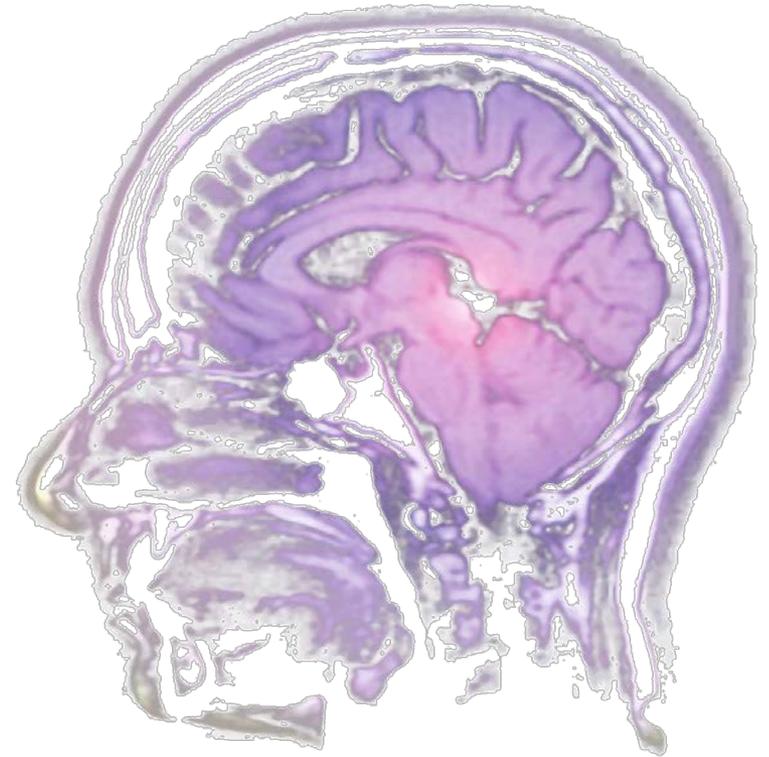


# STAIR

***A starting point for evidence-based translational medicine in stroke***

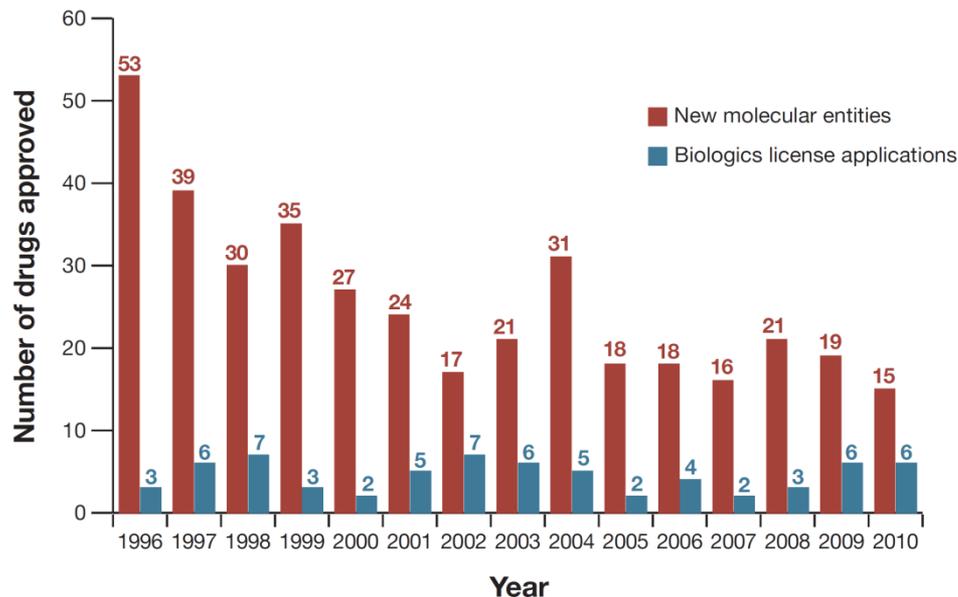


**David Howells**

For the CAMARADES Collaboration

## FDA drug approvals per year

From: Kling, J. Nat. Biotechnol. 29 (2011) 197-200.



## Success by class for compounds first tested in man from 1992-04 through to 2009

Adapted from: DiMasi et al, Clinical Pharmacology and Therapeutics 87 (2010) 272-227.

Therapeutic class	n	Approved molecules	Current success rate (%)
Antineoplastic/immunologic	254	18	7.1
Cardiovascular	134	4	3.0
CNS	235	9	3.8
GI/metabolism	120	4	3.3
Musculoskeletal	88	8	9.1
Respiratory	83	4	4.8
Systemic anti-infective	122	19	15.6
Miscellaneous	189	21	11.1

## Estimates of the cash and capitalized cost of drug development

From: Morgan et al, Health Policy 100 (2011) 4-17.

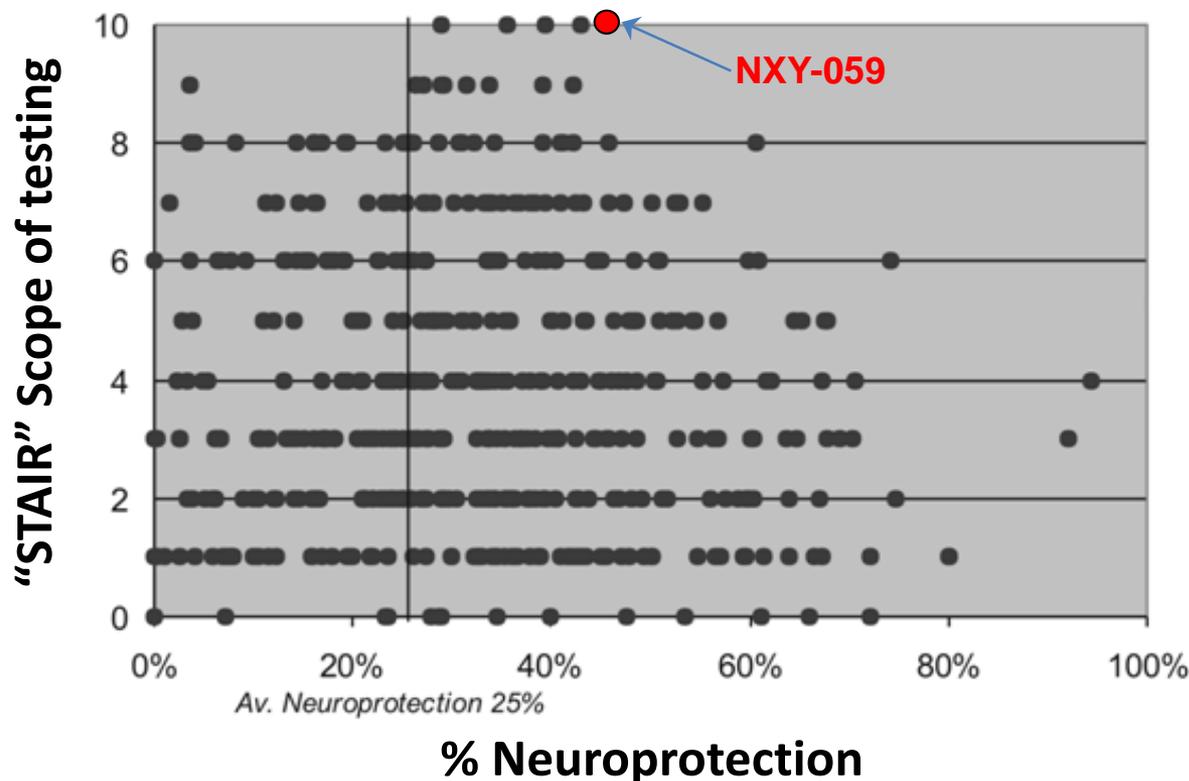
	Hansen and Chien	DiMasi	DiMasi et al.	DiMasi* and Grabowski
Drugs first tested from..	1963 to 1975	1970 to 1982	1983 to 1994	1990 to 2003
<i>Cash</i>				
Pre-clinical	\$46	\$111.0	\$149.8	\$164.7
Clinical	\$46	\$81.5	\$349.0	\$573.0
Total	\$92	\$192.5	\$498.8	\$737.7
<i>Capitalized</i>				
Pre-clinical	\$89	\$263.7	\$414.6	\$481.9
Clinical	\$73	\$127.5	\$578.0	\$964.9
Total	\$161	\$391.2	\$992.6	\$1446.8
<i>Assumptions</i>				
Success rate	12.0%	23.0%	21.5%	21.5%
Cost of capital	8.0%	9.0%	11.0%	11.5%

Million US\$

# 1,026 Experimental Treatments in Acute Stroke

Victoria E. O'Collins, B.Sci,<sup>1</sup> Malcolm R. Macleod, MRCP, PhD,<sup>3</sup> Geoffrey A. Donnan, MD, FRACP,<sup>2</sup>  
Laura L. Horky, MD, PhD,<sup>2</sup> Bart H. van der Worp, MD, PhD,<sup>4</sup> and David W. Howells, PhD<sup>1</sup>

Ann Neurol 2006;59:467-477



1. Laboratory setting: 2+ labs
2. Animal species: 2+ species
3. Health of animals: comorbidities
4. Sex of animals: Male and female
5. Reperfusion: tMCAo and pMCAo models
6. Time window: 1 hour post occlusion +
7. Dose response: 2+ doses
8. Route of delivery: Realistic
9. Functional and histological outcome
10. Long term effect: 4+ weeks

## NXY-059 for Acute Ischemic Stroke

Kennedy R. Lees, M.D., Justin A. Zivin, M.D., Tim Ashwood, Ph.D., Antonio Davalos, M.D., Stephen M. Davis, M.D., Hans-Christoph Diener, M.D., James Grotta, M.D., Patrick Lyden, M.D., Ashfaq Shuaib, M.D., Hans-Göran Hårdemark, M.D., and Warren W. Wasiewski, M.D., for the Stroke–Acute Ischemic NXY Treatment (SAINT I) Trial Investigators\*

### BACKGROUND

NXY-059 is a free-radical–trapping agent that is neuroprotective in animal models of stroke. We tested whether it would reduce disability in humans after acute ischemic stroke.

### METHODS

We conducted a randomized, double-blind, placebo-controlled trial involving 1722 patients with acute ischemic stroke who were randomly assigned to receive a 72-hour infusion of placebo or intravenous NXY-059 within 6 hours after the onset of the stroke. The primary outcome was disability at 90 days, as measured according to scores on the modified Rankin scale for disability (range, 0 to 5, with 0 indicating no residual symptoms and 5 indicating bedbound, requiring constant care).

### RESULTS

Among the 1699 subjects included in the efficacy analysis, NXY-059 significantly improved the overall distribution of scores on the modified Rankin scale, as compared with placebo ( $P=0.038$  by the Cochran–Mantel–Haenszel test). The common odds ratio for improvement across all categories of the scale was 1.20 (95 percent confidence interval, 1.01 to 1.42). Mortality and rates of serious and nonserious adverse events were each similar in the two groups. NXY-059 did not improve neurologic functioning as measured according to the National Institutes of Health Stroke Scale (NIHSS): the difference between the two groups in the change from baseline scores was 0.1 point (95 percent confidence interval,  $-1.4$  to  $1.1$ ;  $P=0.86$ ). Likewise, no improvement was observed according to the Barthel index ( $P=0.14$ ). In a post hoc analysis of patients who also received alteplase, NXY-059 was associated with a lower incidence of any hemorrhagic transformation ( $P=0.001$ ) and symptomatic intracranial hemorrhage ( $P=0.036$ ).

### CONCLUSIONS

The administration of NXY-059 within six hours after the onset of acute ischemic stroke significantly improved the primary outcome (reduced disability at 90 days), but it did not significantly improve other outcome measures, including neurologic functioning as measured by the NIHSS score. Additional research is needed to confirm whether NXY-059 is beneficial in ischemic stroke. (ClinicalTrials.gov number, NCT00119626.)

Lees et al, *NEJM* (2006) 354, 588-600

## NXY-059 for the Treatment of Acute Ischemic Stroke

Ashfaq Shuaib, M.D., Kennedy R. Lees, M.D., Patrick Lyden, M.D., James Grotta, M.D., Antonio Davalos, M.D., Stephen M. Davis, M.D., Hans-Christoph Diener, M.D., Tim Ashwood, Ph.D., Warren W. Wasiewski, M.D., and Ugochi Emeribe, Ph.D., for the SAINT II Trial Investigators\*

### BACKGROUND

The free-radical–trapping agent NXY-059 showed promise as a neuroprotectant in the Stroke–Acute Ischemic NXY Treatment I (SAINT I) trial, reducing disability when given to patients who had acute ischemic stroke. We sought confirmation of efficacy in a second, larger trial.

### METHODS

We enrolled 3306 patients with acute ischemic stroke in a randomized, double-blind trial to receive a 72-hour infusion of intravenous NXY-059 or placebo within 6 hours after the onset of stroke symptoms. Our primary end point was the distribution of disability scores on the modified Rankin scale at 90 days. We examined scores on neurologic and activities-of-daily-living scales as secondary end points. We also tested the hypothesis that NXY-059 would reduce alteplase-related intracranial hemorrhages.

### RESULTS

The efficacy analysis was based on 3195 patients. Prognostic factors were well balanced between the treatment groups. Mortality was equal in the two groups, and adverse-event rates were similar. The distribution of scores on the modified Rankin scale did not differ between the group treated with NXY-059 (1588 patients) and the placebo group (1607 patients;  $P=0.33$  by the Cochran–Mantel–Haenszel test; odds ratio for limiting disability, 0.94; 95% confidence interval [CI], 0.83 to 1.06). Analysis of categorized scores on the modified Rankin scale confirmed the lack of benefit: the odds ratio for trichotomization into modified Rankin scale scores of 0 to 1 versus 2 to 3 versus 4 to 6 was 0.92 (95% CI, 0.80 to 1.06). There was no evidence of efficacy for any of the secondary end points. Among patients treated with alteplase, there was no difference between the NXY-059 group and the placebo group in the frequency of symptomatic or asymptomatic hemorrhage.

### CONCLUSIONS

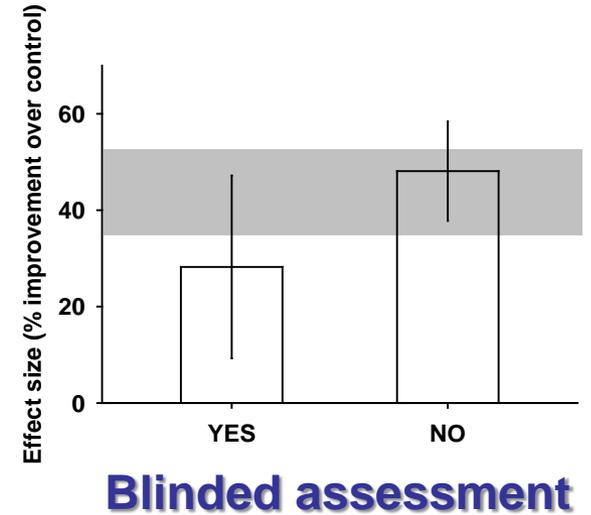
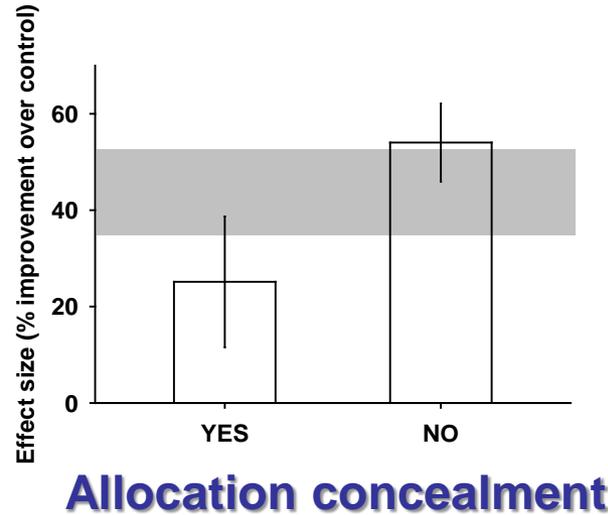
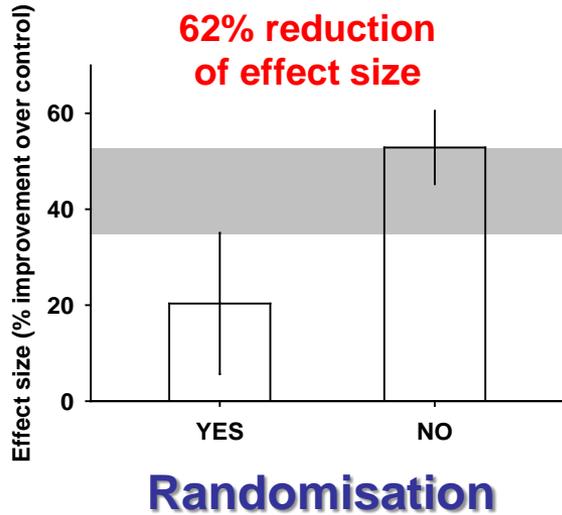
NXY-059 is ineffective for the treatment of acute ischemic stroke within 6 hours after the onset of symptoms. (ClinicalTrials.gov number, NCT00061022.)

Shuaib et al, *NEJM* (2007) 357, 562-571

## Systematic review and meta-analysis

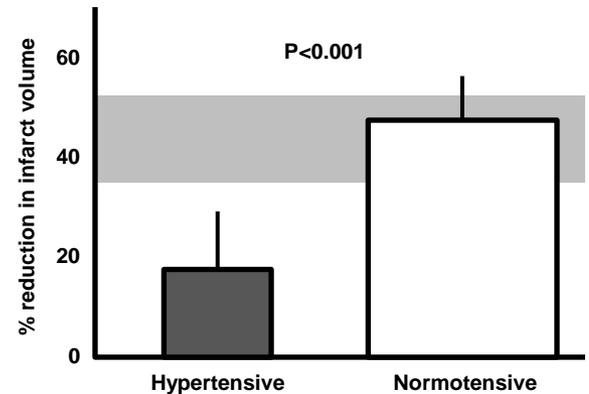
# Bias & NXY-059

- 11 publications, 29 experiments, 408 animals
- Improved outcome by 44% (35-53%)



## Co-morbidity

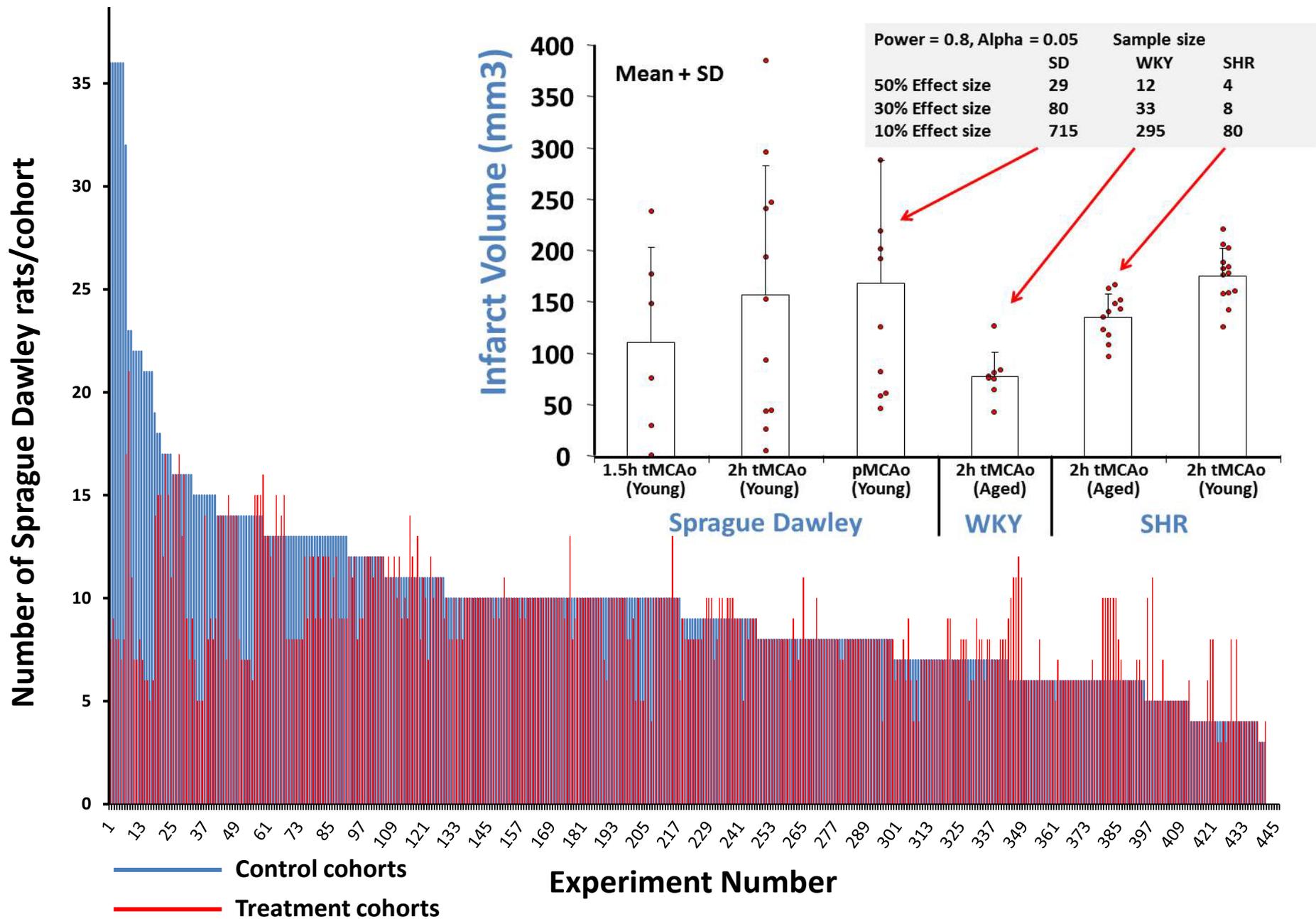
- 7% of studies used animals with hypertension
- 77% of patients in SAINT II had a history of hypertension at study entry



Macleod et al, Stroke (2008) 39, 2824-2829



# 446 Neuroprotection Experiments in Sprague Dawley rats



# 3M Combination Trial

## Selection from 1026 candidates:

- Key target mechanisms;
- Reported efficacy in animal stroke;
- Cost and availability;
- Stability;
- Mode of delivery;
- Safety.

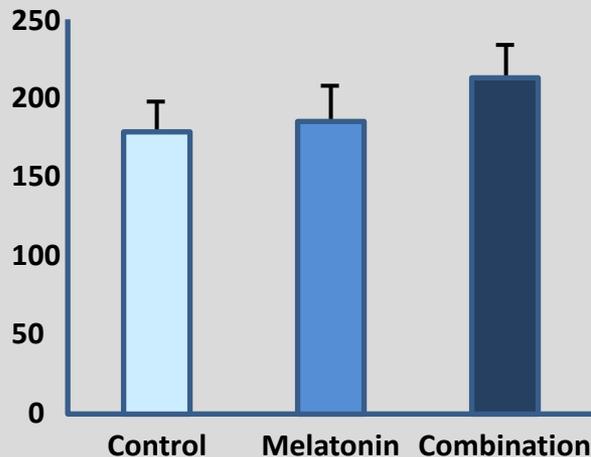
## Meta-analysis

Magnesium (Excitotoxicity)  
(M=25.9%, 95%CI=23.6-28.1%)

Melatonin (Anti-oxidant)  
(M=40.0%, 95%CI=38.0-42.1%).

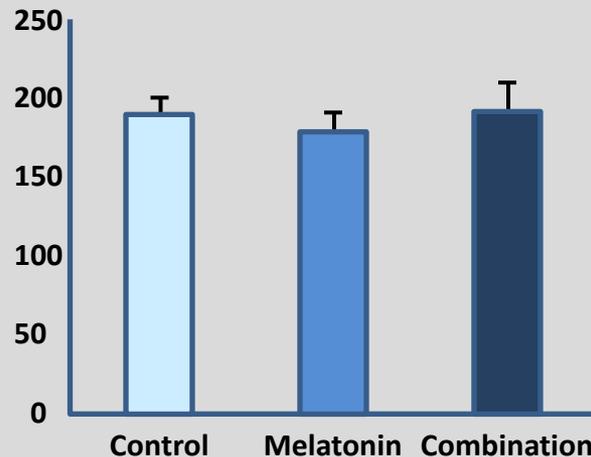
Minocycline (Anti-inflammatory)  
(M=30.6%, 95%CI=28.9-32.3%).

### Old rats, 2hr tMCAo



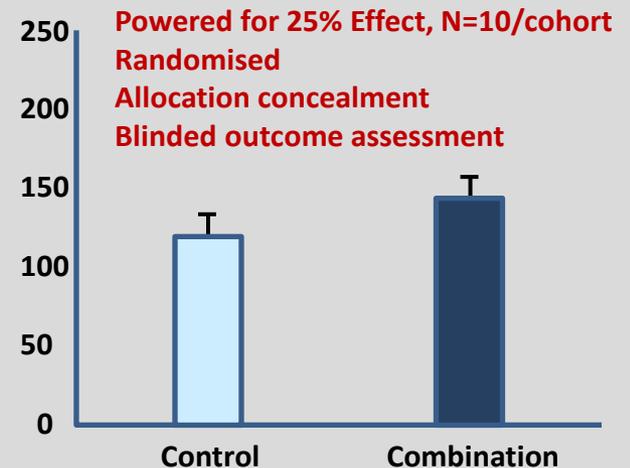
Delivery at 3 hrs

### Young rats, 2hr tMCAo



Delivery at 3 hrs

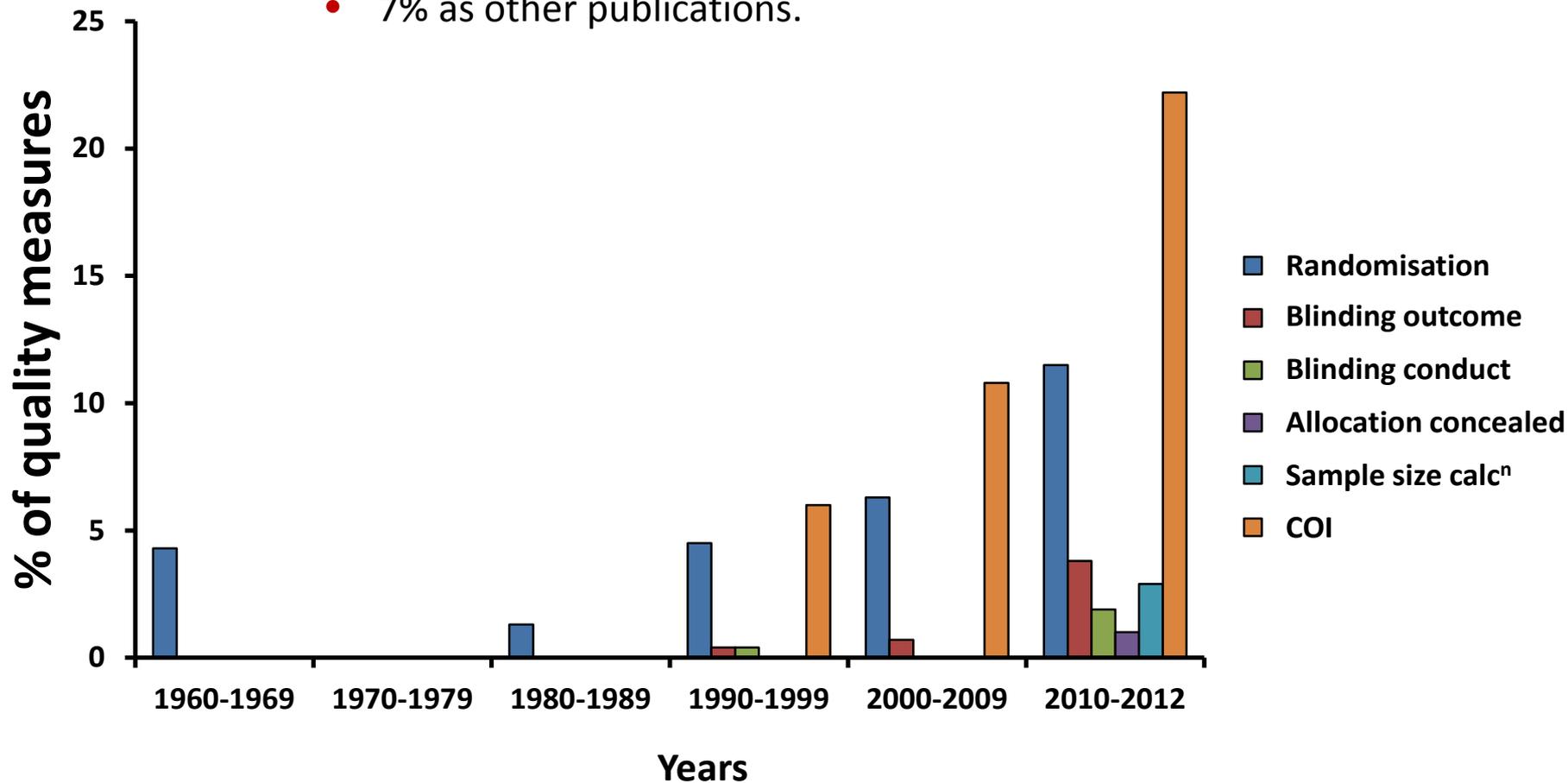
### Young rats, 1.5hr tMCAo



Delivery at occlusion

# 1000 papers randomly retrieved from PubMed

- 55% of articles identified as primary research,
- 32% as reviews,
- 5% as opinion/editorial articles,
- 1% as systematic reviews,
- 7% as other publications.



# Good Laboratory Practice

## Preventing Introduction of Bias at the Bench

Malcolm M. Macleod; Marc Fisher; Victoria O'Collins; Emily S. Sena; Ulrich Dirnagl;  
Philip M.W. Bath; Alistair Buchan; H. Bart van der Worp; Richard Traystman; Kazuo Minematsu;  
Geoffrey A. Donnan; David W. Howells

# Stroke

JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Stroke  
Association<sup>SM</sup>

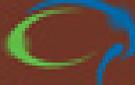
A Division of American  
Heart Association



Journal of  
Cerebral Blood Flow  
& Metabolism



# International Journal of Stroke

  
World Stroke  
Organization

# Update of the Stroke Therapy Academic Industry Roundtable Preclinical Recommendations

Marc Fisher, MD; Giora Feuerstein, MD; David W. Howells, PhD; Patricia D. Hurn, PhD; Thomas A. Kent, MD; Sean I. Savitz, MD; Eng H. Lo, PhD; for the STAIR Group  
*Stroke* 2009 40(6): 2244-50.

## **Scope of pre-clinical evaluation**

- Adequate dose-response curve
- Define the time window in a well-characterized model
- Blinded, physiologically controlled reproducible studies
- Histological and functional outcomes assessed acutely and long-term
- Initial rodent studies, then consider gyrencephalic species
- Permanent occlusion then transient in most cases

## **Recommendations for ensuring good scientific inquiry**

- Sample size calculation
- Inclusion and exclusion criteria
- Randomisation
- Allocation concealment
- Reporting of animals excluded from analysis
- Blinded assessment of outcome
- Reporting potential conflicts of interest and study funding



Collaborative Approach to Meta Analysis and

# •C•A•M•A•R•A•D•E•S•

Review of Animal Data from Experimental Stroke

- **Malcolm MacLeod**
- **Emily Sena**
- **Gillian Currie**
- **Hanna Vesterinen**
- **Peter Sandercock**
- **Ulrich Dirnagl**
- **Ana Antonic**
- **Jennifer Lees**
- **Kieren Egan**
- **Simon Koblar**
- **Verna Aykanat**
- **Mikael Jerndal**
- **Kalle Fosberg**
- **Thomas Linden**
- **Michael Nilsson**
- **Philip Bath**
- **Geoffrey Donnan**



# Cost of Stroke

## Stroke incidence

- Developed world population ~ 1.2bn
- Estimated stroke incidence 300-500 per 100,000
- Conservative estimate = 360,000-600,000/year

## Lifetime cost

- 1990 US data suggest ~\$100,000
- 2004 Australian data suggest ~\$60,000
- 2009 UK data suggest ~\$95,000

## Annual cost to developed world

- Conservative estimate = **\$21.6 – \$60.0 bn/year**

**tPA currently helps ~10% of ischemic stroke patients**