

Failures of Translation in SAH and stroke: What can be learned?

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Disclosures

AstraZeneca

Difficulties in translation of acute brain injury trials

The *CONSCIOUS* trial in SAH:

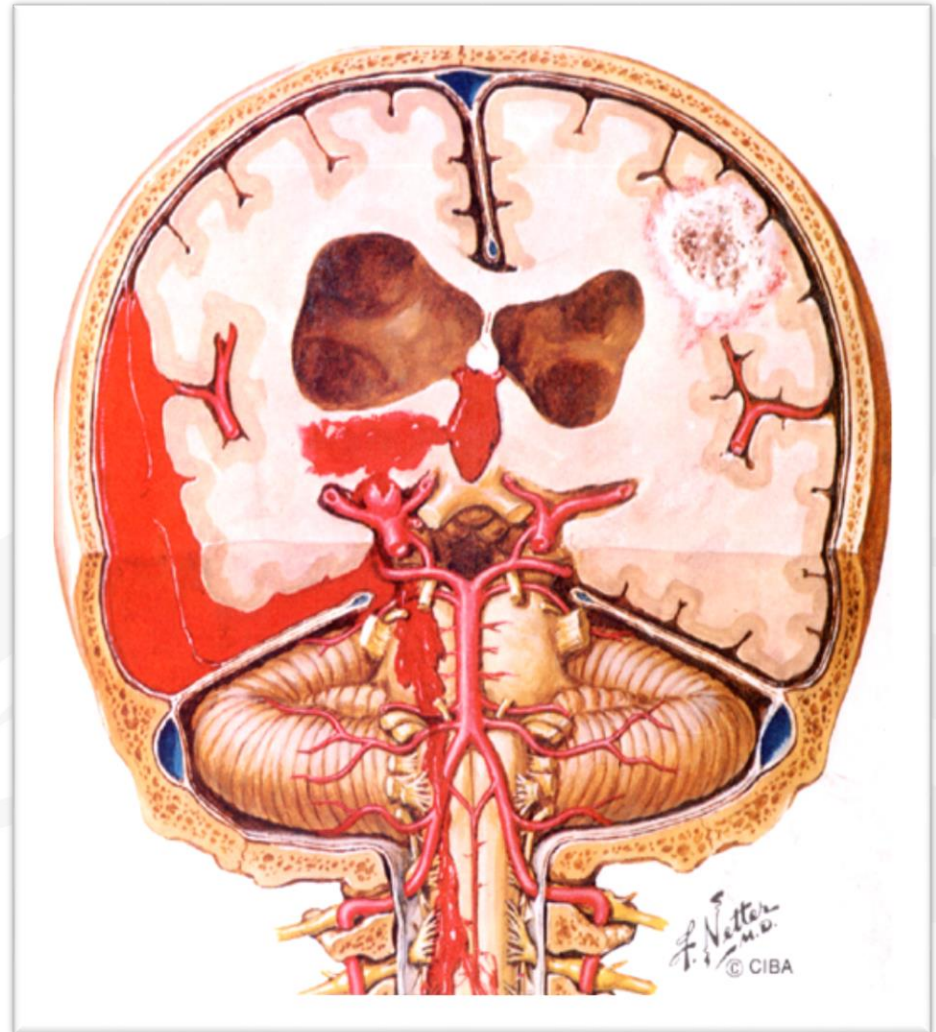
- A suspect surrogate and failure to translate

The *SOCRATES* trial in stroke prevention:

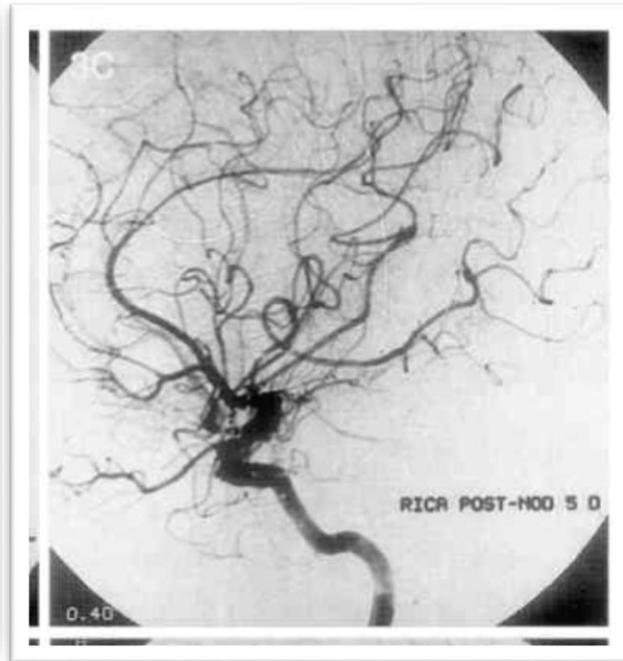
- An ill-fated endpoint

Neurological Complications of SAH

- Parenchymal hemorrhage
- Obstructive hydrocephalus
- Ischemic Stroke
- Seizures
- Hyponatremia
- Delayed cerebral ischemia



Vasospasm as a cause of delayed ischemic deficit



Vasospasm is predicted by subarachnoid clot burden

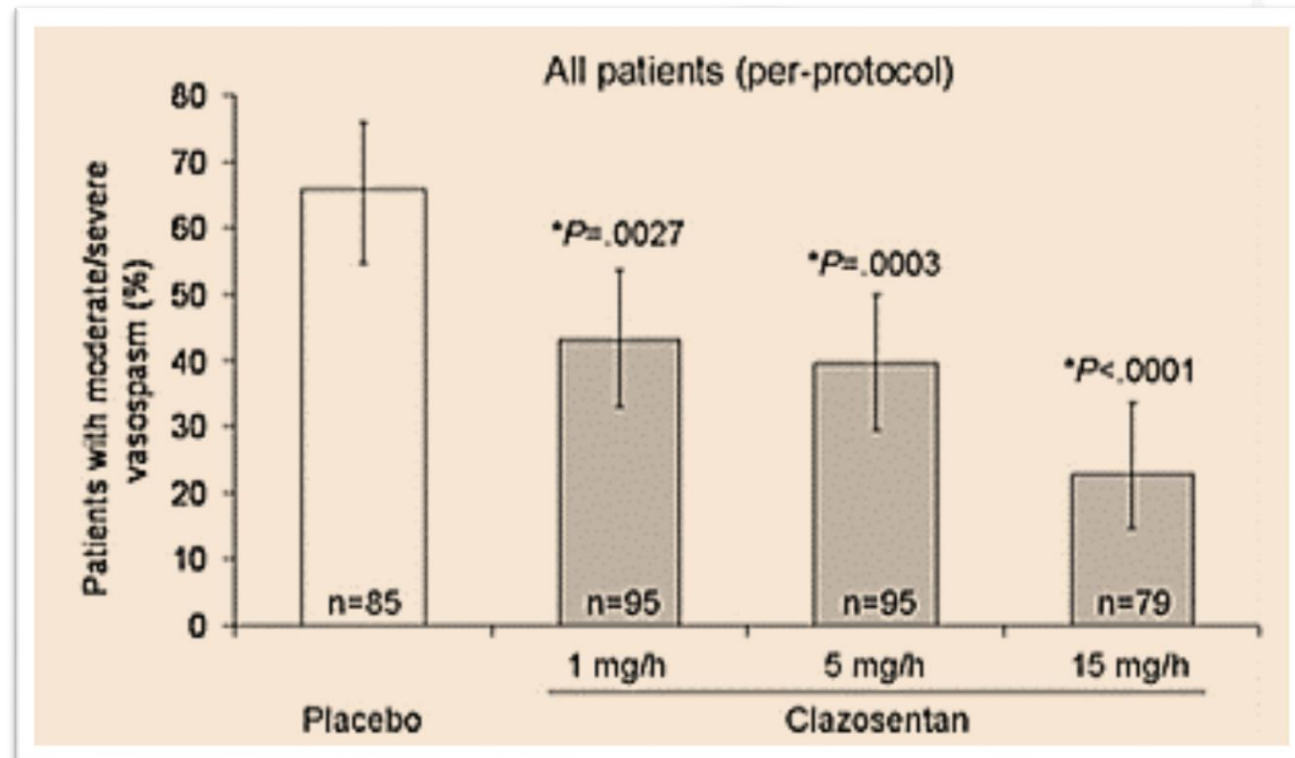
- Oral Nimodipine remains standard of care
- Imperfect correlation between angiographic and clinical findings

CONSCIOUS 1

- Clozasantan: A 21 amino acid peptide demonstrated to be potent endothelin receptor antagonist
- 413 patient RCT treatment for 14 days of treatment at 3 doses (1, 5, 15 mg/h)
- Surrogate endpoint: moderate- severe vasospasm by angiography at 7-11 days

CONSCIOUS 1: A successful trial...

Reduced moderate to severe vasospasm from 66% to 23%



Mcdonald et al., *Stroke*, 2008

...or was it?

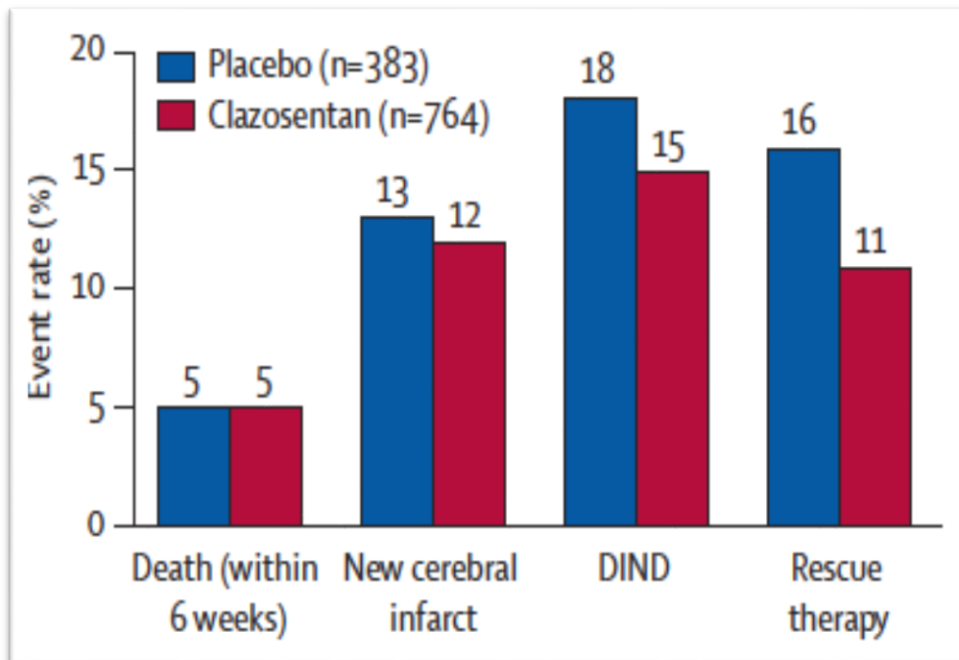
Characteristic	Placebo (n=96)	Clazosentan		
		1 mg/hour (n=107)	5 mg/hour (n=110)	15 mg/hour (n=96)
Hypotension	3 (3)	6 (6)	13 (12)	11 (12)
Anemia	16 (17)	27 (25)	32 (29)	19 (20)
Lung complications	26 (27)	47 (44)	48 (44)	37 (39)
Pulmonary edema	1 (1)	11 (10)	14 (13)	10 (10)
Acute respiratory distress syndrome	2 (2)	6 (6)	8 (7)	8 (8)
Pleural effusion	5 (5)	13 (12)	14 (13)	13 (14)
Pneumonia	14 (15)	21 (20)	25 (23)	13 (14)

Characteristic	Placebo (n=96)	Clazosentan		
		1 mg/hour (n=107)	5 mg/hour (n=110)	15 mg/hour (n=96)
Death, vegetative, or severe disability	30 (31)	28 (26)	30 (27)	33 (34)
Exact 95% CI	22–42%	18–36%	19–37%	25–45%
Absolute risk reduction		–5%	–4%	3%
Exact 95% CI		–18–8%	–17–9%	–11–17%
<i>P</i> value (Fisher exact test)		0.44	0.54	0.76
Relative risk reduction		0.16	0.13	–0.10
95% CI (normal approximation)		–0.29–0.46	–0.34–0.43	–0.65–0.27

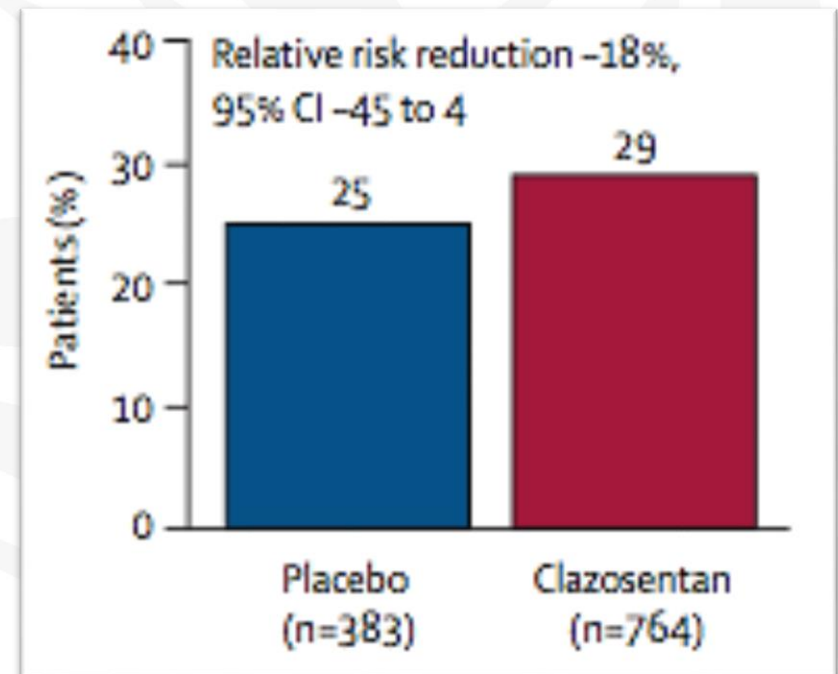
CONSCIOUS 2: A Phase 3 RCT

- 27 countries, 102 sites
- randomized 2:1
- clozasentan (5 mg/kg) vs placebo x 14 days

Reduced vasospasm-related endpoints



Primary endpoint GOS-E



LESSON LEARNED:

Surrogate measures can be misleading

Preclinical models must mimic the clinical setting



Secondary Stroke Prevention: Background

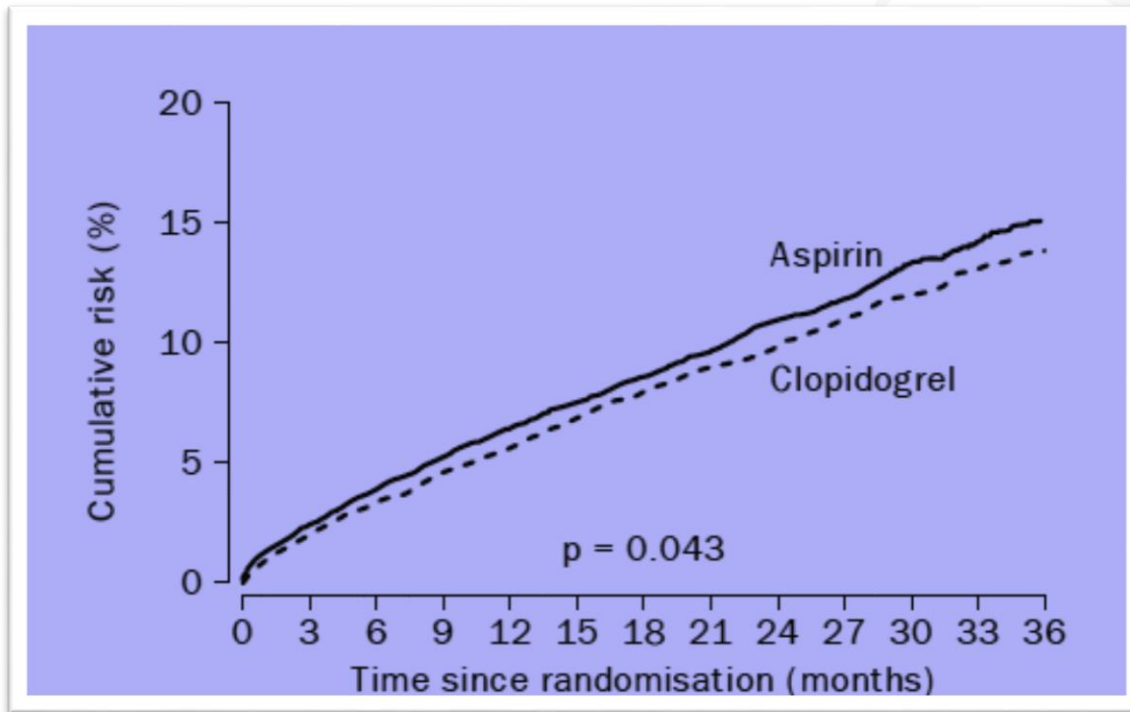
- Risk of stroke greatest acutely after index event
- ASA reduces risk of stroke, MI, or death by 22%
- In large trials, 2-4 weeks of ASA reduces acute risk of secondary stroke (30% RRR, ARR of 0.7%)
- Alternatives to Aspirin:
 - dipyridamole/ASA (ESPS-2)
 - clopidogrel monotherapy (CAPRIE)

Use of composite endpoint in CAPRIE:

- CAPRIE trial (75mg ASA vs. 325 mg clopidogrel) utilized composite endpoint (IS, MI, or vascular death)
- Reduces sample size in event-driven trial and may be appropriate:
 - Underlying biology is similar
 - Differences are in the same direction
 - Homogeneity of treatment effect

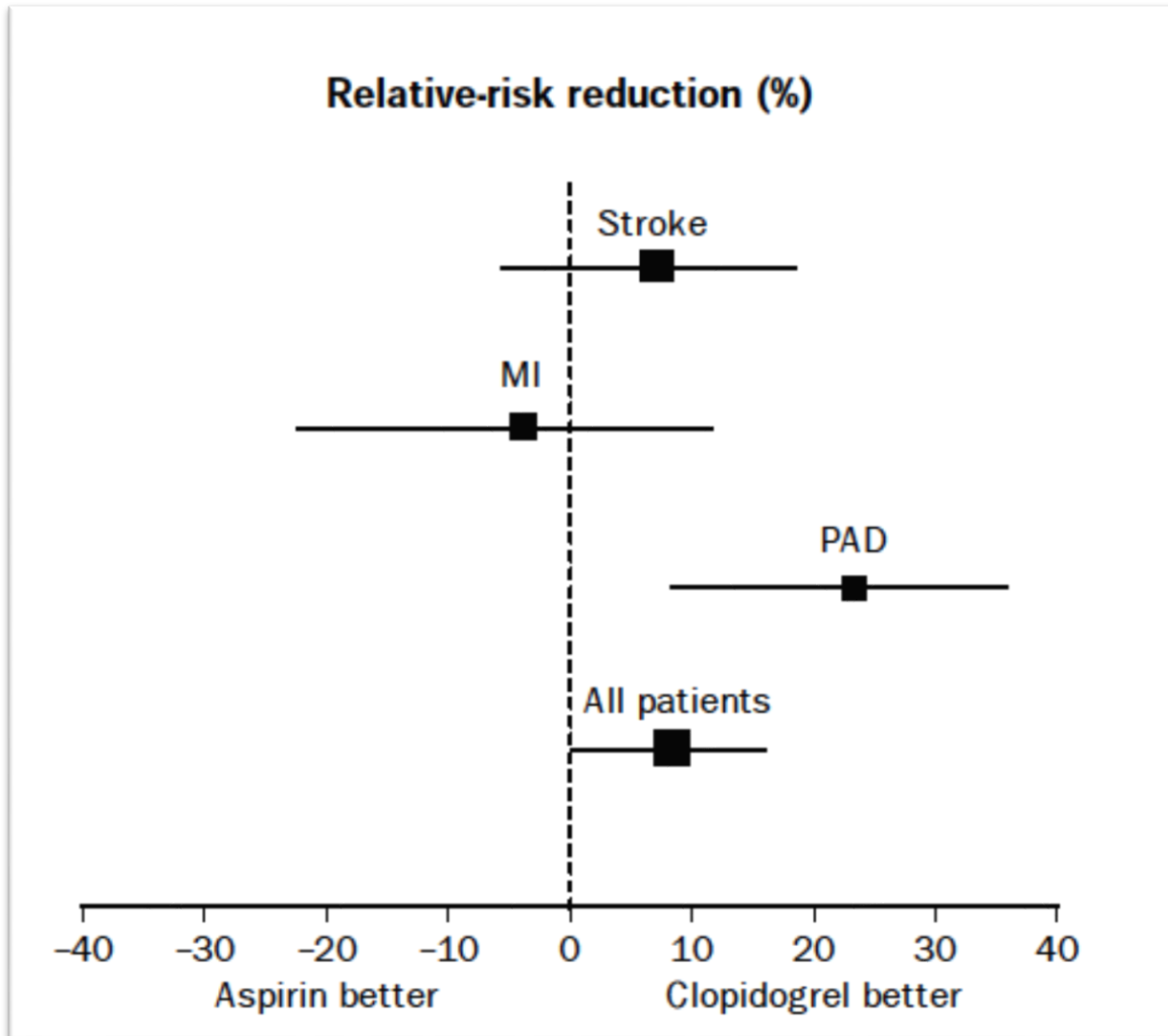
CAPRIE

- n= 19,185 with IS, MI or PAD, followed 1-3 years ;
Intervention: ASA 325 mg qd vs clopidogrel 75 mg qd



Clopidogrel had 5.3% risk of composite endpoint (ischemic stroke, MI, or vascular death) vs 5.8% with ASA (p=0.043)

CAPRIE: SUBGROUP ANALYSIS



Insignificant benefit for stroke:
(7.15 vs 7.7 events/year;
P=0.26)

CAPRIE: Did it work for stroke?

- Overall, 8.7% significant RRR for composite endpoint
- For MI, significance was reached:
relative risk reduction of 19.2% (95% CI: 5.3-31)
- However, non-significant reduction in stroke endpoint
relative risk reduction of 5.2% (95% CI: -7.9-16.7)

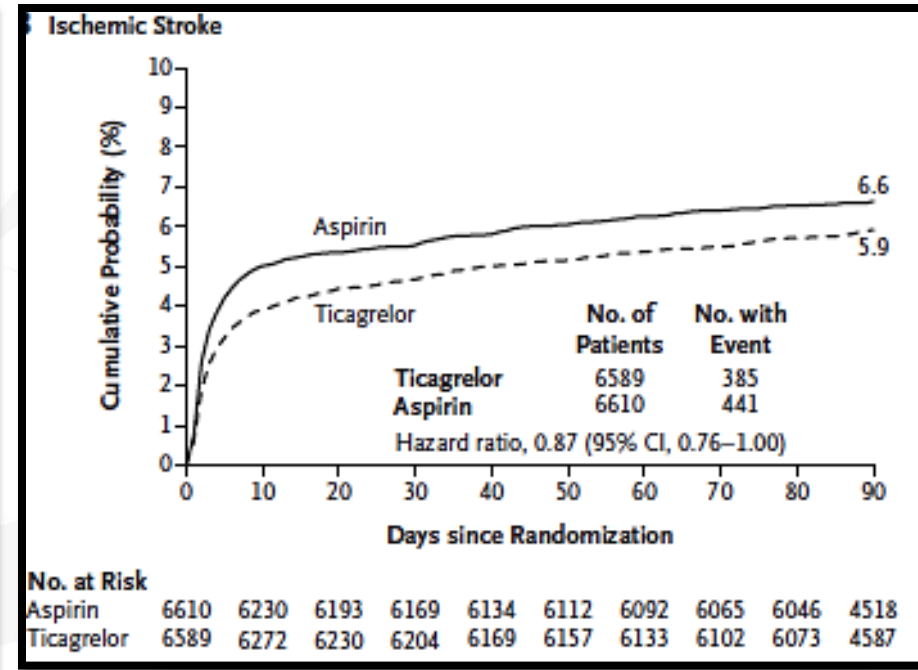
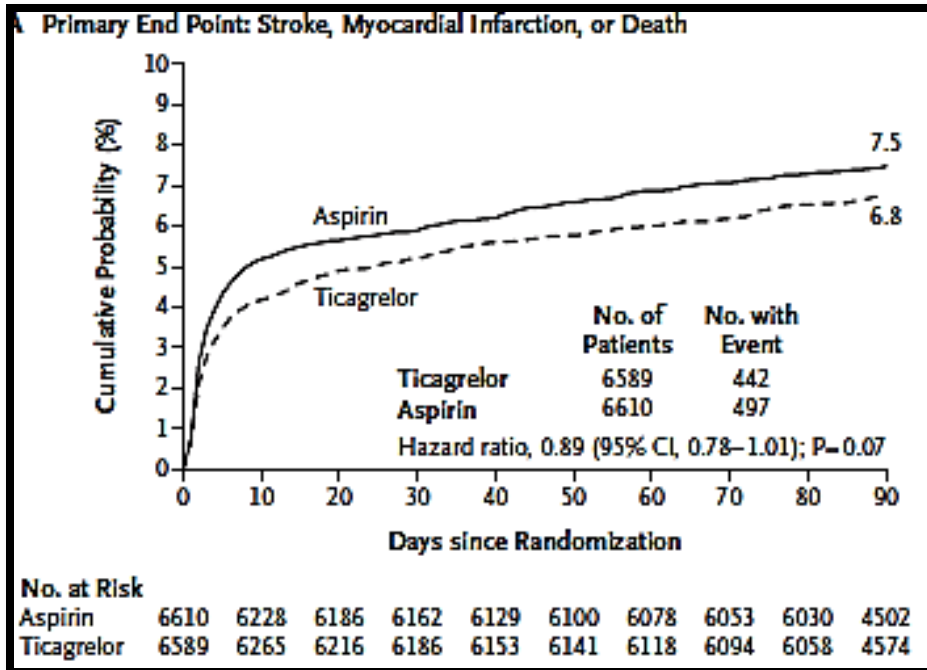
Ticagrelor to prevent secondary stroke: SOCRATES trial

- Unmet need for secondary stroke prevention
- Stroke is particularly high risk within 90 days of index event
- Ticagrelor may be particularly effective in this setting
- ASA is an acceptable comparator (the only one accepted by FDA)

Secondary stroke Prevention: SOCRATES study

- N=13,199 patients (674 centers in 33 countries)
- Patients with TIA or minor stroke randomized to Ticagrelor (180 mg load then 80 mg BID) vs ASA (300 mg load, then 100 qd) for 90 days
- Primary endpoint: stroke, MI, or death within 90 days
- Secondary endpoint (tested in hierarchical sequence) was time to ischemic stroke

SOCRATES RESULTS



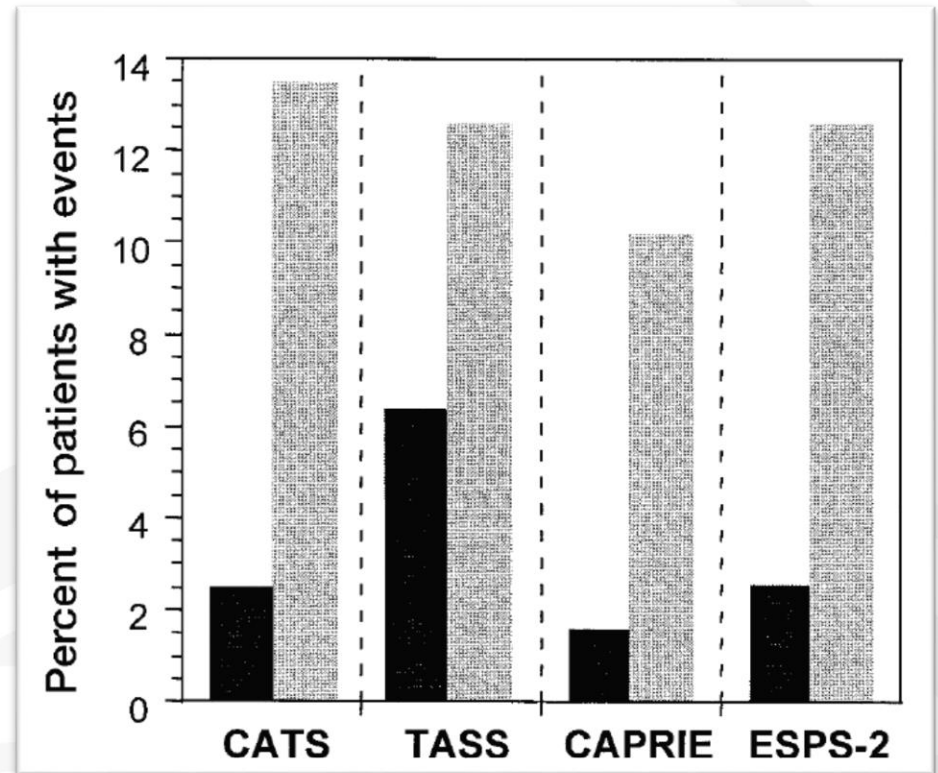
442 (6.7%) vs. 497 (7.5%)
P=0.07

385 (5.9%) vs. 441 (6.76%)
P=0.046

STUDY FAILED

Why did the Composite Fail?

- Underlying biology is not the same
- Stroke is much more common than MI in patients with index event of stroke/TIA
- Stroke effect was masked by other components of composite
- “Death from any cause” failed in prior antiplatelet trials



LESSONS LEARNED:

Composite endpoints can be a double edged sword:

Sometimes it is better to just ask the question

Enrollment challenged by failure to understand patient flow in the US

Conclusions

Importance of establishing preclinical models in the clinical context

Surrogate endpoints can be helpful to establish target engagement or potential clinical efficacy

Trial design can mask a positive finding

Thank You

