Brain Center
Rudolf Magnus

The future of stroke treatment: A European perspective

Bart van der Worp

University Medical Center Utrecht

disclosures

speaker's fees from
Boehringer Ingelheim
Bayer

Brain Center
Rudolf Magnus

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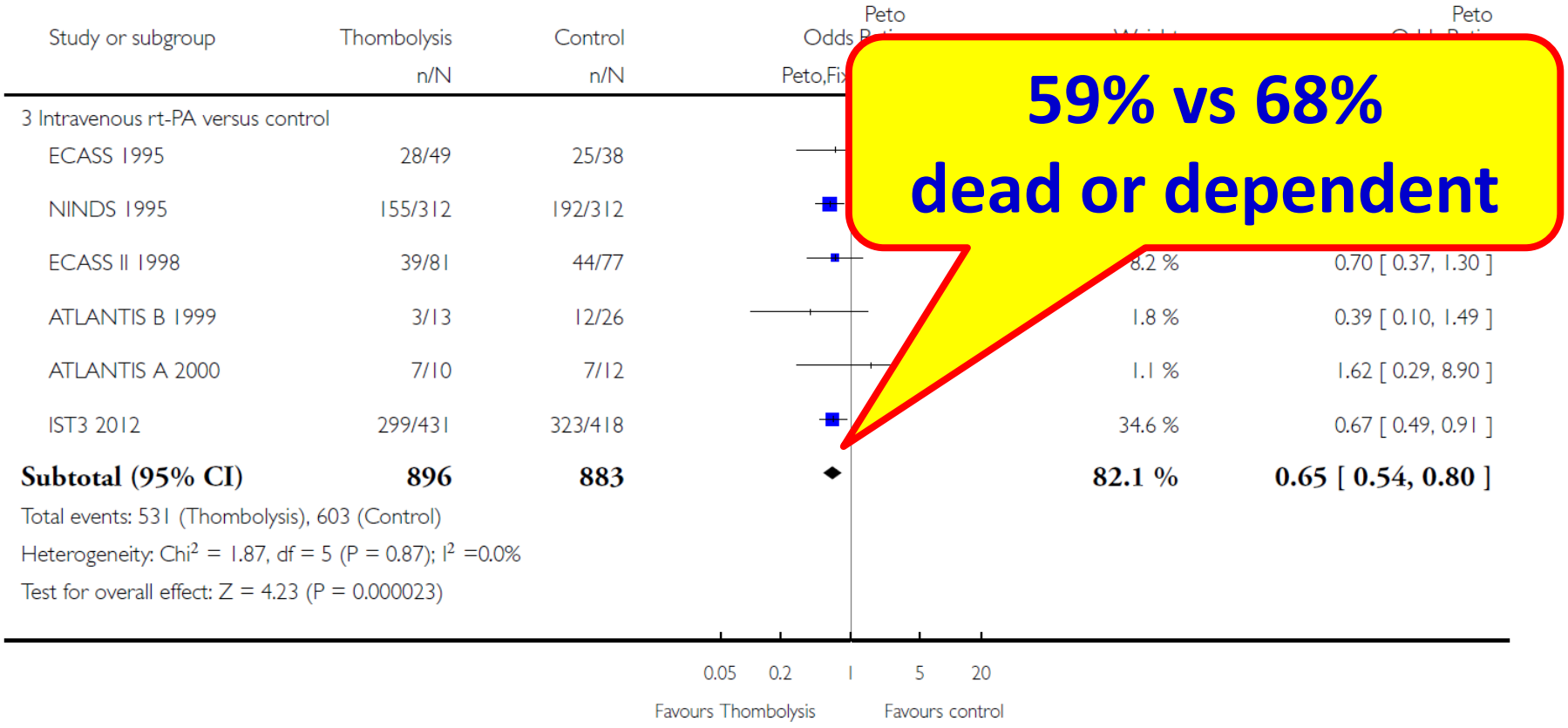
The future of stroke treatment: A dreamer's perspective

Bart van der Worp

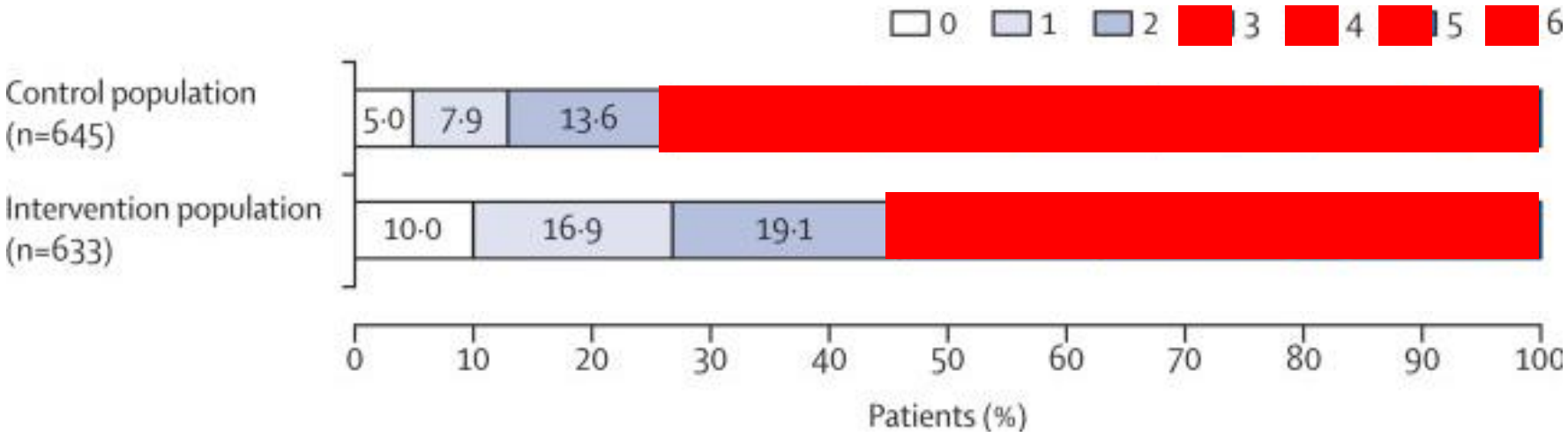
Do we need new or better stroke treatments?

dead or dependent with i.v. alteplase ≤ 3 h



Wardlaw 2014

intra-arterial treatment ≤ 6 h*



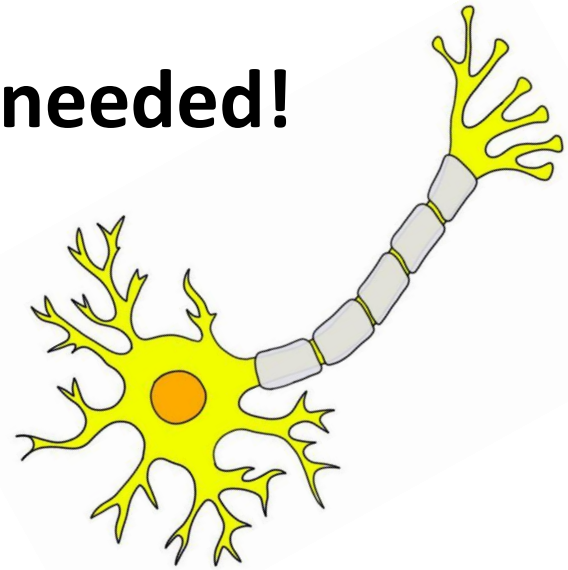
*: minority treated between 6 and 12 h

Goyal 2016

eligible for reperfusion therapy

- intravenous thrombolysis ± 20%
- intra-arterial treatment ± 10%

additional treatment options needed!

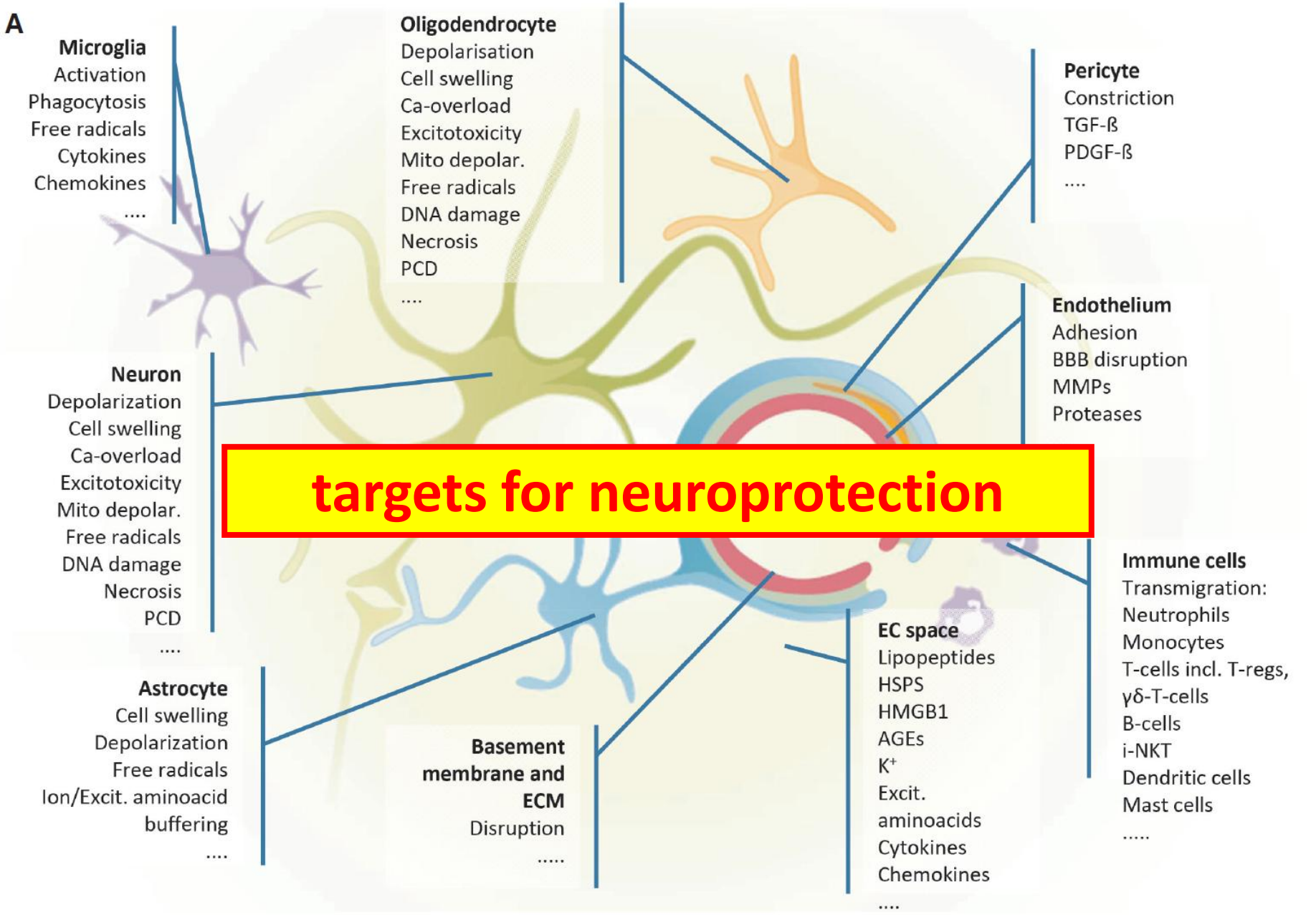


neuroprotection

- = protecting neurons from injury or degeneration
- = keeping neuronal and glial damage under the threshold of symptom manifestation

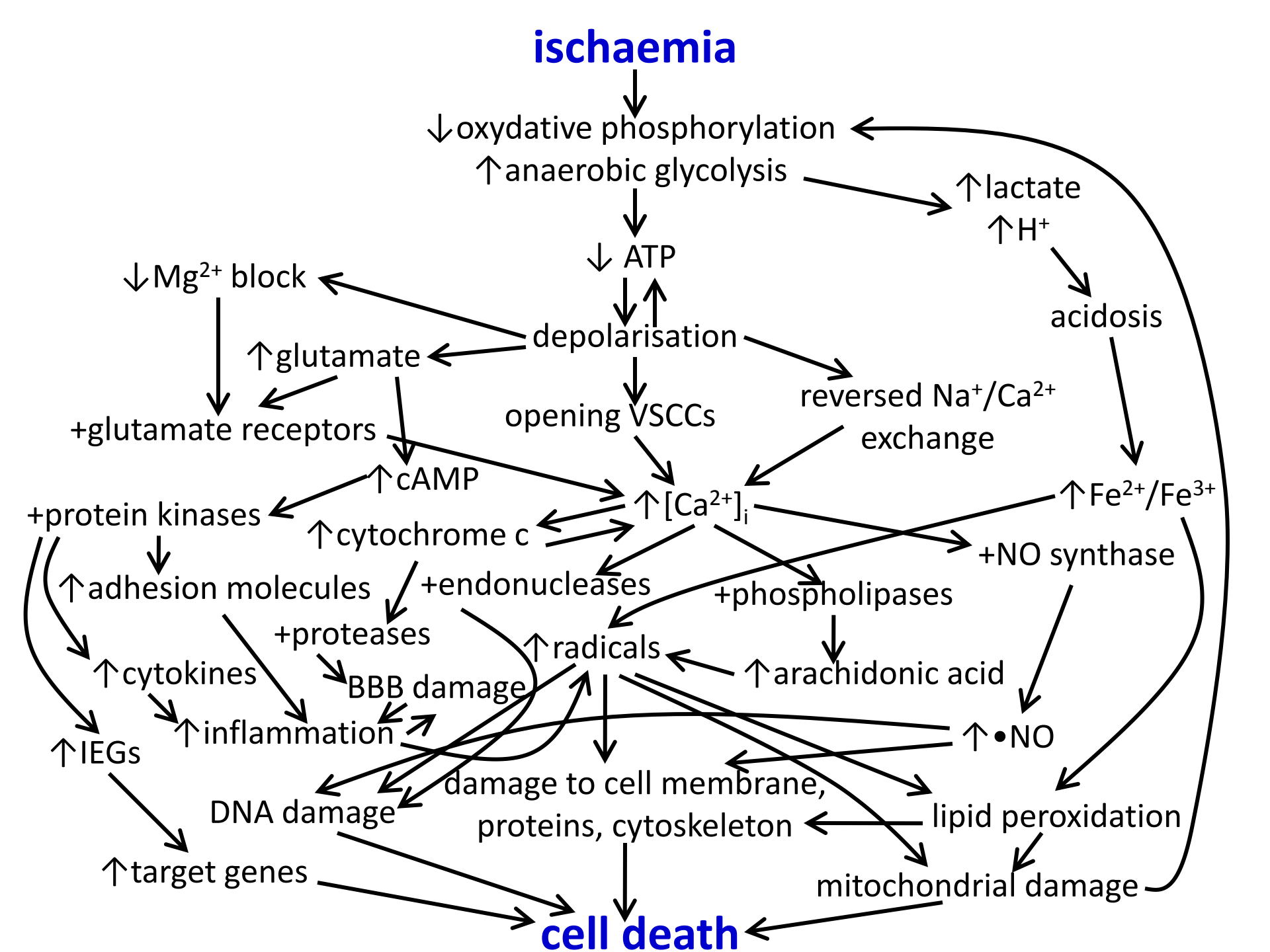
can be aimed at different targets

Chamorro 2016



Dirnagl 2014

reperfusion


ischaemia
↓oxydative phosphorylation
↑anaerobic glycolysis
↑lactate
↑H+
↓ ATP
↓Mg2+ block
depolarisation
acidosis
↑glutamate
reversed Na+/Ca2+ exchange
opening VSCCs
+glutamate receptors
↑cAMP
↑[Ca2+]i
↑Fe2+/Fe3+
+protein kinases
↑cytochrome c
+NO synthase
↑adhesion molecules
+endonucleases
+phospholipases
+proteases
↑radicals
↑cytokines
BBB damage
↑arachidonic acid
↑inflammation
↑•NO
↑IEGs
damage to cell membrane, proteins, cytoskeleton
DNA damage
lipid peroxidation
↑target genes
mitochondrial damage
cell death

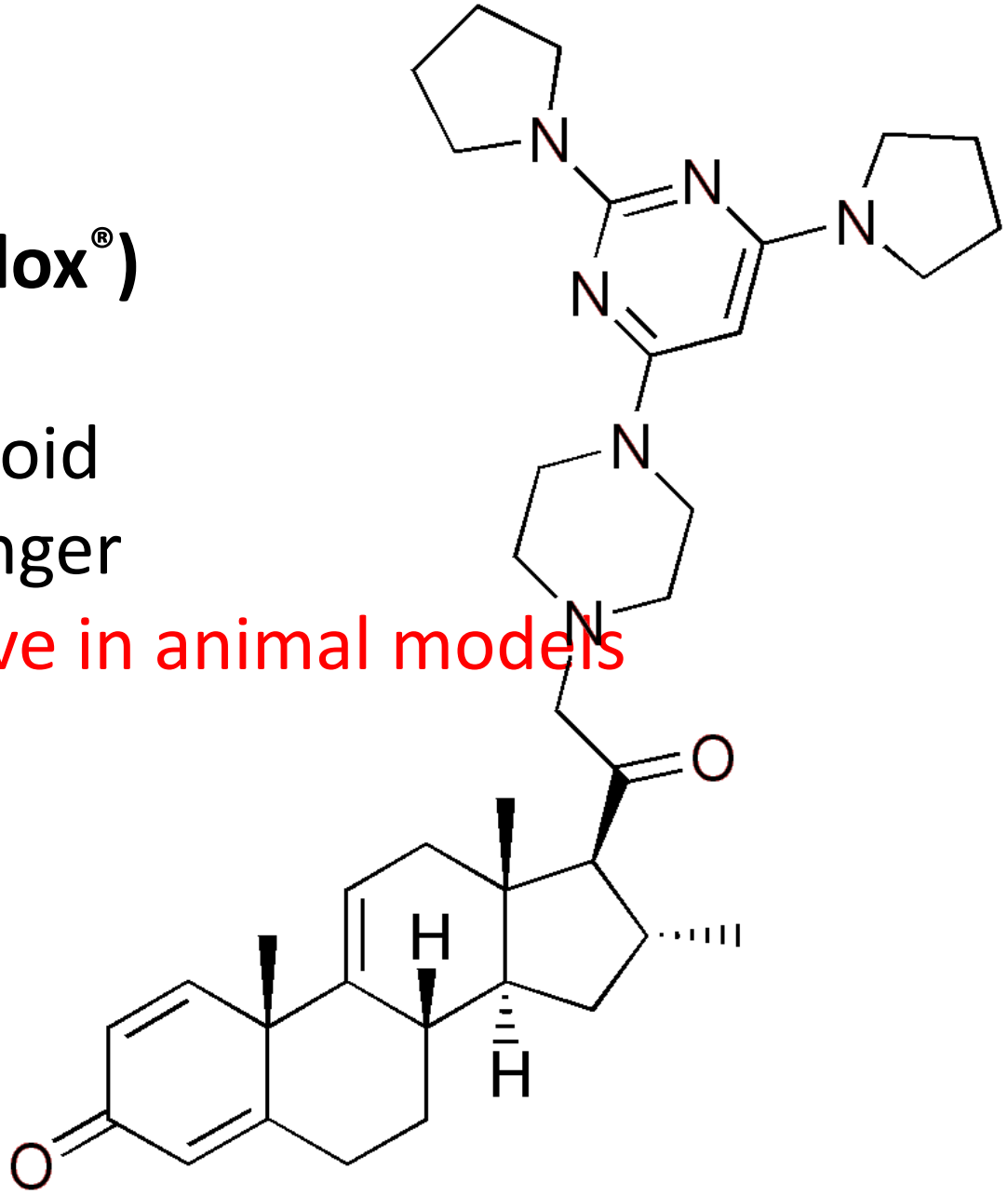
1994

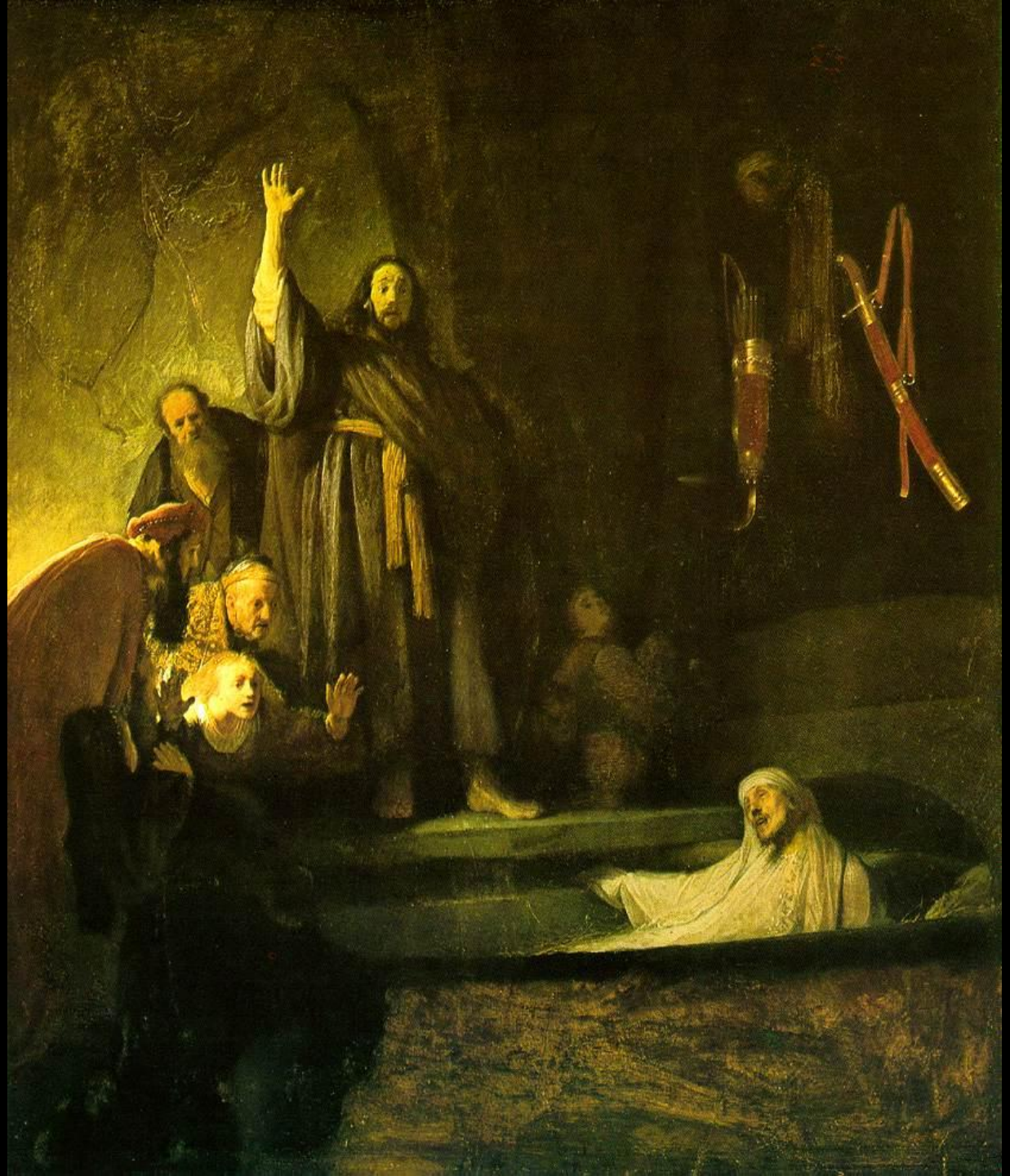
Tirilazad Efficacy Stroke Study (TESS)

- randomised
- double-blind
- international
- acute ischaemic stroke
- tirilazad mesylate vs. placebo
- n = 900
- Upjohn

tirilazad (Freedox®)

- 21-aminosteroid
- radical scavenger
- highly effective in animal models
- “lazaroid”

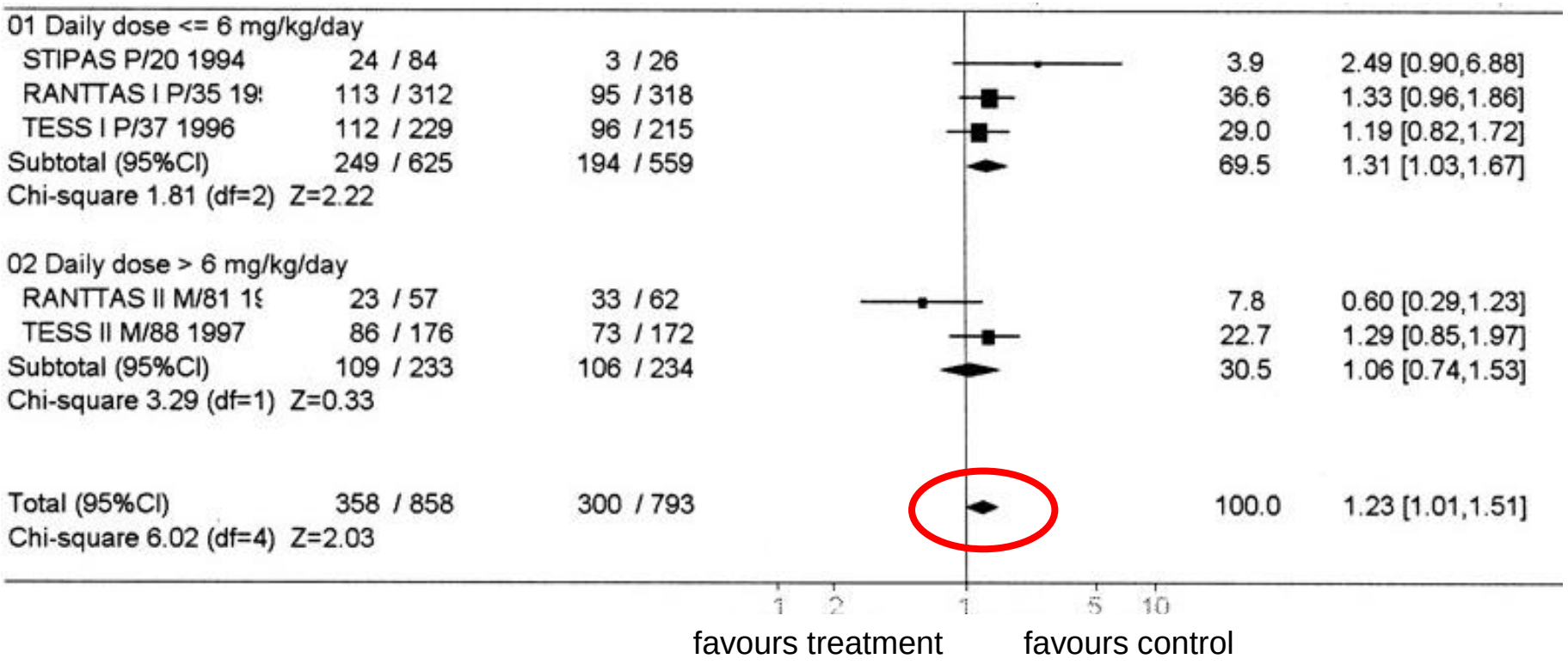




Rembrandt
van Rijn, c 1630

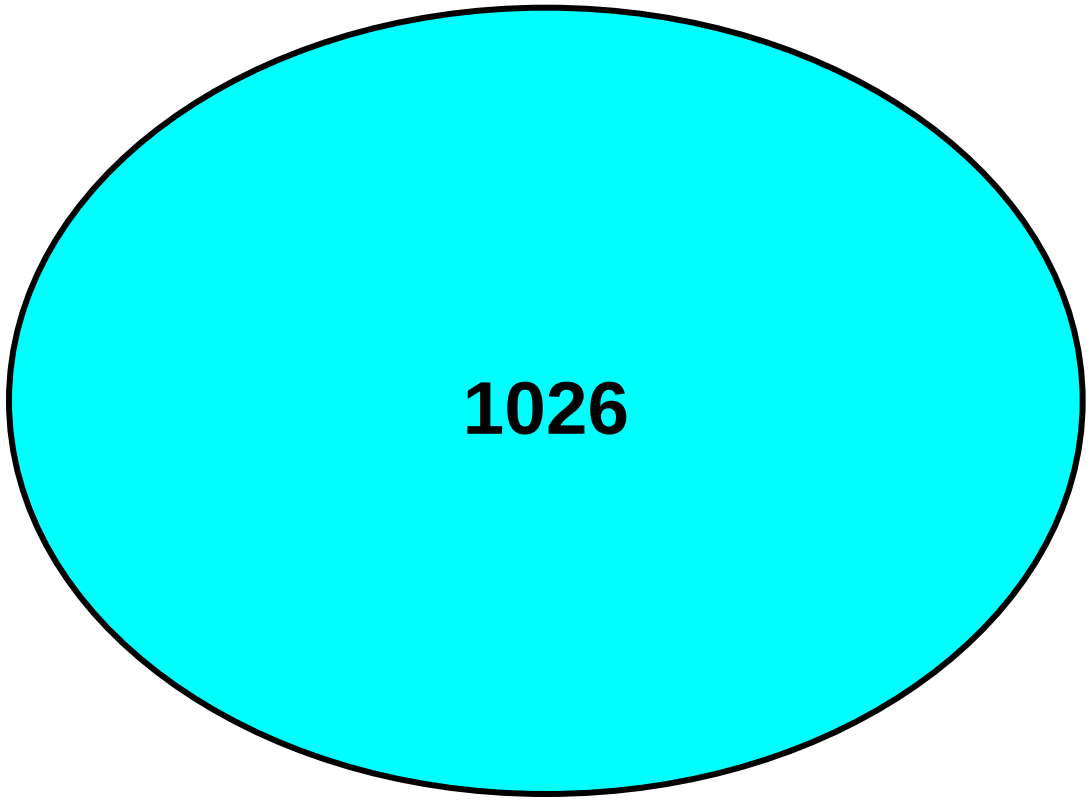

CARLTON

tirilazad meta-analysis 2000



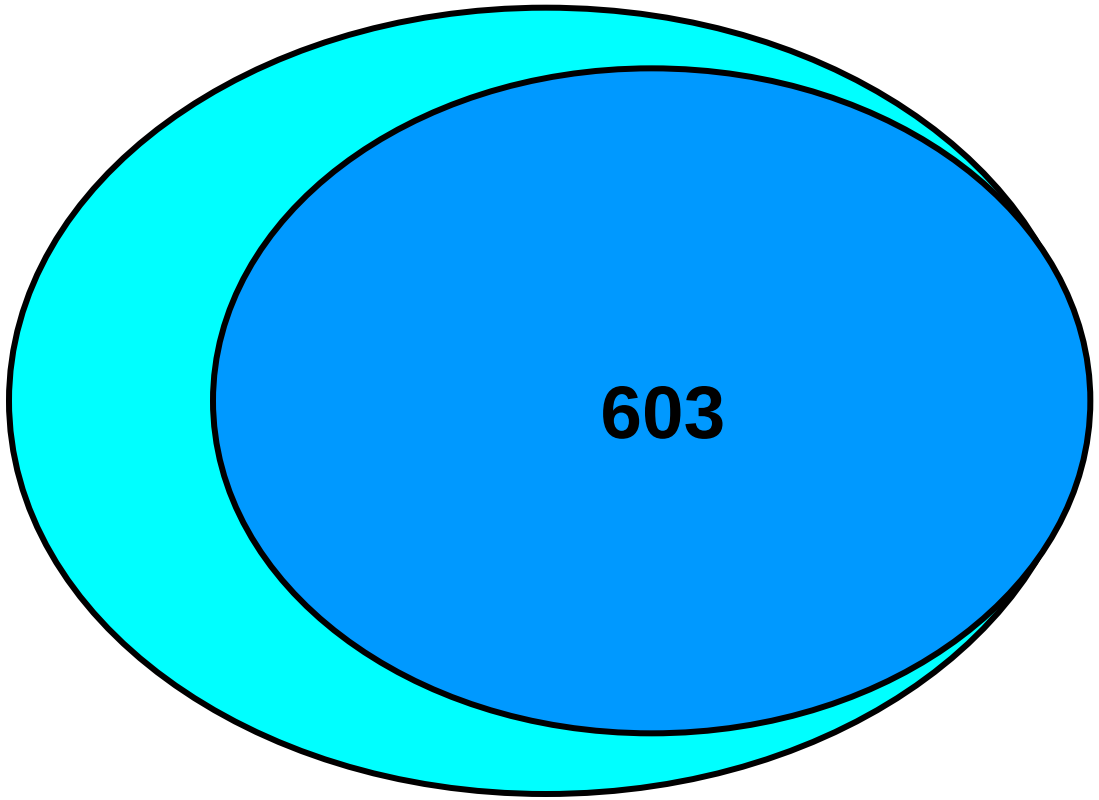
Tirilazad International Steering Committee 2000

tested in animal models of cerebral ischemia



O'Collins 2006

tested in models of focal cerebral ischemia



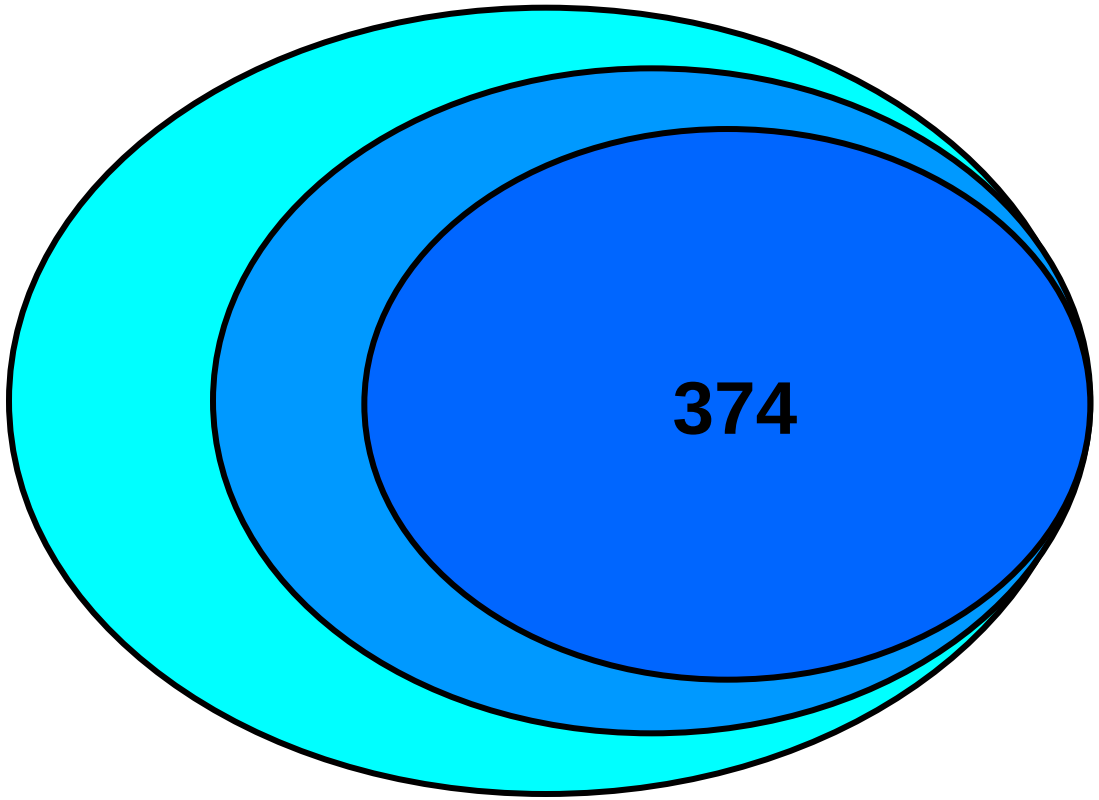
O'Collins 2006

- antioxidants
- calcium antagonists
- anti-inflammatory agents
- thrombolytics
- …

- Polynesian ceremonial beverages
- aged garlic
- sea snail peptides
- Gingko biloba extracts
- …

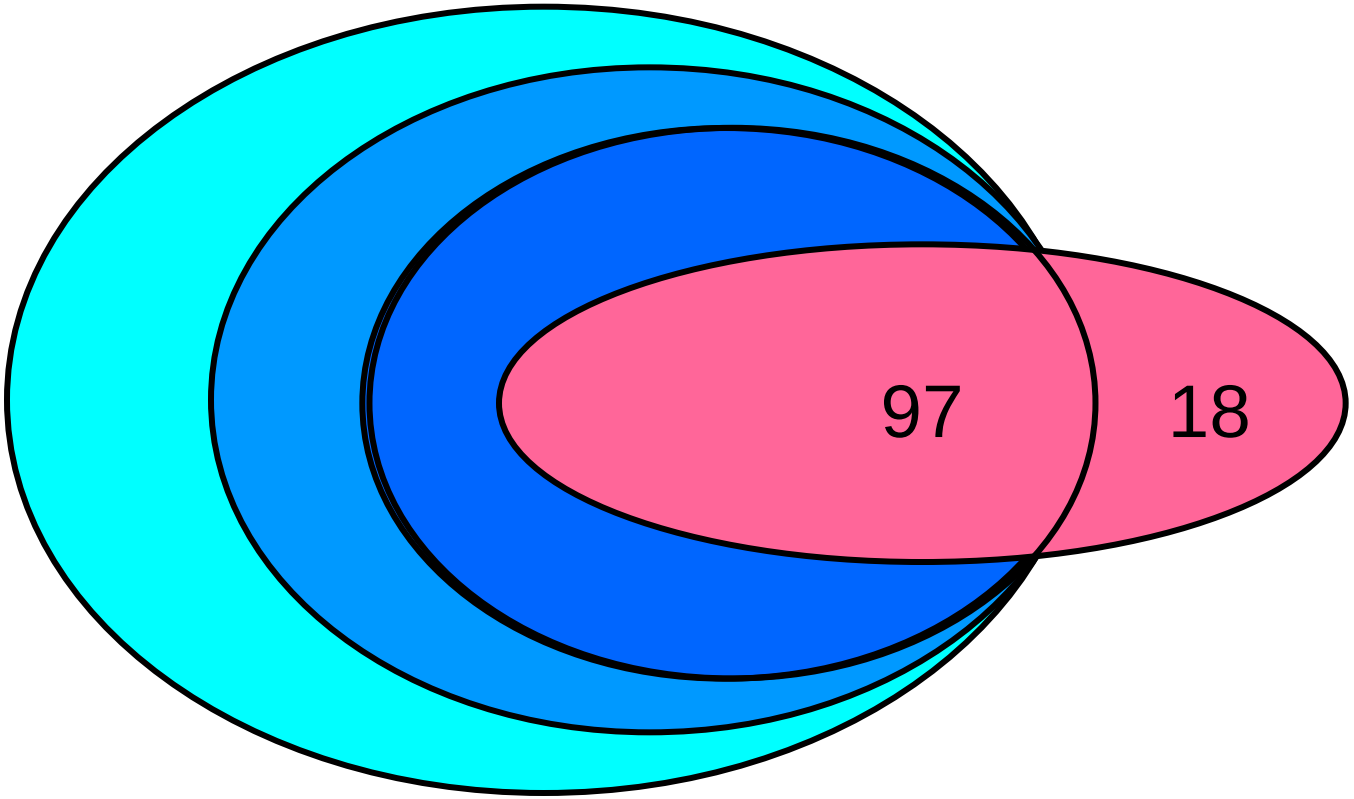
O'Collins 2006

effective in models of focal cerebral ischemia



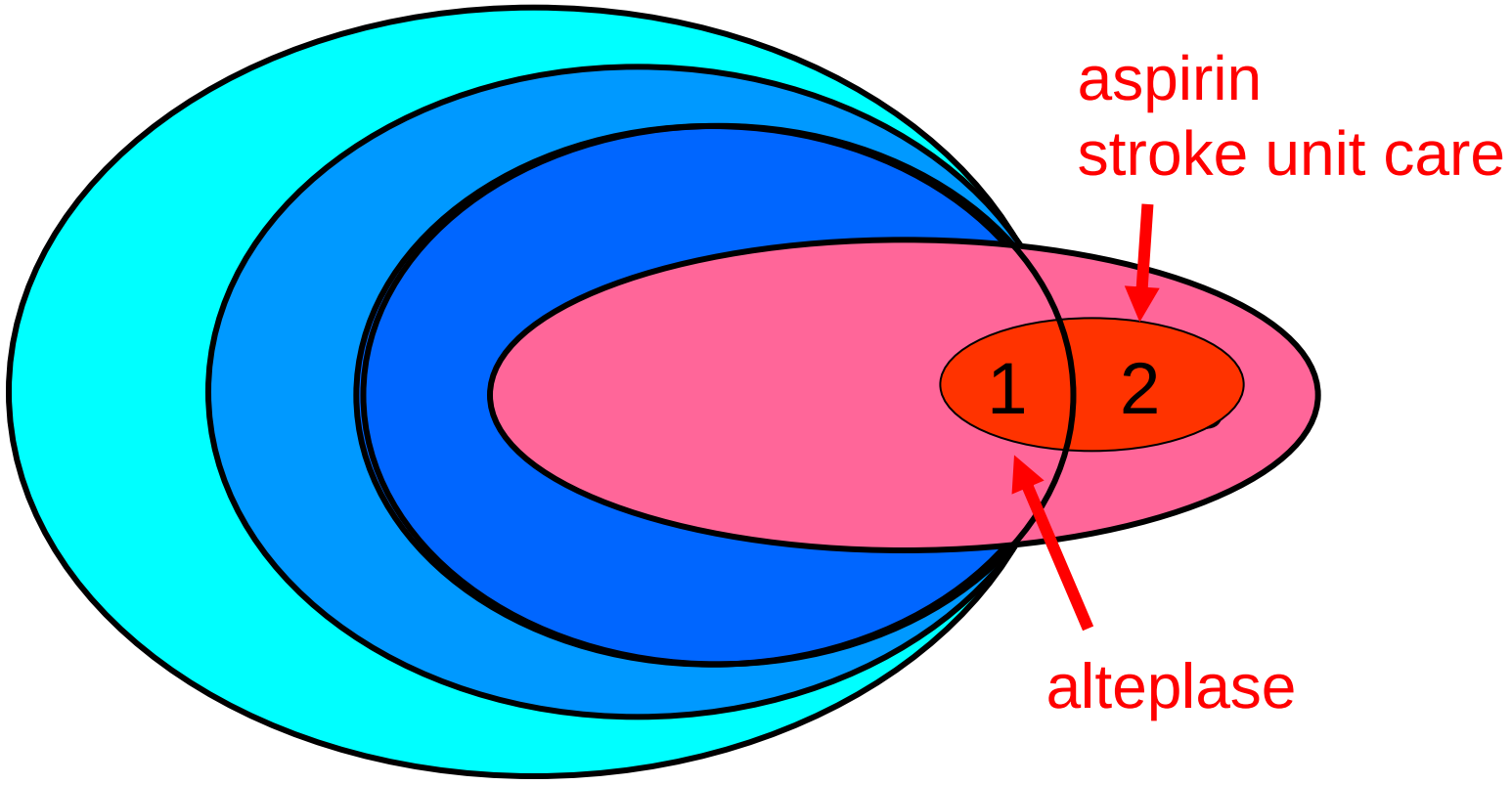
O'Collins 2006

tested in clinical trials of ischaemic stroke



O'Collins 2006

effective in clinical trials of ischaemic stroke



O'Collins 2006

gap between laboratory and clinic

causes

- limitations clinical trials
- limitations animal studies
  - methodology (internal validity)
  - generalisability (external validity)
- publication bias

internal validity

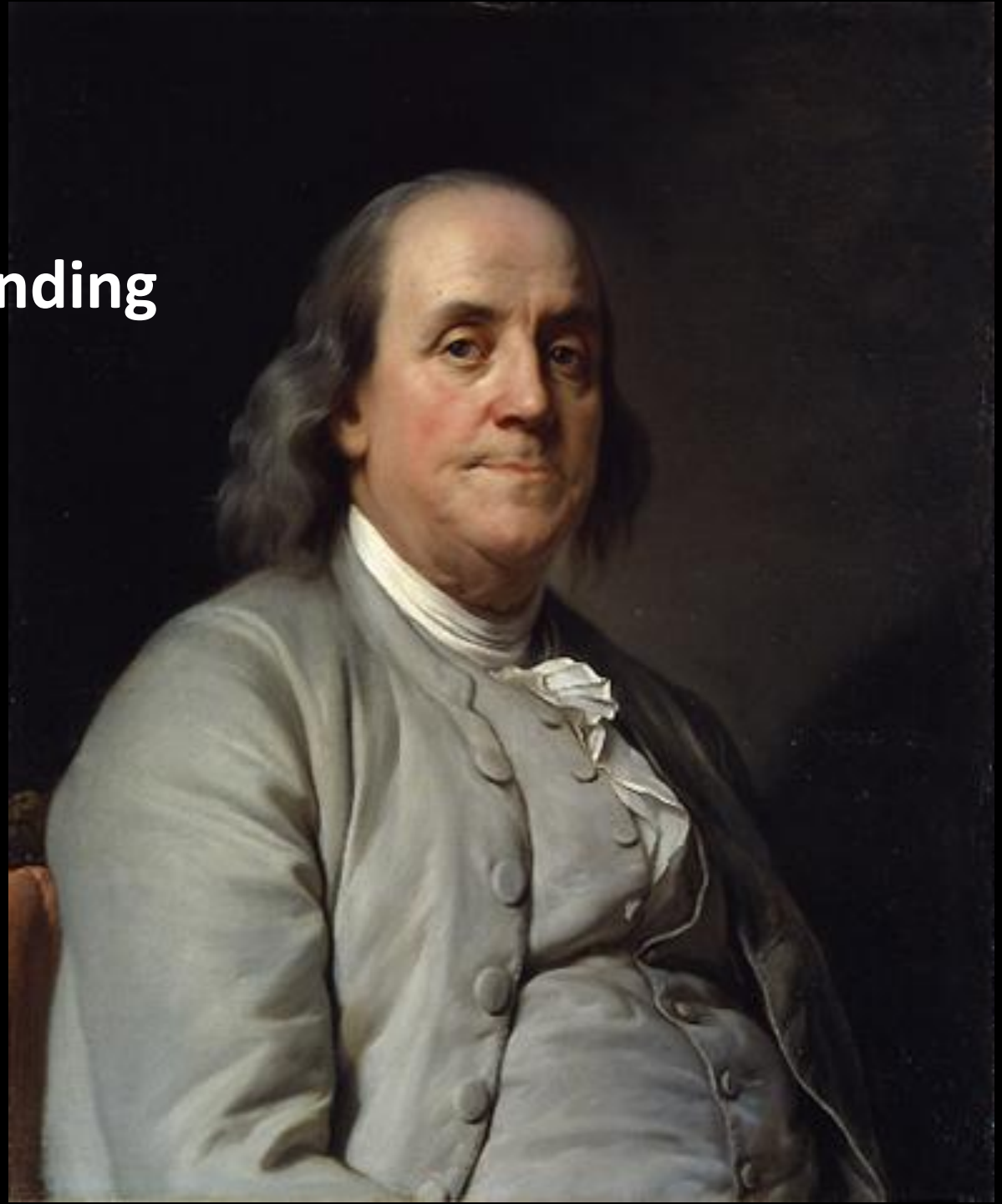
- randomisation
- blinded outcome assessment
- sample size calculation
- …

randomisation

- used in clinical trials since 1948
- main advantage
  - eliminates selection bias

Moher 2010

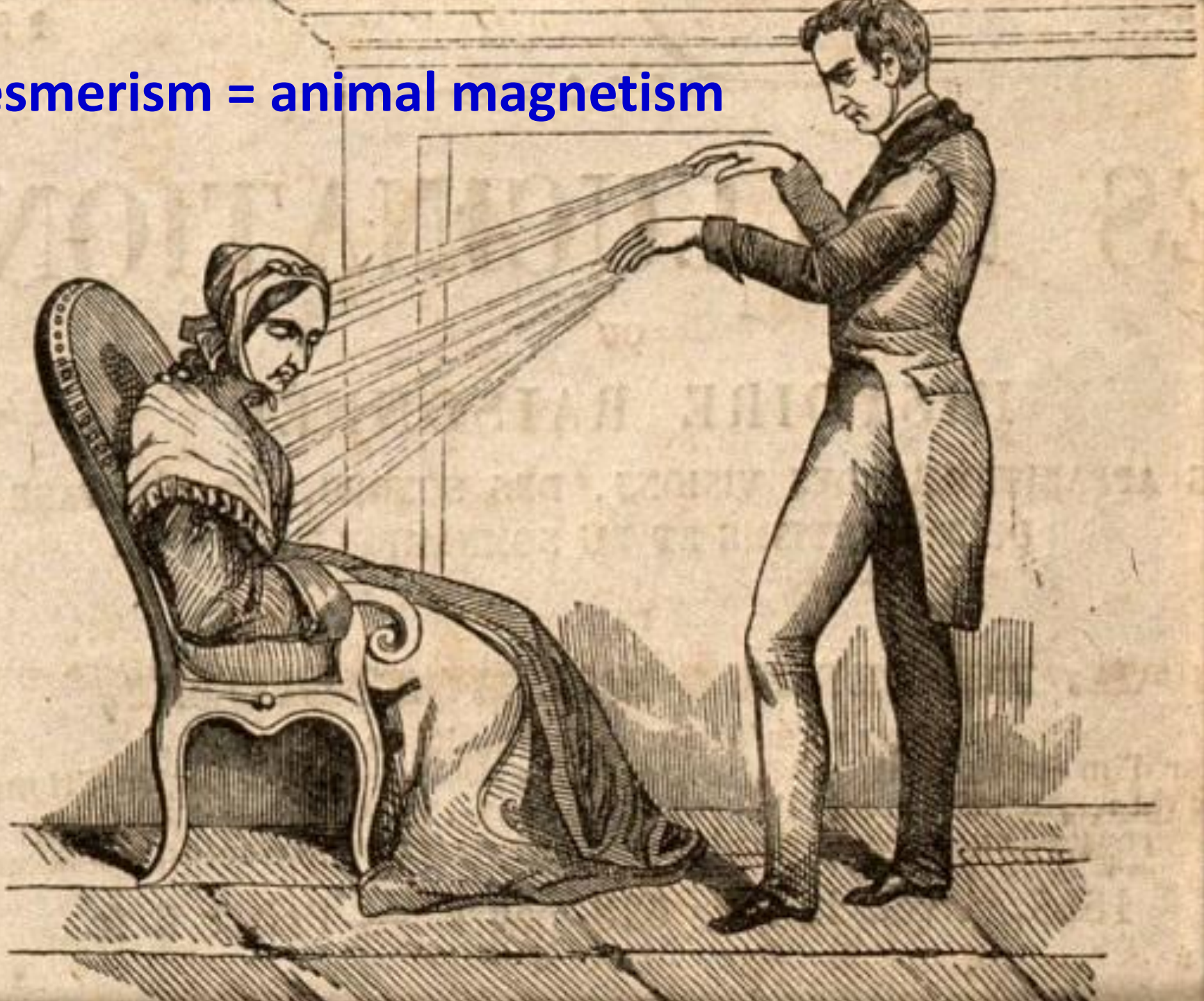
blinding



Benjamin Franklin 1706 - 1790


Louis XVI

Mesmerism = animal magnetism



Kaptchuk 1998

1784

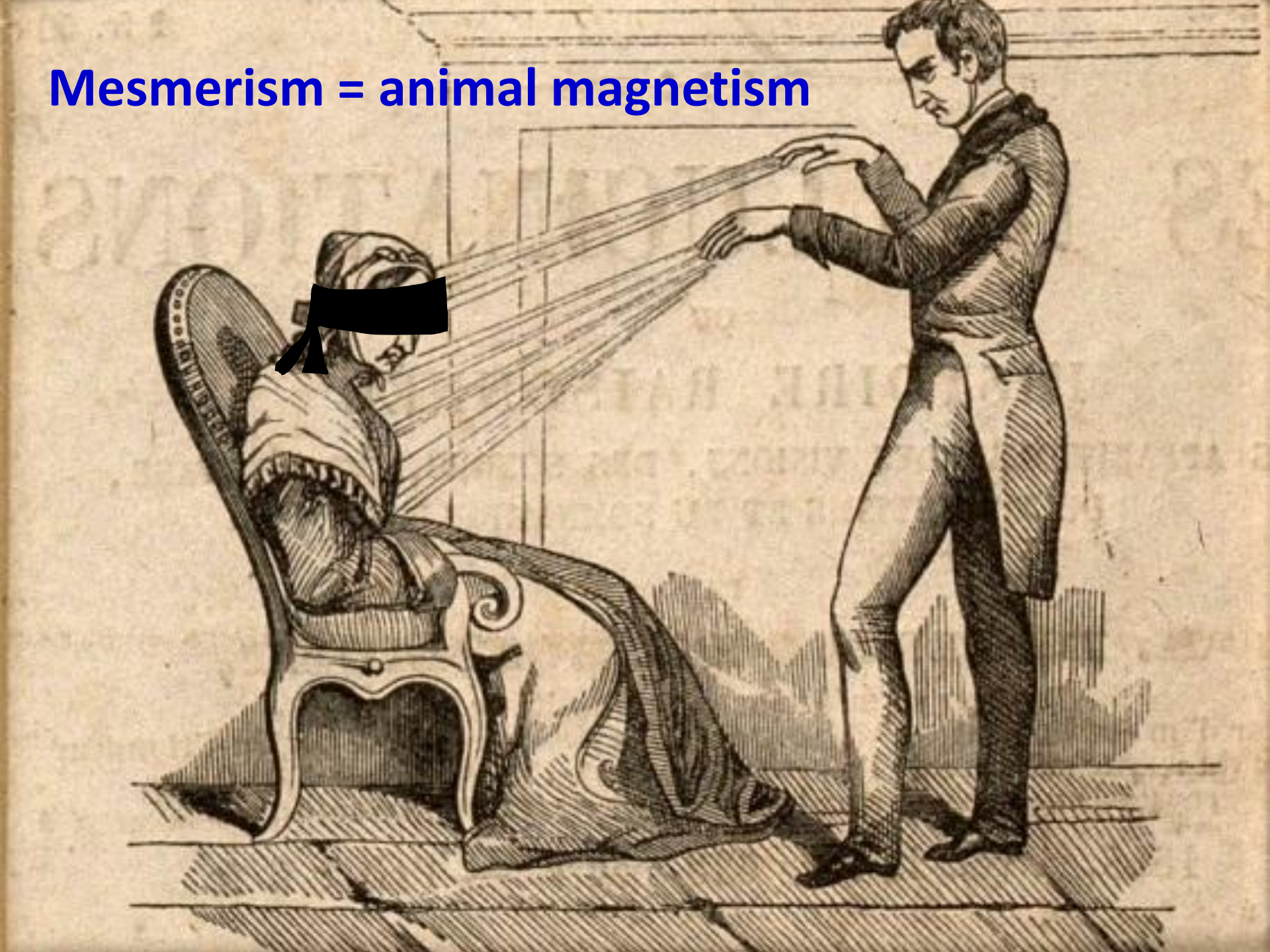
blindfolding of patients

Antoine Lavoisier

Joseph-Ignace Guillotin

Jean-Sylvain Bailly

Mesmerism = animal magnetism



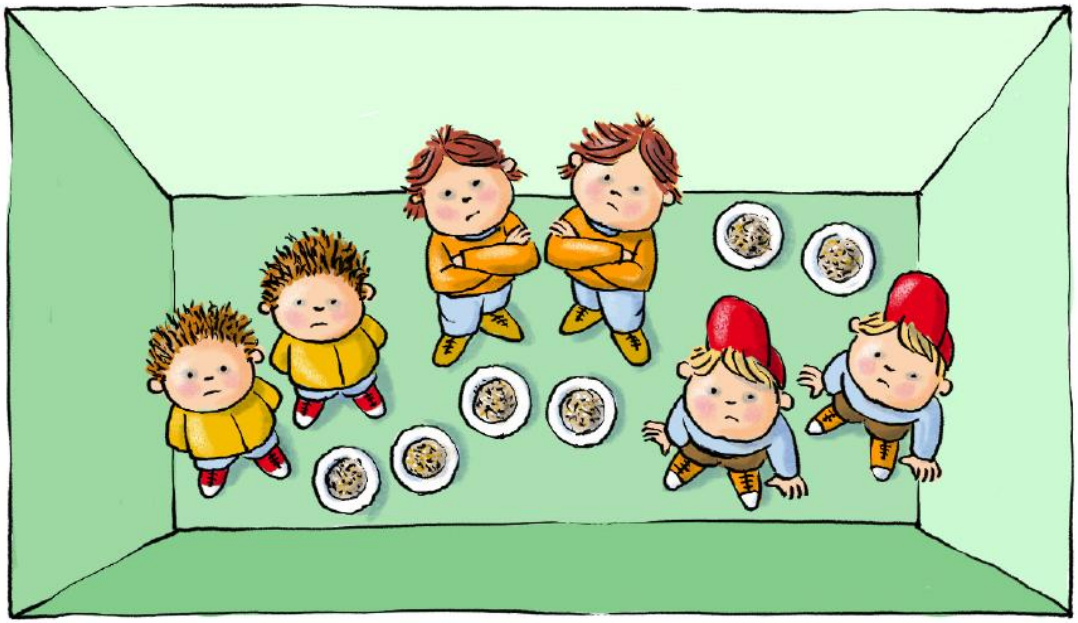
CAMARADES reviews of animal stroke studies

8 reviews
318 studies
11,417 animals

randomisation	34%
blinded outcome assessment	29%
sample size calculation	3%

Van der Worp 2010


generalisability



Dirnagl 2016

Does study quality matter?

- randomisation
- blinding

SR & meta-analysis NXY-059 for stroke

The NEW ENGLAND JOURNAL of MEDICINE

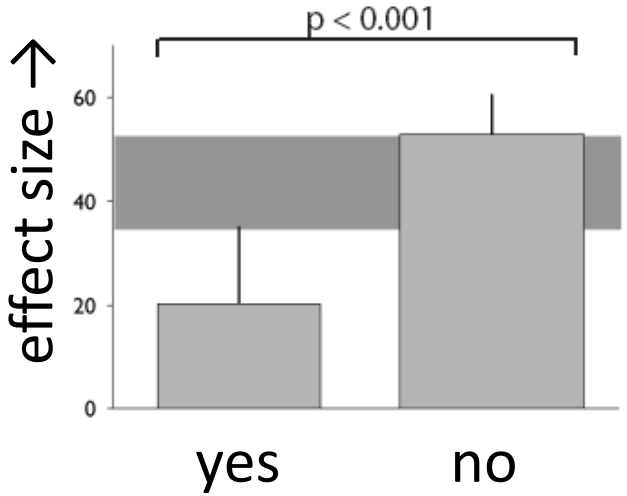
ORIGINAL ARTICLE

NXY-059 for the Treatment of Acute Ischemic Stroke

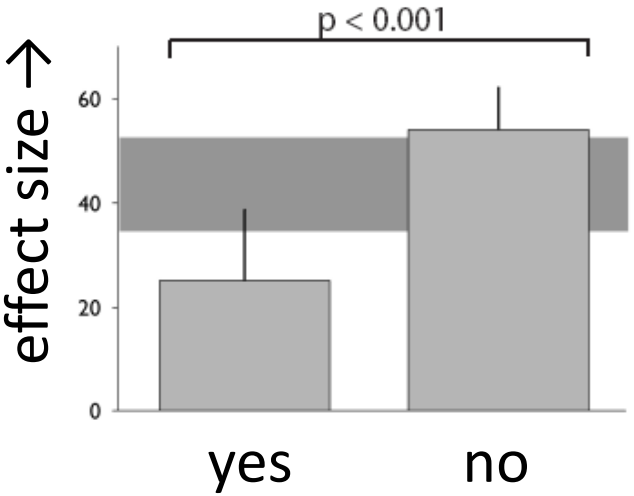
Ashfaq Shuaib, M.D., Kennedy R. Lees, M.D., Patrick Lyden, M.D., James Grotta, M.D., Antonio Davalos, M.D., Stephen M. Davis, M.D., Hans-Christoph Diener, M.D., Tim Ashwood, Ph.D., Warren W. Wasiewski, M.D., and Ugochi Emeribe, Ph.D., for the SAINT II Trial Investigators*

SR & meta-analysis NXY-059 for stroke

randomisation



blinded outcome assessment



Macleod 2008

association ≠ causal relationship

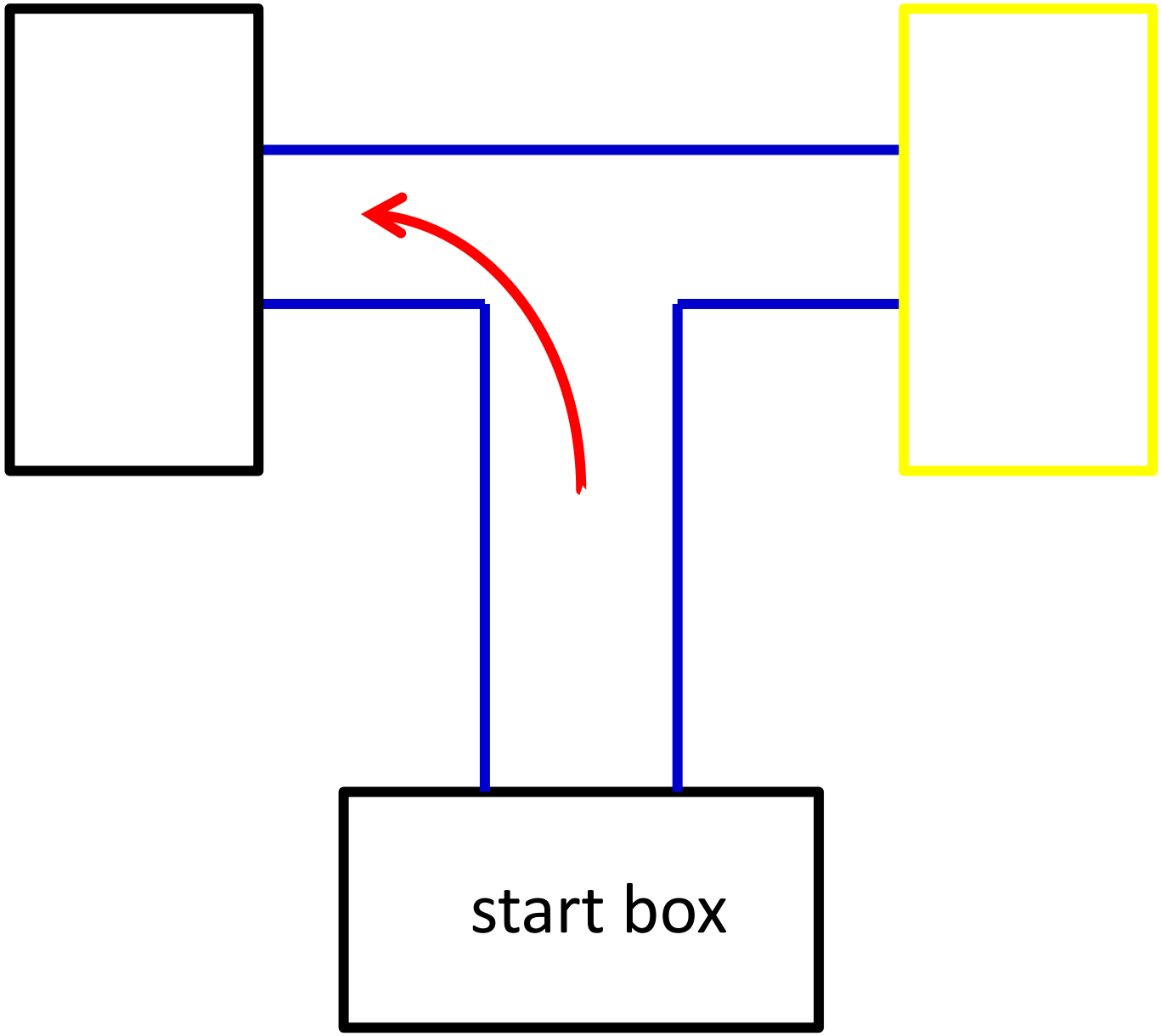
LIST	STATE	AVERAGE POPULATION IQ	PRESIDENT ELECT
1	Connecticut	113	John Kerry
2	Massachusetts	111	John Kerry
3	New Jersey	111	John Kerry
4	New York	109	John Kerry
5	Rhode Island	107	John Kerry
6	Hawaii	106	John Kerry
7	Maryland	105	John Kerry
8	New Hampshire	105	John Kerry
9	Illinois	104	John Kerry
10	Delaware	103	John Kerry
11	Minnesota	102	John Kerry
12	Vermont	102	John Kerry
13	Washington	102	John Kerry
14	California	101	John Kerry
15	Pennsylvania	101	John Kerry
16	Maine	100	John Kerry
17	Virginia	100	George Bush
18	Wisconsin	100	John Kerry
19	Colorado	99	George Bush
20	Iowa	99	George Bush
21	Michigan	99	John Kerry
22	Nevada	99	George Bush
23	Ohio	99	George Bush
24	Oregon	99	John Kerry
25	Alaska	98	George Bush
26	Florida	98	George Bush
27	Missouri	98	George Bush
28	Kansas	96	George Bush
29	Nebraska	95	George Bush
30	Arizona	94	George Bush
31	Indiana	94	George Bush
32	Tennessee	94	George Bush
33	North Carolina	93	George Bush
34	West Virginia	93	George Bush
35	Arkansas	92	George Bush
36	Georgia	92	George Bush
37	Kentucky	92	George Bush
38	New Mexico	92	George Bush
39	North Dakota	92	George Bush
40	Texas	92	George Bush
41	Alabama	90	George Bush
42	Louisiana	90	George Bush
43	Montana	90	George Bush
44	Oklahoma	90	George Bush
45	South Dakota	90	George Bush
46	South Carolina	89	George Bush
47	Wyoming	89	George Bush
48	Idaho	87	George Bush
49	Utah	87	George Bush
50	Mississippi	85	George Bush

“The effect of experimenter bias on the performance of the albino rat”

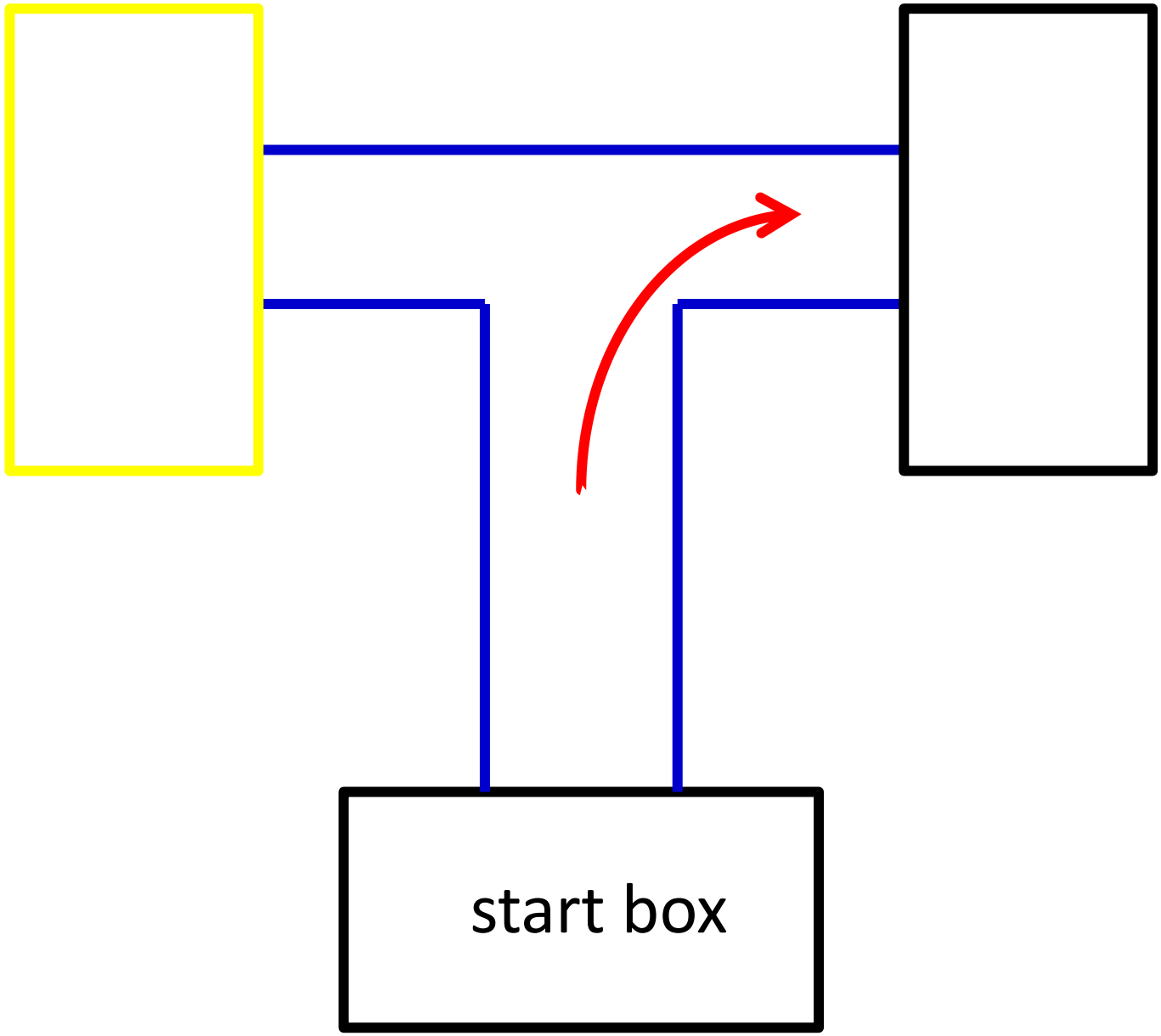
- 12 students
- 60 rats

- students trained rats on T-maze task
- 10 trials / day for 5 days

Rosenthal & Fode 1963



Rosenthal & Fode 1963



Rosenthal & Fode 1963

students randomised

- “maze-bright” rats
- “maze-dull” rats

- outcome measure: # correct responses

Rosenthal & Fode 1963

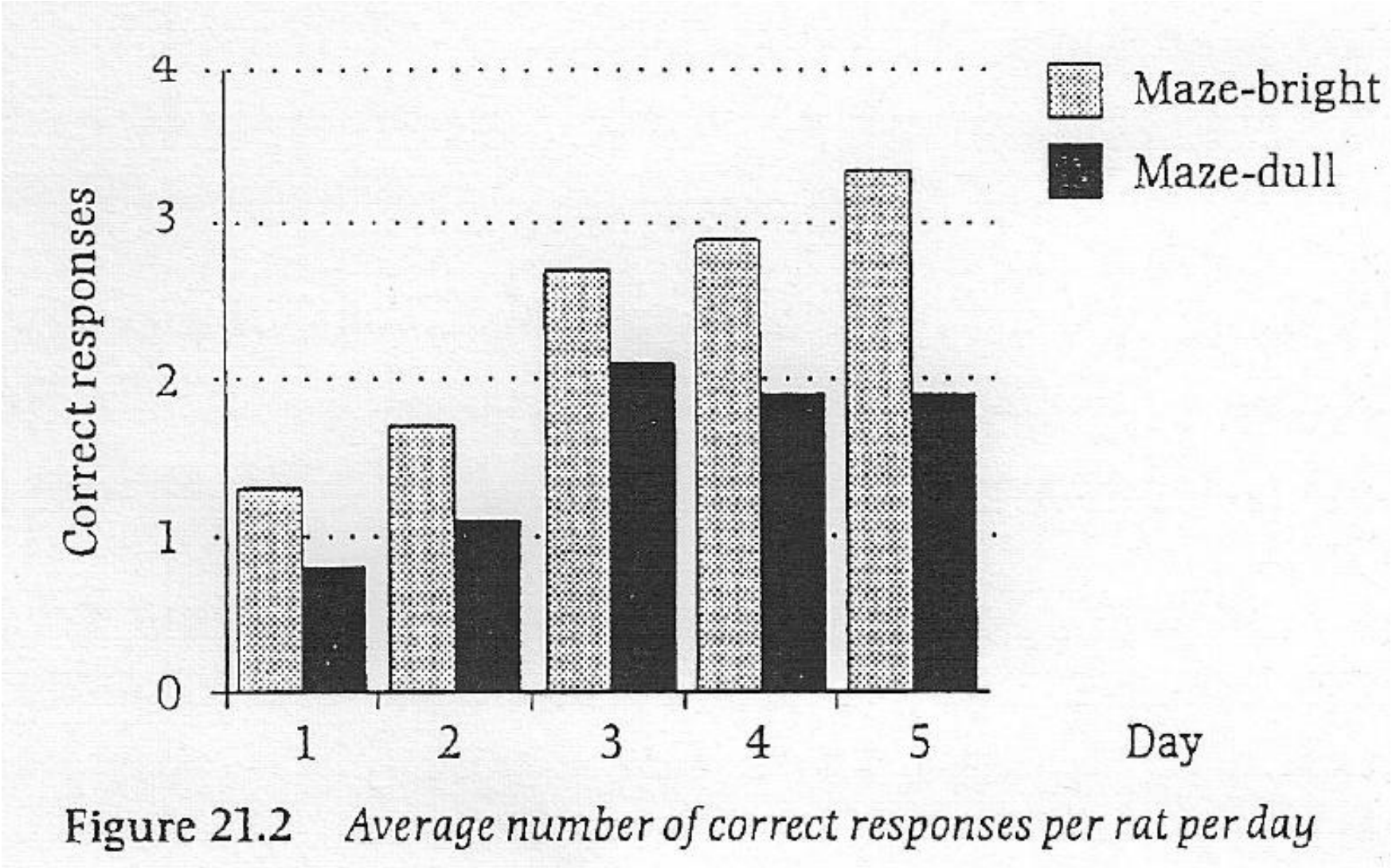


Figure 21.2 *Average number of correct responses per rat per day*

Rosenthal & Fode 1963

post-experimental questionnaire

maze-bright rats

- cleaner
- brighter
- more tame
- more pleasant

Rosenthal & Fode 1963

conclusion

- researchers too easily find what they are looking for
- → detection bias

- solution: **blinded outcome assessment**

options for improvement

reporting guidelines

CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials

Kenneth F Schulz,[1] Douglas G Altman,[2] David Moher,[3] for the CONSORT Group

options for improvement

reporting guidelines

OPEN ACCESS Freely available online

PLoS BIOLOGY

Perspective

Improving Bioscience Research Reporting: The ARRIVE Guidelines for Reporting Animal Research

Carol Kilkenny[1*], William J. Browne[2], Innes C. Cuthill[3], Michael Emerson[4], Douglas G. Altman[5]

a message from the President to those who continue to perform animal stroke studies of poor quality:

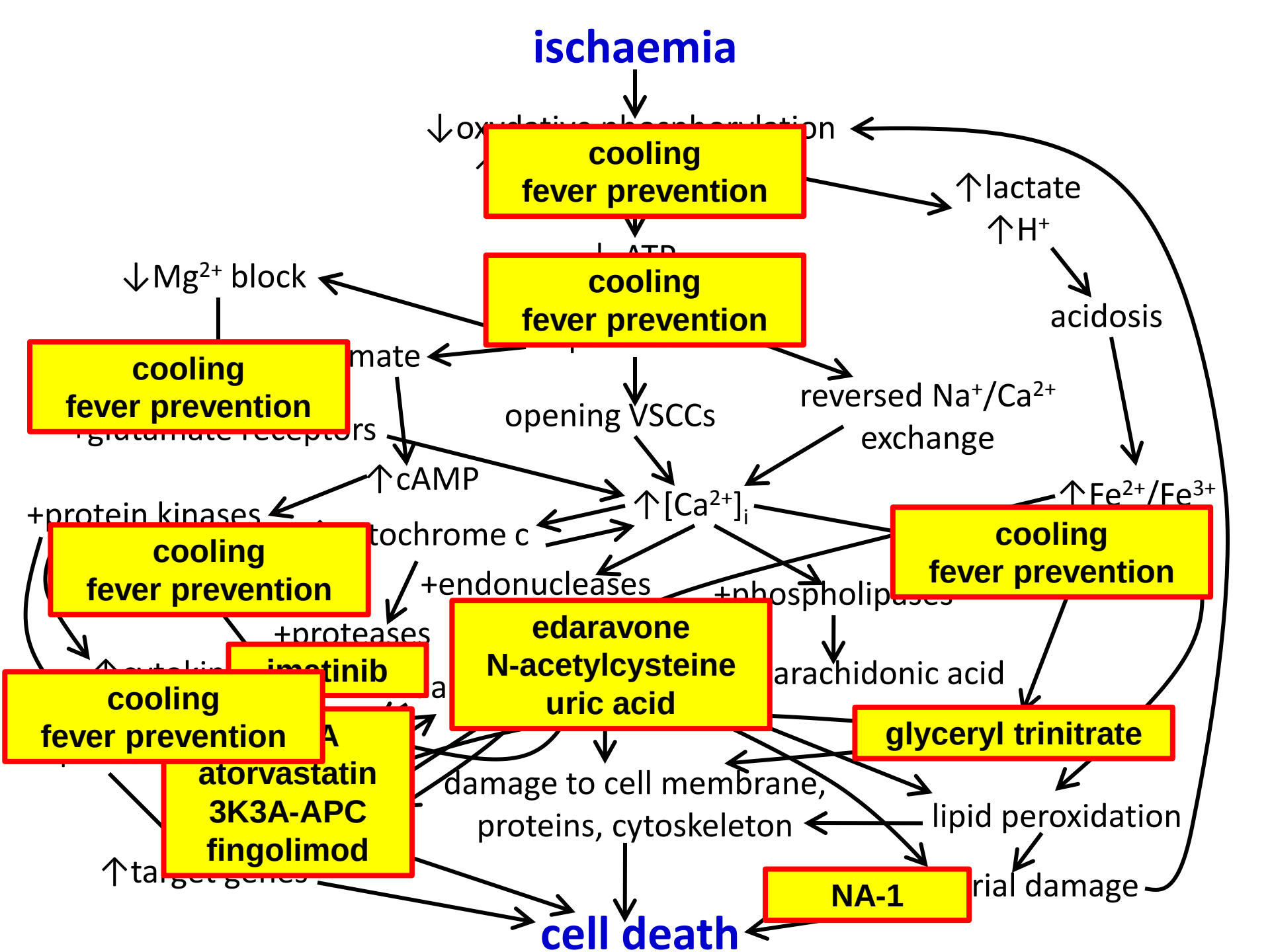

E PLURIBUS UNUM

requirements for testing in clinical trial

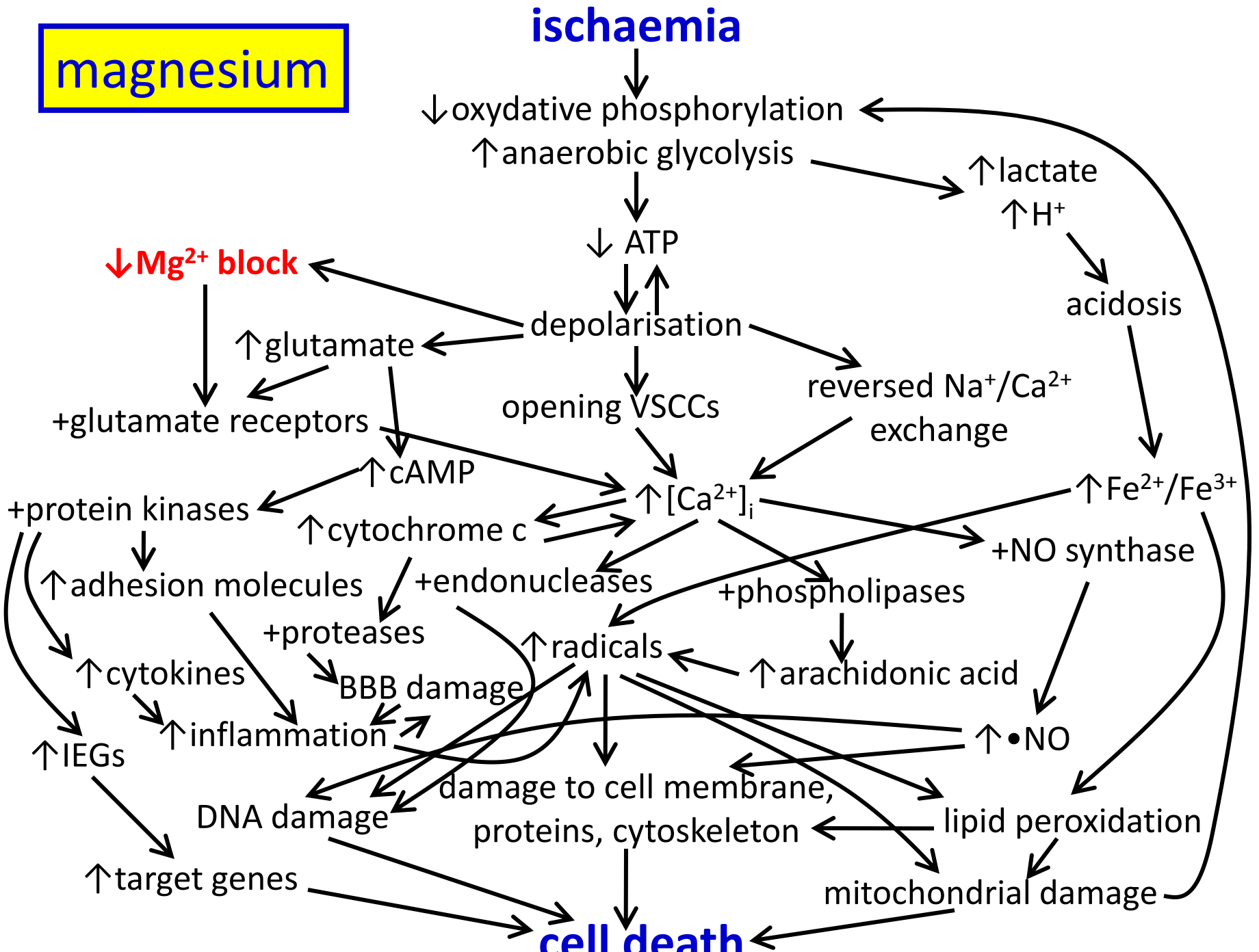
animal studies

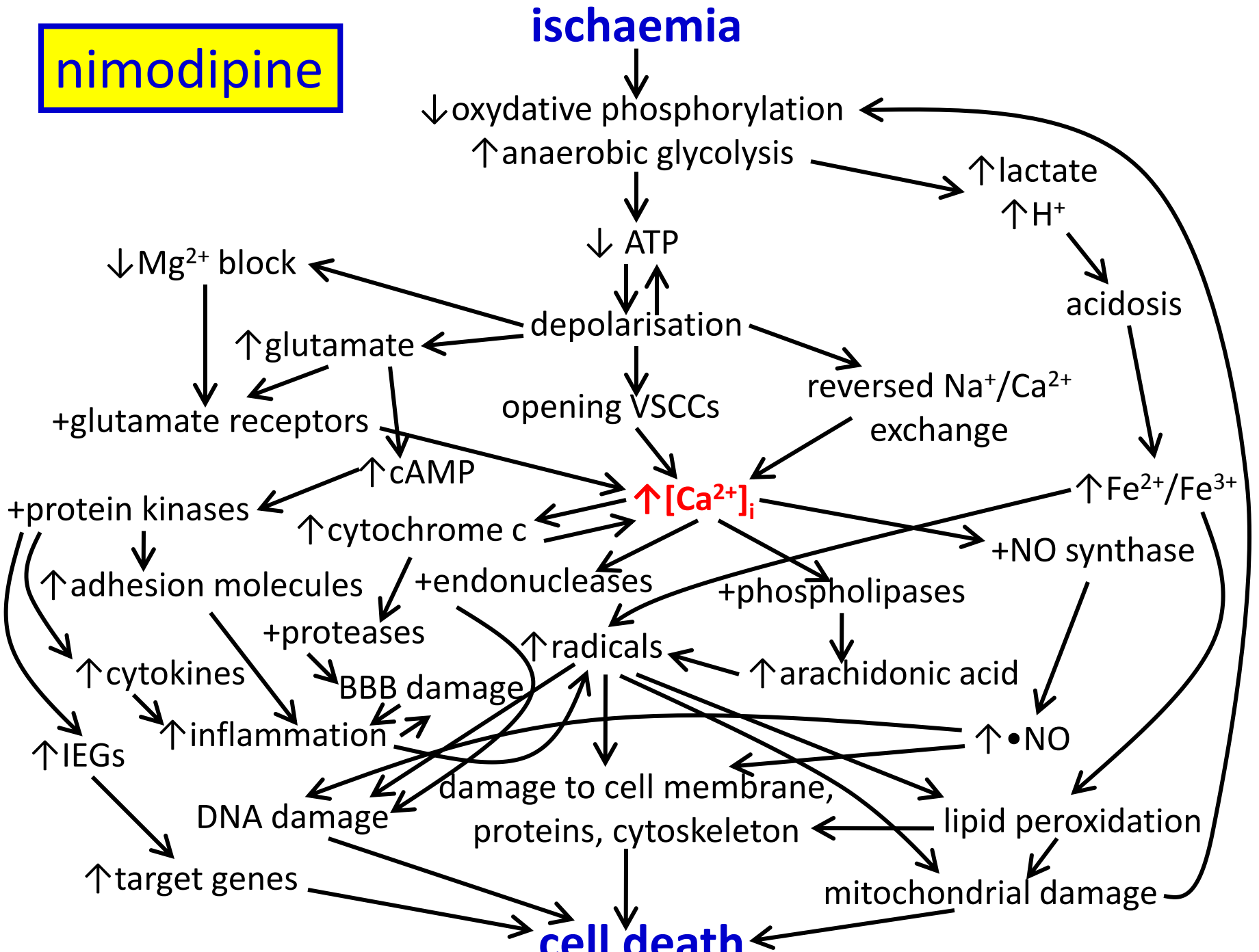
- good quality of evidence
- broad range of evidence
  - multi-centre phase III animal trial?
- no relevant impact of publication bias
- benefit under conditions of clinical trial

- safe & feasible


ischaemia
cooling
fever prevention
↑lactate
↑H+
↓Mg2+ block
cooling
fever prevention
acidosis
cooling
fever prevention
opening VSCCs
reversed Na+/Ca2+
exchange
↑cAMP
↑[Ca2+]i
↑Fe2+/Fe3+
+protein kinases
cooling
fever prevention
+endonucleases
cooling
fever prevention
+proteases
edaravone
N-acetylcysteine
uric acid
arachidonic acid
cooling
fever prevention
glyceryl trinitrate
atorvastatin
3K3A-APC
fingolimod
damage to cell membrane,
proteins, cytoskeleton
lipid peroxidation
NA-1
cell death


hypothermia
©ssnet.cz


magnesium
ischaemia
↓oxydative phosphorylation
↑anaerobic glycolysis
↑lactate
↑H+
↓ ATP
↓Mg2+ block
acidosis
depolarisation
↑glutamate
reversed Na+/Ca2+
exchange
opening VSCCs
+glutamate receptors
↑cAMP
↑[Ca2+]i
↑Fe2+/Fe3+
+protein kinases
↑cytochrome c
+NO synthase
↑adhesion molecules
+endonucleases
+phospholipases
+proteases
↑radicals
↑cytokines
BBB damage
↑arachidonic acid
↑inflammation
↑•NO
↑IEGs
damage to cell membrane,
proteins, cytoskeleton
DNA damage
lipid peroxidation
↑target genes
mitochondrial damage
cell death


nimodipine
ischaemia
↓oxydative phosphorylation
↑anaerobic glycolysis
↑lactate
↑H+
↓ ATP
↓Mg2+ block
depolarisation
acidosis
↑glutamate
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↑radicals
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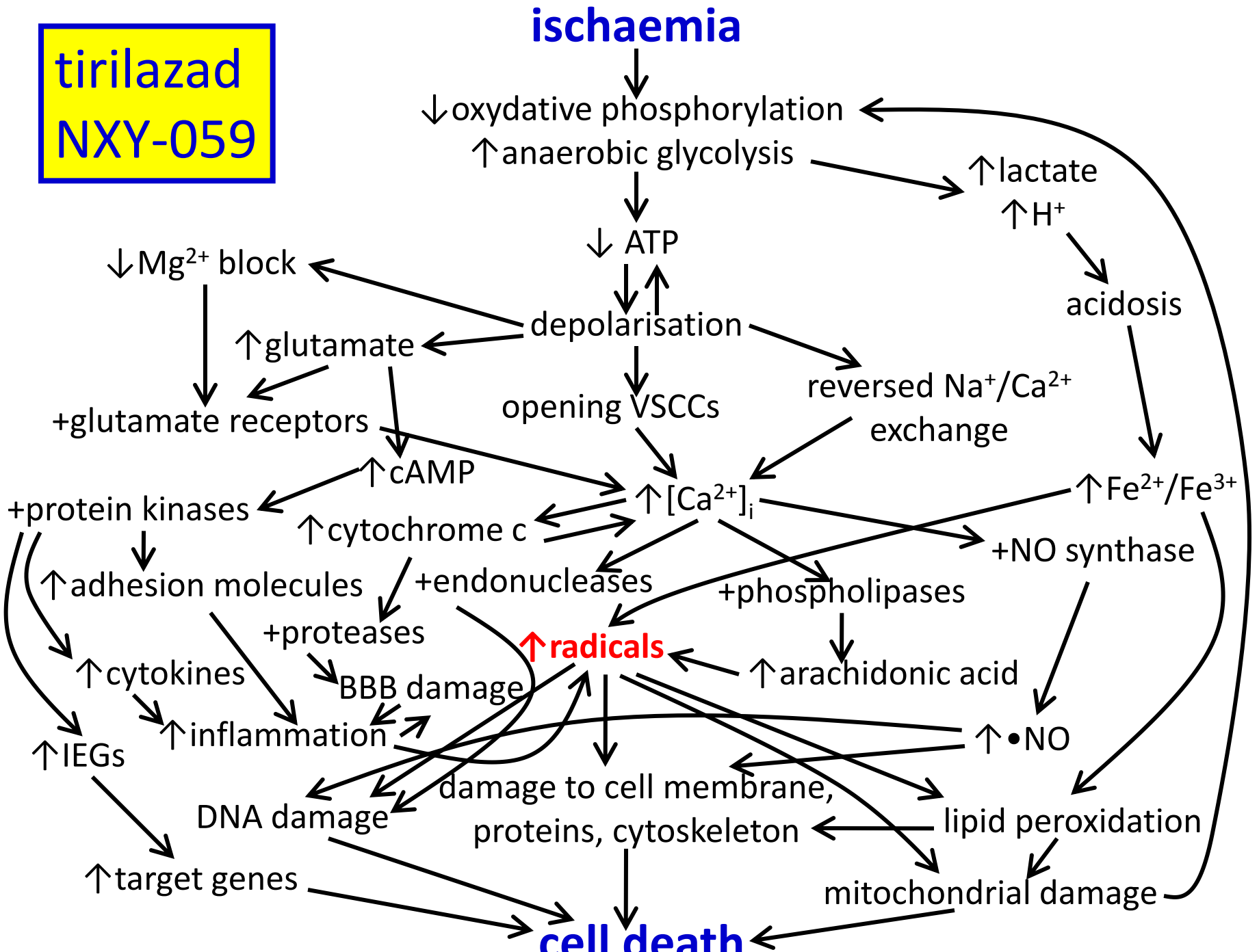
↑arachidonic acid
↑inflammation
↑•NO
↑IEGs
damage to cell membrane, proteins, cytoskeleton
DNA damage
lipid peroxidation
↑target genes
mitochondrial damage
cell death


tirilazad
NXY-059
ischaemia
↓oxydative phosphorylation
↑anaerobic glycolysis
↑lactate
↑H+
↓ ATP
↓Mg2+ block
depolarisation
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damage to cell membrane,
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DNA damage
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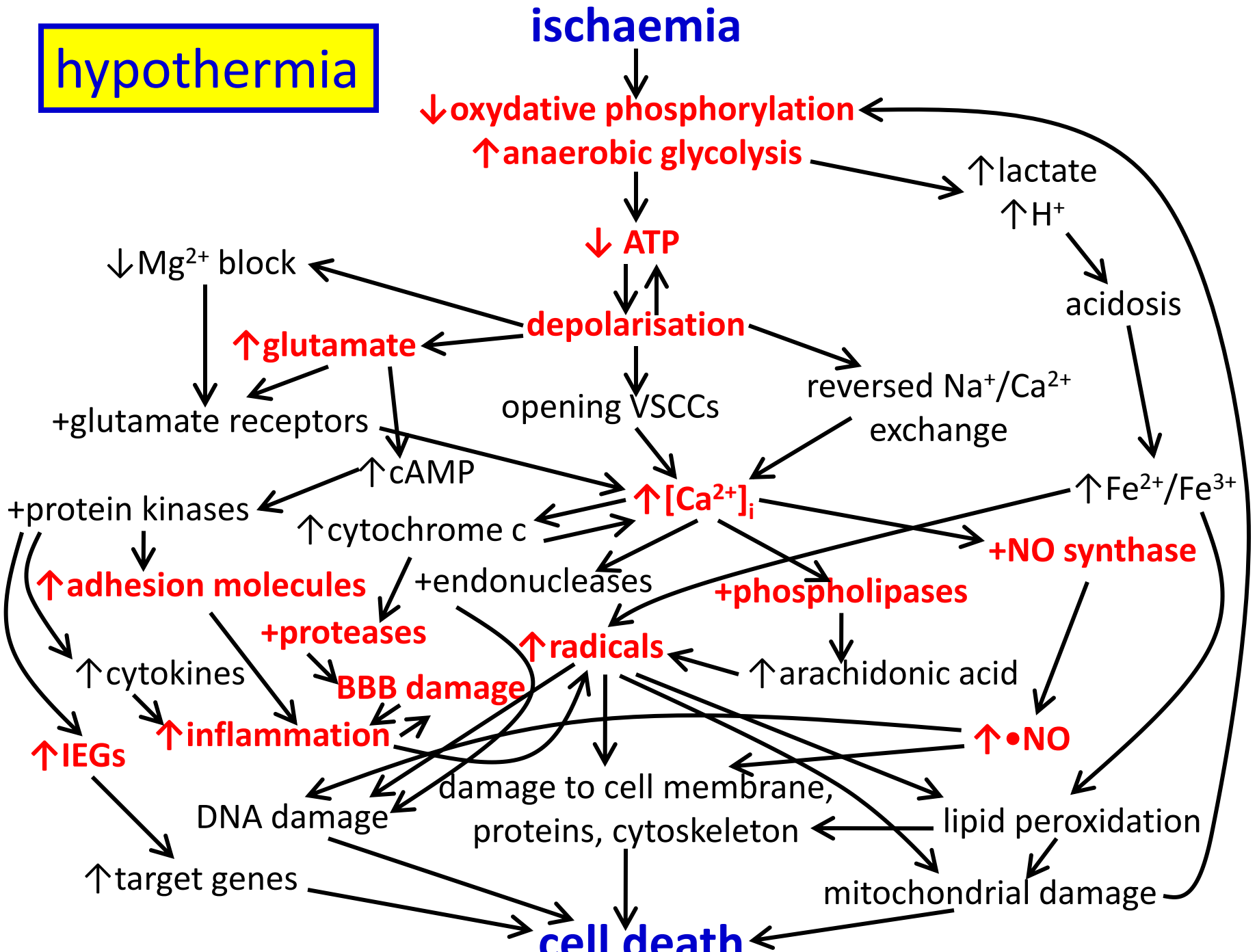
cell death


hypothermia
ischaemia
↓oxydative phosphorylation
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↑H+
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BBB damage
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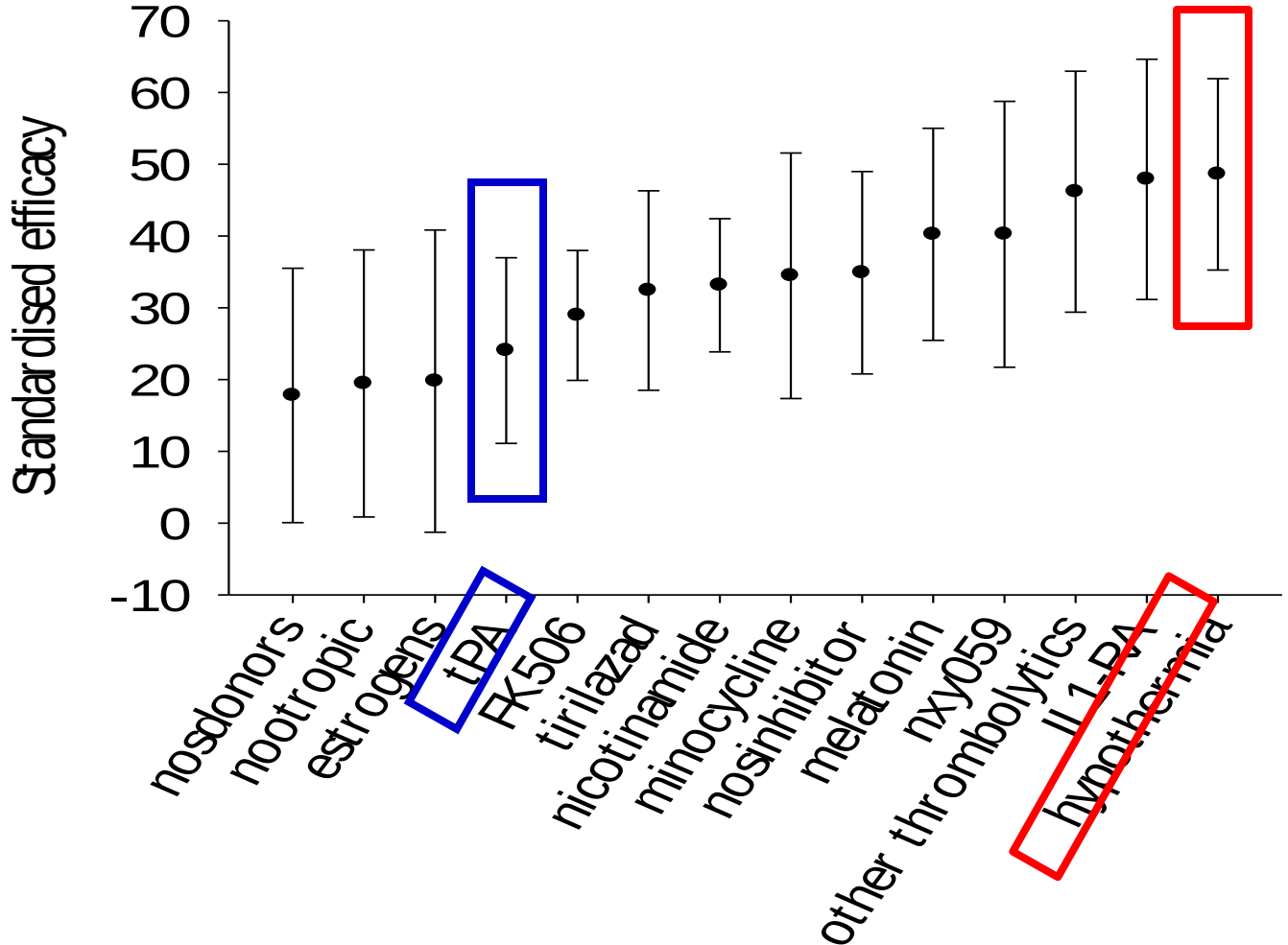
damage to cell membrane, proteins, cytoskeleton
DNA damage
lipid peroxidation
↑target genes
mitochondrial damage
cell death

systematic reviews of animal stroke models



Sena 2010

cooling to 32 – 34˚C in clinical trials

<u>effective in:</u>

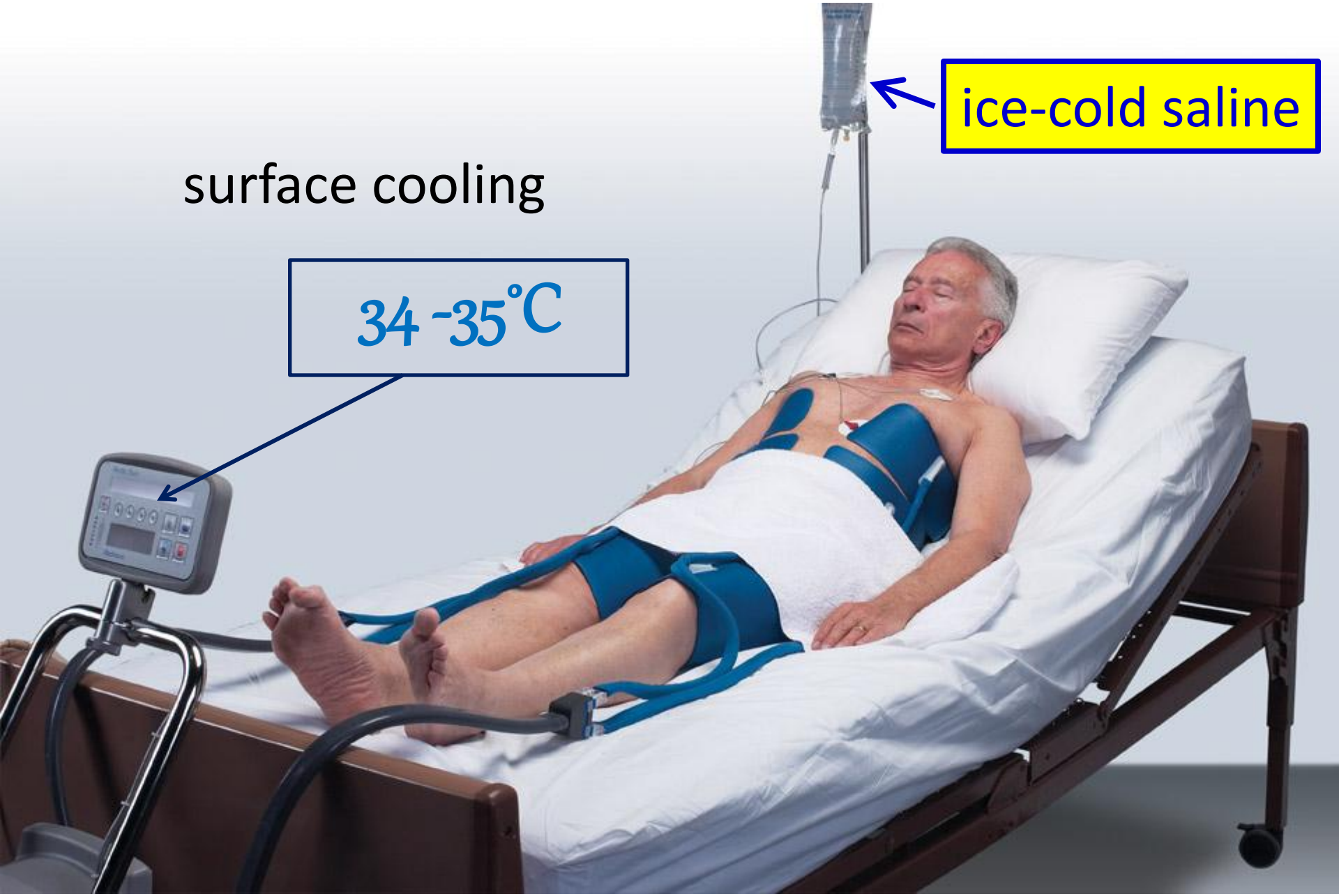
- postanoxic encephalopathy
- neonatal hypoxic-ischaemic brain damage

<u>not effective in:</u>

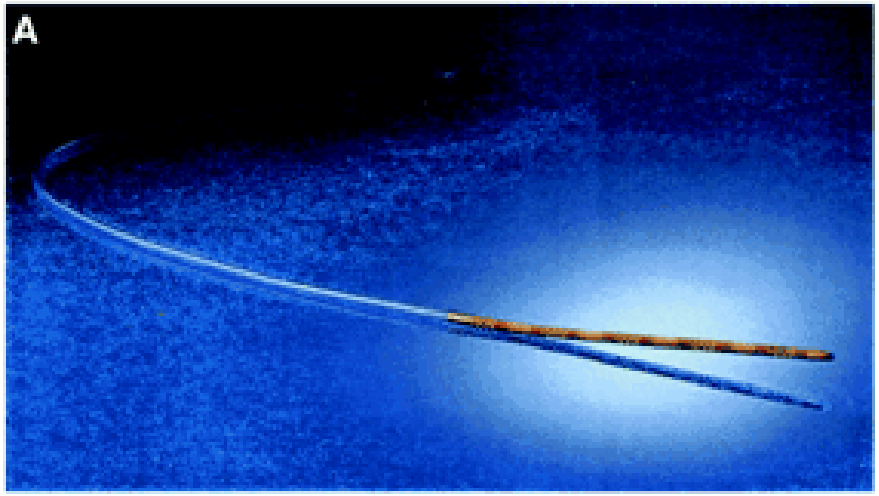
- traumatic brain injury
- bacterial meningitis

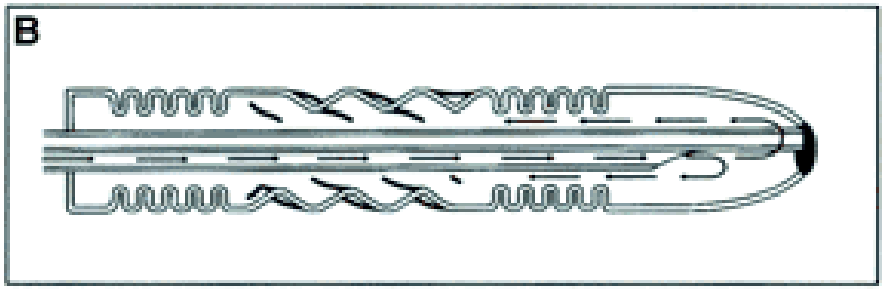
HCASG 2002
Bernard 2002
Shankaran 2005
Andrews 2015
Mourvillier 2013

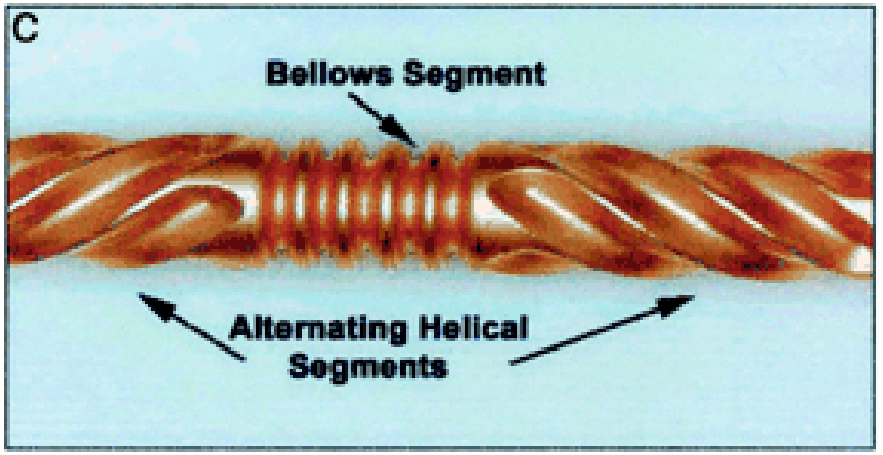
methods to cool stroke patients


ice-cold saline
surface cooling
34 -35°C

intravascular cooling







Mack 2003

Can be done by neurologist!

clinical trials in acute ischaemic stroke

	year	n cooled
COOL-AID	2004	18
NOCSS	2006	22
ICTuS-L	2010	28
MHAIS	2013	18
COOLIST	2016	16
ICTUS 2	2016	63
		165

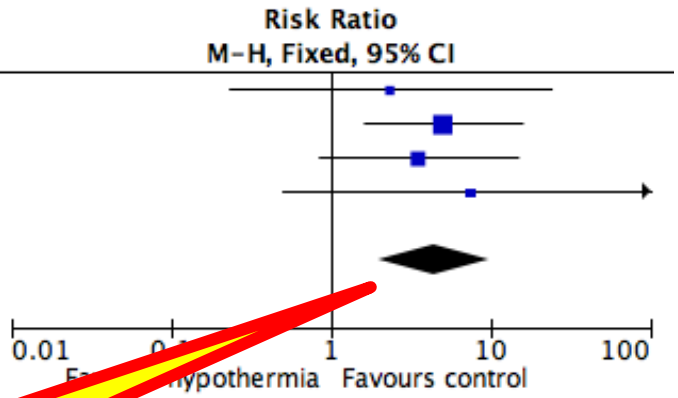
De Georgia 2004, NOCSS unpublished, Hemmen 2010, Piironen 2014, Geurts 2016; Lyden 2016

pneumonia

Study or Subgroup	Hypothermia Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
de Georgia 2004	2	18	1	21	14.2%	2.33 [0.23, 23.66]	2004
Hemmen 2010	14	28	3	30	44.5%	5.00 [1.61, 15.57]	2010
Piironen 2014	7	18	2	18	30.7%	3.50 [0.84, 14.61]	2014
Geurts 2015	8	15	0	6	10.7%	7.44 [0.49, 111.82]	2015
Total (95% CI)		**79**		**75**	**100.0%**	**4.42 [1.99, 9.83]**	
Total events	31		6				

Heterogeneity: $Chi^2 = 0.58$, $df = 3$ ($P = 0.90$); $I^2 = 0\%$

Test for overall effect: $Z = 3.65$ ($P = 0.0003$)



hypothermia: 39%
controls: 8%

Geurts 2016

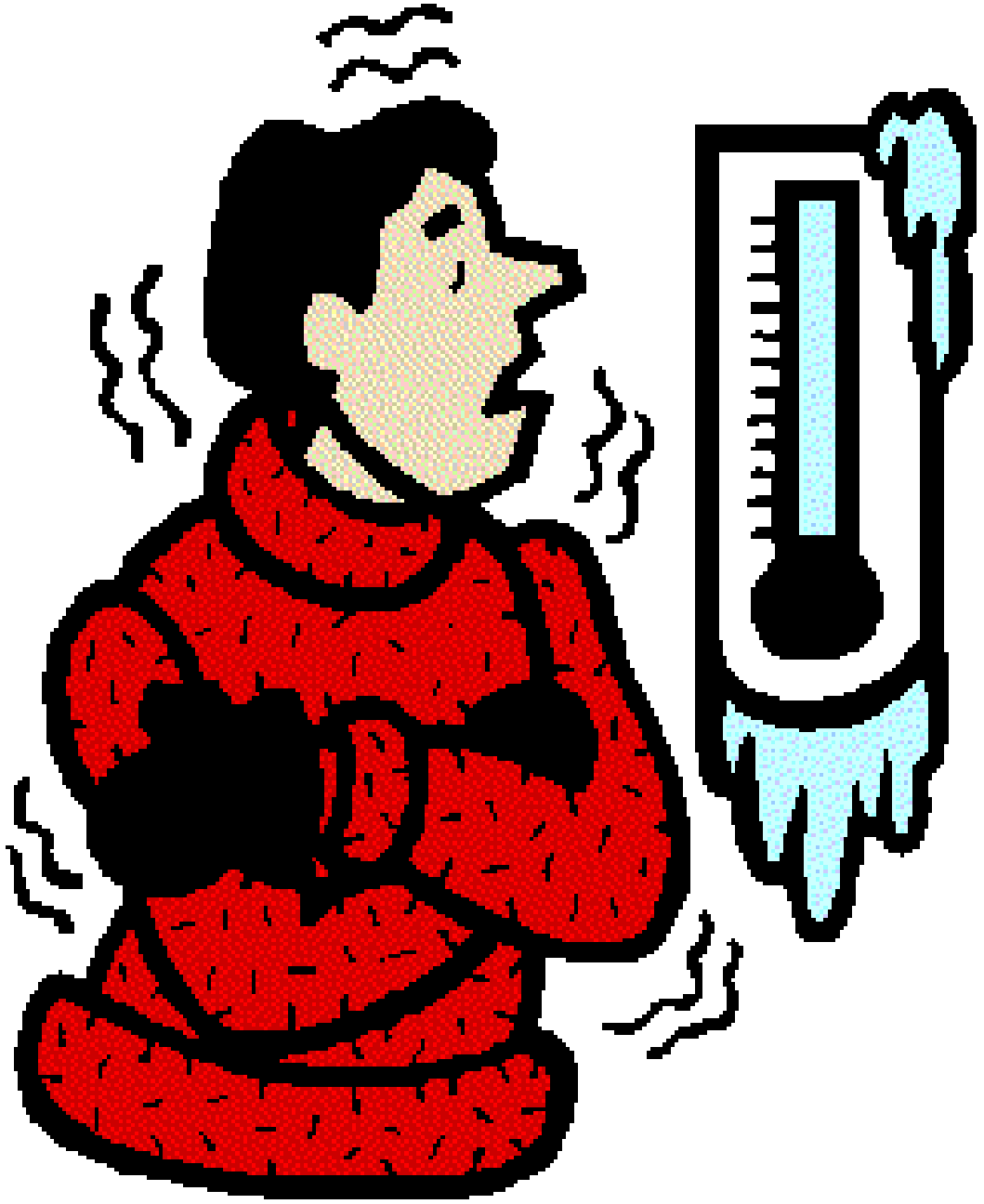
a multi-centre, randomised, controlled, clinical trial of hypothermia for acute ischaemic stroke

EuroHYP-1

trial design

- randomised, multicentre, international
- open, blinded outcome assessment
- 800 awake patients with ischaemic stroke
- cooling to 34 - 35°C for 12 h
- start ≤ 6 h of onset
  AND < 2.5 h of thrombolysis
- 1st inclusion November 2013

pethidine
(= meperidine)
buspirone



something more simple?

effect of fever in animal models

→ 43% increase infarct size

De Jonge i.p.

temperatures > 37.5°C after stroke:

- 1/3 of patients on day 1
- associated with poor outcome

- guidelines recommend(ed) treatment of fever
- → may be too late
- prevention of fever better??

Jauch 2013; Steiner 2014; Hemphill 2015; Ntaios 2015


500

paracetamol trial - PAIS

- 1400 patients with acute stroke
- paracetamol 6 x 1 g for 3 days vs. placebo
- start ≤ 12 h from symptom onset

Den Hertog 2009

results PAIS trial

treatment with paracetamol →

- body temperature ↓ 0.3˚C
- temperature > 37.5˚C at 24 h: 30% → 15%

Den Hertog 2009

improvement with paracetamol at 3 months

aOR: 1.21 (0.97 – 1.51)

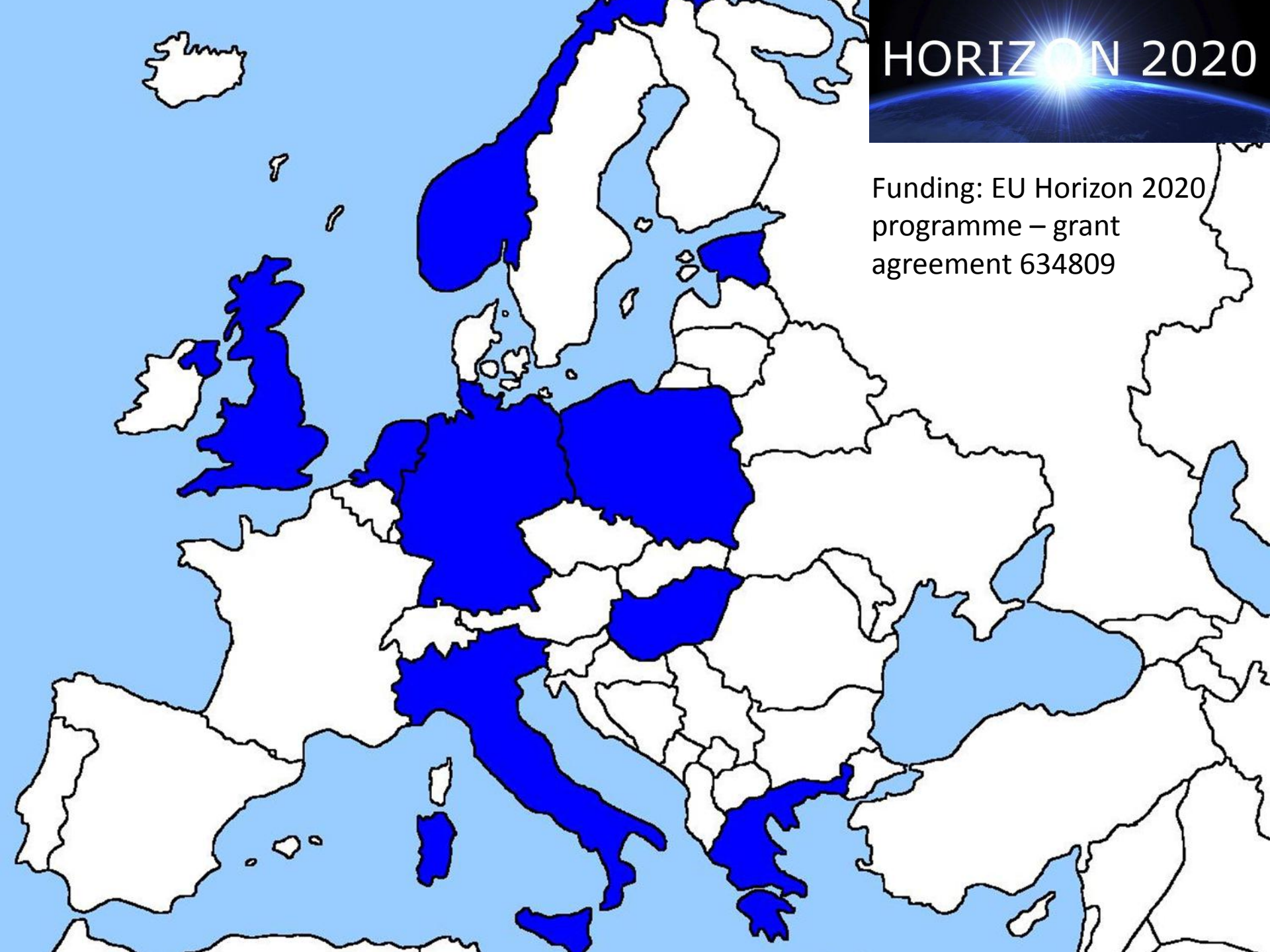
if true:

- extremely safe, simple, and cheap treatment

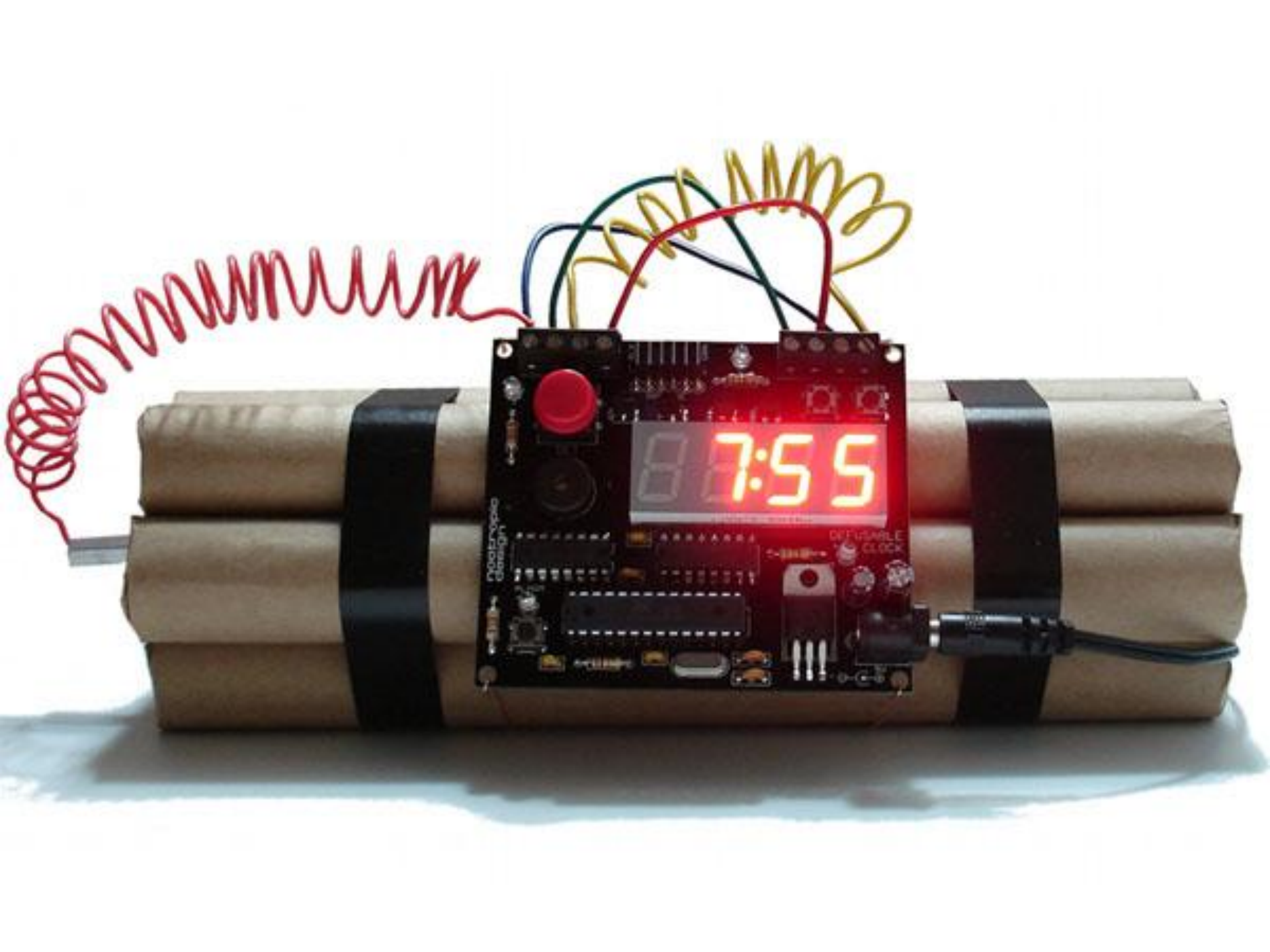
Den Hertog, Lancet Neurol 2009

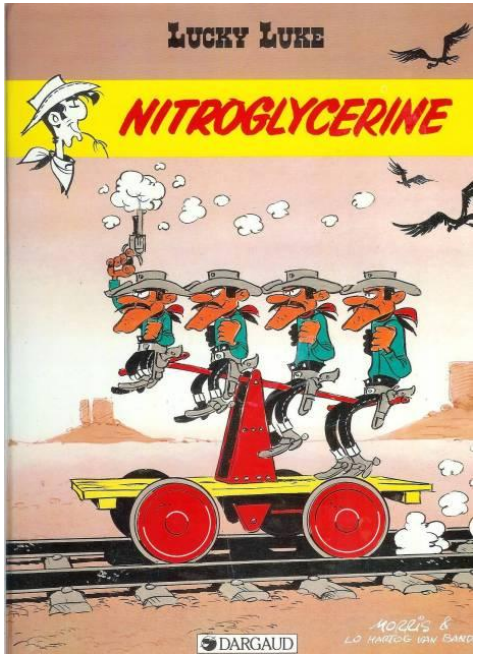
PRECIOUS: PREvention of Complications to Improve OUtcomes in elderly patients with acute Stroke

- PROBE, 2*2*2 factorial
- n = 3800 (ischaemic stroke and ICH)
- open treatment, start ≤ 24 h, for 4 days
  - ceftriaxone – 2 g daily
  - paracetamol – 4 g daily
  - metoclopramide – 30 mg daily
- primary endpoint: mRS @ 90 days



Funding: EU Horizon 2020 programme – grant agreement 634809


7:55



nitroglycerine

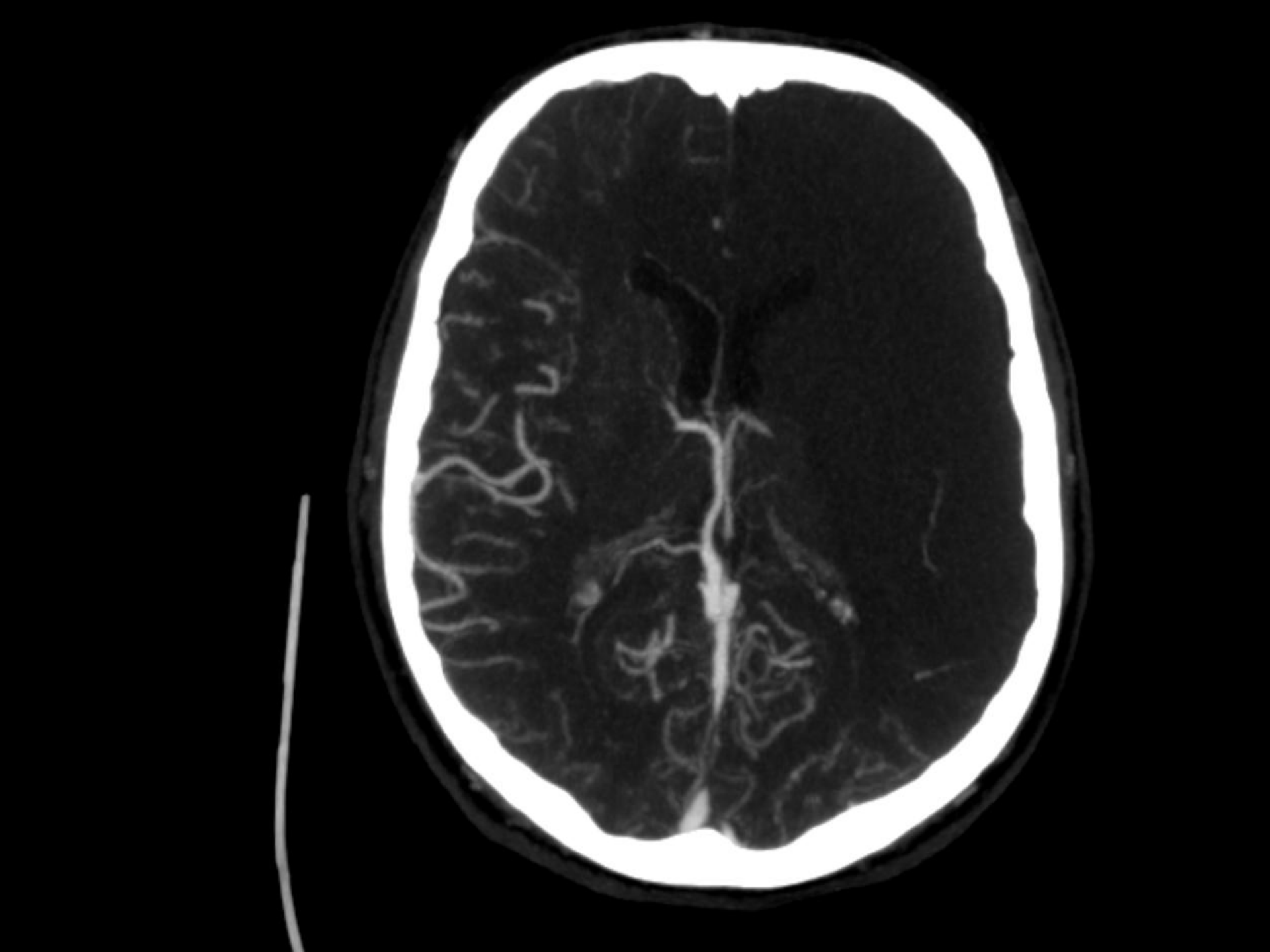
= glyceryl trinitrate (GTN)

- NO donor
- systemic and cerebral vasodilator

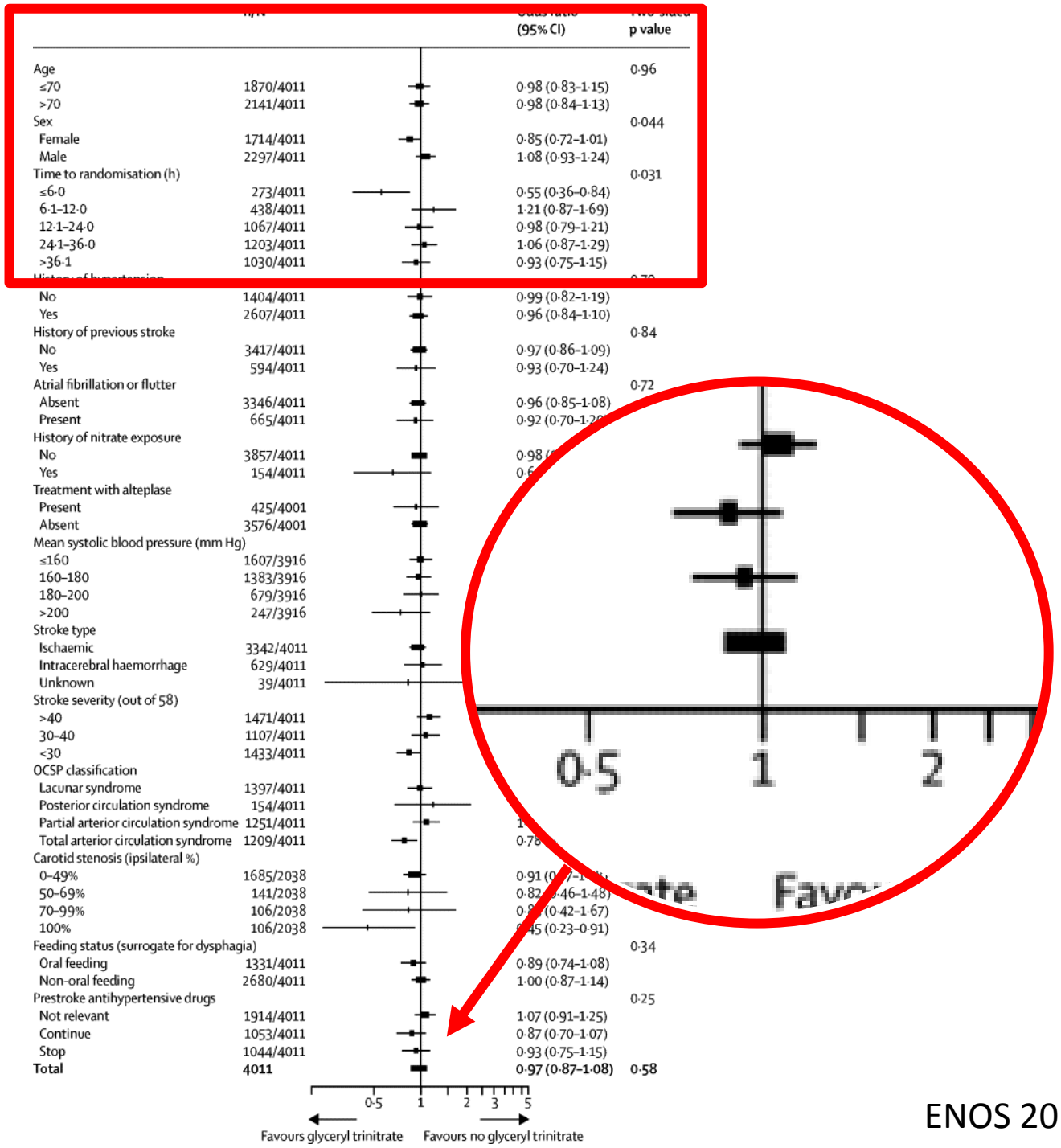
<u>NO donors in animal studies</u>

↑ cerebral blood flow

↓ infarct size

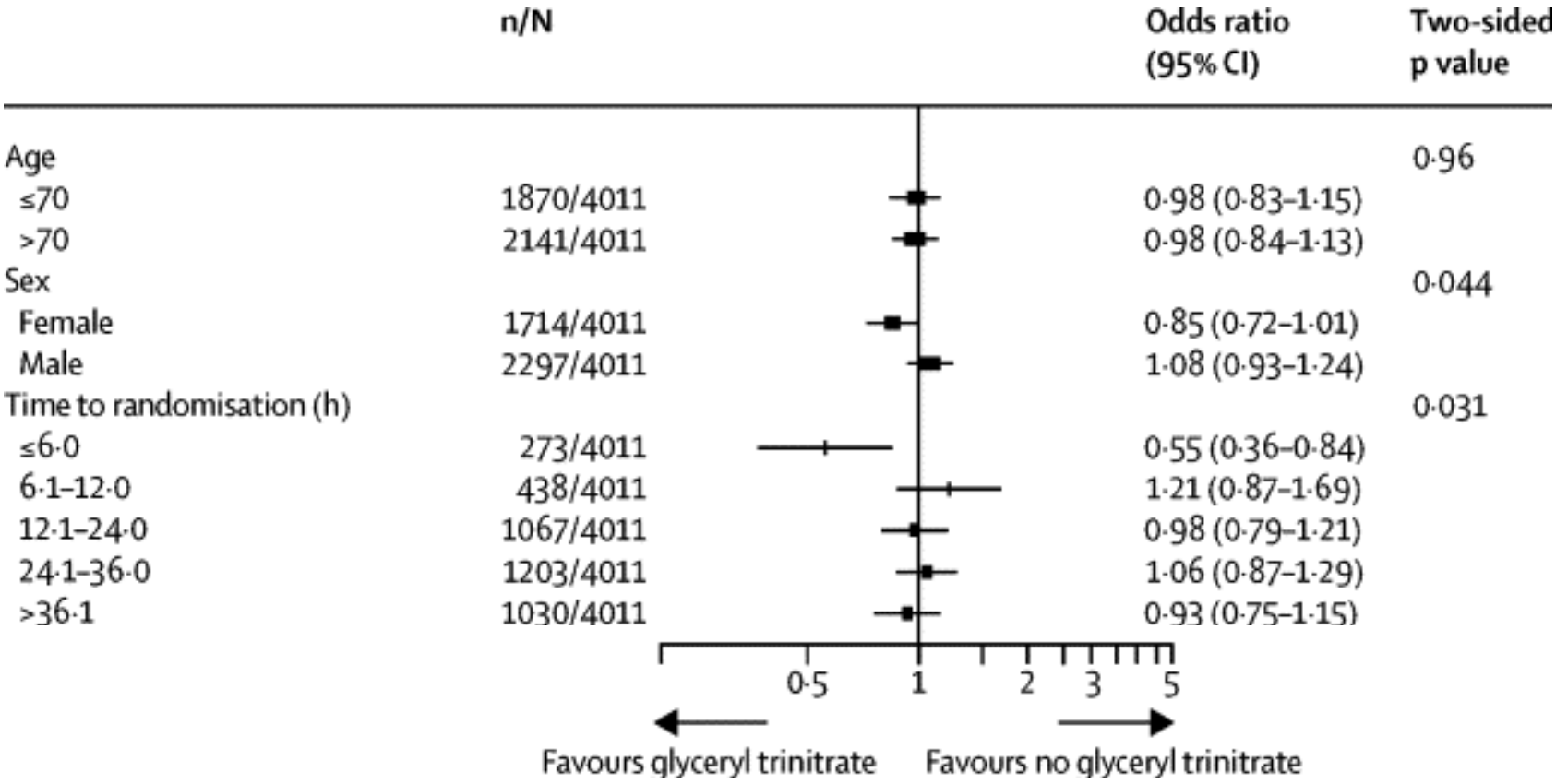


ENOS



ENOS 2015

ENOS



ENOS 2015

GTN – ambulance trial

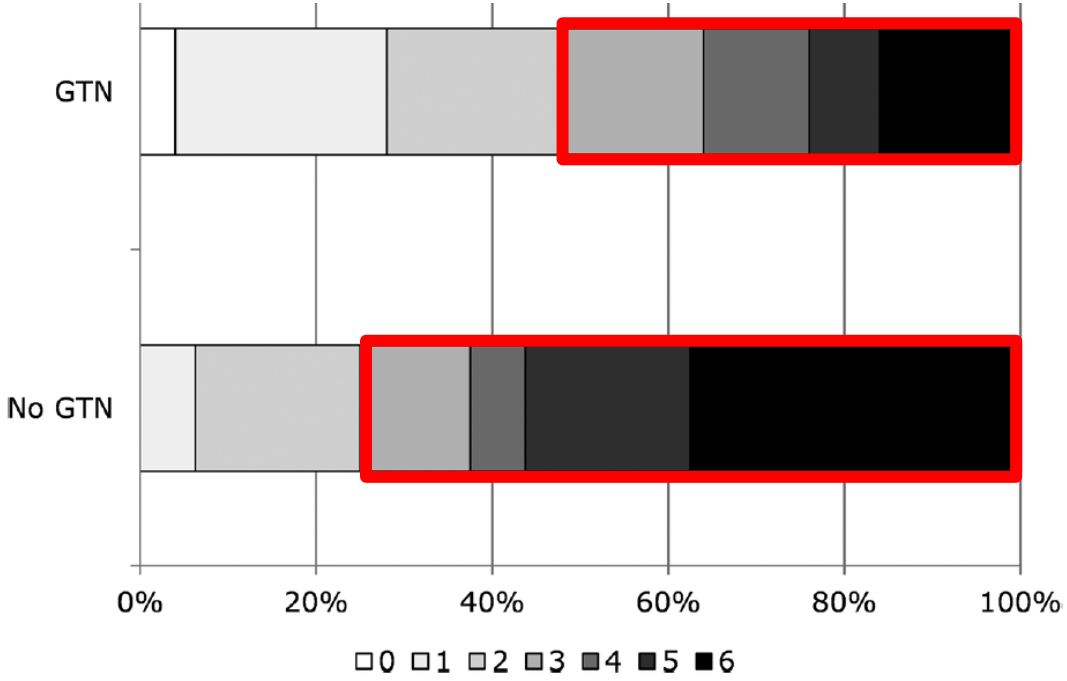
RIGHT

- n = 41
- start GTN ≤ 4 h
- ambulance setting

Ankolekar 2013

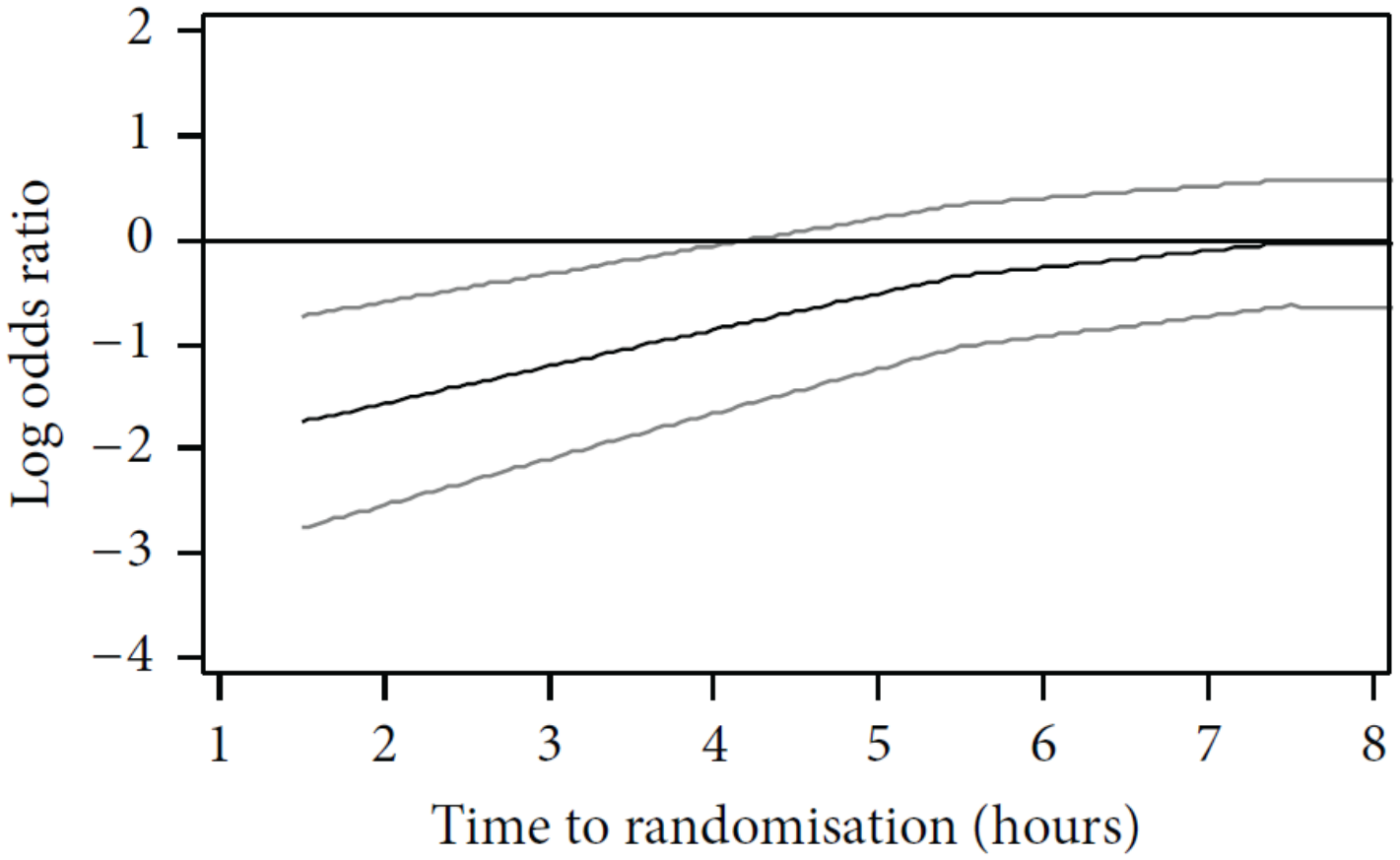
GTN – ambulance trial

- feasible & safe
- RR_{sys} @ 15 min: 180 → 153 mm Hg



Ankolekar 2013

mRS vs. time to start of treatment



MR ASAP

GTN trials

- PROBE, phase III
- adult patients with suspected stroke
- transdermal GTN in a dose of 5 mg/day vs. standard care
- start in the ambulance, ≤ 4 or 3 h

funded by the dutch heart foundation

Hartstichting

conclusions

- neuroprotection is not dead
- translation from bench to bedside may improve with better interaction between the laboratory and the clinic
- promising treatments are currently tested in clinical trials


Van Gogh 1890

ESOC 2018

4th European Stroke Organisation Conference

16-18 May 2018 | Gothenburg, Sweden

ESO - The Voice of Stroke in Europe