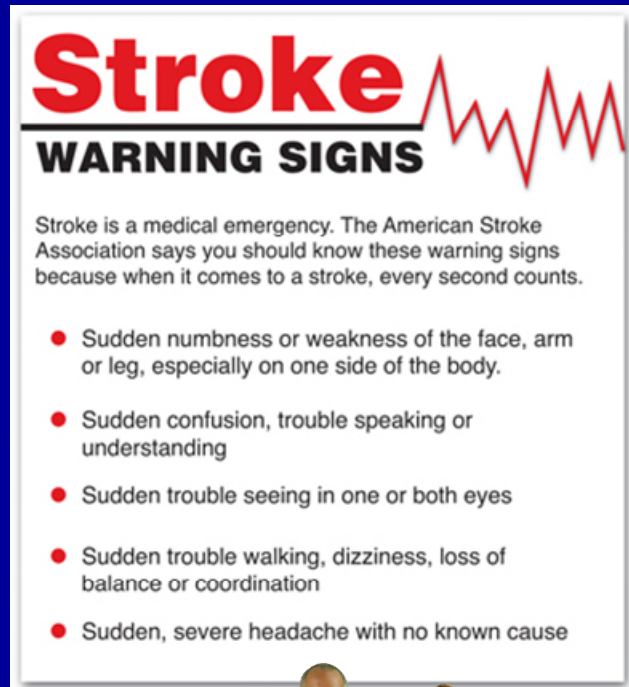
## What Is This Really About?

## Follow The Money...Healthcare is a Business!



# FIBRINOLYSIS IN ACUTE ISCHEMIC STROKE

## Skeptical Summary



- There is a subset of stroke patients who will benefit from fibrinolysis
- We cannot accurately and safely identify that subset of patients
- NINDS re-validation?
  - Unethical to withhold beneficial treatment
  - But not unethical to continue to capture more patients outside of protocol (e.g., wake-up stroke, coumadin/DOAC, 9hrs, endovasc-24hrs)



# FIBRINOLYSIS IN ACUTE ISCHEMIC STROKE

“Once again, U.S. has most expensive, least effective health care system in survey”

Lenny Bernstein: The Washington Post 16 June 2014

	AUS	CAN	FRA	GER	NETH	NZ	NOR	SWE	SWIZ	UK	US
<b>OVERALL RANKING (2013)</b>	4	10	9	5	5	7	7	3	2	1	11
<b>Quality Care</b>	2	9	8	7	5	4	11	10	3	1	5
Effective Care	4	7	9	6	5	2	11	10	8	1	3
Safe Care	3	10	2	6	7	9	11	5	4	1	7
Coordinated Care	4	8	9	10	5	2	7	11	3	1	6
Patient-Centered Care	5	8	10	7	3	6	11	9	2	1	4
<b>Access</b>	8	9	11	2	4	7	6	4	2	1	9
Cost-Related Problem	9	5	10	4	8	6	3	1	7	1	11
Timeliness of Care	6	11	10	4	2	7	8	9	1	3	5
<b>Efficiency</b>	4	10	8	9	7	3	4	2	6	1	11
<b>Equity</b>	5	9	7	4	8	10	6	1	2	2	11
<b>Healthy Lives</b>	4	8	1	7	5	9	6	2	3	10	11
<b>Health Expenditures/Capita, 2011**</b>	\$3,800	\$4,522	\$4,118	\$4,495	\$5,099	\$3,182	\$5,669	\$3,925	\$5,643	\$3,405	\$8,508

Notes: \* Includes ties. \*\* Expenditures shown in \$US PPP (purchasing power parity); Australian \$ data are from 2010.

Source: Calculated by The Commonwealth Fund based on 2011 International Health Policy Survey of Sicker Adults; 2012 International Health Policy Survey of Primary Care Physicians; 2013 International Health Policy Survey; Commonwealth Fund *National Scorecard 2011*; World Health Organization; and Organization for Economic Cooperation and Development, *OECD Health Data, 2013* (Paris: OECD, Nov. 2013).

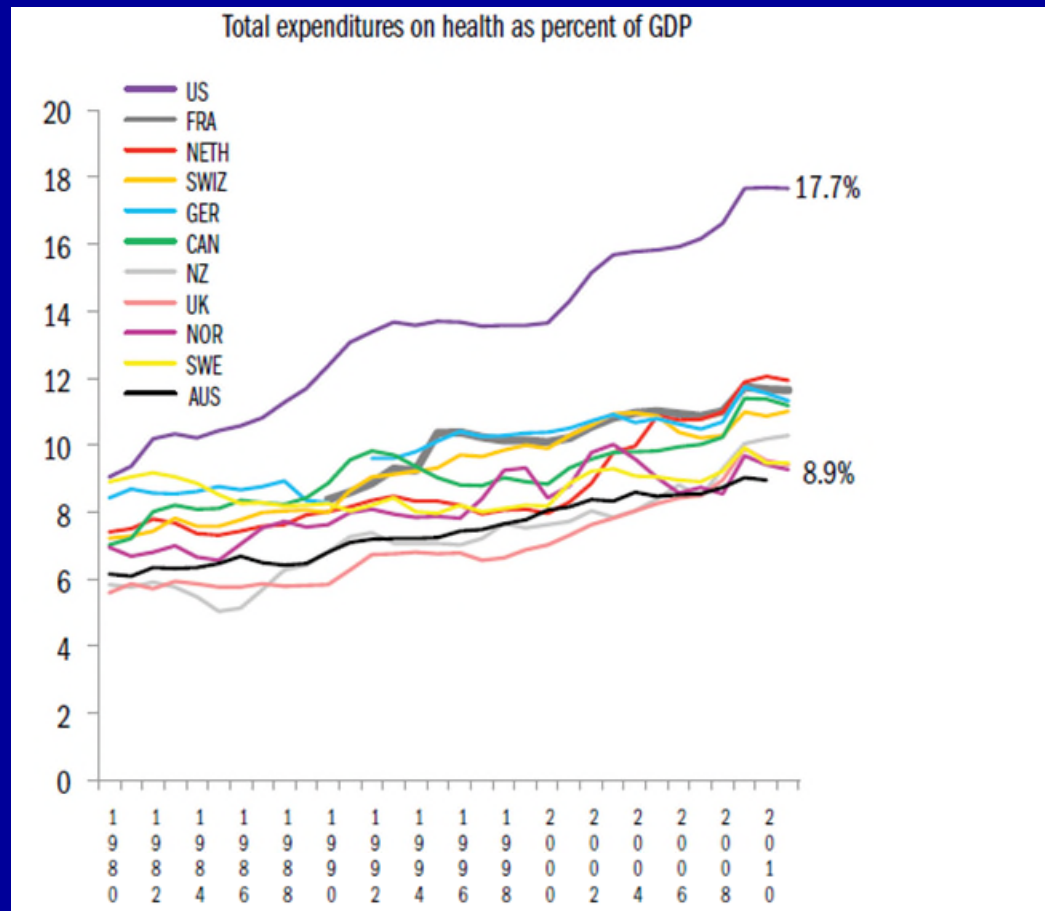
The Washington Post



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The Washington Post

# FIBRINOLYSIS IN ACUTE ISCHEMIC STROKE

Woolf, S.H., et al, US HEALTH DISADVANTAGE RELATIVE TO OTHER HIGH-INCOME COUNTRIES: FINDINGS of NATIONAL RESEARCH COUNCIL/INSTITUTE OF MEDICINE  
REPORT JAMA 309(8):771, February 27, 2013

- National Research Council and the Institute of Medicine: “US Health International Perspective: Shorter Lives Poorer Health”
- ***US spends more on healthcare than other developed nations (18% GDP)***
- ***Health outcomes are generally worse than other high-income countries***
- US ranks at or near the bottom in a broad range of metrics, including:
  - Life expectancy up to the age of 75
  - Mortality prior to the age of five
  - Death due to vehicle crashes
  - Adolescent pregnancy
  - Sexually transmitted infections
  - Prevalence of HIV and AIDS
  - Prevalence of obesity
  - Prevalence of diabetes
  - Death to ischemic heart/pulmonary disease, drug-related mortality
- NRC/IOM states origin of dismal standings in metrics include:
  - Lack of universal health insurance coverage
  - Weaker foundation in primary care
  - Barriers to access and affordable care
  - Suboptimal care coordination, quality and safety
  - Greater propensity for unhealthy behaviors
  - Greater calorie intake
  - Increased likelihood of drug abuse
  - Less frequent use of seatbelts
  - Less frequent safe sex practices among adolescents



# FIBRINOLYSIS IN ACUTE ISCHEMIC STROKE

## BLUF Summary

- There is a subset of AIS patients who will benefit from tPA thrombolysis
- We cannot, with any degree of accuracy, identify those stroke patients who will benefit



# FIBRINOLYSIS IN ACUTE ISCHEMIC STROKE

## Dodgy Effectiveness







# Fibrinolysis in Acute Ischemic Stroke--*Redux*: A Skeptical Perspective

“...still a man hears what he wants to hear  
and disregards the rest...”

‘The Boxer’ Paul Simon and Art Garfunkel, 1969



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