Thrombolytic Therapy in Acute Stroke

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Disclosure:

I do not have any financial or other affiliation with any commercial organization that may have a direct or indirect connection to the content of my presentation.

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THROMBOLYTIC THERAPY FOR ACUTE ISCHEMIC STROKE BEYOND THREE HOURS

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Overview:

- Null Hypothesis and Skepticism
- Thrombolysis for Acute CVA
- 12 Major RCTs
- Community Setting
- Systematic Reviews
- Conclusion

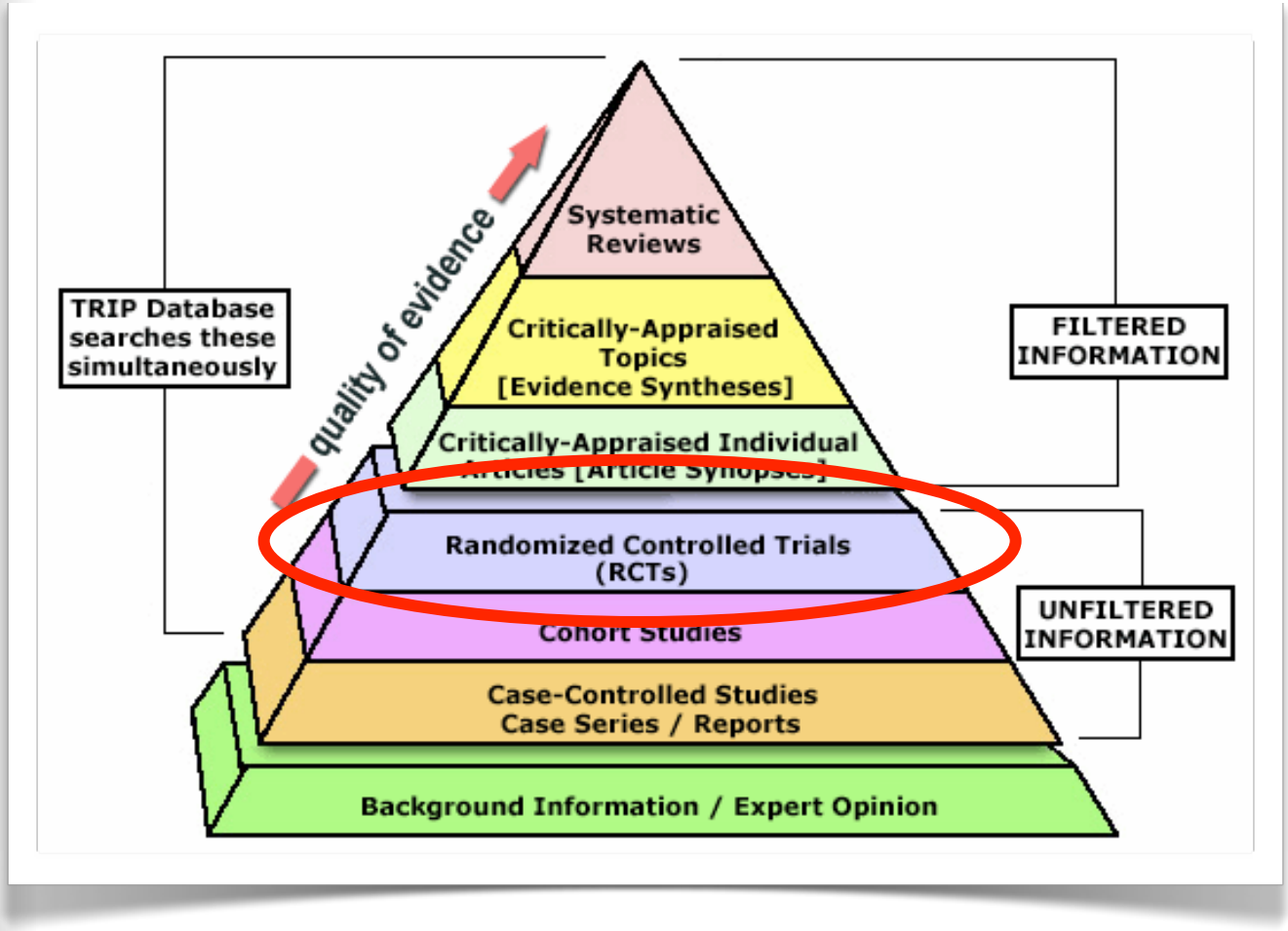
Null Hypothesis:

- Statement that the thing being studied produces no effect or makes no difference
- Burden of proof is upon those who make a positive claim.

Skepticism:

- Skepticism is an overall approach that requires all information to be well supported by evidence

Levels of Evidence: 12 RCTs

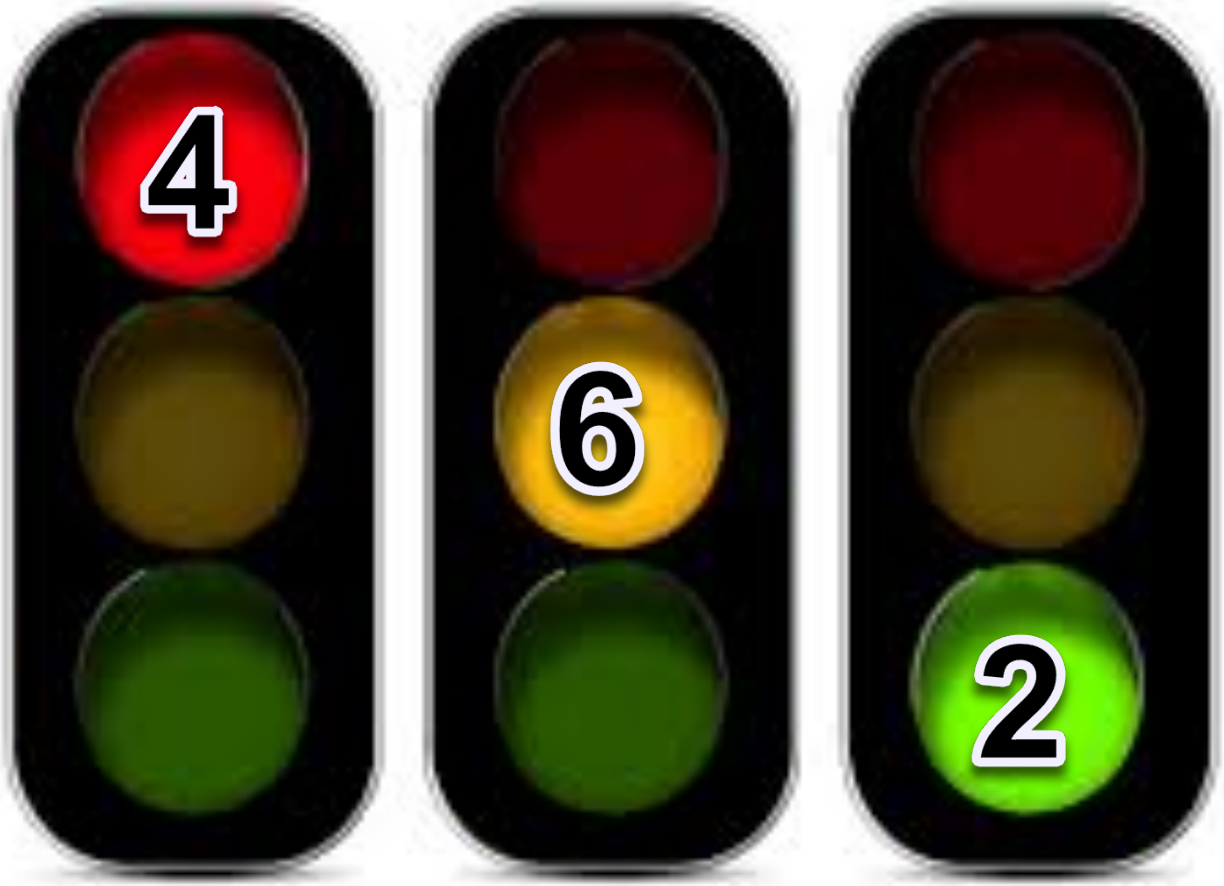


Thrombolysis for Acute Embolic Stroke

- CVA leading cause disability and death
- Sussman et al 1958
- Dosage trials began in the 1980's
- Therapeutic trials began to be published in the 1990's
  - 12 major RCTs to date

Red, Yellow and Green Light

12 Major RCTs



MAST-Italy (1995) Lancet

- 6hr window
- N=622 (1.5MU Strepto)
  - Increased early death (OR 2.7)
  - *"Marginal"* reduction of severe disability at 6 months
- **Overall no benefit**

ECASS I (1995) JAMA

- 6hr window
- N=620 (1.1mg/kg tPA)
  - Favored tPA at 90d
  - More bleeds in tPA
  - No difference in 30d mortality
  - More deaths in 90d with tPA
- **Benefit does not outweigh the risk**

NINDS-I (1995) NEJM

- 3hr window
- N=291 (0.9mg/kg tPA)
- **No difference at 24 hours**
  - Improvement of 4 points over base-line values in NIHSS
- **No overall benefit**

NINDS-II (1995) NEJM

- 3hr window
- N=333 (0.9mg/kg tPA)
- **13% Absolute Benefit at 90d**
  - <2 mRS 26% vs. 39% tPA
- **6% Absolute Harm (ICH)**
  - No difference in overall mortality at 3 months (21% vs. 17% tPA)
- **NNT=8**

MAST-Europe (1996) NEJM

- 6hr window (mod-severe stroke, MCA territory only)
- N=310 (1.5MU strepto)
  - No difference combined disability/ death at 6 months
  - Increased ICH (21% vs. 3%)
  - Increased mortality (47% vs. 38%)
- **Stopped Early Due to ICH and Mortality** (plan n=600)

ASK (1996) JAMA

- 4hr window
- N=340 (1.5MU strepto)
  - No difference combined disability/ death at 3 months
  - Slight decrease disability
  - Slight increased mortality
- **Stopped Early Due to Mortality** (plan n=600)

ECASS II (1998) Lancet

- 0-3hr and 3-6hr
- N=800 (0.9mg/kg tPA)
- **No difference mRS at 3 months**
  - Increase: Parechymal bleed, ICH and early death due to ICH
  - No difference in 30d or 90d mortality
  - No difference between treat <3hr or 3-6hr (**did not confirm NINDS-2**)
- **No overall benefit**

ATLANTIS-B (1999) JAMA

- 3-5hrs
- N=613 (0.9mg/kg tPA)
  - No benefit 90d NIHSS
  - Increase in ICH (7% vs. 1%)
  - Increase mortality (11% vs. 7%)
- **Stopped Early *"unlikely to prove beneficial"*** (plan n=968)

ATLANTIS-A (2000) Stroke

- 0-6hrs (N=142) 0.9mg/kg tPA
- Stopped enrolling 0-3 based on NINDS
  - Favor Lytic at 24hr (40% vs. 21%)
  - Favor Placebo 1/12 (75% vs. 60%)
  - Increase ICH (11% vs. 0%)
  - Increase Death (23% vs. 7%)
- **Stopped Early for Harm** (plan n=300)

ECASS III (2008) NEJM

- 3-4.5hr window
- N=821 (0.9mg/kg tPA)
- **6.4 Absolute Benefit 90d**
  - **<2 mRS 45.2% vs. 52.4% tPA**
- **9.4% Absolute Harm (ICH)**
  - **17.6% vs. 27% tPA**
- No difference mortality 90d
- **NNT=15**

DIAS-2 (2009) Lancet Neuro

- 3-6hrs (N=193) Desmoteplase
- Low and high dose vs. placebo
- Reversible ischemic penumbra on MR or CT
  - No difference outcomes
  - Increase in mortality for high dose group (not statistically)
  - Stopped high dose early for harm
- **No overall benefit**

IST-3 (2012) Lancet

- 6hrs window
- N=3,035 (0.9mk/kg tPA)
  - Alive and independent at 6 months **NO DIFFERENCE**
  - ICH 7% vs. 1% at 7d
  - Death 11% vs. 7% at 7d
  - Death 6 months no difference
- **No overall benefit**

IST-3 (2012) Lancet

Authors Conclusions:

"despite the early hazards, thrombolysis within 6h improved functional outcome. Benefit did not seem to be diminished in elderly patients."

IST-3 (2012) Lancet

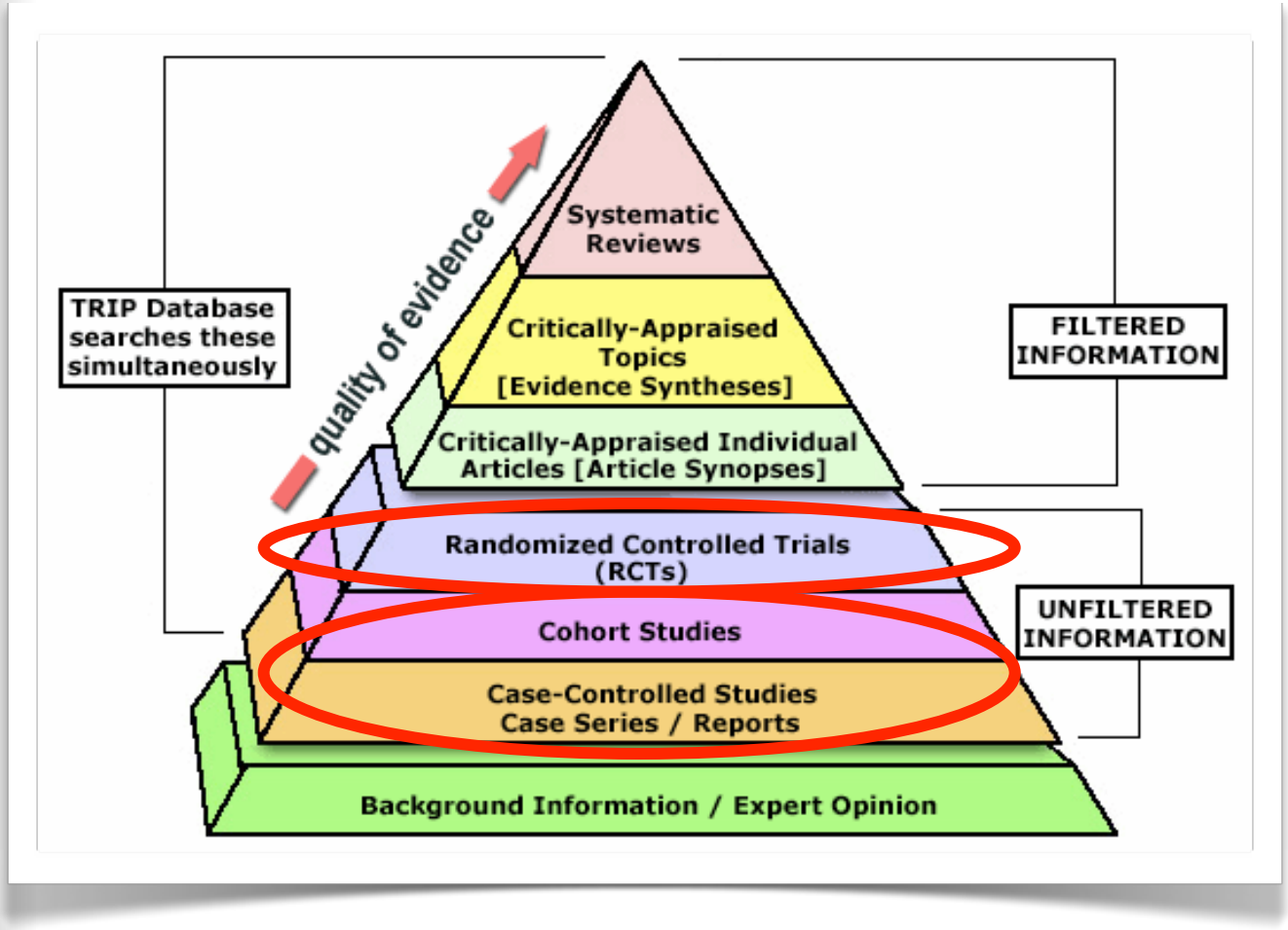
- Pragmatic, open-label (blinding)
- Small blinded (300) favored control
- Only pts docs thought would benefit (bias)
- Missed target by 50%
- After 7yrs they moved the goal post
- Another Stats was brought in to *"persuade"*
- Came up with 2ndary outcome with ordinal logistic regression analysis
- Primary end point was NEGATIVE
- Reported as a positive study - **???**

IST-3 (2012) Lancet

Ken's Opposite Spin:

"tPA harmed 1 in 25 early (death), the bleed rate went up 600% (relative) and there was no benefit seen at 6 months (primary outcome)."

Levels of Evidence: Observational Studies



Cleveland (2000) JAMA

- 29 community hospitals
- 3,948 admits and 70 (1.8%) tPA
- 50% protocol violators
- ICH 22%
- **Mortality 5.1% vs 15.7% tPA**

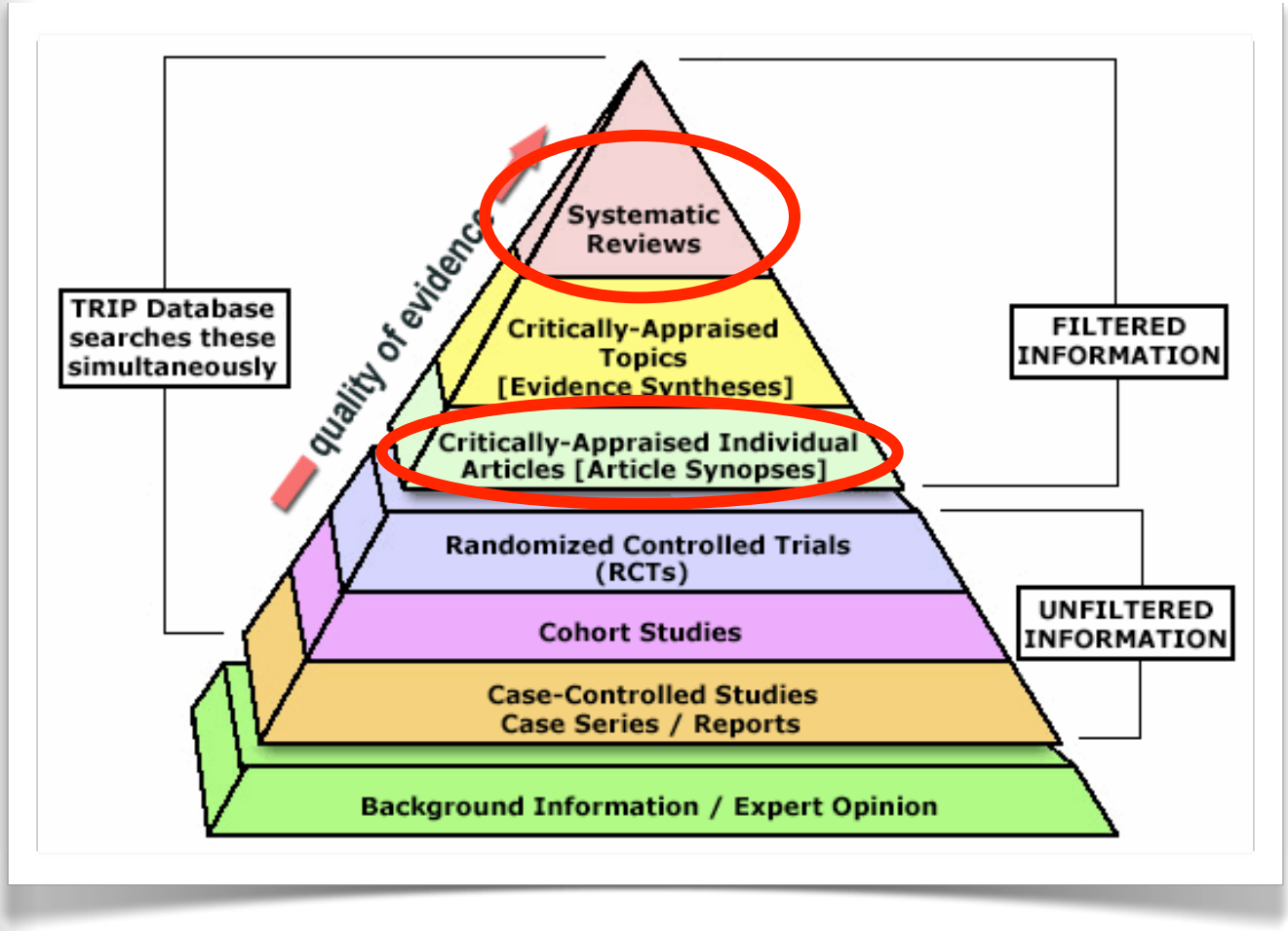
CASES (2005) CMAJ

- 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**

SITS: MOST (2007) Lancet

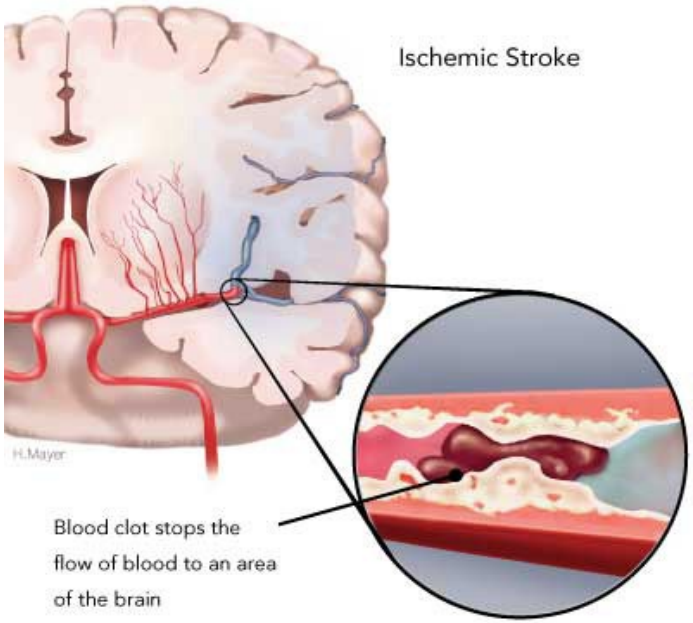
- Prospective Observational Trial of safety and efficacy of tPA<3hr
- N=6,483 from 285 centres
  - 7% ICH at 7 days
  - 11% mortality at 90d
- tPA is safe and effective
- **HOWEVER:**
  - Excluded protocol violators
  - Outcome data missing from >15%

Levels of Evidence:



Time is Brain?

- Window of opportunity



Time is Not Brain:

NEUROLOGY/ORIGINAL RESEARCH

A Graphic Reanalysis of the NINDS Trial

Hoffman et al Ann Emerg Med 2009

- *"Our graphs fail to support the time-is-brain hypothesis."*

Thrombolysis for acute ischaemic stroke (Review)

Wardlaw JM, Murray V, Berge E, del Zoppo GJ

THE COCHRANE COLLABORATION®

Wardlaw et al Cochrane 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 (or dose or route of administration) "*

Dose and Drug:

Thrombolysis (different doses, routes of administration and agents) for acute ischaemic stroke (Review)

Wardlaw JM, Koumellis P, Liu M

THE COCHRANE COLLABORATION®

- **Wardlaw et al Cochrane 2013**
  - No evidence that one lytic agent or dose is better than another
  - *"the evidence is inadequate to conclude whether lower doses of thrombolytic agents are more effective than higher doses, or whether one agent is better than another"*

"Multiple" RCT Showing Benefit <4.5hrs:

Trial	Journal	Time	Primary Benefit	Harm
NINDS -II (n=333)	NEJM 1995	<3hr	~13% absolute benefit mRS at 90d	Increase ICH
ECASS-III (n=821)	NEJM 2008	3-4.5hr	7% absolute benefit OR=1.34 (95% 1.02-1.76)	Increase ICH

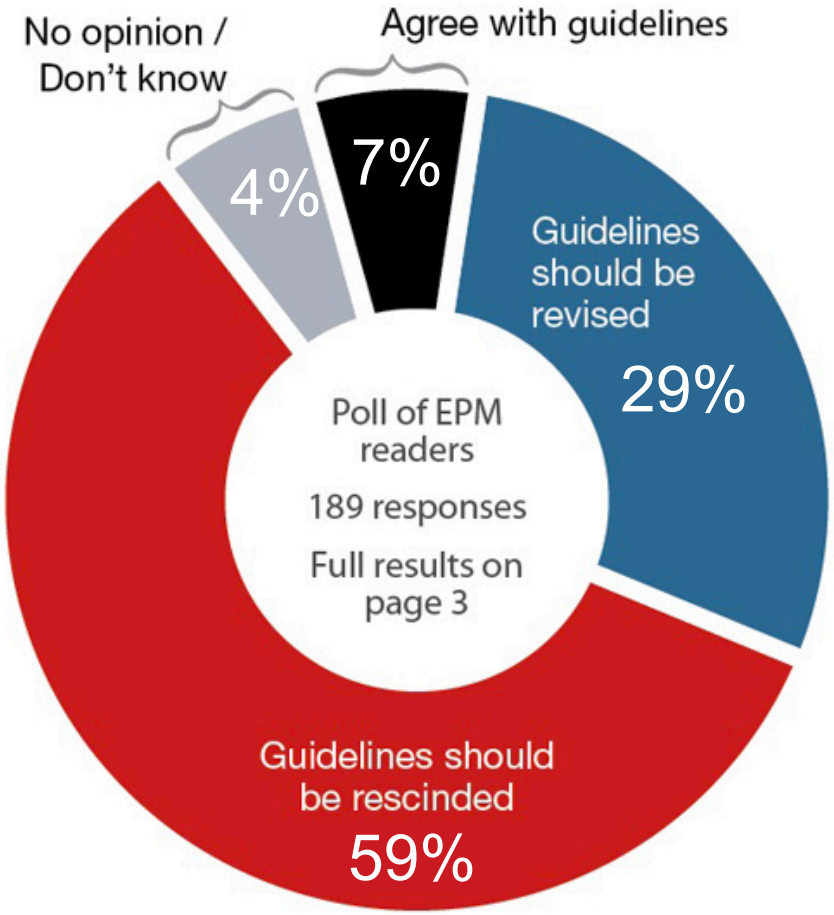
Trial	Journal	Time	Primary Benefit	Harm
MAST -Italy (n=622)	Lancet 1995	<6hr	**None**	Increased early death
ECASS-I (n=620)	JAMA 1995	<6hr	**None**	Benefit not outweigh the risk
NINDS-I (n=291)	NEJM 1995	<3hr	**None**	No difference
MAST - Eu (n=310)	NEJM 1996	<6hr	**None**	**Stopped** early due to harm
ASK (n=340)	JAMA 1996	<4hr	**None**	**Stopped** early due to harm
ECASS-II (n=800)	Lancet 1998	<6hr	**None**	No difference
ATLANTIS-B (n=613)	JAMA 1999	3-4hr	**None**	**Stopped** *early "unlikely to prove beneficial"*
ATLANTIS-A (n=142)	Stroke 2000	<6hr	**None**	**Stopped** early due to harm
DIAS-2 (n=193)	Lancet 2009	3-9hr	**None**	No difference
IST-3 (n=3035)	Lancet 2012	<6hr	**None**	No difference

CAEP Guidelines:

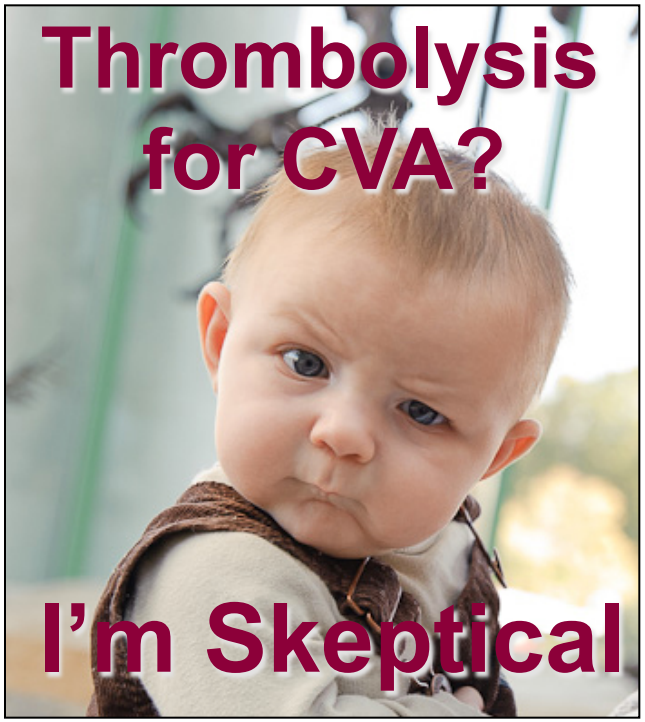
- *Further evidence is necessary to support the widespread application of stroke thrombolysis outside research settings.*
- *Until it is clear that the benefits of this therapy outweigh the risks, thrombolytic therapy for acute stroke should be restricted to use within formal research protocols or in monitored practice protocols that adhere to the NINDS eligibility criteria.*

ACEP

tPA should be offered to all patients who qualify in the less- than-3-hour time window.



Conclusion:



- Not ready to reject the Null Hypothesis

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