# 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

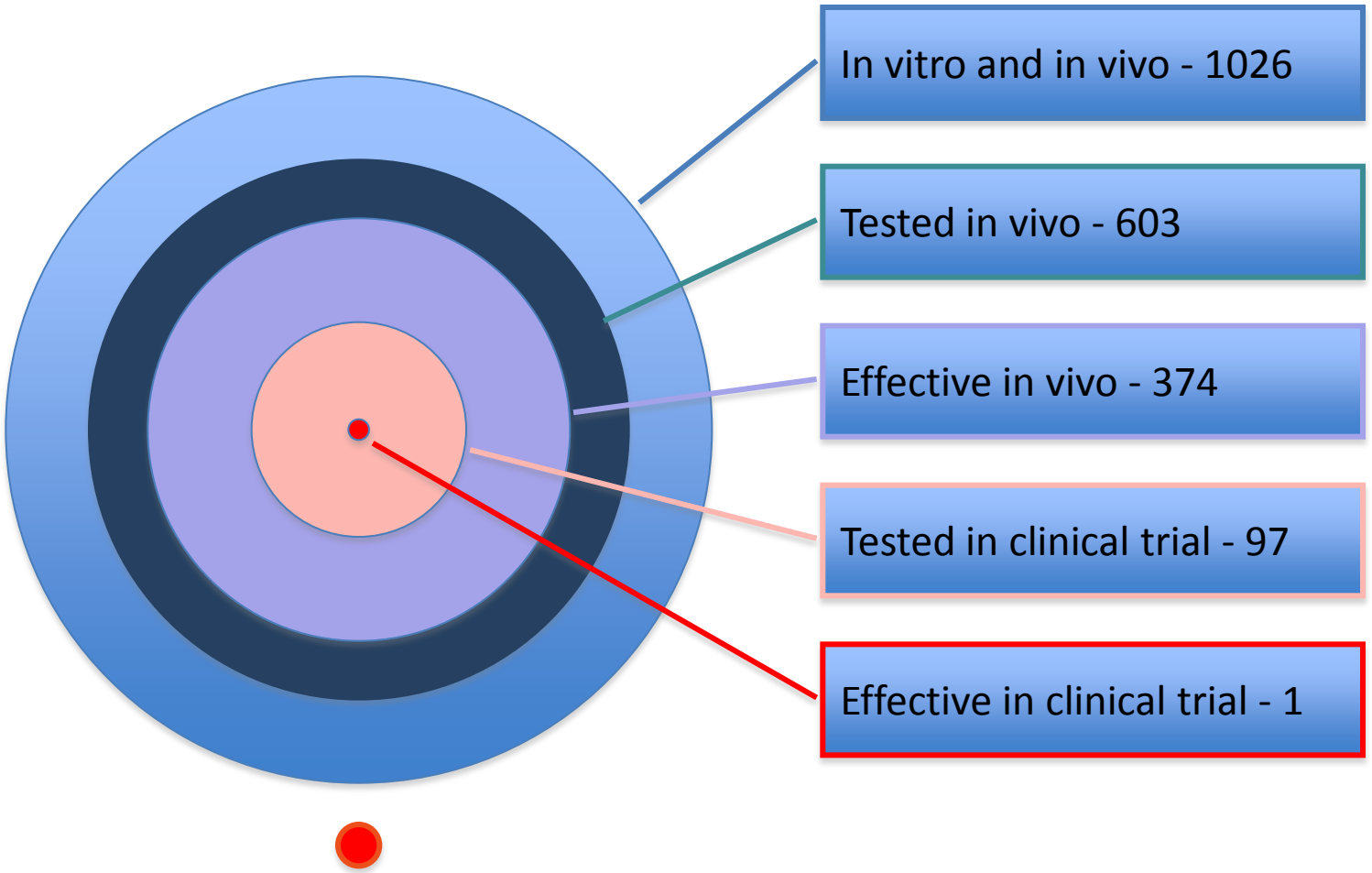
**Influence in models**

- 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

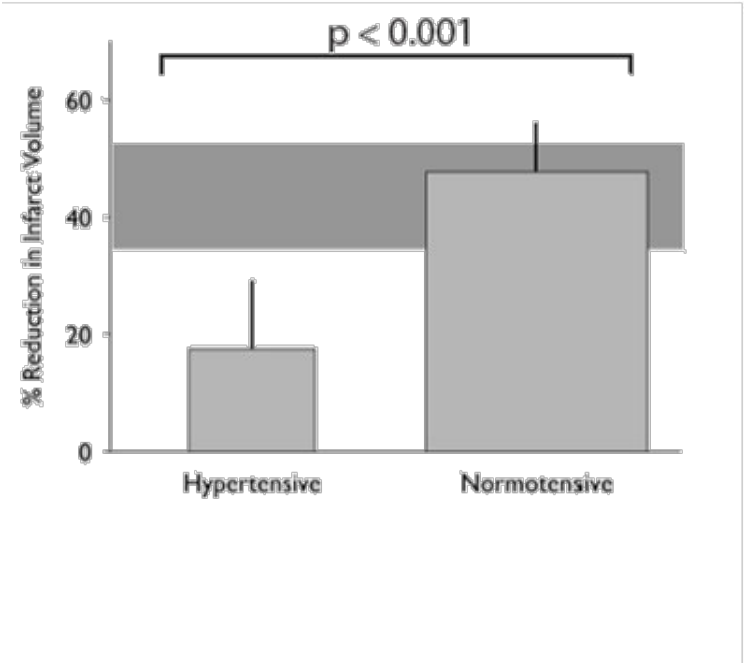



O' Collins et al, 2006

# High blood pressure in animal stroke studies – NXY-059

**Hypertension:**

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



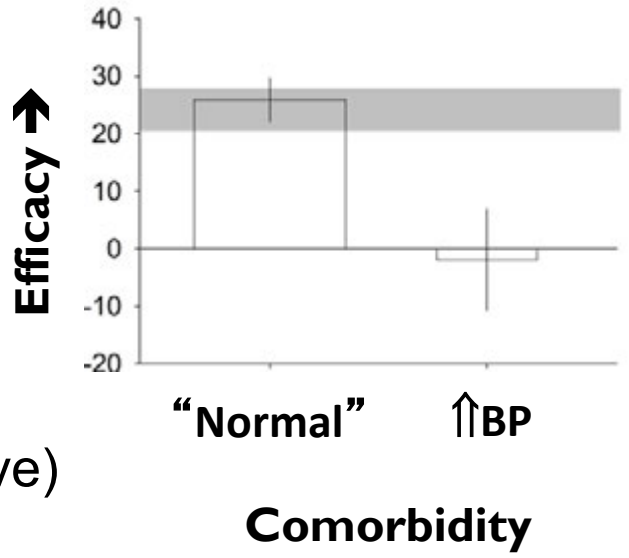
# High blood pressure in animal stroke studies – tPA

**Infarct Volume:**

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

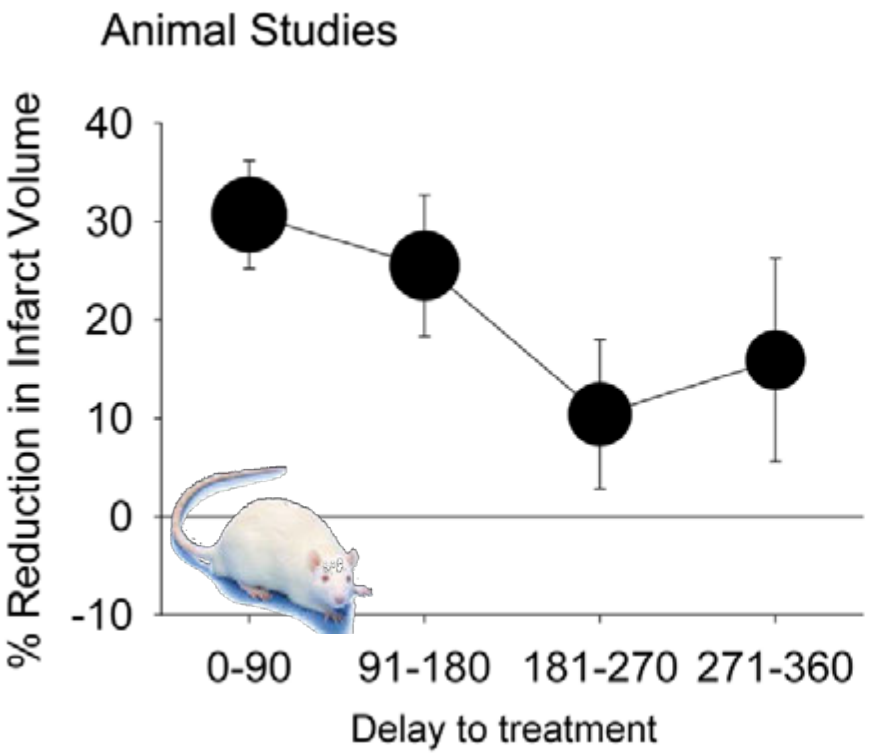
**Hypertension:**

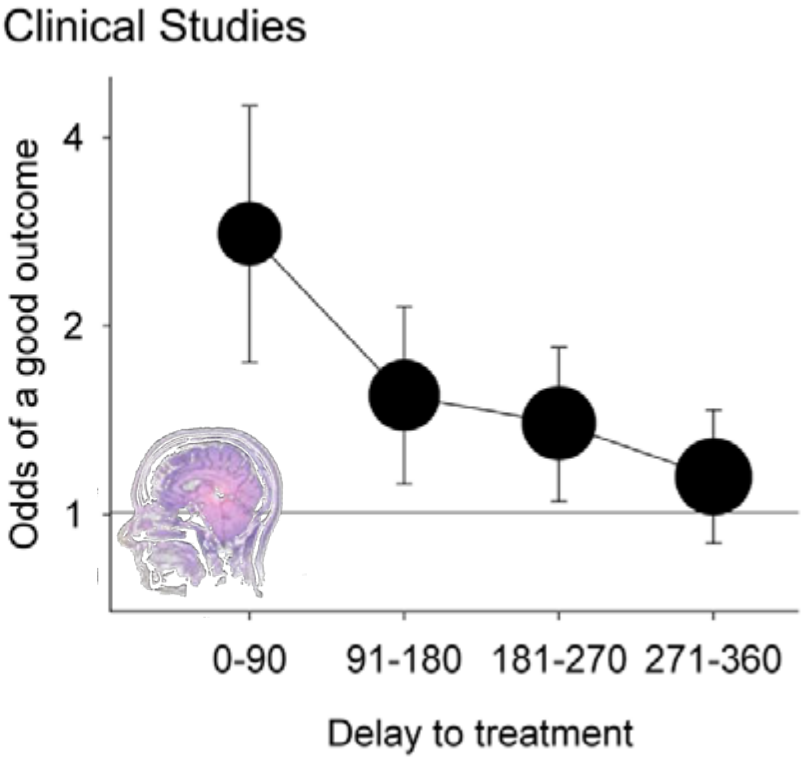
- 9% of animal studies
- Specifically exclusion criterion in (positive) NINDS study



# 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

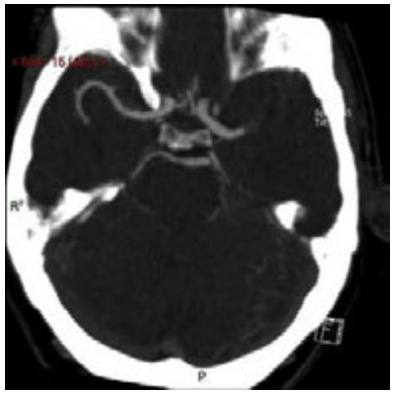

Animal Studies
% Reduction in Infarct Volume
40
30
20
10
0
-10
0-90
91-180
181-270
271-360
Delay to treatment

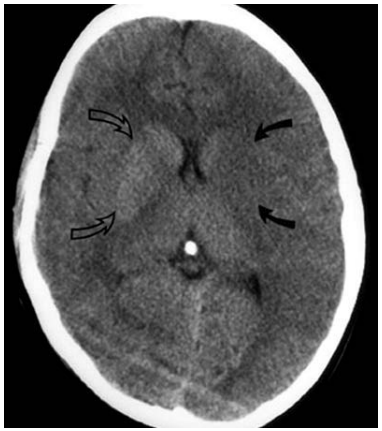

Clinical Studies
Odds of a good outcome
4
2
1
0-90
91-180
181-270
271-360
Delay to treatment

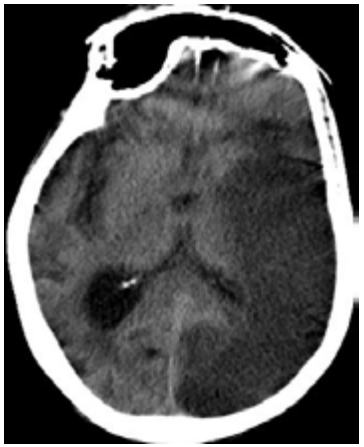
# Cooling for stroke

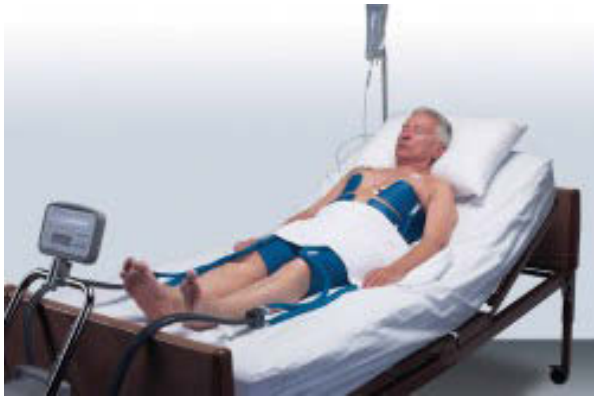
- Cooling seems to work in patients who have brain injury due to cardiac arrest
- There's lots of stories about individual patients who should have extensive brain damage but don't
- Many labs use cooling as a positive control in their animal studies
- Preliminary evidence from clinical trials in stroke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

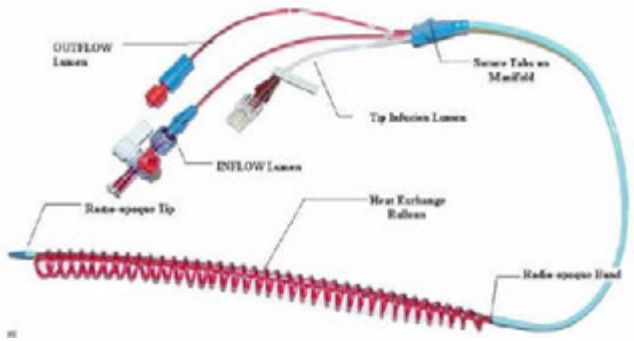
# How to become cool



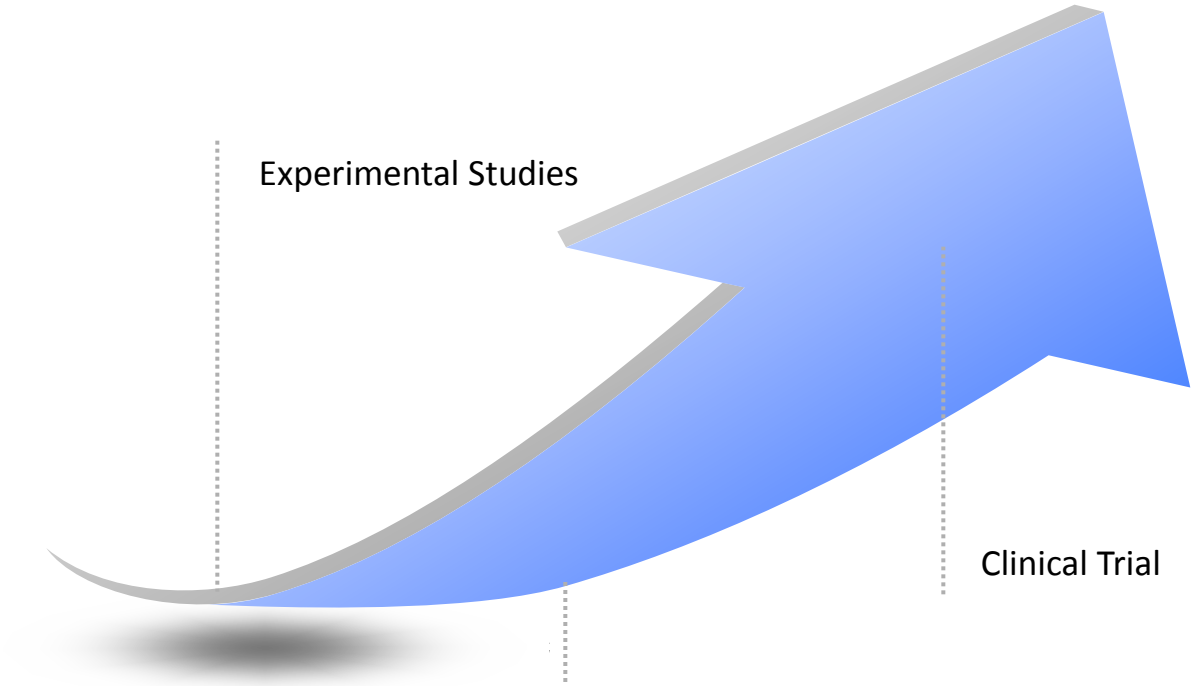








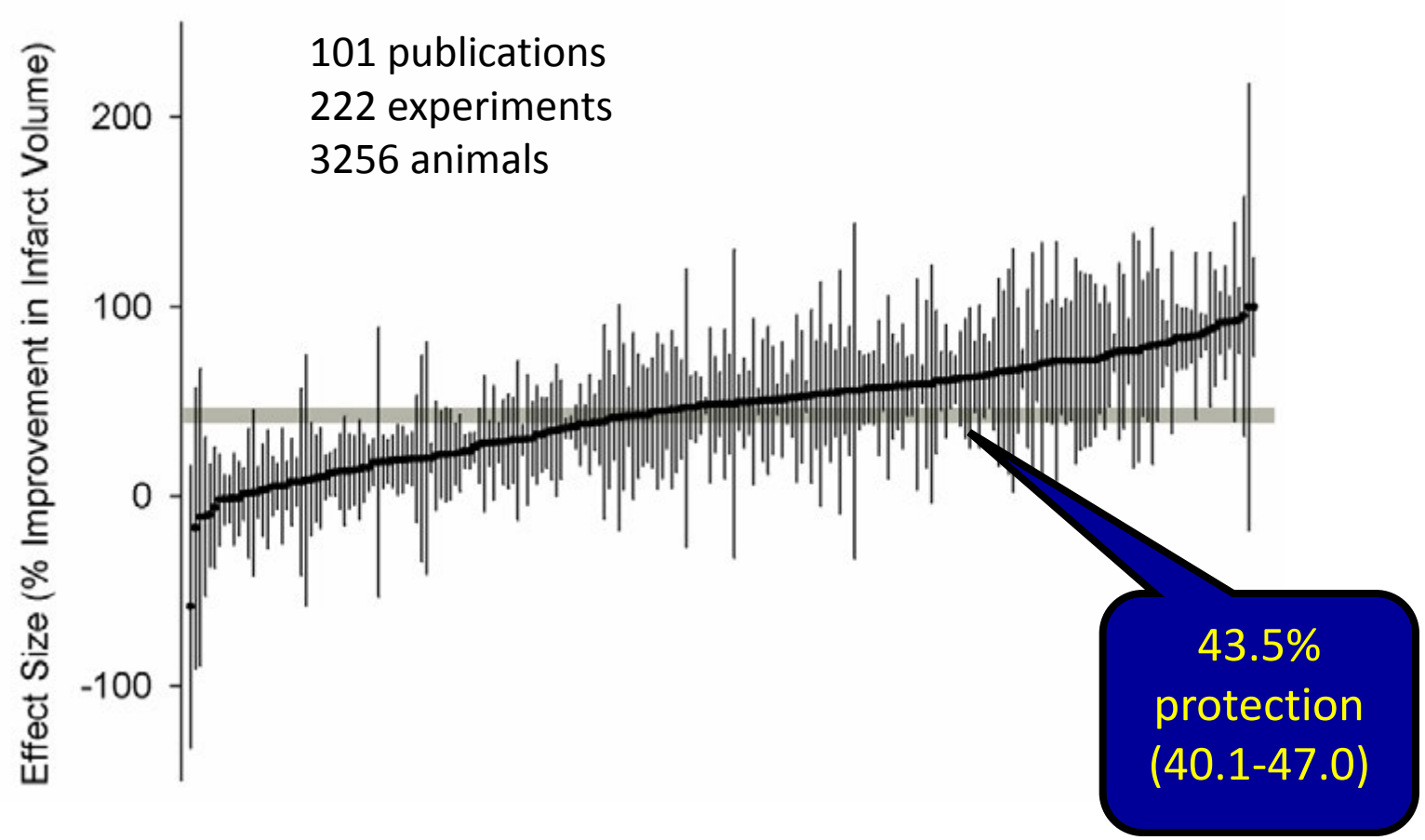
# Evidence based trial design



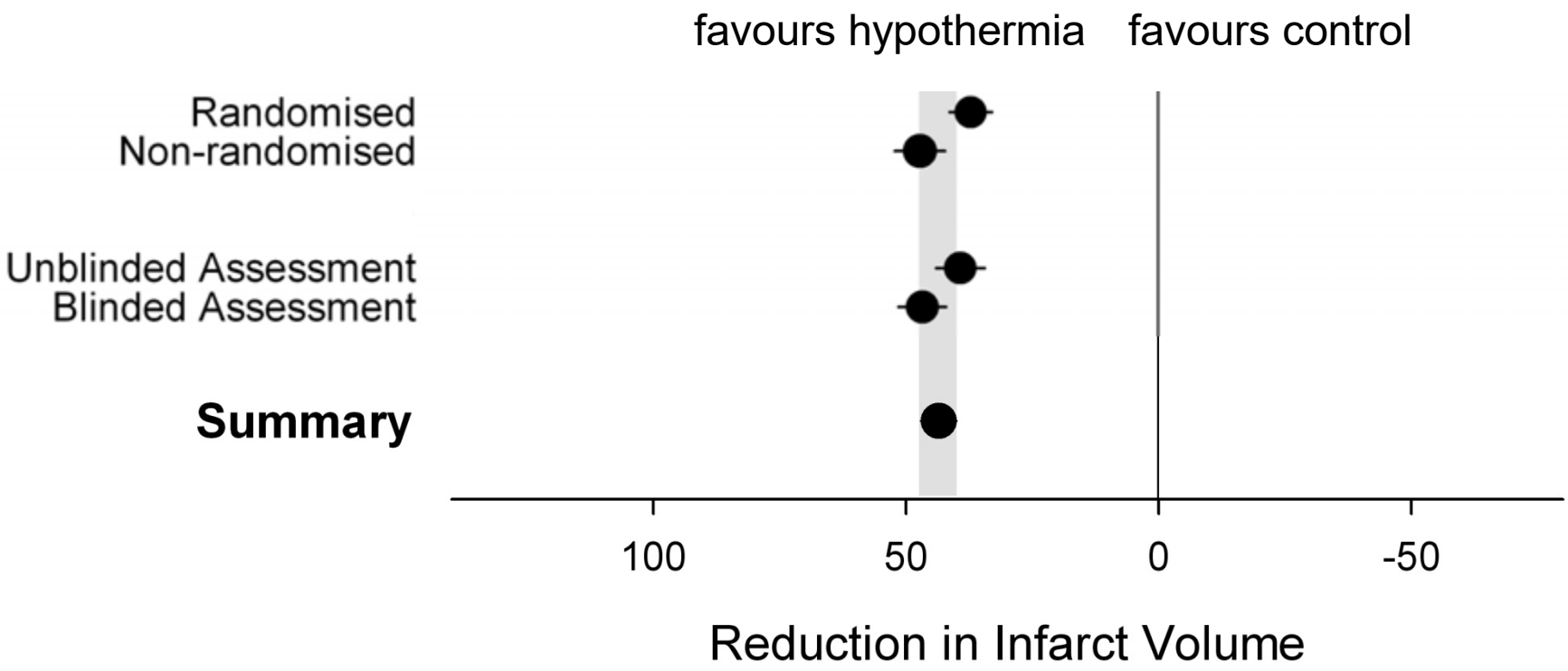

Systematic review and meta-analysis

- 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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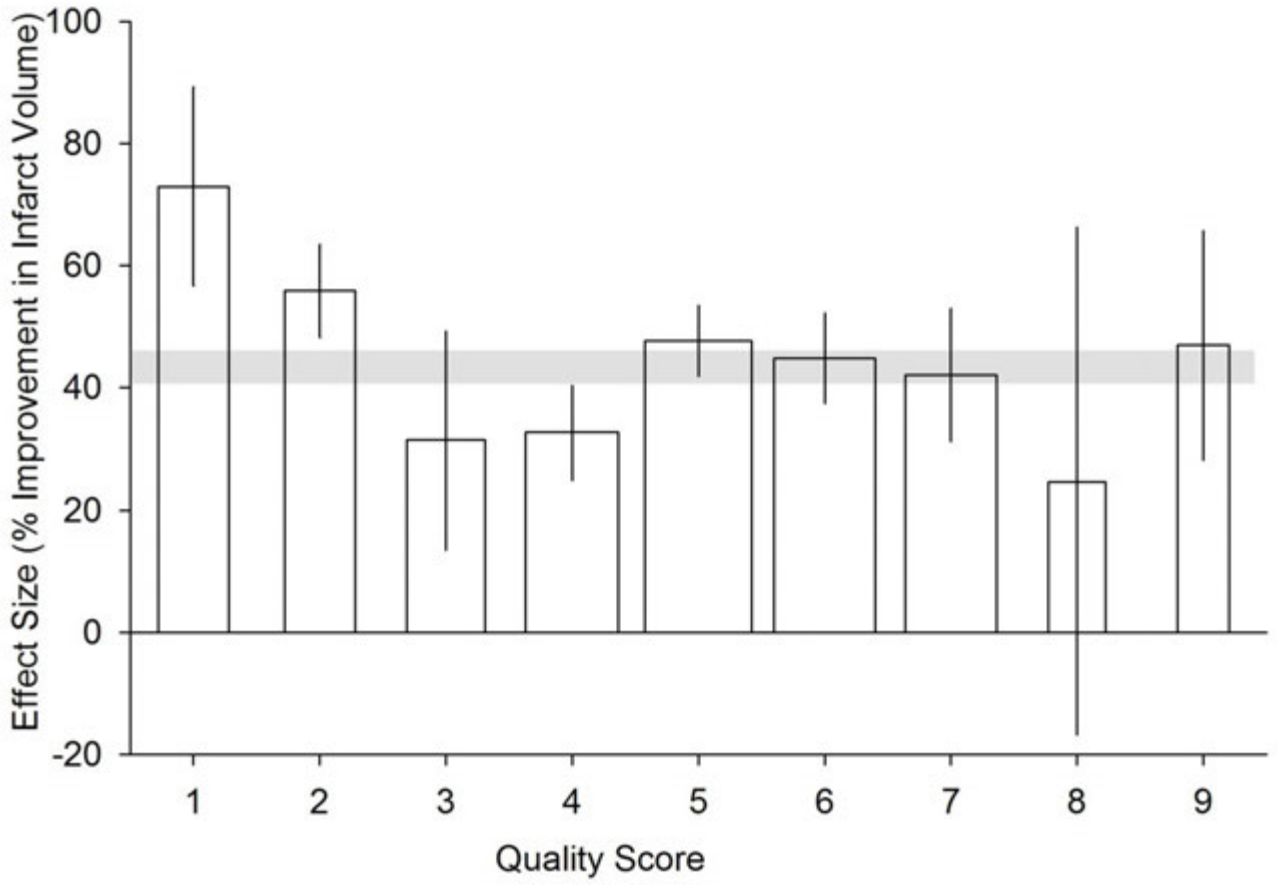
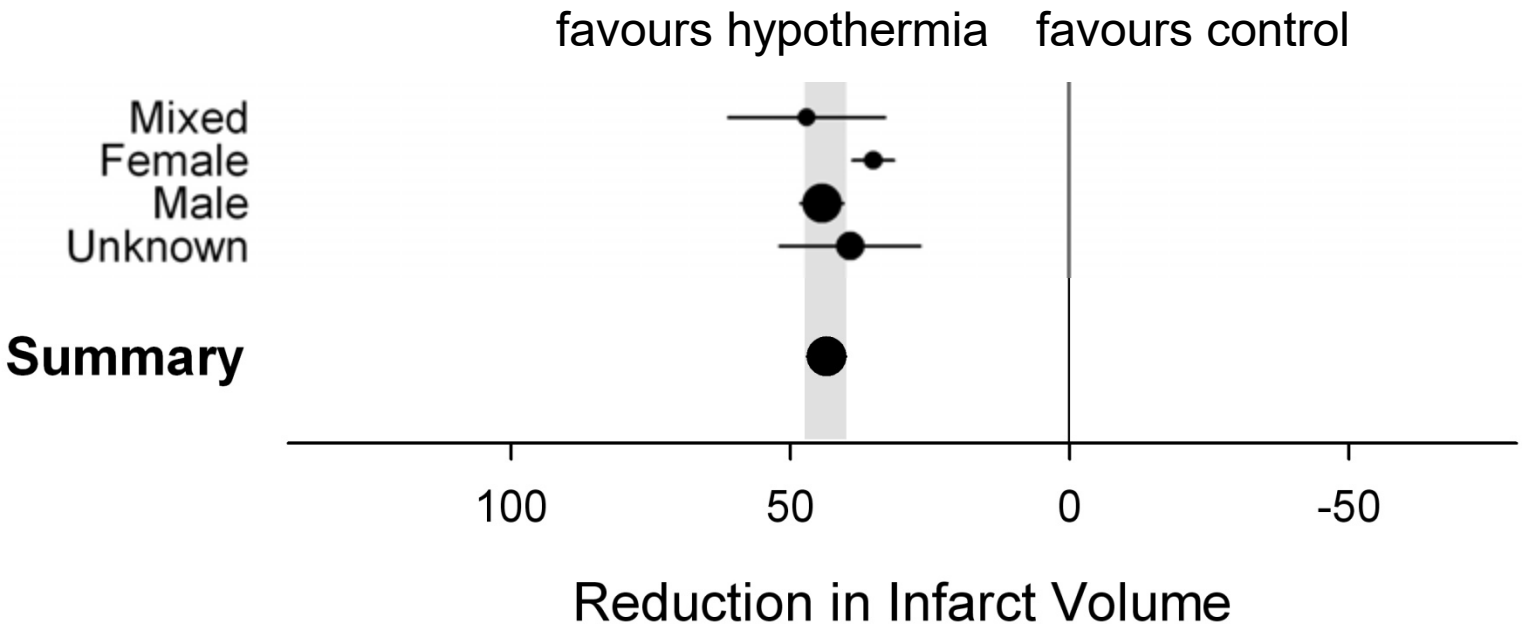


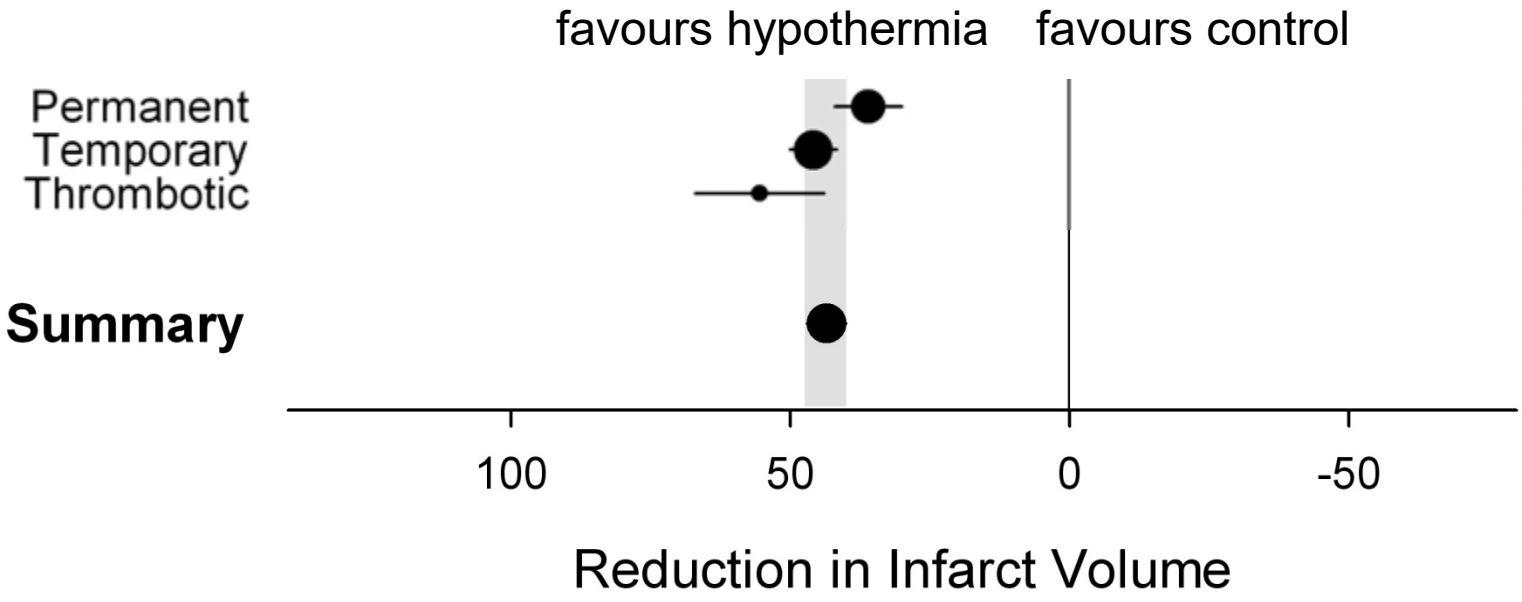
# What is the range of evidence?

sex



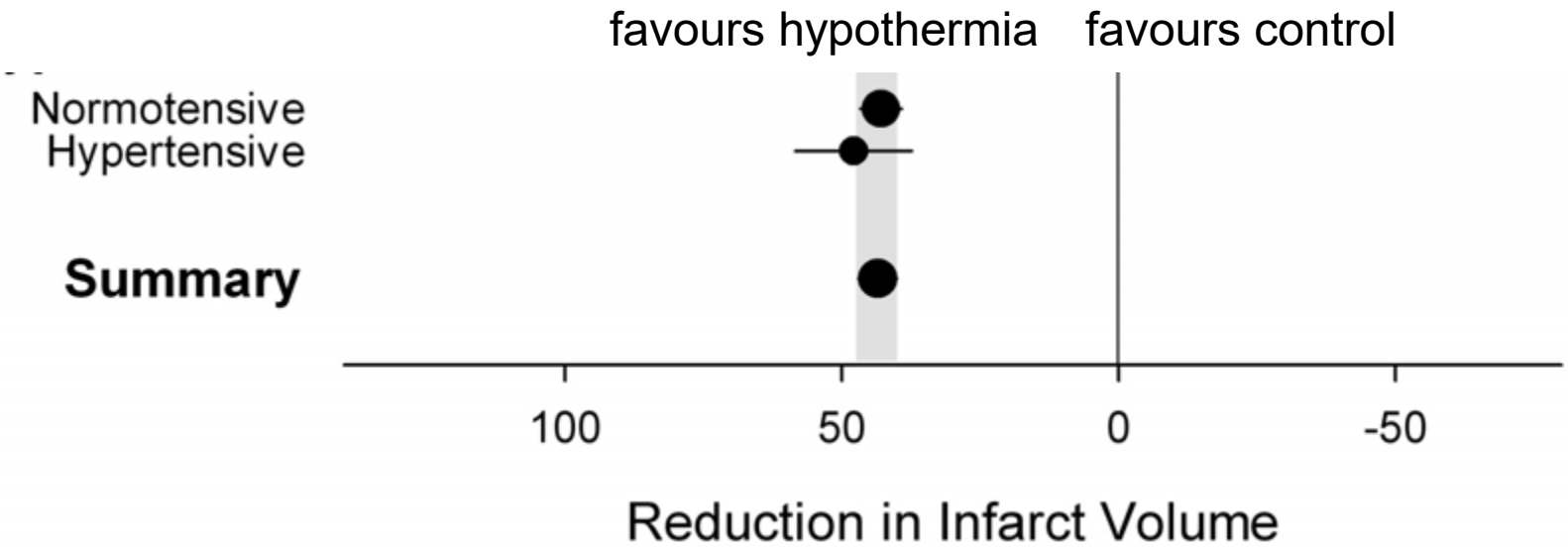
# What is the range of evidence?

duration of ischaemia



# What is the range of evidence?

presence of hypertension

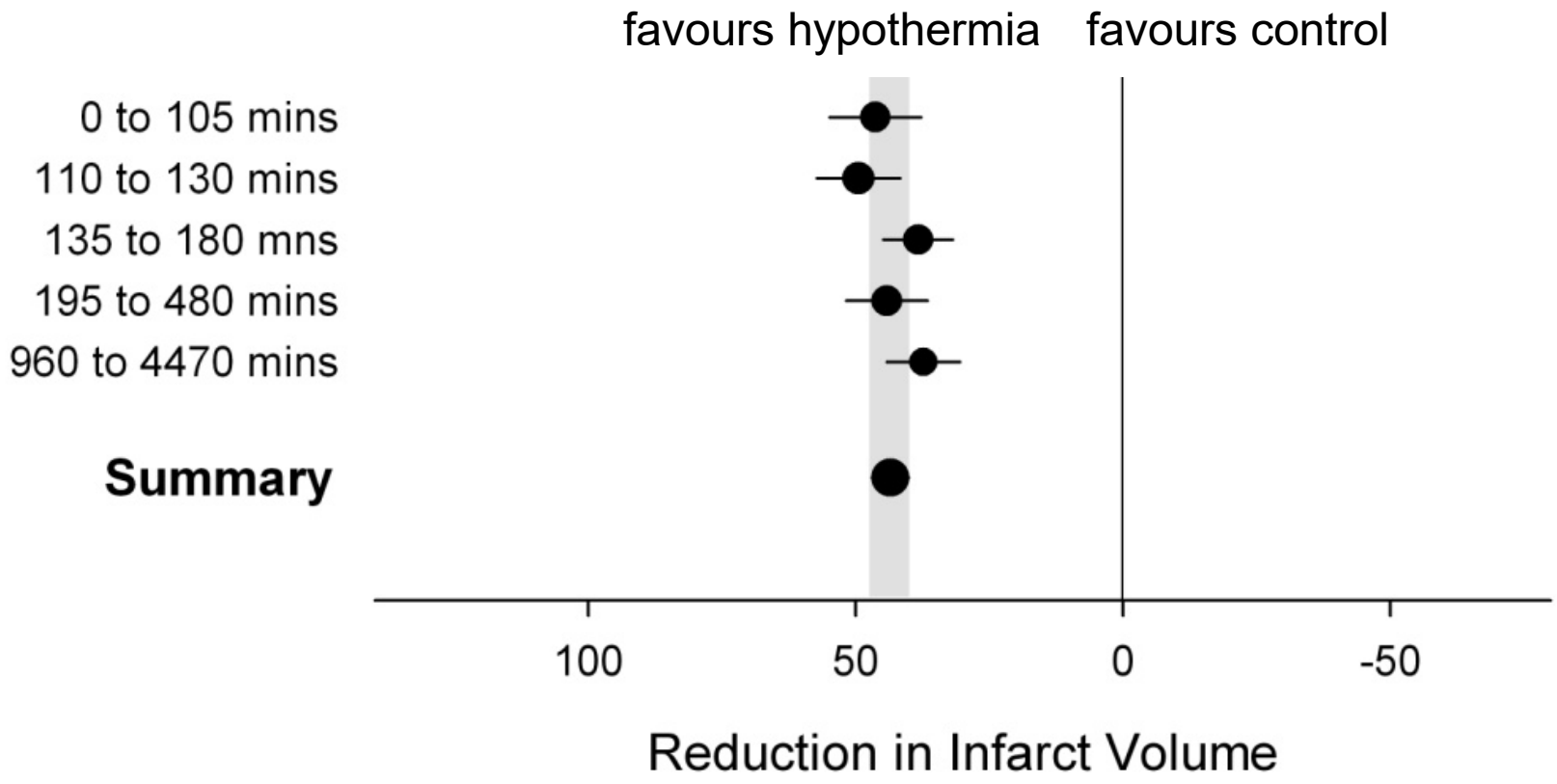


# Is there evidence of a publication bias?

| 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%** |

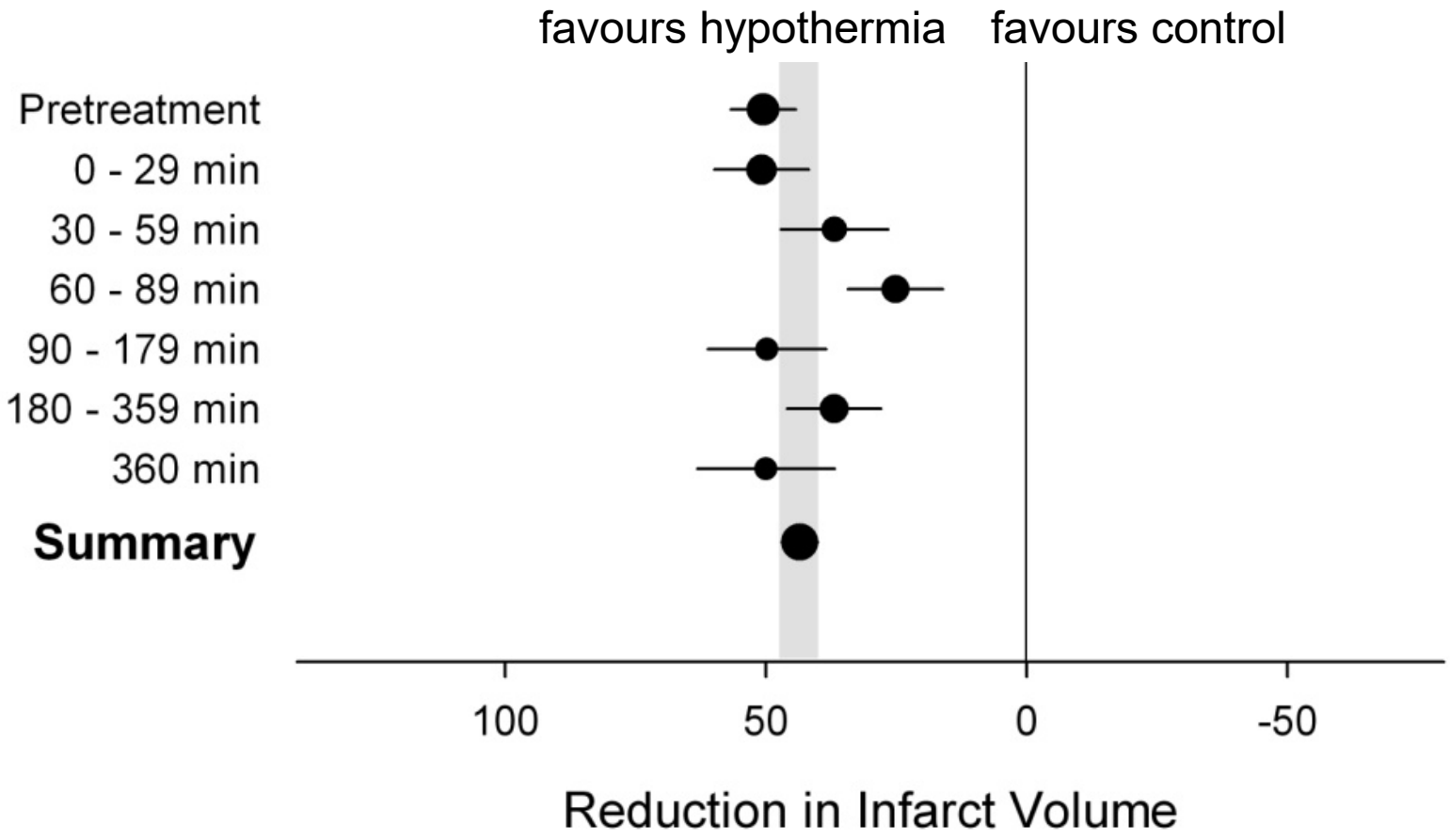
# What are the conditions of maximum efficacy?

## duration of hypothermia



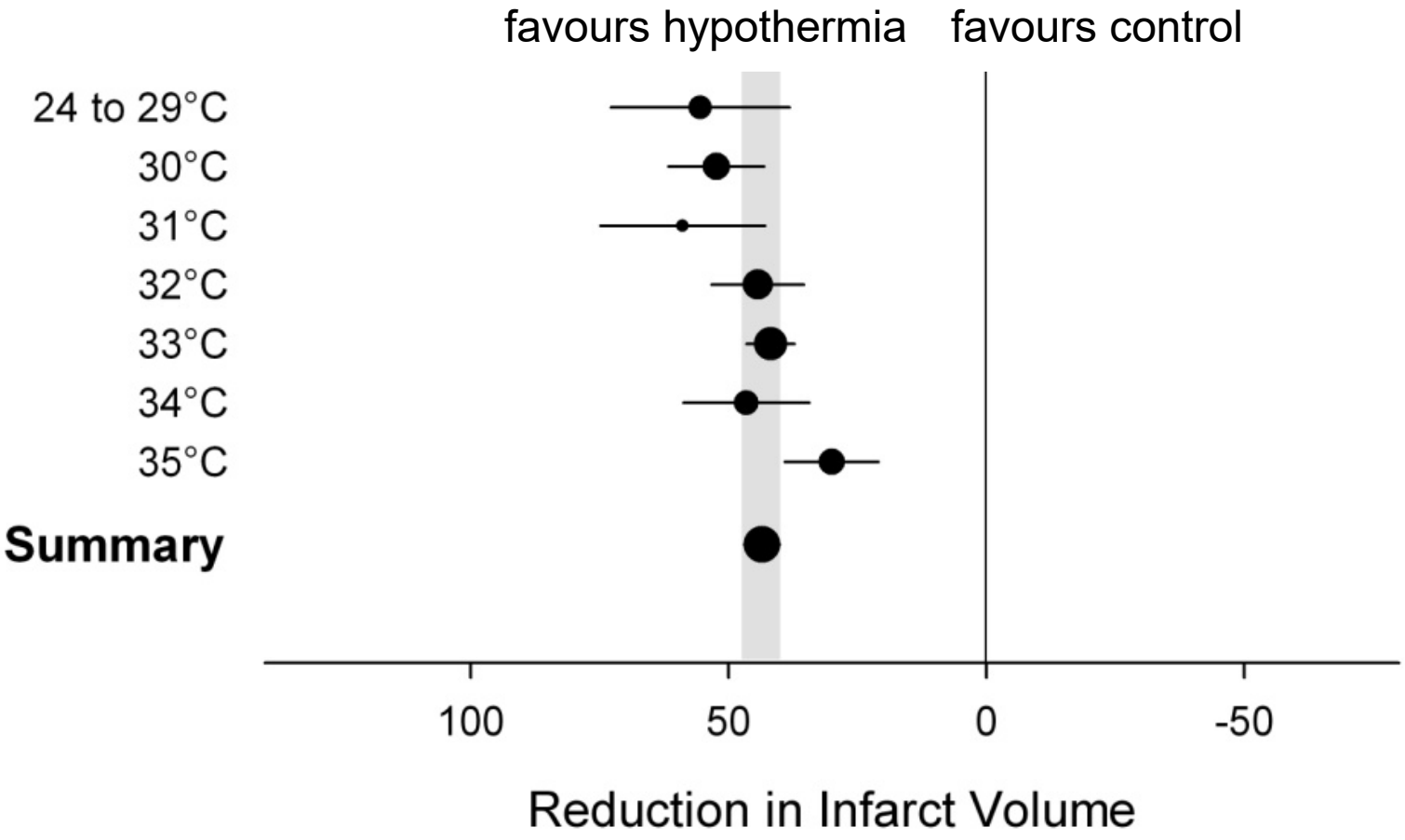
# What are the conditions of maximum efficacy?

## 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