DIPARTIMENTO DI NEUROSCIENZE
SALUTE MENTALE E ORGANI DI SENSO
NESMOS

SAPIENZA
UNIVERSITÀ DI ROMA

Ipotermia e Neuroprotezione: quali frontiere terapeutiche

XXVI Congresso nazionale SINV
Lecce

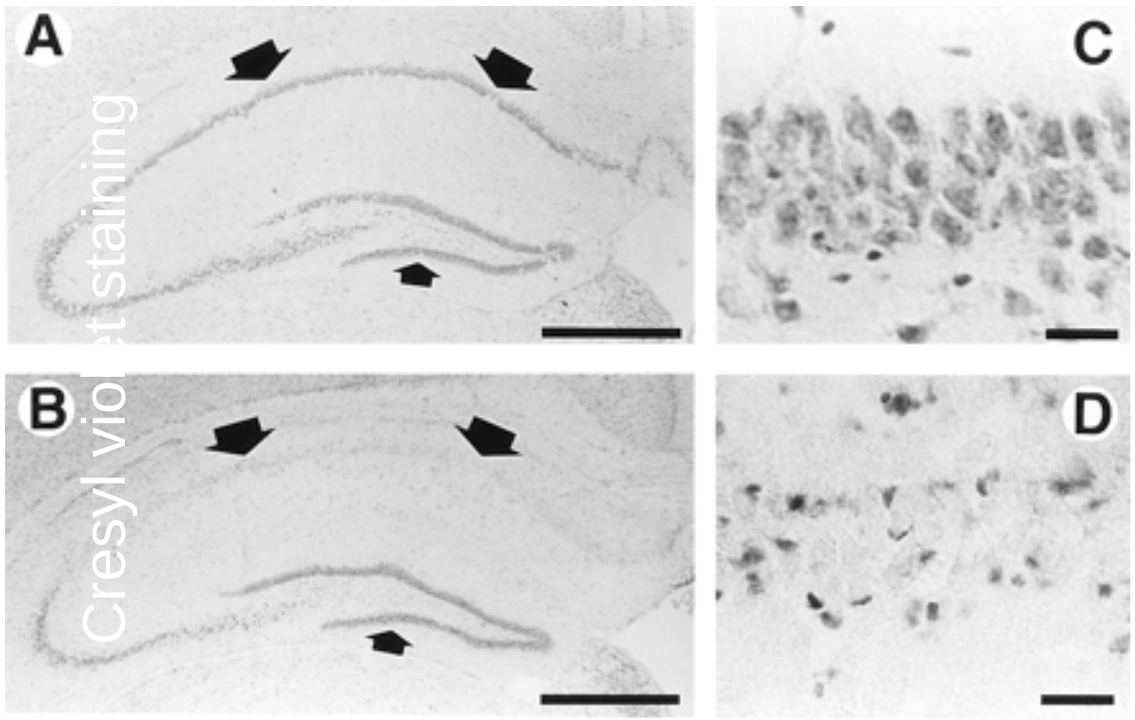
Francesco Orzi

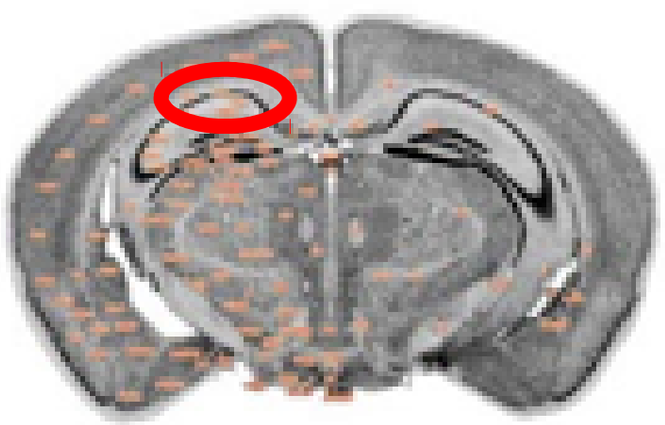
Maturation Phenomenon

Changes in CA1 after 5 min ischemia, in the gerbil

ore dopo riperfusione

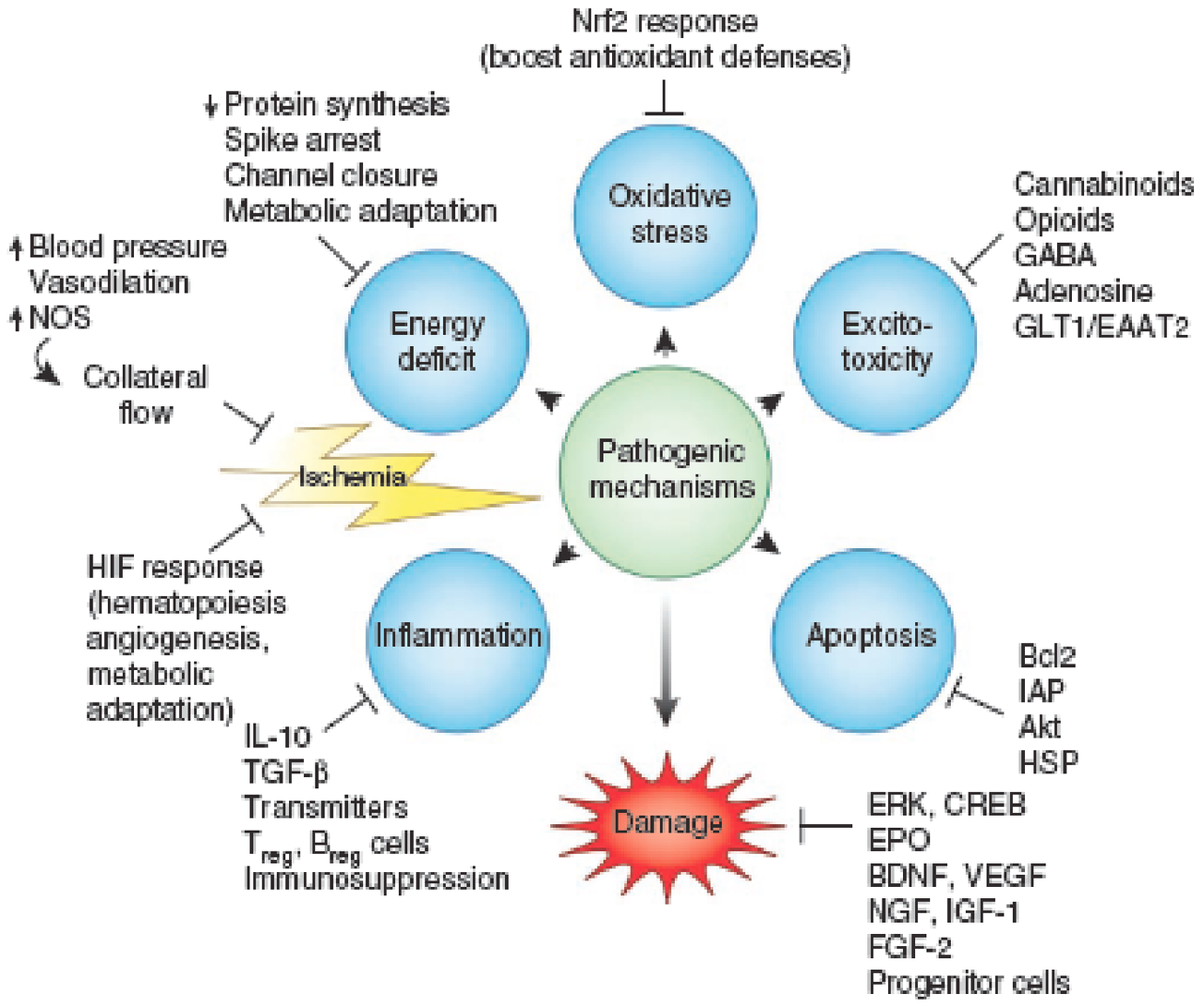
7 giorni dopo riperfusione





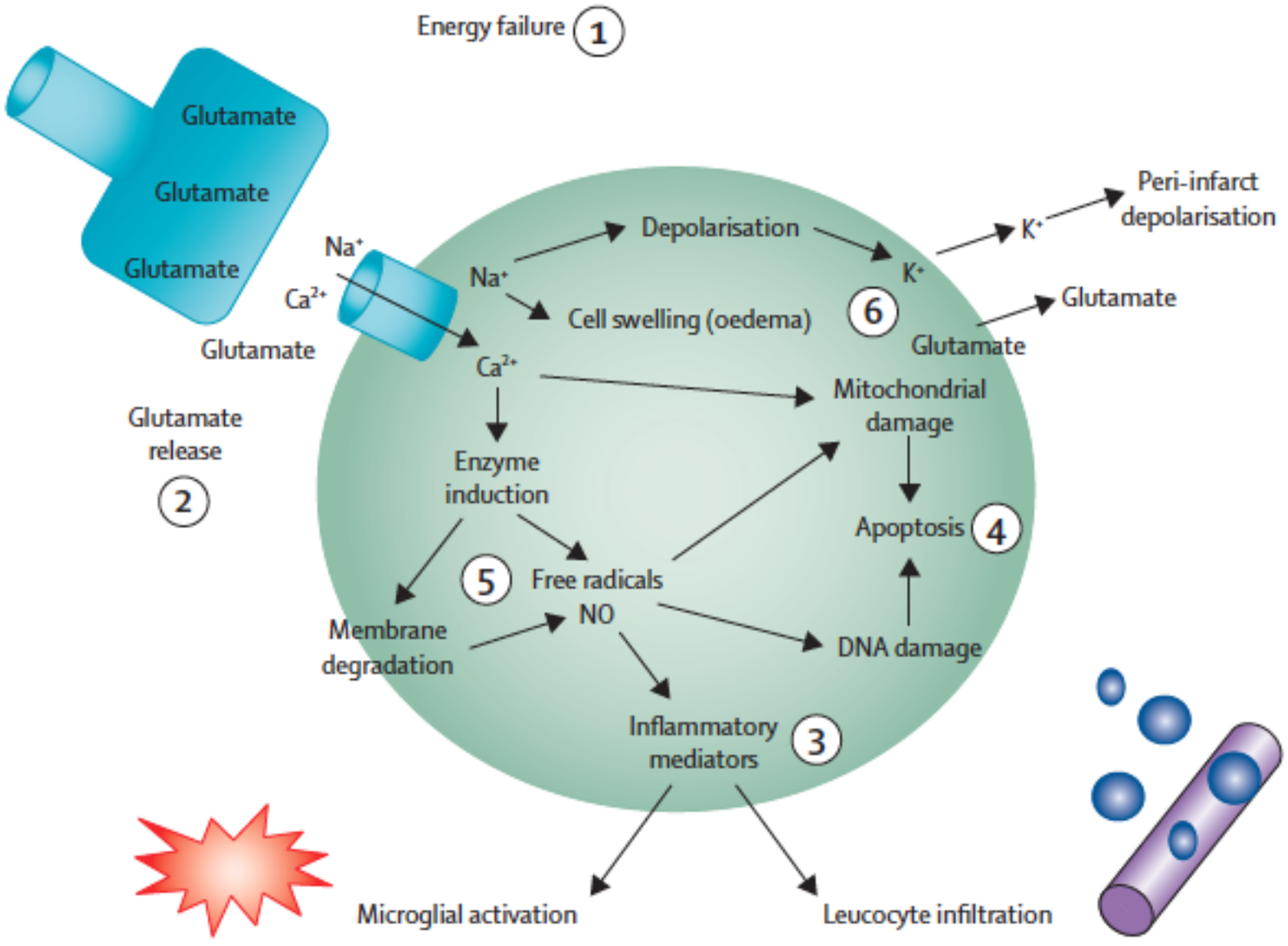
Suzuki et al, 1983

Complex Scenario



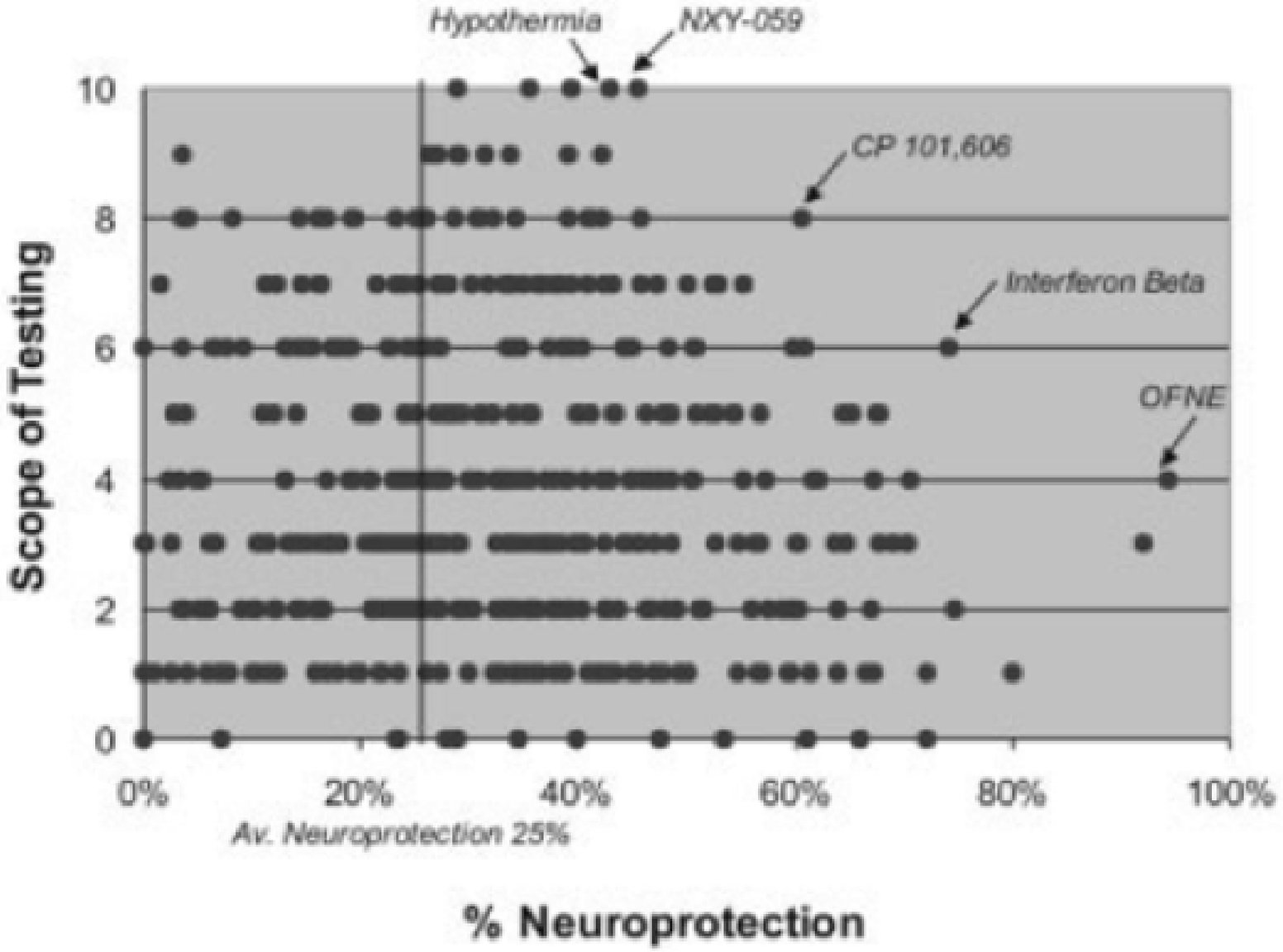
Iadecola & Anrather, Nat Med July 2011

neuroprotective mechanisms of hypothermia



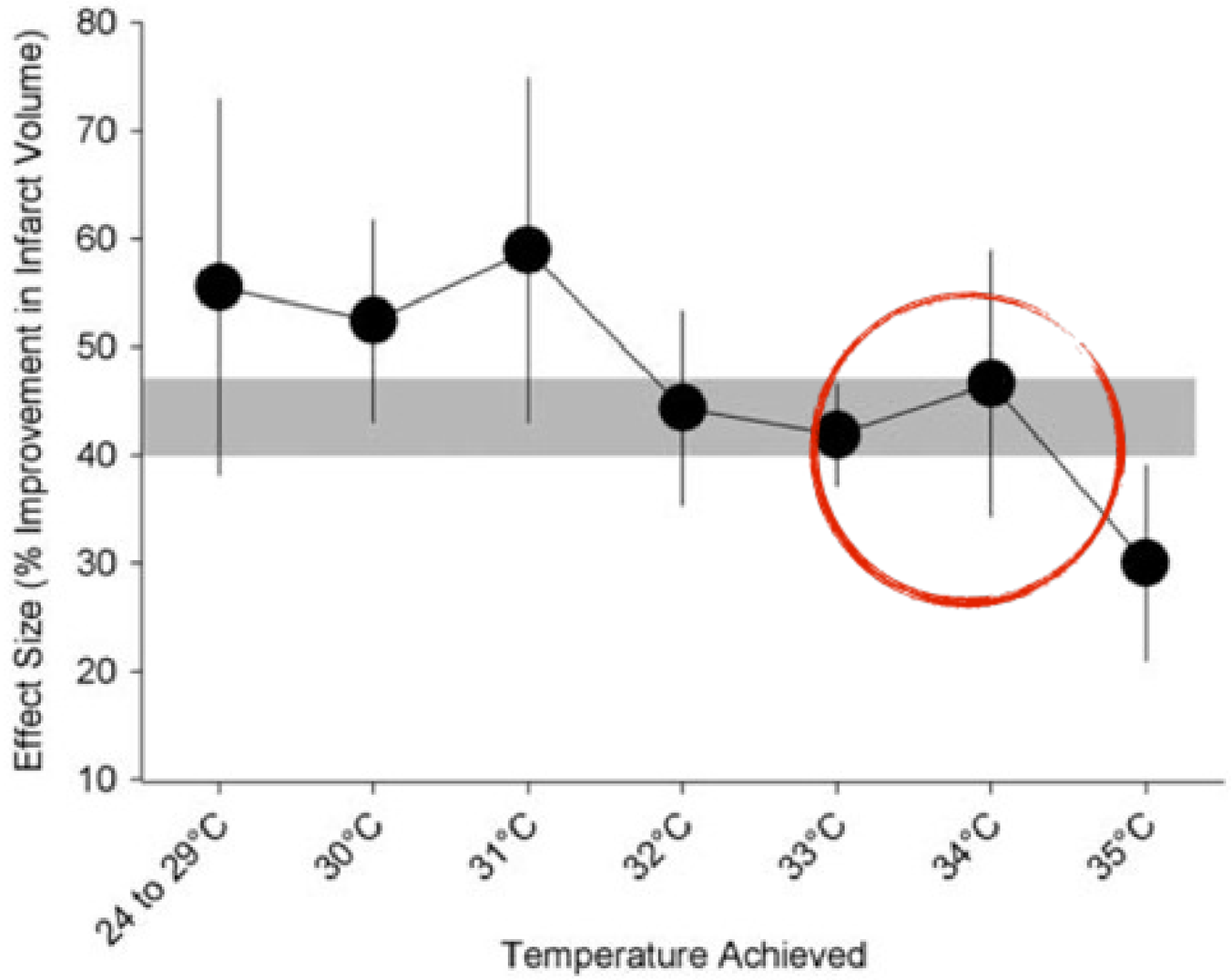
Tzu-Ching Wu, James C Grotta; Lancet Neurol 2013

STAIR scoring and extent of neuroprotection



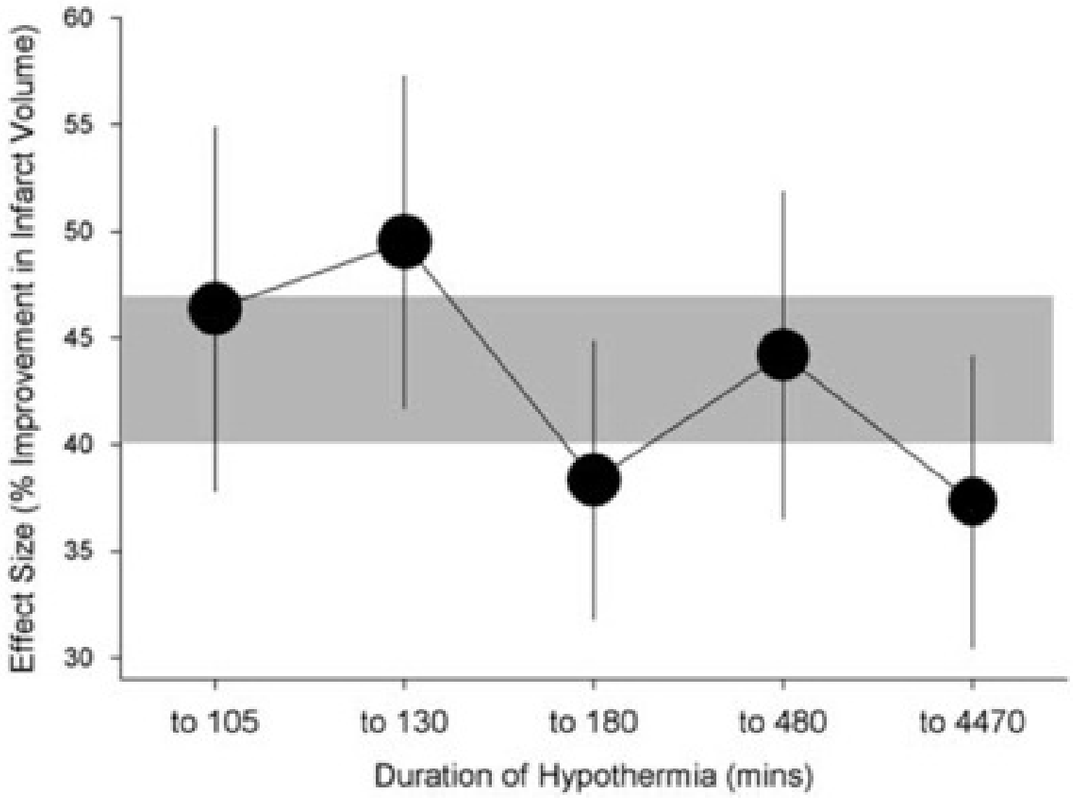
O'Collins et al, Ann Neurol 2006

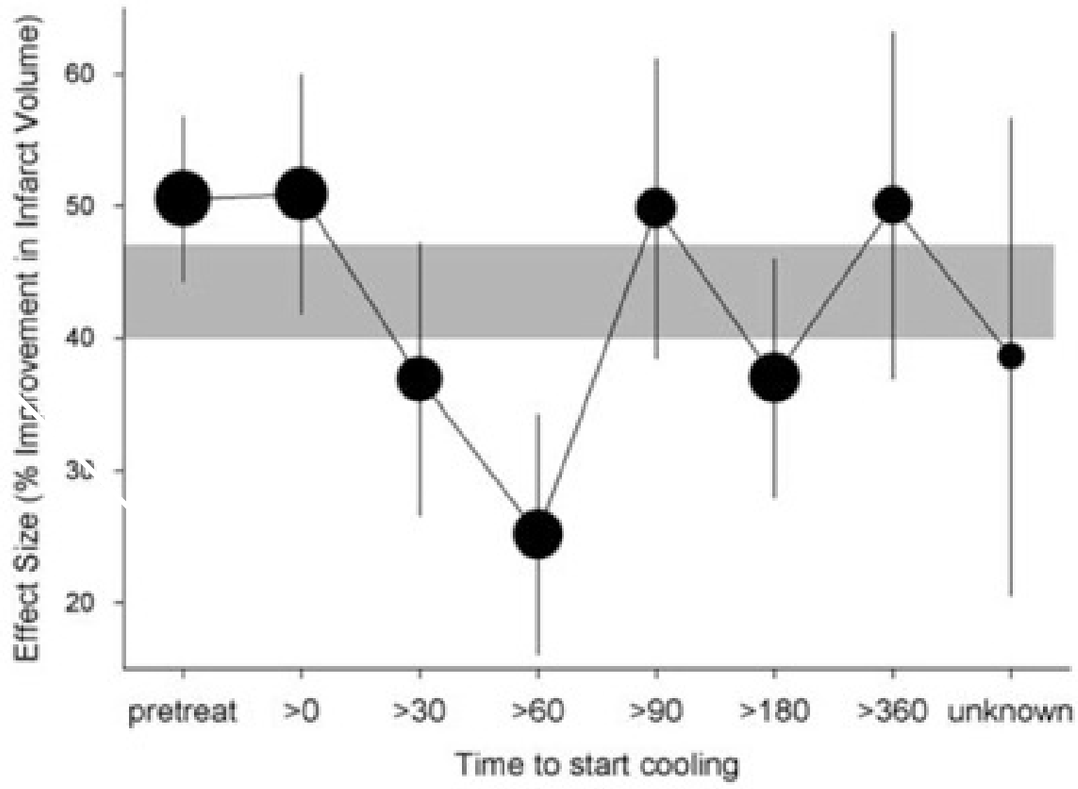
effect vs temperature depth



van der Worp et al, J Cereb Blood Flow Metab. 2010

effect vs duration or window

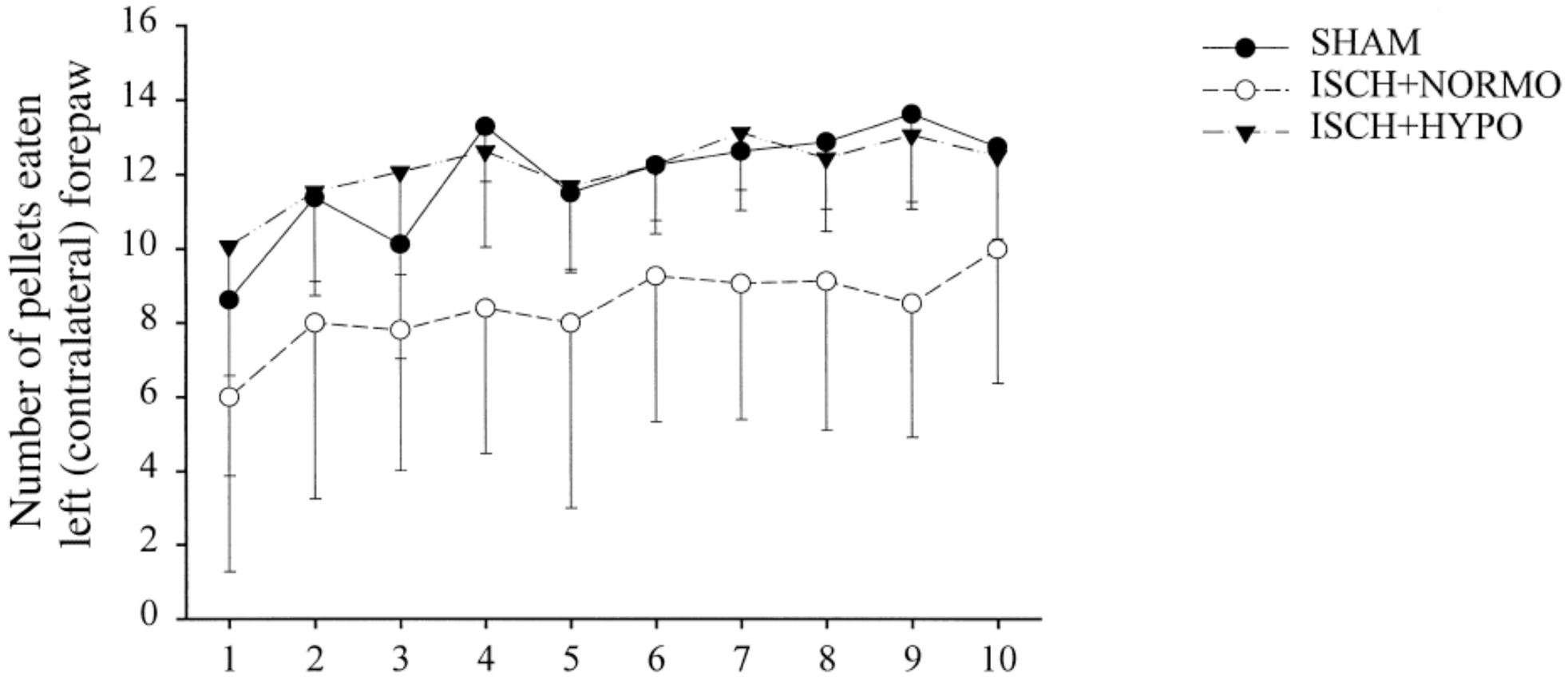




van der Worp et al, J Cereb Blood Flow Metab. 2010

long-term behavioral effects

repeated testing at 30-35 days following 90min MCAO, 33°C for 24h



Colbourne et al. J Cereb Blood Flow Metab, Vol. 20, No. 12, 2000

Cooling seems to promote survival mechanisms

- brain-derived neurotrophic factor (BDNF) (Vosler et al., 2005; D'Cruz et al., 2002)
- glial-derived neurotrophic factor (GDNF) (Schmidt et al., 2004)
- neurotrophin (Boris-Moller et al., 1998)
- maturation of neural progenitor cell (Xiong et al., 2011; Silasi et al., 2011), or cell proliferation (Saito et al., 2010; Silasi et al., 2011; Imada et al., 2010)
- … but findings are inconsistent (Lasarzik et al., 2009; Kanagawa et al., 2006; Bennet et al., 2007)

take home message

from animal models

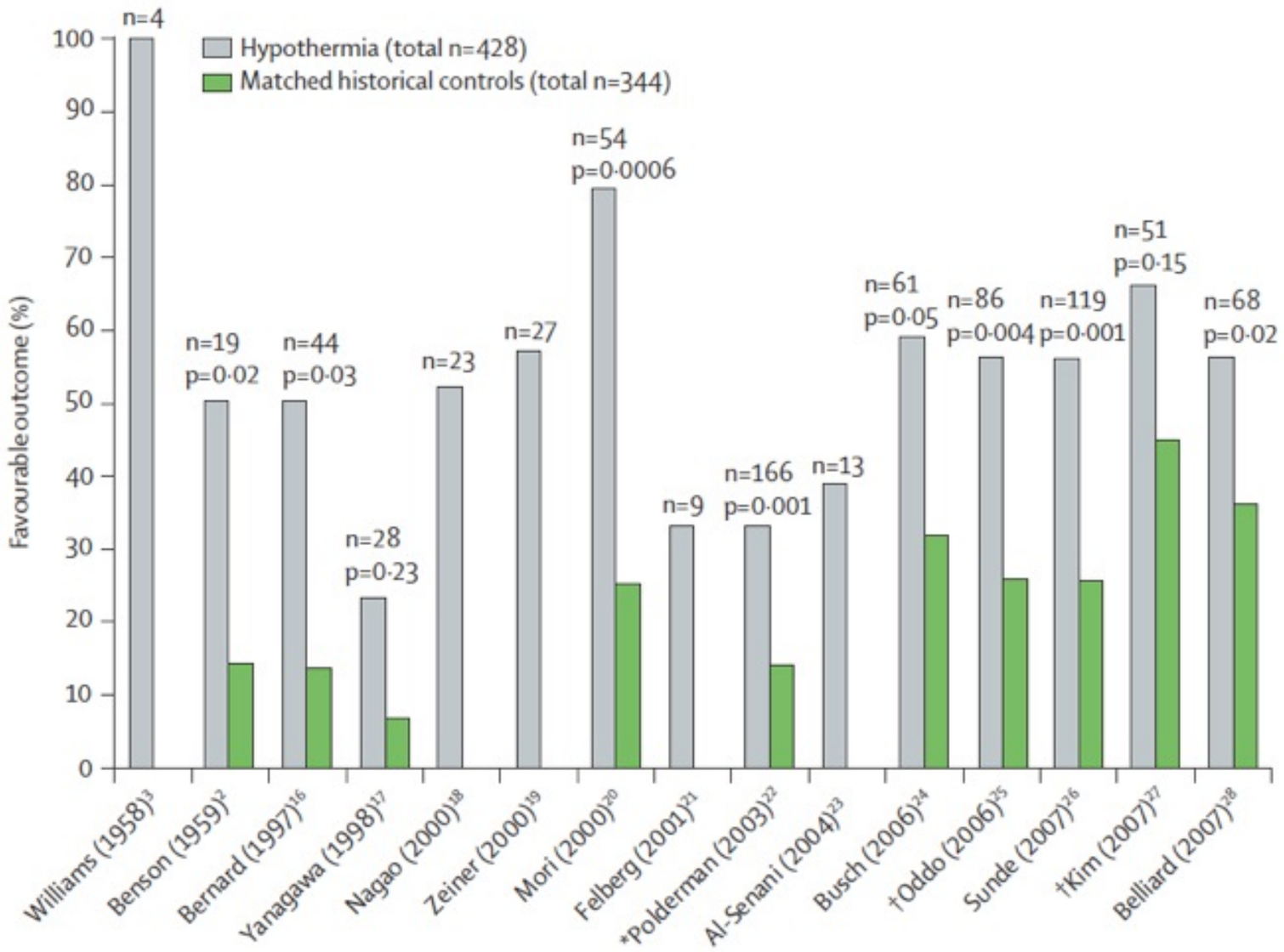
moderate hypothermia represents one of the most solidly evidence-based neuroprotective strategies available Hemmen and Lyden, 2007 in focal and global cerebral ischemia Ginsberg et al., 1992; Ginsberg and Belayev, 2005; Colbourne et al., 1997; Barone et al., 1997; Corbett and Thornhill, 2000; Huh et al., 2000; Gunn et al., 2005

infarct volume is still reduced by about 1/3 with cooling to 35°C, or with window up to 6h

open questions

- duration, deep, time of initiation
- most studies in **young, healthy** animals
- rewarming
- whether it **merely delays** the damage process

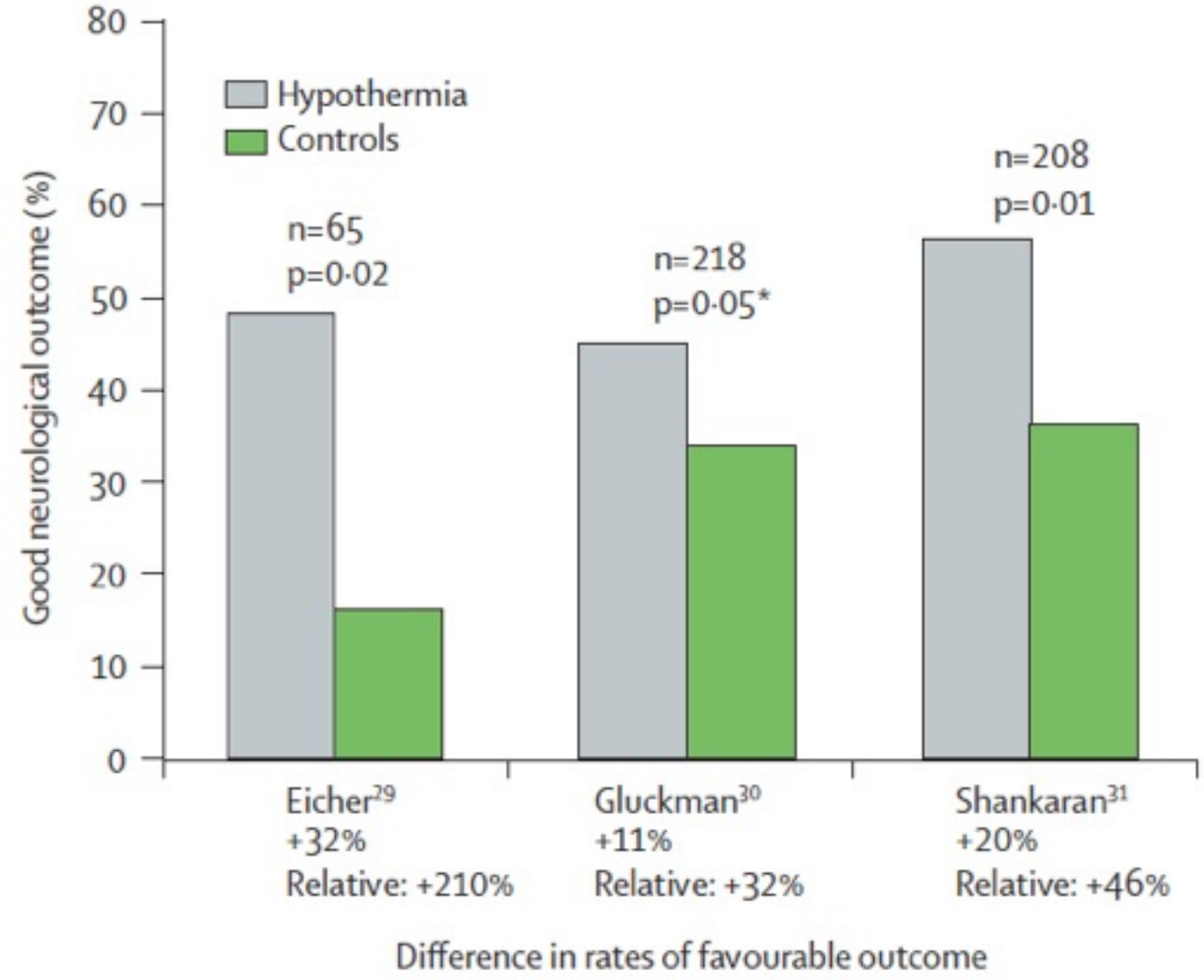
Non-Randomized Studies in Cardiac Arrest



Polderman, Lancet 2008

RCT in perinatal asphyxia

- window 6h from birth
- target 33-35°C for 48-72h



Polderman, Lancet 2008; 371: 1955–69

take home message

from humans (cardiac arrest and perinatal asphyxia)

- benefit from cooling to 32–34°C for 12–24 (cardiac arrest) or 48-72h (perinatal asphyxia);
- questions: window, duration, depth of cooling

side effects

< 34º sedation and mechanical ventilation
< 33º platelet dysfunction
< 30º cardiac arrhythmias, hypotension

Polderman and Herold 2009
Bernard et al 2002 (Cardiac Arrest)
Jacobs et al 2007 (Perinatal Hpoxic-Ischemic Encephalopathy)

Stroke Trials

Early (1996-2001) studies

Reference	Treated patients	Control patients	Method of cooling	Target temperature (°C)	Time required to reach target temperature (h)	Time from onset of stroke to start of cooling (h)	Duration of cooling
Naritomi[80]	4	0	Cooling blankets, alcohol compresses	33	..	5	..
Schwab[81]	25	0	Cooling blankets, cold infusions, cold washing	33	3–7	14±7	2–3 days
Georgiardis[82]	6	0	Intravenous cooling device	33	3±1	28±17	2–3 days
COOL AID[83]	10	9	Cooling blankets, ice water and alcohol rubs	32±1	4±2	6±1	1–4 days
Schwab[84]	50	0	Cooling blankets, alcohol and ice bags	32–33	4–11	22±9	1–3 days
Kammersgaard[85]	17	56	Cooling blankets	35·5	4	3±4	6 h

Olsen et al, Lancet Neurol 2003

COOL AID

surface cooling

- n 10 + 9 controls (open, pilot study)
- Inclusion NIHSS >15 (**intubated, sedated, and drug-paralyzed**)
- depth target 32 C° (in 3-5h; bladder) Overshot in 9 pts: lowest 28.4°C
- duration 12-72h
- window (6h) 3.5 ± 1.5 h
- tPA in 6 pts (IV or IA)
- Outcome mRS 90 days
- **result** “feasible and safe” (3 deaths in the hypothermia group)

Krieger et al, Stroke 2001

The Copenhagen Stroke Study

surface cooling

- n 17+56 matched controls
- depth 35.5 C° duration 6h
- window (12h) 3.5 ± 1.5 h
- Outcome mortality and impairment (SSS 6 months)
- drugs phetidine
- **result** “no poor outcome”

Kammersgaard et al, Stroke 2000

Trials

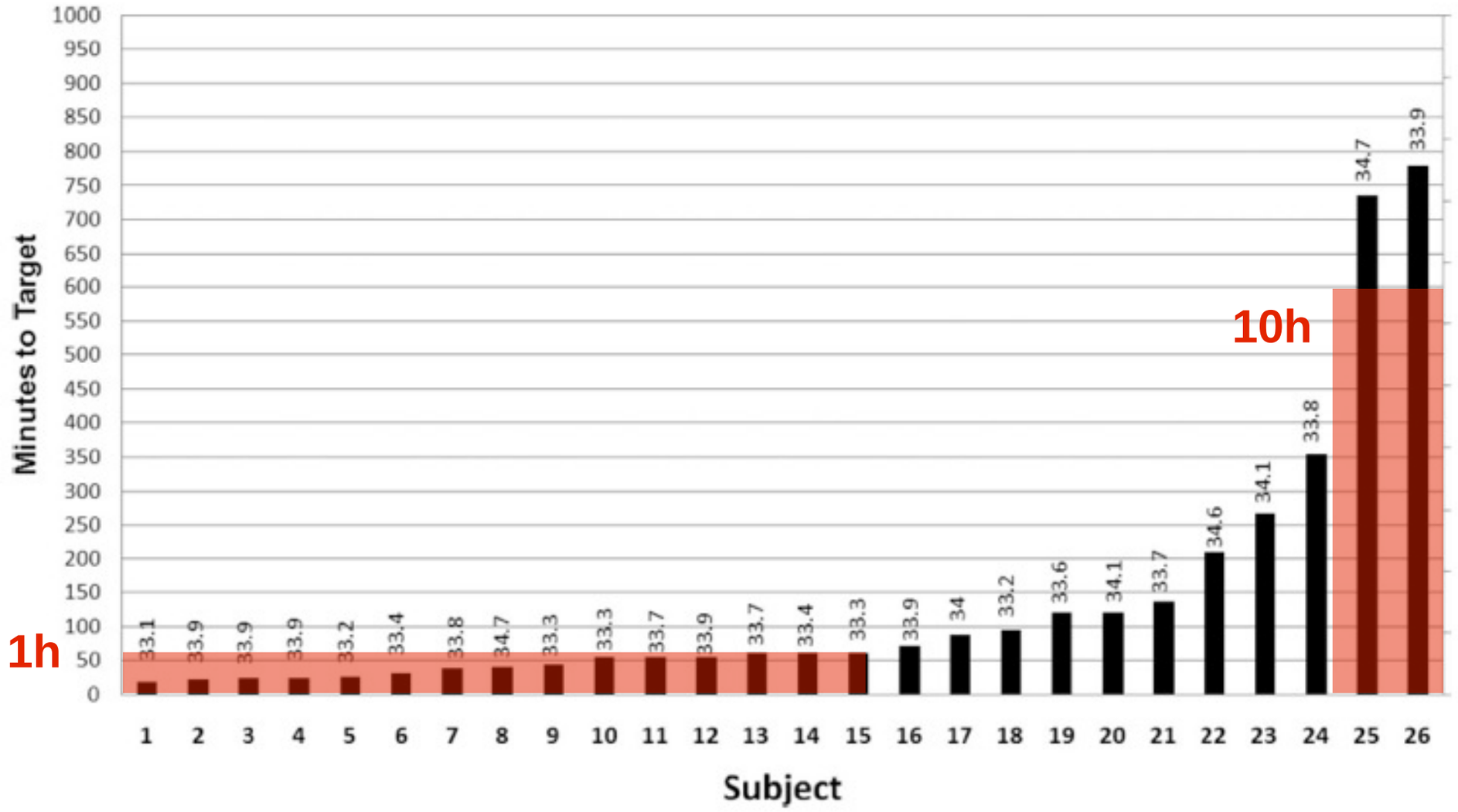
- COOL AID (2004)
  - 33°C for 24h within 12h, using iv cooling
- Ice-cold saline
  - for the induction of mild hypothermia in patients with acute ischemic stroke: a pilot study (2009)
- Caffeinol + Hypothermia (2009)
  - 33-34.5°C for 24h within 3h, surface cooling
- ICTuS-L (2010)
  - combination of iv thrombolysis and iv cooling to 33°C
- PAIS (2011)
  - Paracetamol for normalization of temperature
- HAIST-E
  - MR spectroscopy to measure brain temperature, to 35 or 33°C
- MASCOT
  - surface cooling to 33°C in 40 ventilated patients
- COAST II
  - ev cooling to 35°C with ice cold saline induction in pts thrombolysis
- HAIS-SE
  - surface vs ev cooling within 4.5h with t-PA, to 34°C for 12-24h, rewarming 0.2°C/h

IctusL (randomized, controlled)

- n 28+30 control, with or without iv or ia rtPA (6 groups)
- inclusion NIHSS ≥7
- depth 33°C (Innercool Intravenous System)
- duration 24h; rewarming 12h, rate 0.3°C/h
- window <6h (median time to target was 7h); 30-180min after tPA
- **tPA** <3h or <6h
- outcome NIHSS at 3 months
- drugs meperidine (∞ 1g/24h) + buspirone + warming blankets
- **result** "feasible and safe" (pneumonia)

Hemmen et al, Stroke 2010

ICTuS-L
Time to target temperature



Hemmen et al, Stroke 2010

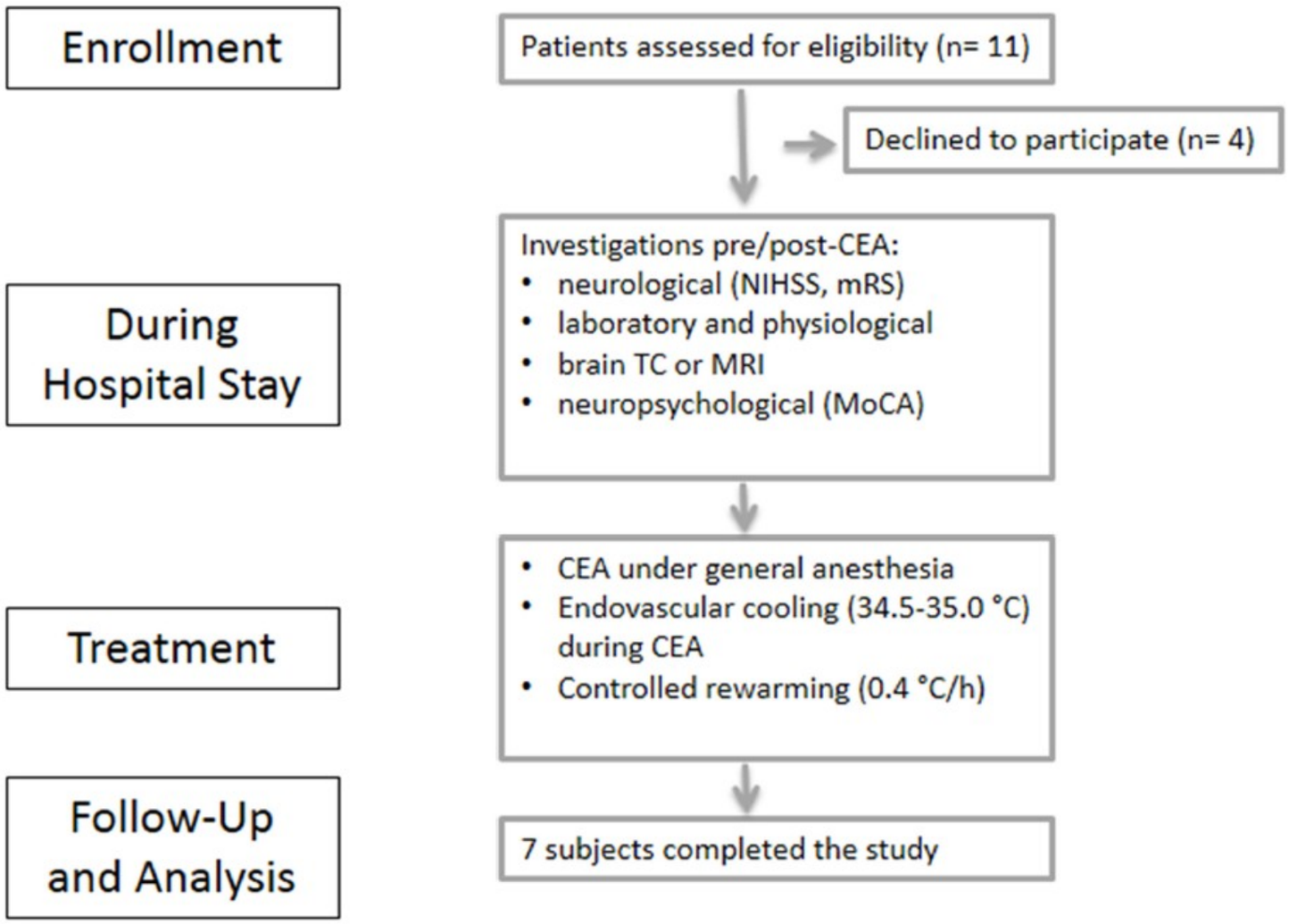
take home message

from phase II trials

- cooling to 34–35°C is safe
- shivering is a relevant variable
- iv ice-saline is an effective starting procedure
- pneumonia main adverse effect

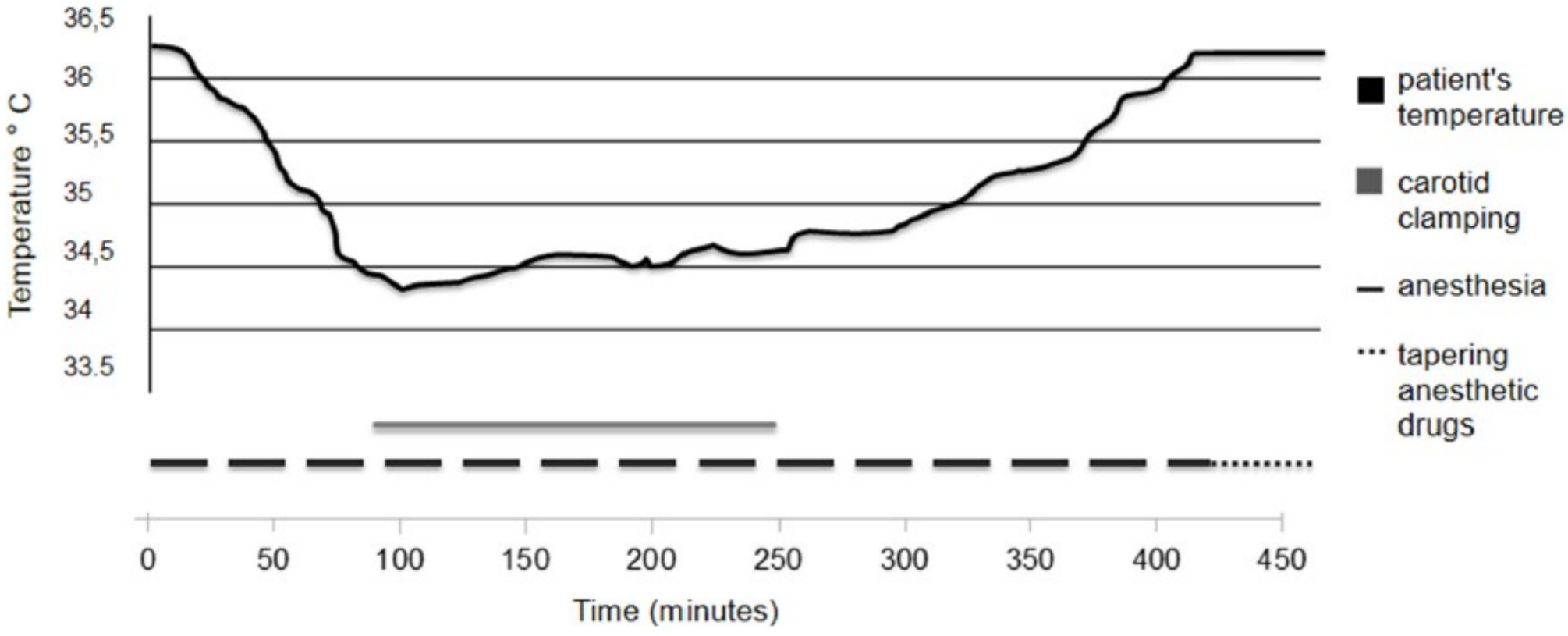
- question: duration

Hypothermia during Carotid Endarterectomy



Candela et al, PLOS 2016

Representative time course of body temperature during and following CEA



Candela et al, PLOS 2016

EuroHYP-1

EuroHYP-1: European multicentre, randomised, phase III clinical trial of therapeutic hypothermia plus best medical treatment versus best medical treatment alone for acute ischaemic stroke

EuroHYP-1 is funded by the European Commission within the 7th Framework Programme

EuroHYP-1: Primary Objective

- To determine whether systemic cooling to 34 - 35°C improves functional outcome in patients with acute ischaemic stroke

EuroHYP-1: Inclusion Criteria

- Acute ischemic stroke
- **NIHSS 6 – 18**
- GCS motor response subscale score ≥ 5
- Age ≥ 18 years
- written informed consent
- start treatment < **6 hours** after stroke onset AND
- < 90 min **after start thrombolysis / thrombectomy** at trial site OR
- < 90 min after admission (patients not receiving thrombolysis OR receiving thrombolysis at a different site and transferred to trial site)
- mRS score ≤ 2 prior to onset of stroke

EuroHYP-1: Exclusion Criteria

- Rapidly resolving stroke symptoms
- SaO2 <94% under nasal oxygen administration, other severe resp. disorder
- ICH/ tumor/ encephalitis or other cause of symptoms on CT/MRI
- Hemorrhagic transformation not an excl. crit., *except parenchymal hematoma >30% of infarction, space-occupying effect, or remote bleeding*
- Bradycardia (<40 bpm)
- Severe cardiac failure (NYHA ≥ III)
- Any acutely life-threatening conditions other than ischemic stroke
- MAO-inhibitors <14d; use of other medication interacting with pethidine or buspirone e.g. ritonavir, phenytoin, cimetidine, phenothiazines, opioids, partial opioid agonists
- Acute alcohol intox; Opioid addiction
- Known hypersensitivity to pethidine/ buspirone
- Skin damage at the sites intended to be used for cooling

… ongoing

n= 87

no AE, likely safe

shivering is an issue