Brain cooling in acute stroke

SSNF Perth 2015

Developing new treatments for old diseases

Understand

- Understand what causes the disease
- Understand which biological processes are pivotal and which are not

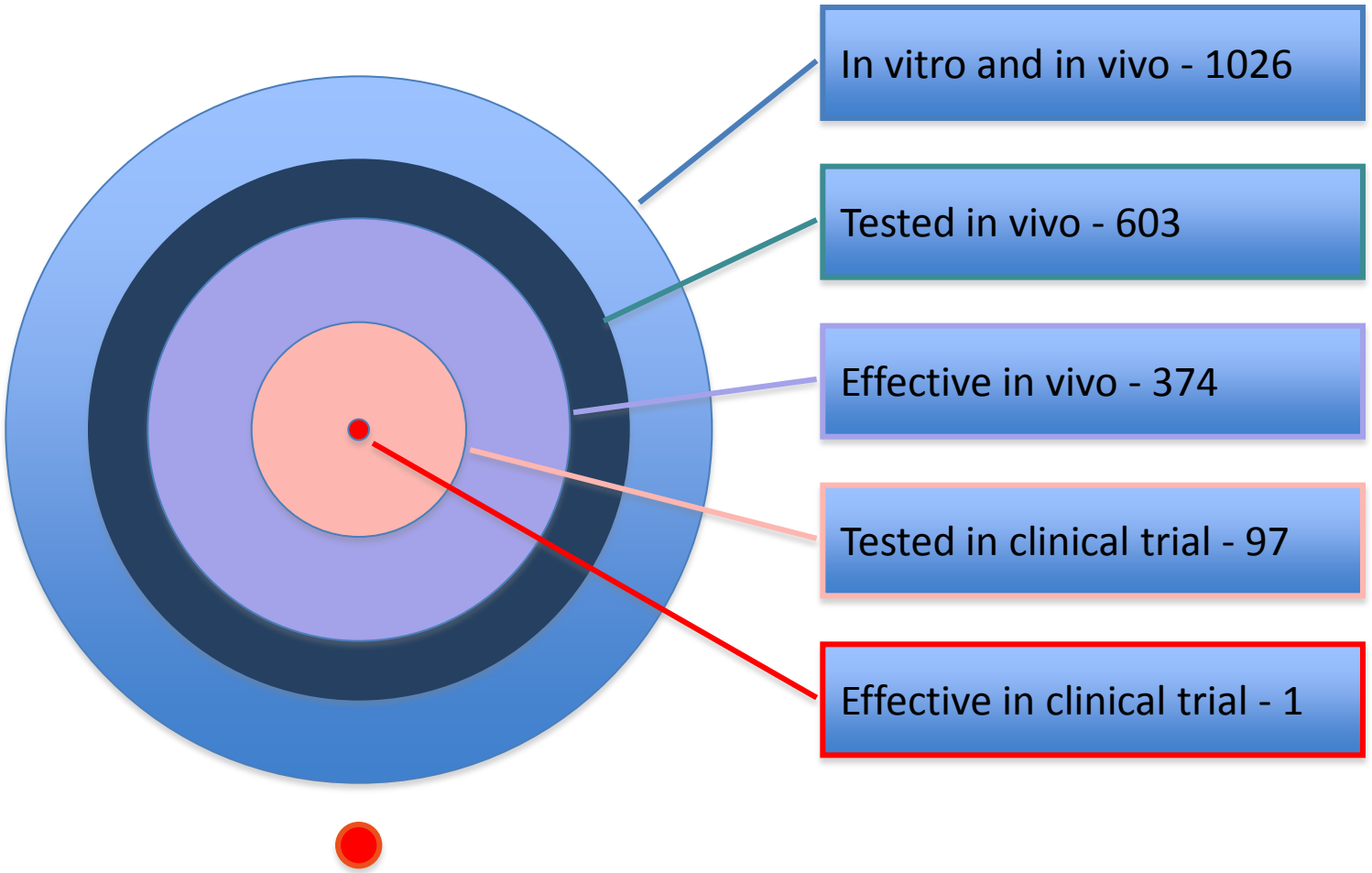
Influence in models

- Be able to change these processes in experiments
- Be able to change outcome in disease models
- Know your treatment is probably safe

Prevent in real life

- Show, in clinical trials, that the treatment changes outcome
- Show that the treatment works in the real world

1026 interventions in experimental stroke

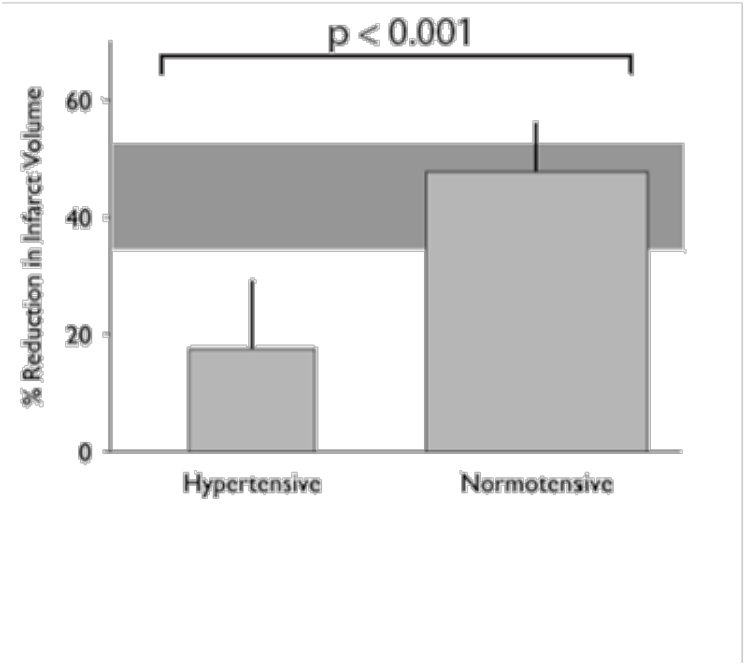


O'Collins et al, 2006

High blood pressure in animal stroke studies – NXY-059

Hypertension:

- 7% of animal studies
- 77% of patients in the (neutral) SAINT II study



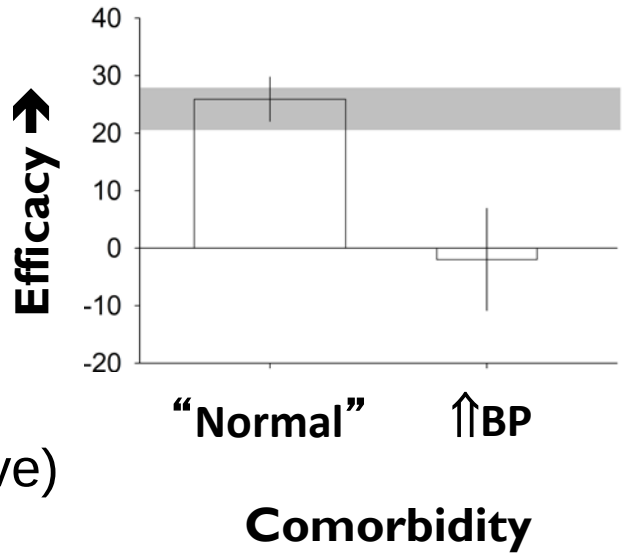
High blood pressure in animal stroke studies – tPA

Infarct Volume:

- 113 publications
- 212 experiments
- 3301 animals
- Improved outcome by 24% (20-28)

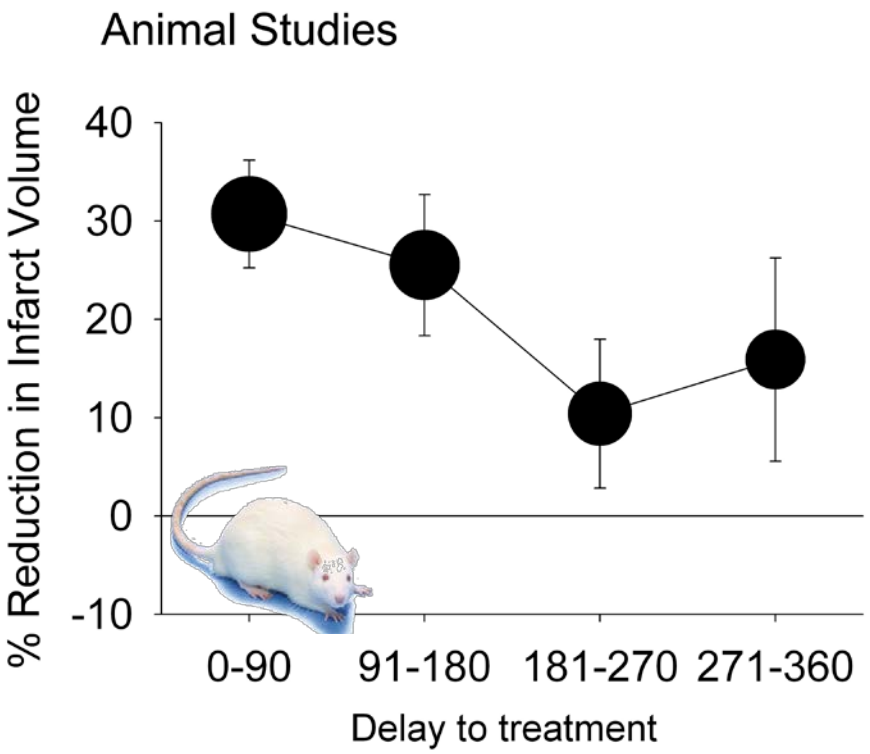
Hypertension:

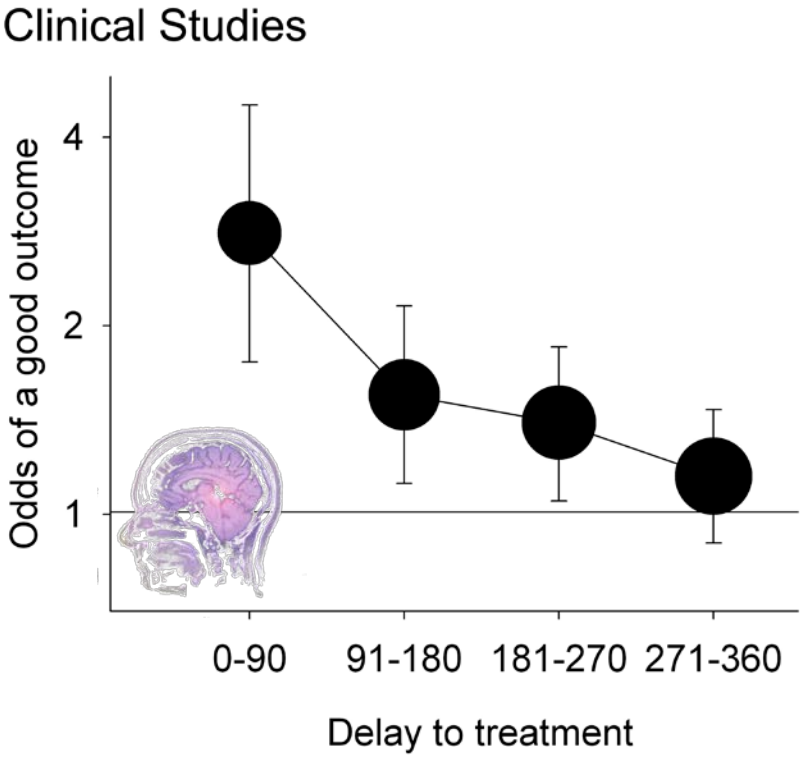
- 9% of animal studies
- Specifically exclusion criterion in (positive) NINDS study



Time to treatment in animal stroke studies

- Both tPA and tirilazad appear to work in animals
- tPA works in humans but tirilazad doesn't
- Time to treatment: tPA:
  - Animals – median 90 minutes
  - Clinical trial – median 90 minutes
- Time to treatment: tirilazad
  - Animals – median 10 minutes
  - Clinical trial - >3 hrs for >75% of patients

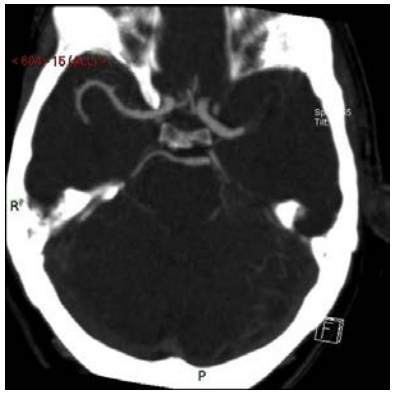

Animal Studies
% Reduction in Infarct Volume
40
30
20
10
0
-10
0-90
91-180
181-270
271-360
Delay to treatment

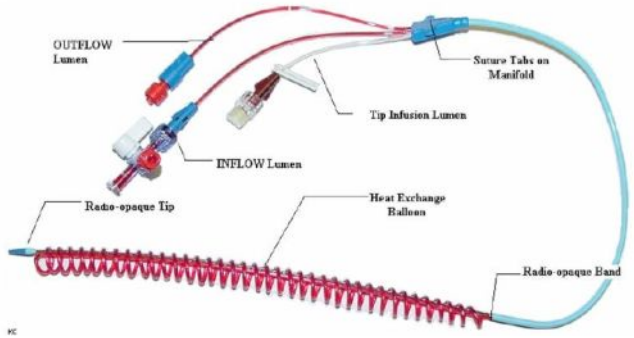

Clinical Studies
Odds of a good outcome
4
2
1
0-90
91-180
181-270
271-360
Delay to treatment

Cooling for stroke

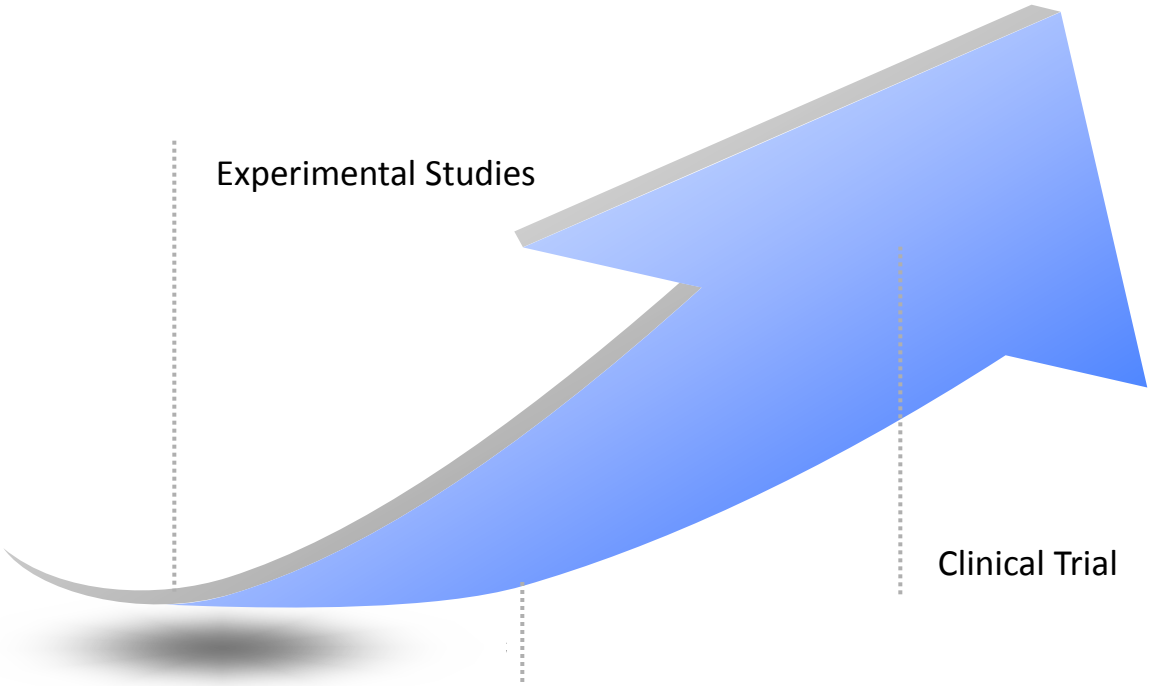
- Cooling seems to work in patients who have brain injury due to cardiac arrest
- There's lots of stories about individual patients who should have extensive brain damage but don't
- Many labs use cooling as a positive control in their animal studies
- Preliminary evidence from clinical trials in stroke is encouraging

How to become cool





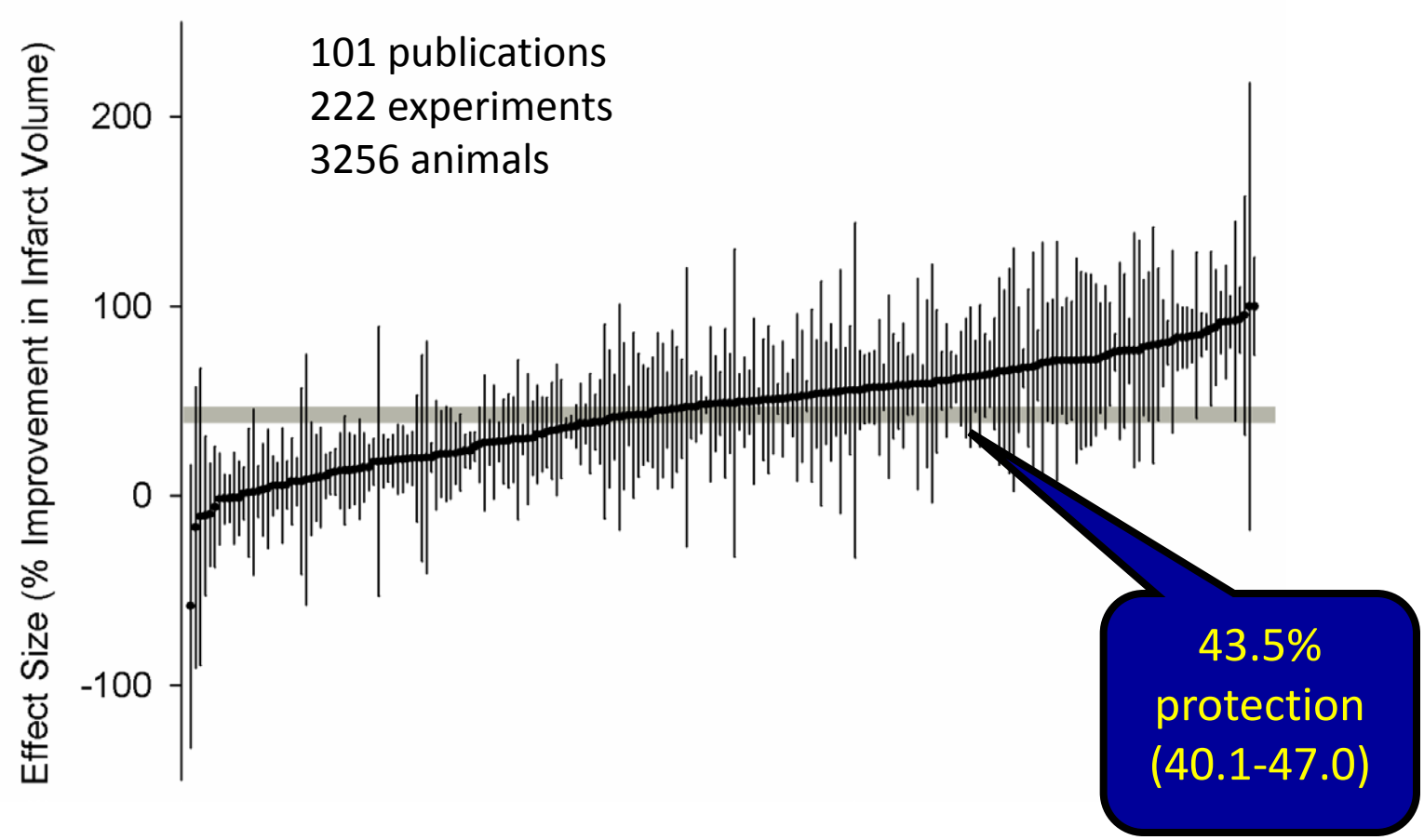
Evidence based trial design



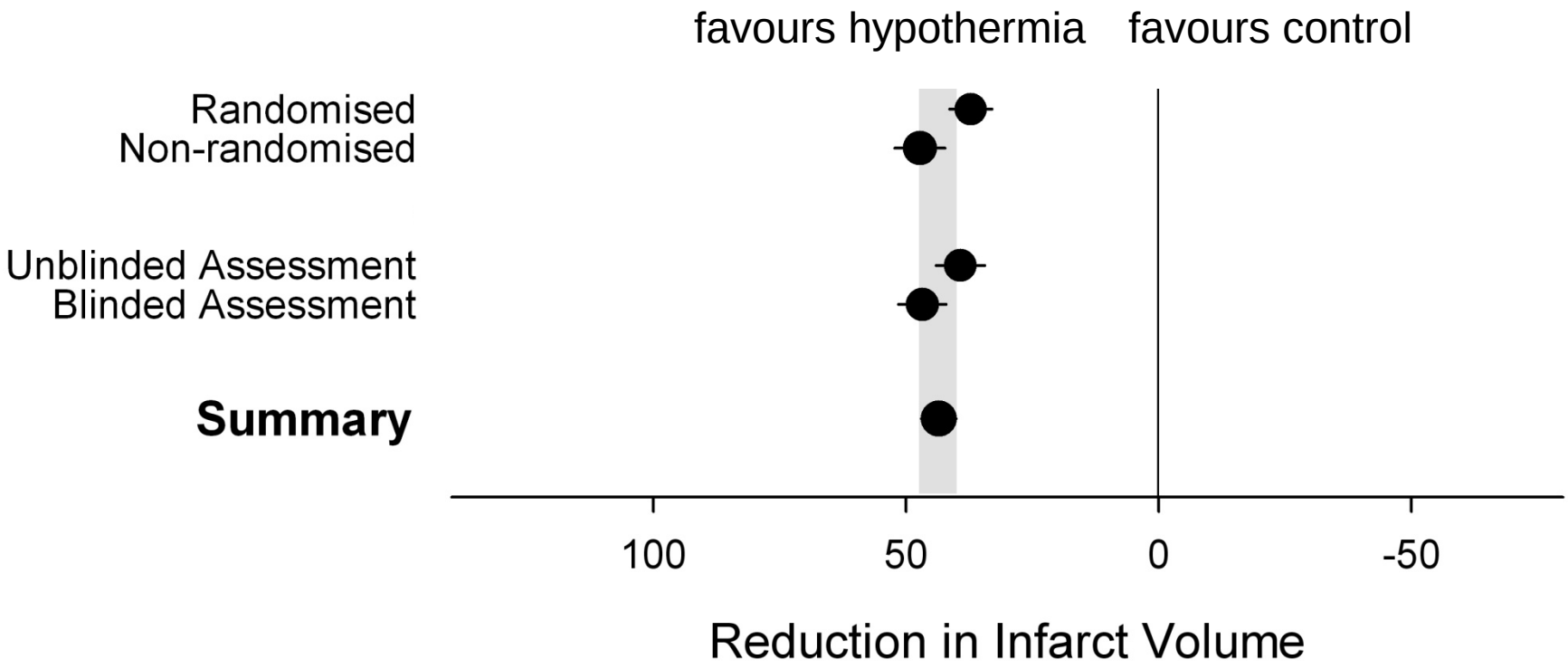
Systematic review and meta-analysis

- how powerful is the treatment?
- what is the quality of evidence?
- what is the range of evidence?
- is there evidence of a publication bias?
- What are the conditions of maximum efficacy?

How powerful is the treatment in animals?



What is the quality of evidence?



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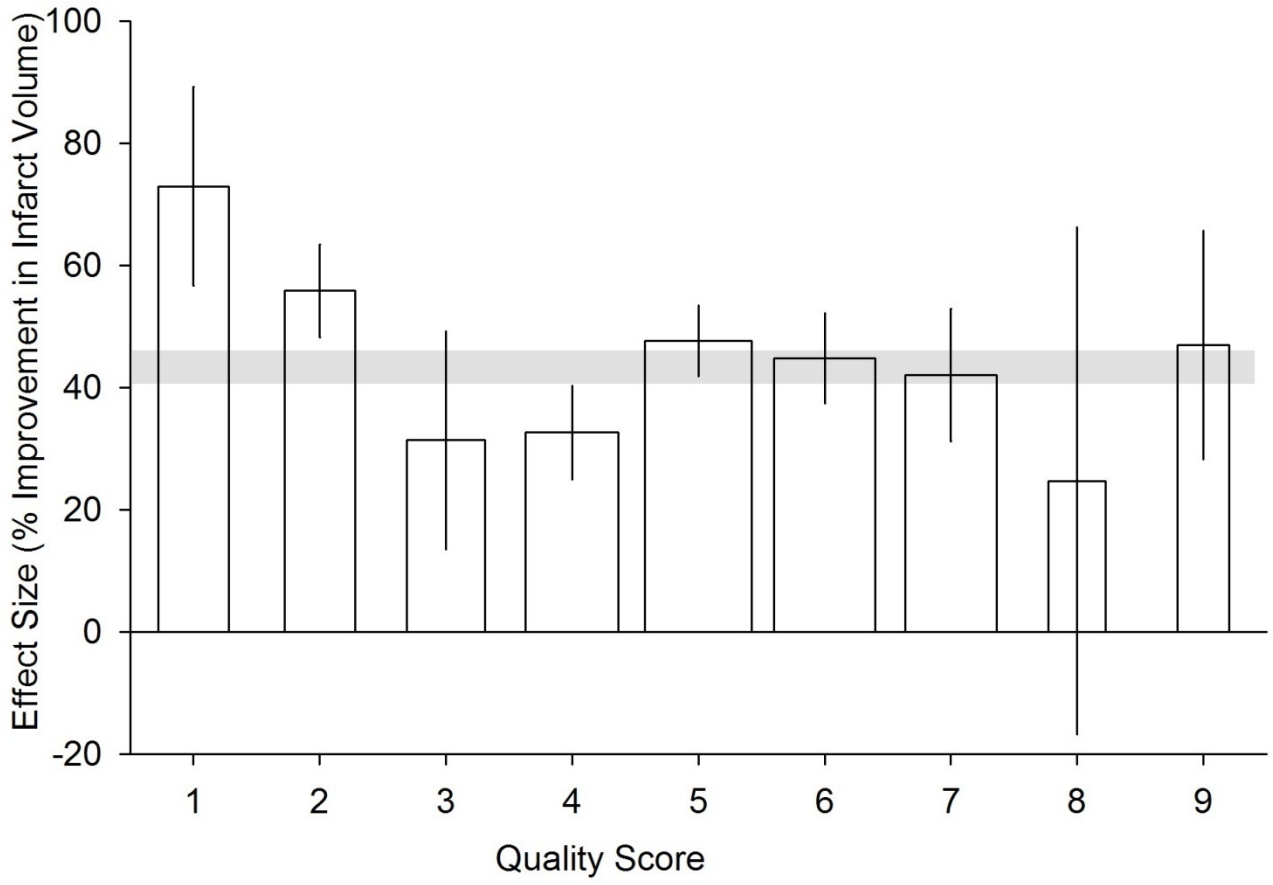
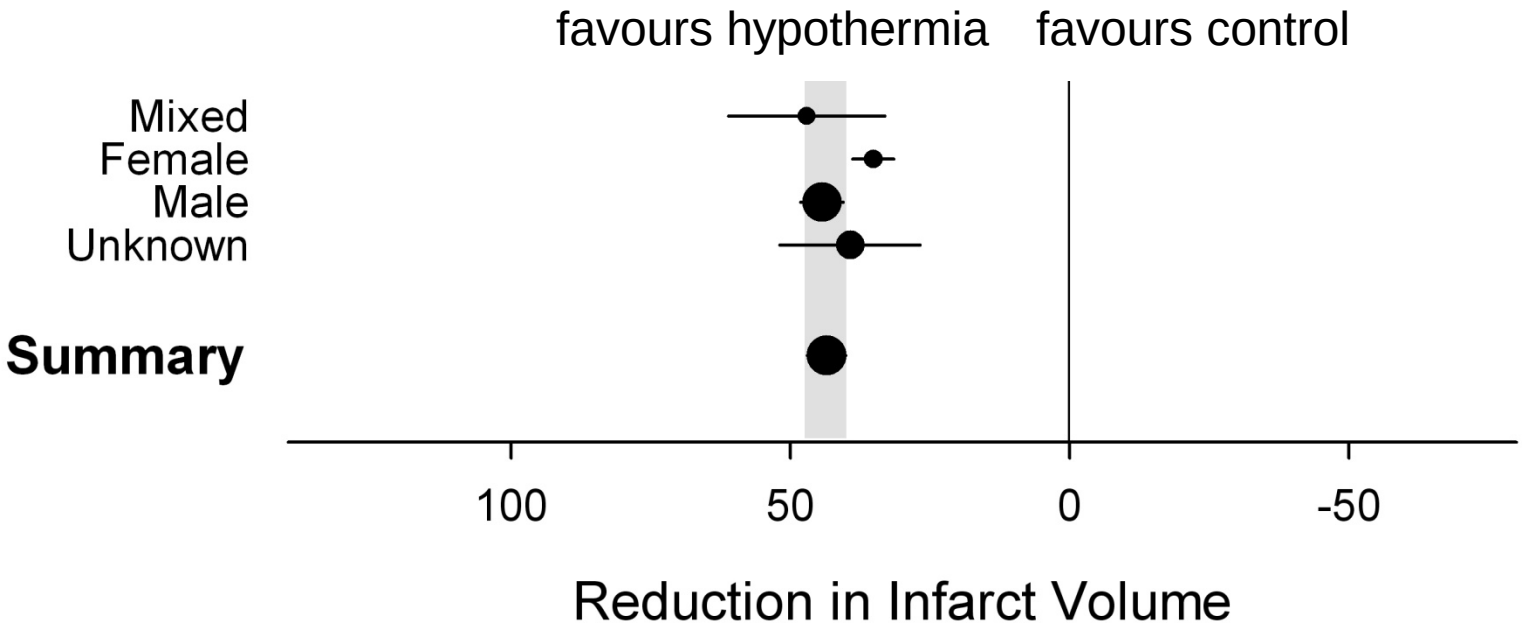


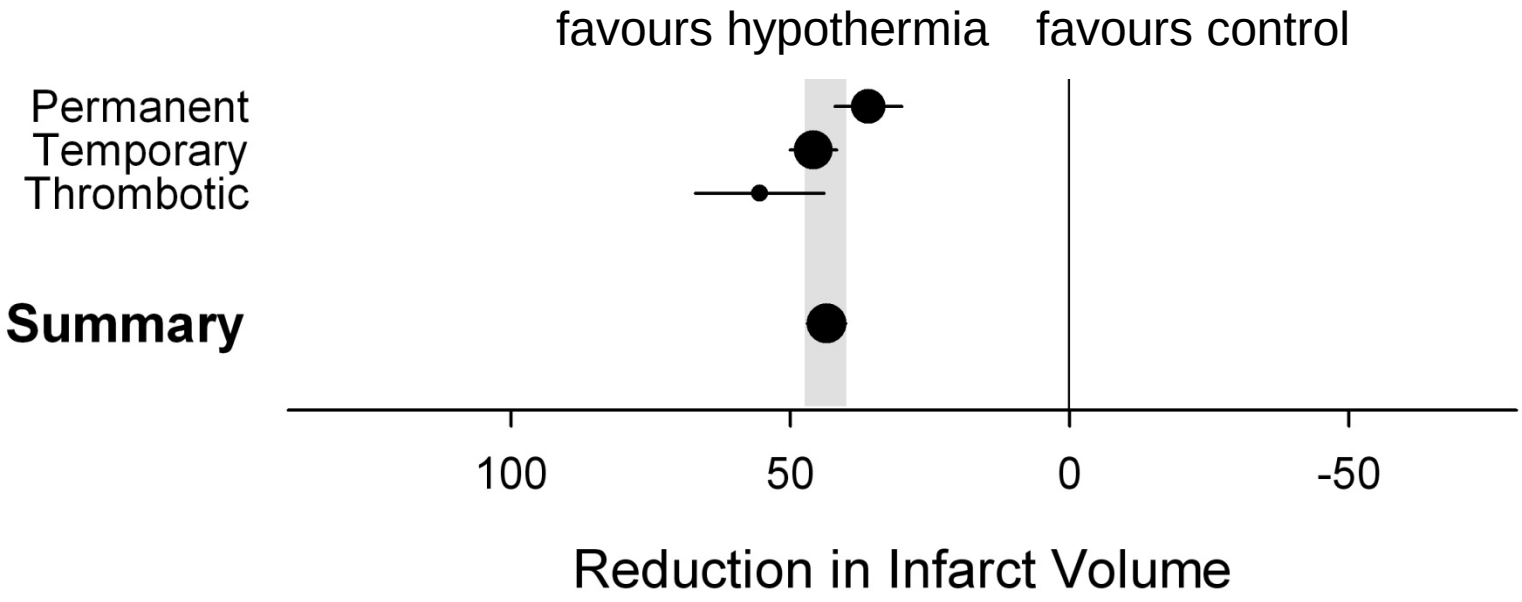
What is the range of evidence?

sex



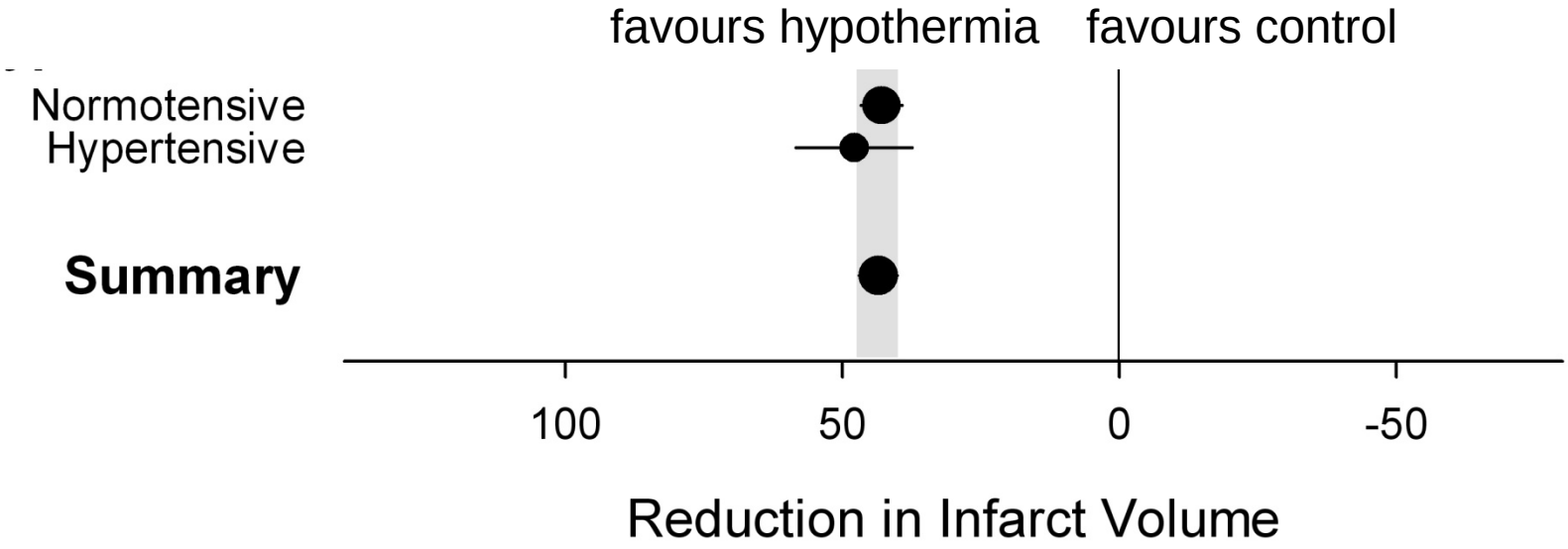
What is the range of evidence?

duration of ischaemia



What is the range of evidence?

presence of hypertension

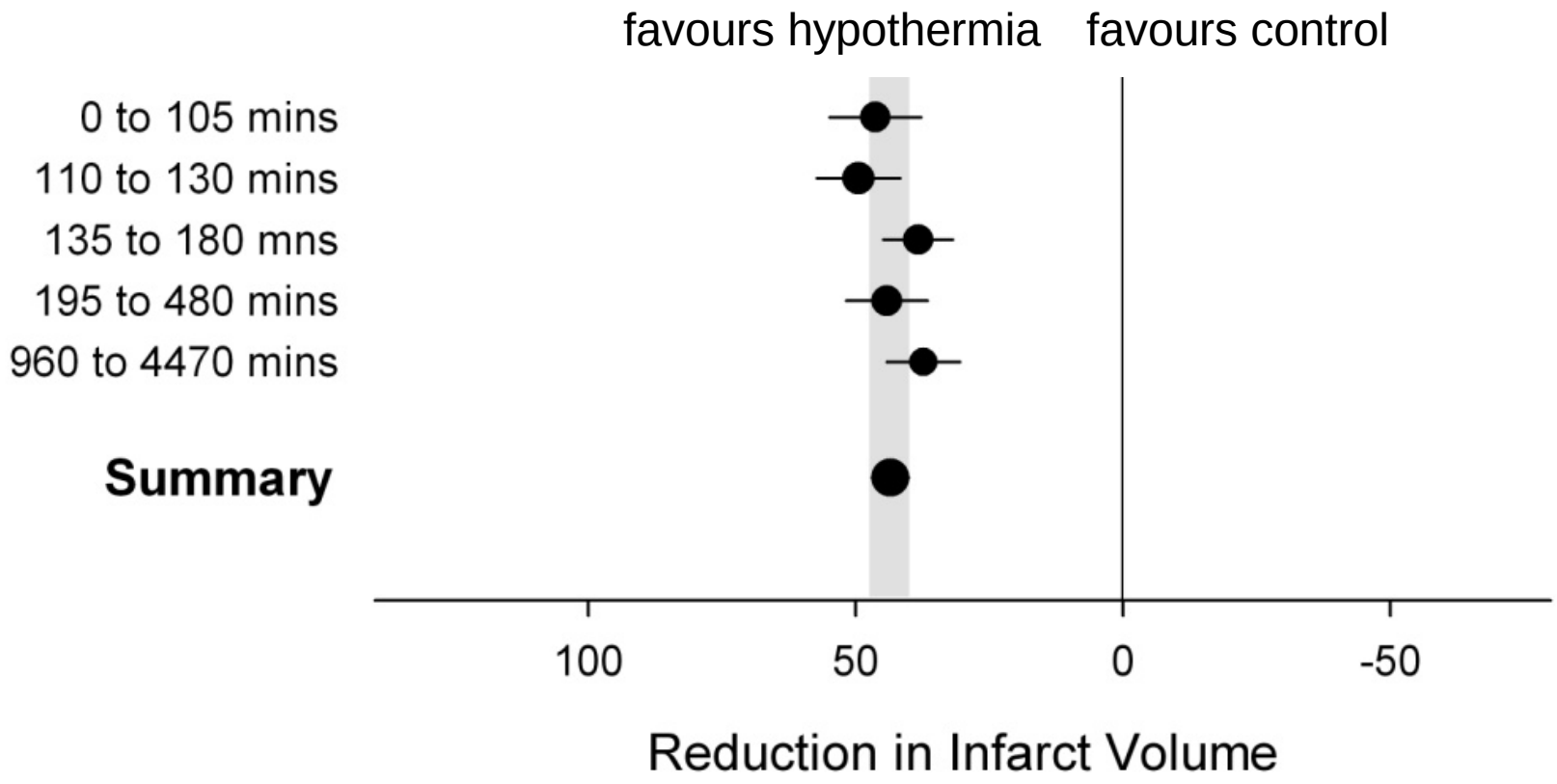


Is there evidence of a publication bias?

Intervention	Reported Effect Size (95%CI)	Bias with Egger Regression	Bias with METATRIM	Additional %Studies Considered "Missing"	METATRIM Adjusted Effect Size (95%CI)	Absolute Overstatement of Efficacy	Relative Over-statement of Efficacy
Estrogens	26.7% (20.4%–33.0%)	+	+	24	11.9% (4.6%–19.2%)[a]	14.8% (8.0%–21.6%)	124.4%
FK506	32.0% (27.8%–36.3%)	+	+	30	21.9% (17.5%–26.3%)[a]	10.1% (5.8%–14.4%)	46.1%
Growth factors	29.7% (25.9%–33.4%)	+	+	14	25.1% (21.2%–28.9%)[a]	4.6% (0.9%–8.3%)	18.3%
Hypothermia	43.5% (40.1%–47.0%)	+	+	20	35.4% (31.7%–39.1%)[a]	8.1% (4.5%–11.6%)	22.9%
IL1-RA	38.2% (31.2%–45.1%)	+	+	36	25.4% (18.4%–32.4%)[a]	12.8% (5.9%–19.7%)	50.4%
Melatonin	42.1% (35.7%–48.5%)	+	+	14	41.0% (34.8%–47.3%)	1.1% (−5.1% to 7.4%)	2.7%
Minocycline	30.9% (24.1%–37.6%)	+	−	0	No adjustment		—
Nicotinamide	29.2% (23.0%–35.5%)	+	+	24	21.8% (14.9%–28.6%)[a]	7.4% (0.8%–13.9%)	33.9%
NOS donors	21.4% (13.7%–29.1%)	+	+	25	14.0% (6.4%–21.6%)[a]	7.4% (−0.1% to 14.9%)	52.9%
NOS inhibitors	22.2% (17.1%–27.3%)	+	+	13	14.7% (8.9%–20.6%)[a]	7.5% (2.0%–13.0%)	51.0%
NXY-059	43.8% (34.7%–52.8%)	+	−	0	No adjustment		—
Piracetam and related compounds	29.6% (16.1%–44.4%)	+	−	0	No adjustment		
Stem cells	29.6% (23.7%–35.4%)	+	−	0	No adjustment		—
Tirilazad	31.9% (23.1%–40.7%)	+	−	0	No adjustment		—
tPA	22.5% (19.2%–25.9%)	+	+	5	19.9% (16.4%–23.3%)	2.6% (−0.7% to 6.0%)	13.1%
Other Thrombolytics	46.6% (35.7%–57.5%)	+	−	0	No adjustment		-
Pooled analysis	**31.3% (29.7%–32.8%)**	**+**	**+**	**214[b]**	**23.8% (22.2%–25.5)[a]**	**7.5% (5.9%–9.1%)**	**31.1%**

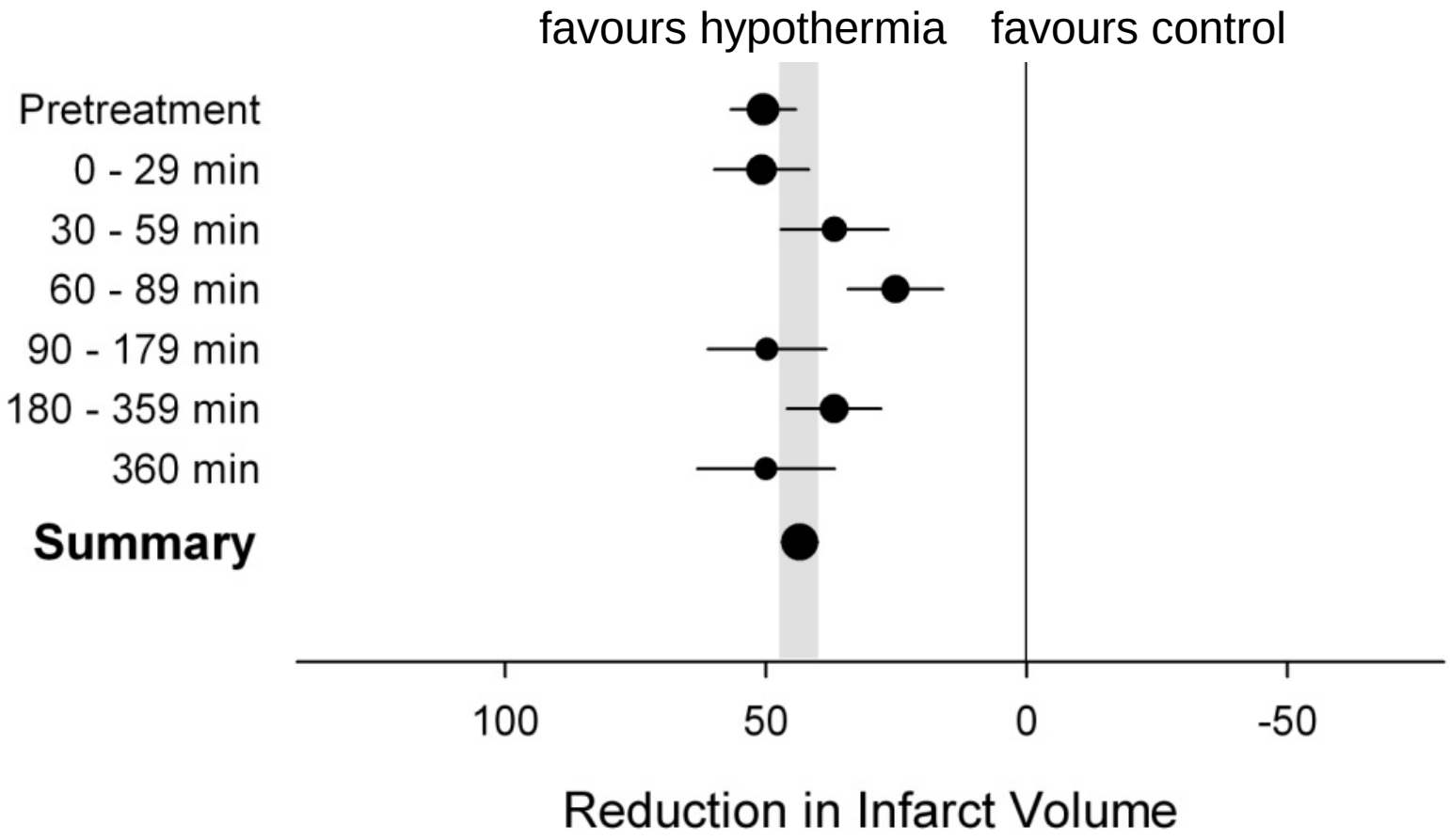
What are the conditions of maximum efficacy?

duration of hypothermia



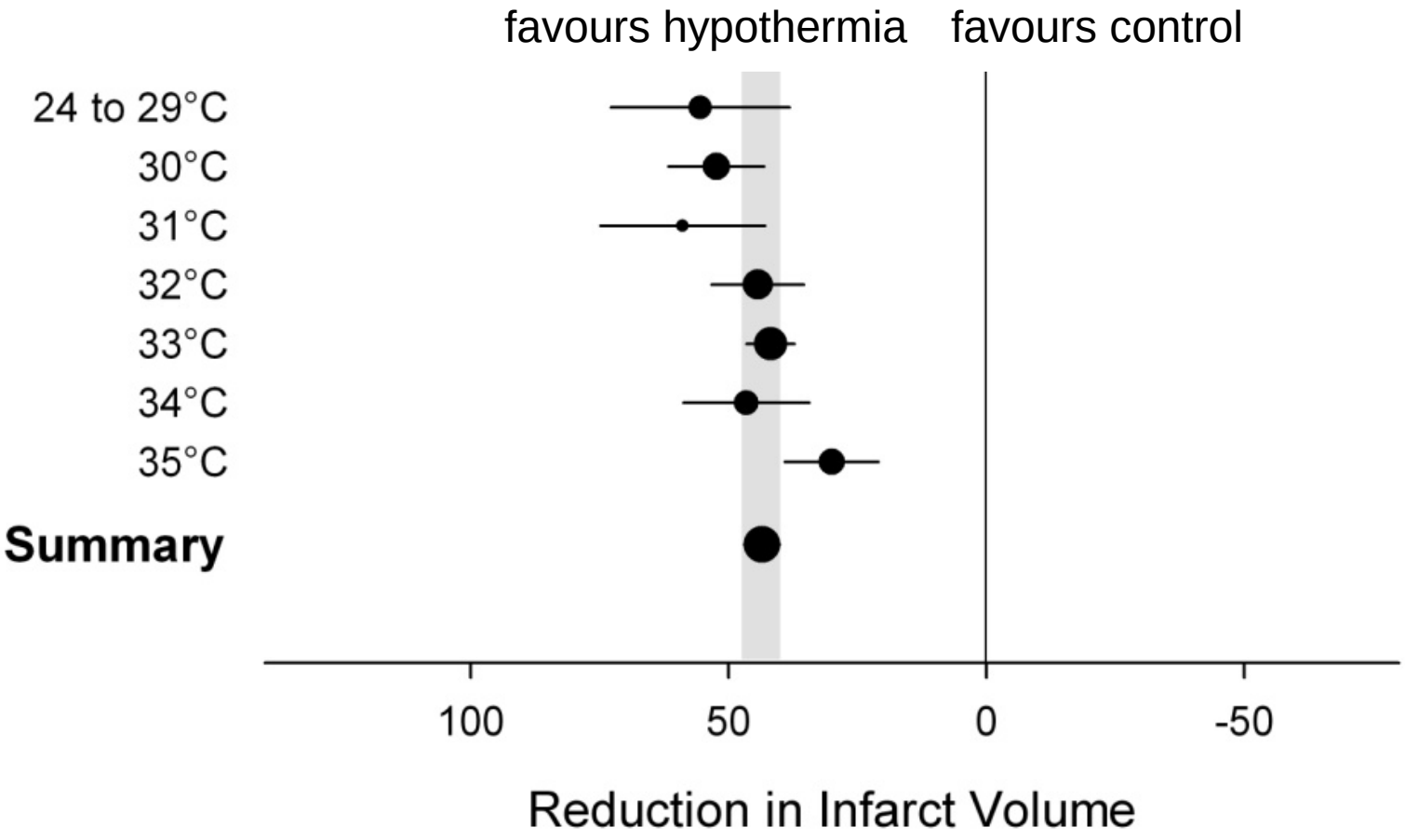
What are the conditions of maximum efficacy?

delay to treatment



What are the conditions of maximum efficacy?

depth of hypothermia



EuroHYP-1
Knowledge translation table

Criterion	Animal data	EuroHYP-1
How powerful is the treatment?	>40% improvement in outcome	Powered to detect 7% improvement in outcome
What is the quality of evidence?	Efficacy maintained in high quality studies	Randomised, blinded outcome assessment, intensely monitored
Is there evidence of a publication bias?	Yes, but >35% improvement in adjusted outcome	Registered
What is the range of evidence?	Good: sex, duration, delay to treatment, intensity, hypertension, reperfusion	Patients >18yo with acute ischaemic stroke, NIHSS 6 to 20, treated within 6hrs
What are the conditions of maximum efficacy?	Temperature dependent: otherwise robust across dimensions	Target 34-35˚ C

EuroHYP-1

- International randomised controlled clinical trial of modest cooling in patients with stroke
- Evidence based trial design
  - entry within 6 hours of stroke onset
  - Cooling to 34 to 35°C
  - Patients with hypertension allowed
  - Cooling for 24 hours

Chest Heart & Stroke Scotland

SEVENTH FRAMEWORK PROGRAMME

EuroHYP-1

- FP7 funding of €11m awarded from 01/02/12
- Target 50 – 70 centres in more than 15 countries
- First patient recruited November 2013
- 1500 patient target over 4 years
- Results late 2017

Chest Heart & Stroke Scotland

SEVENTH FRAMEWORK PROGRAMME

Recruitment

Performance by country

	Germany	UK	Denmark	France	Spain
Centre months open	277.77	70.33	16.10	7.63	8.60
Patients Randomised	20	14	3	1	3
Patients per centrre Month	0.072	0.199	0.186	0.131	0.349

Protocol amendments

- Reduced duration of cooling
- Reduced target sample size
  - Improved ascertainment of mRS
  - mRS shift analysis
  - Covariate adjustment

Thank you

- If you are interested in joining the trial, contact Bridget.Colam@ed.ac.uk