



# Traumatic brain injury, therapeutic hypothermia and the POLAR trial



Tony Smith, Medical Director, St John

# TBI and therapeutic hypothermia

- Quickly review treatment of TBI
  - Where therapeutic hypothermia currently 'sits'
- Review evidence for hypothermia
  - Not an exhaustive literature search
- POLAR trial
- Questions



# Traumatic brain injury

- Significant mortality and morbidity following trauma
- Largest cause of in-hospital mortality
- Largest cause of disability in survivors
- Enormous cost
  - The patient
  - Their family
  - Society





# Treating patients with TBI

- Currently based on
  - Preventing secondary injury
  - Operating on mass lesions
  - Controlling ICP and optimising CPP (therapeutic hypothermia often used)
- No good evidence that we do makes a big difference



# What we do know

- Steroids kill people
- Early decompressive craniectomy doesn't help
  - May make long term outcomes worse
- Hypertonic saline pre-hospital doesn't help
- Hyperventilation probably makes outcomes worse
- Secondary injury makes outcomes worse



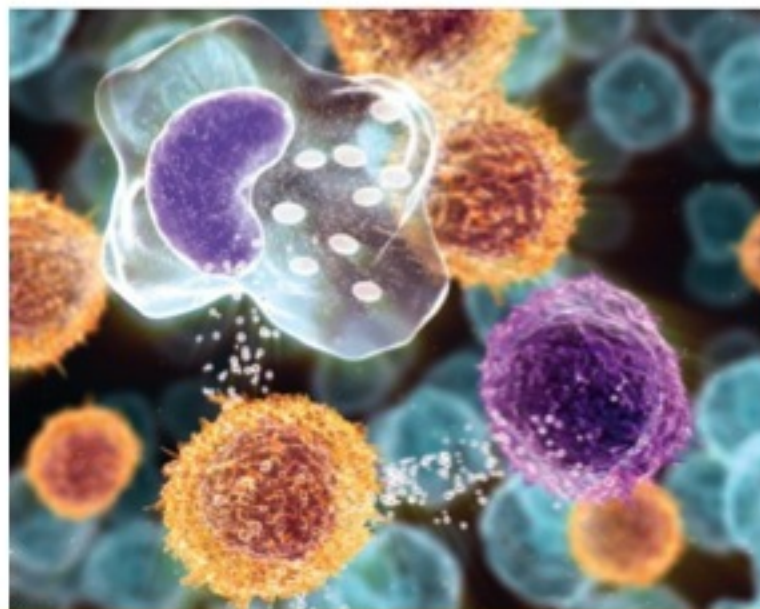
# What we don't know

- If treating ICP really helps
  - What ICP or CPP to target
- What 'degree' of secondary injury is important
  - Some attempts to reduce secondary injury may cause harm
- If hypothermia helps
  - If so, at what temperature and for how long



# Hypothermia and TBI

- We like to pretend we understand what is going on...
  - Swelling, bleeding and bruising
  - Altered autoregulation and blood flow
  - 'Leaky' blood brain barrier
  - White cell activation, inflammatory state and free radicals
  - Activation of necrotic and apoptotic pathways
- Hypothermia
  - Reduces swelling and lowers ICP
  - Reduces inflammatory response
  - Lowers cerebral metabolic rate





# Hypothermia and TBI

- Hypothermia also
  - Increases bleeding
  - Lowers cardiac output
  - Increases infection risk
  - Reduces gut activity
  - Reduces renal tubular function
  - Requires additional anaesthesia, equipment and nursing expertise



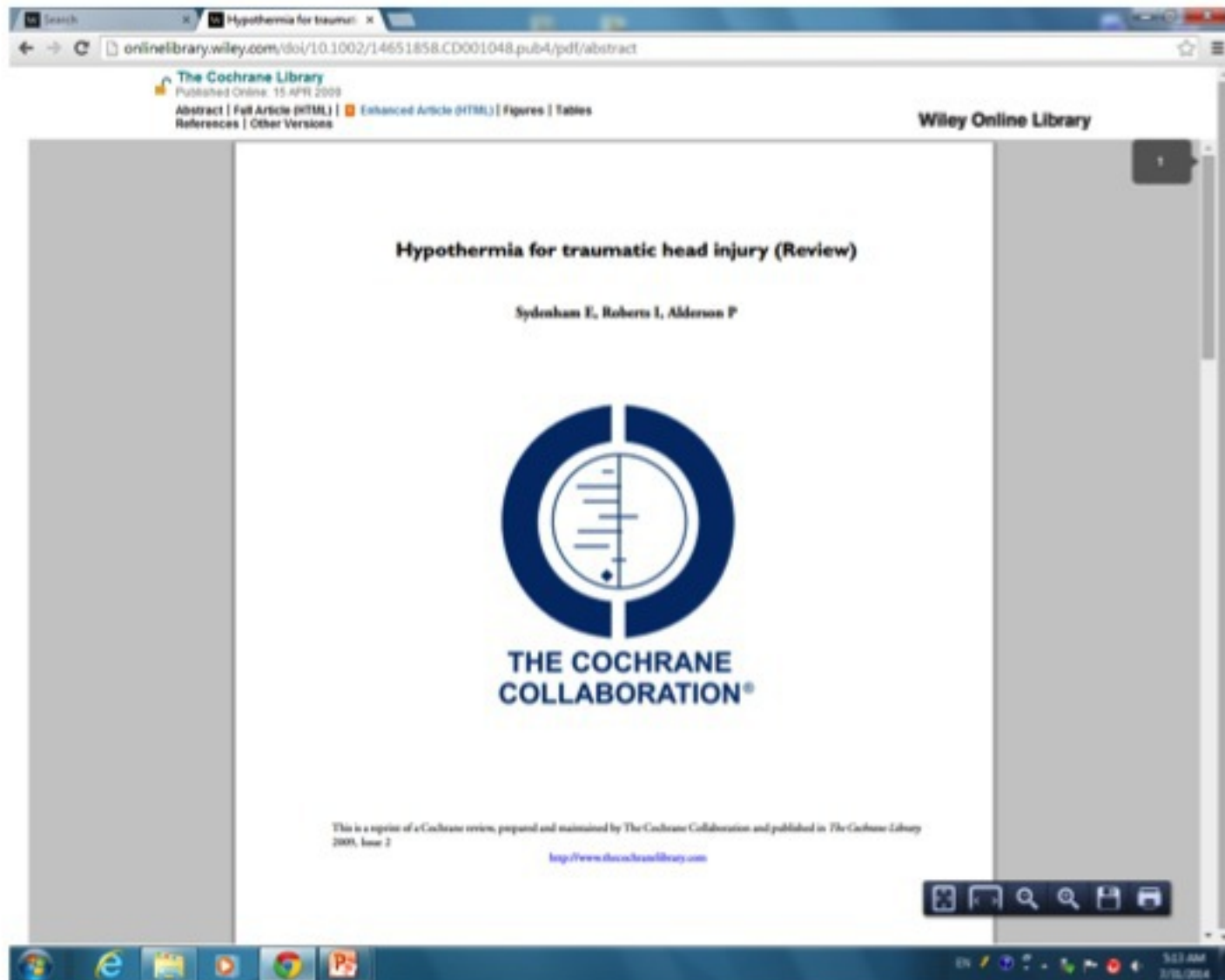


## Hypothermia and other conditions

- Hypothermia improves outcomes
  - Following out of hospital cardiac arrest
  - Neonates with hypoxic ischaemic encephalopathy
- We cannot translate this evidence into patients with TBI



# Evidence for hypothermia and TBI



# Cochrane 2009

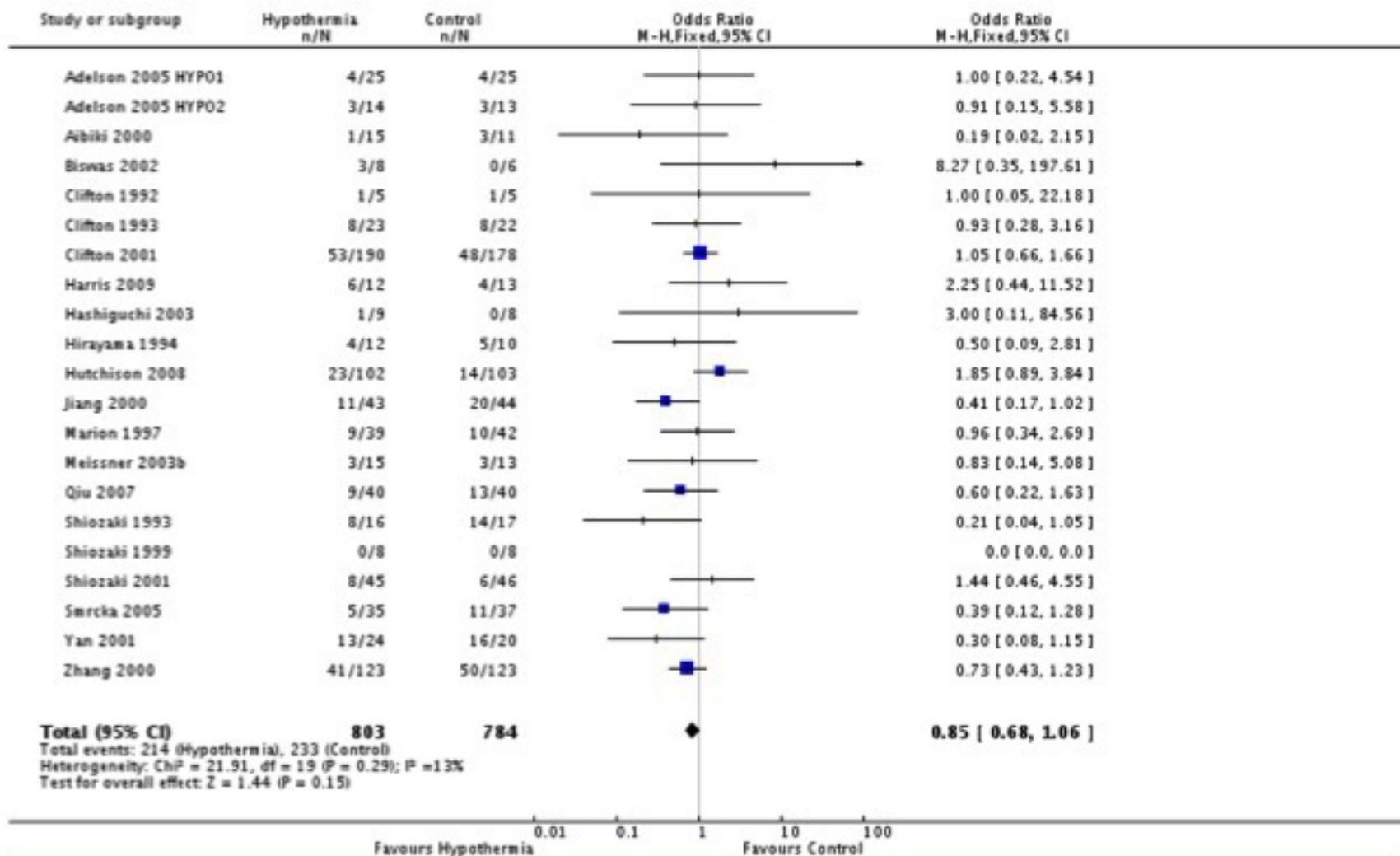
## > Concluded

- > No evidence for hypothermia to be routinely used
- > No good evidence hypothermia improves outcomes
- > Low quality trials produced the most apparent benefit
- > High quality trials produced the least apparent benefit



# Cochrane 2009

Review: Hypothermia for traumatic head injury  
Comparison: 1 immediate hypothermia versus normothermia  
Outcome: 1 Death at final follow-up





Crossley et al. *Critical Care* 2014, **18**:R75  
<http://ccforum.com/content/18/2/R75>

**RESEARCH****Open Access**

# A systematic review of therapeutic hypothermia for adult patients following traumatic brain injury

Samantha Crossley<sup>1</sup>, Jenny Reid<sup>1</sup>, Rachel McLatchie<sup>1</sup>, Judith Hayton<sup>1</sup>, Clair Clark<sup>1</sup>, Margaret MacDougall<sup>2</sup> and Peter JD Andrews<sup>3\*</sup>

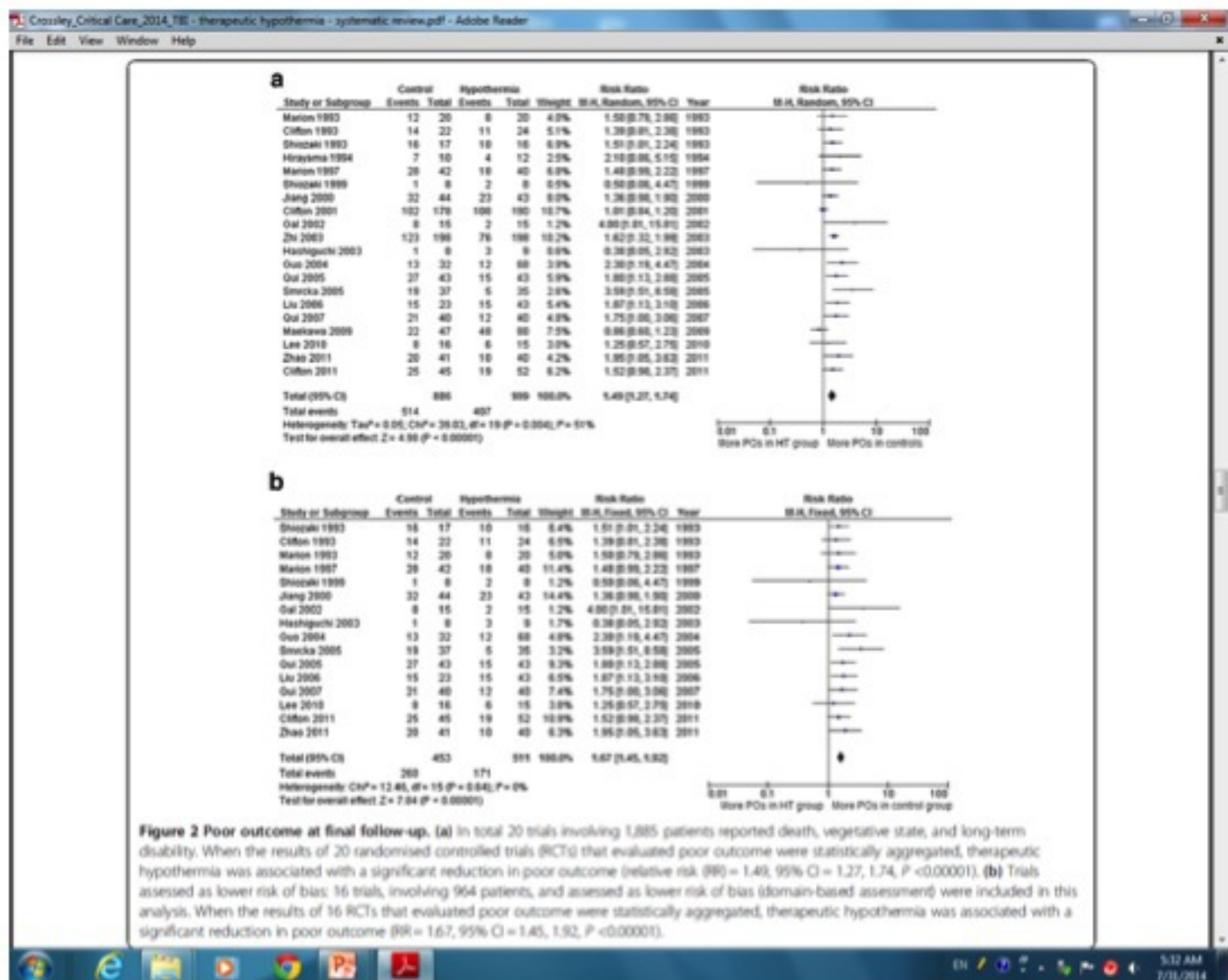
**Abstract**

**Introduction:** Research into therapeutic hypothermia following traumatic brain injury has been characterised by small trials of poor methodological quality, producing variable results. The Cochrane review, published in 2009, now requires updating. The aim of this systematic review is to assess the effectiveness of the application of therapeutic hypothermia to reduce death and disability when administered to adult patients who have been admitted to hospital following traumatic brain injury.

**Methods:** Two authors extracted data from each trial. Unless stated in the trial report, relative risks and 95% confidence intervals (CIs) were calculated for each trial. We considered  $P < 0.05$  to be statistically significant. We combined data from all trials to estimate the pooled risk ratio (RR) with 95% confidence intervals for death, unfavourable outcome, and pneumonia. All statistical analyses were performed using RevMan 5.1 (Cochrane IMS, Oxford, UK) and Stata (Intercooled Version 12.0, StataCorp LP). Pooled RRs were calculated using the Mantel-Haenszel estimator. The random effects model of DerSimonian and Laird was used to estimate variances for the Mantel-Haenszel and inverse variance estimators.

**Results:** Twenty studies are included in the review, while 18 provided mortality data. When the results of 18 trials that evaluated mortality as one of the outcomes were statistically aggregated, therapeutic hypothermia was associated with a significant reduction in mortality and a significant reduction in poor outcome. There was a lack of statistical evidence for an association between use of therapeutic hypothermia and increased onset of

# Systematic review, Crit Care 2014



# Systematic review, Crit Care 2014

## ➤ Concluded

- Some evidence to suggest hypothermia may be beneficial
- Majority of trials are of low quality
- Largest treatment effect in single center studies
- Smallest treatment effect in multi-centre studies

## ➤ My conclusion

- Summary of the evidence, not useful for guiding treatment
- May be efficacious but not effective.....



# Huh?

- Efficacious

- Works in an ideal world under ideal circumstances

- Effective

- Works in the real world under usual circumstances



**"It's not a great mission statement,  
but we'll revise it if things get better."**



# So where does this leave us?

- Still a lot of uncertainty
  - Too many small trials
  - Too many single center trials
- The POLAR trial

I THOUGHT I WAS  
INTERESTED IN UNCERTAINTY  
BUT NOW I'M NOT SO SURE



# The POLAR trial

The screenshot shows a web browser window displaying the ClinicalTrials.gov website. The address bar shows the URL: [clinicaltrials.gov/ct2/show/study/NCT00987688](http://clinicaltrials.gov/ct2/show/study/NCT00987688). The page title is "The Prophylactic Hypothermia Trial to Lessen Traumatic Brain Injury (POLAR-RCT)". The page content includes a search bar, navigation links, and detailed information about the trial.

**ClinicalTrials.gov**  
A service of the U.S. National Institutes of Health

Search for studies:    
Example: "Heart attack" AND "Los Angeles"  
[Advanced Search](#) [Help](#) [Studies by Topic](#) [Glossary](#)

[Find Studies](#) [About Clinical Studies](#) [Submit Studies](#) [Resources](#) [About This Site](#)

Home > Find Studies > Study Record Detail Text Size ▾

## The Prophylactic Hypothermia Trial to Lessen Traumatic Brain Injury (POLAR-RCT)

**This study is currently recruiting participants.** (see [Contacts and Locations](#))

*Verified April 2012 by Australian and New Zealand Intensive Care Research Centre*

**Sponsor:**  
Australian and New Zealand Intensive Care Research Centre

**Collaborators:**  
Australian and New Zealand Intensive Care Society Clinical Trials Group  
National Health and Medical Research Council, Australia  
Victorian Transport Accident Commission  
Monash University  
Délégation à la Recherche Clinique et à l'Innovation (DRCI) CHU Besançon

**Information provided by (Responsible Party):**  
Siouxzy Morrison, Australian and New Zealand Intensive Care Research Centre

**ClinicalTrials.gov Identifier:**  
NCT00987688

First received: September 29, 2009  
Last updated: January 1, 2014  
Last verified: April 2012  
[History of Changes](#)

[Full Text View](#) [Tabular View](#) [No Study Results Posted](#) [Disclaimer](#) [How to Read a Study Record](#)

**Purpose**

Traumatic brain injury (TBI) is a leading cause of death and long term disability, particularly in young adults. Studies from Australia have

# The POLAR trial

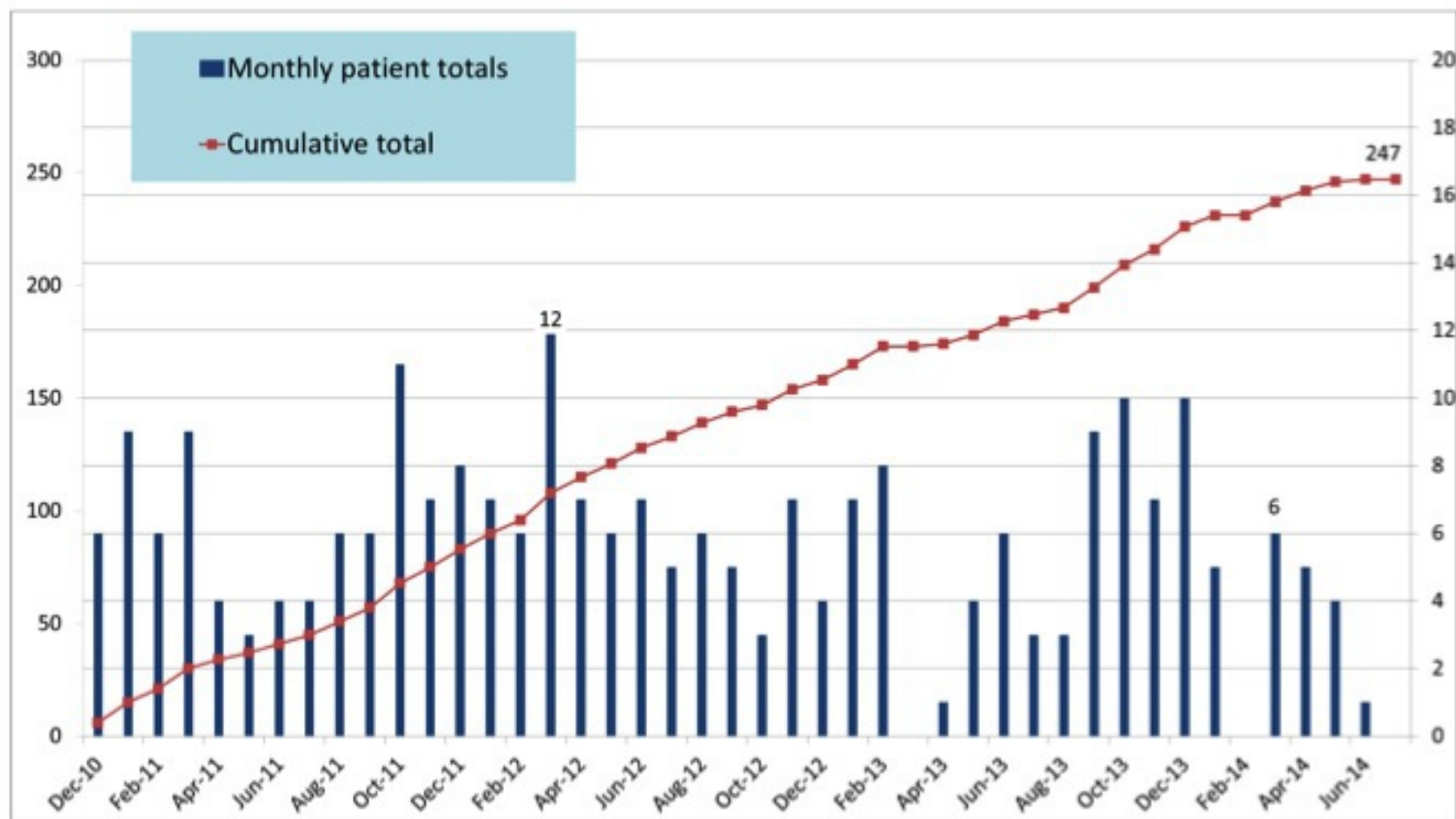
- Prospective randomised trial of prophylactic hypothermia in patients with severe TBI
- Multi-centre
- 500 patients
- Intervention: 33 degrees, 72 hours plus usual therapy
- Control: 36.5-37.5 degrees, 72 hours plus usual therapy
- Primary outcome is GOSE at 6 months
- Secondary outcomes
  - Mortality
  - Adverse events
  - Quality of life

# The POLAR trial

- Inclusion criteria
  - GCS less than 9
  - Age 18-60 years
  - Intubated or about to be intubated
- Randomisation can occur pre-hospital or in-hospital
- Exclusion criteria
  - Drugs or alcohol thought to be predominant cause of coma
  - More than 3 hours since injury
  - Intubated without drugs
  - Shock
  - GCS 3 and unreactive pupils
  - Penetrating trauma
  - Taking an anti-coagulant

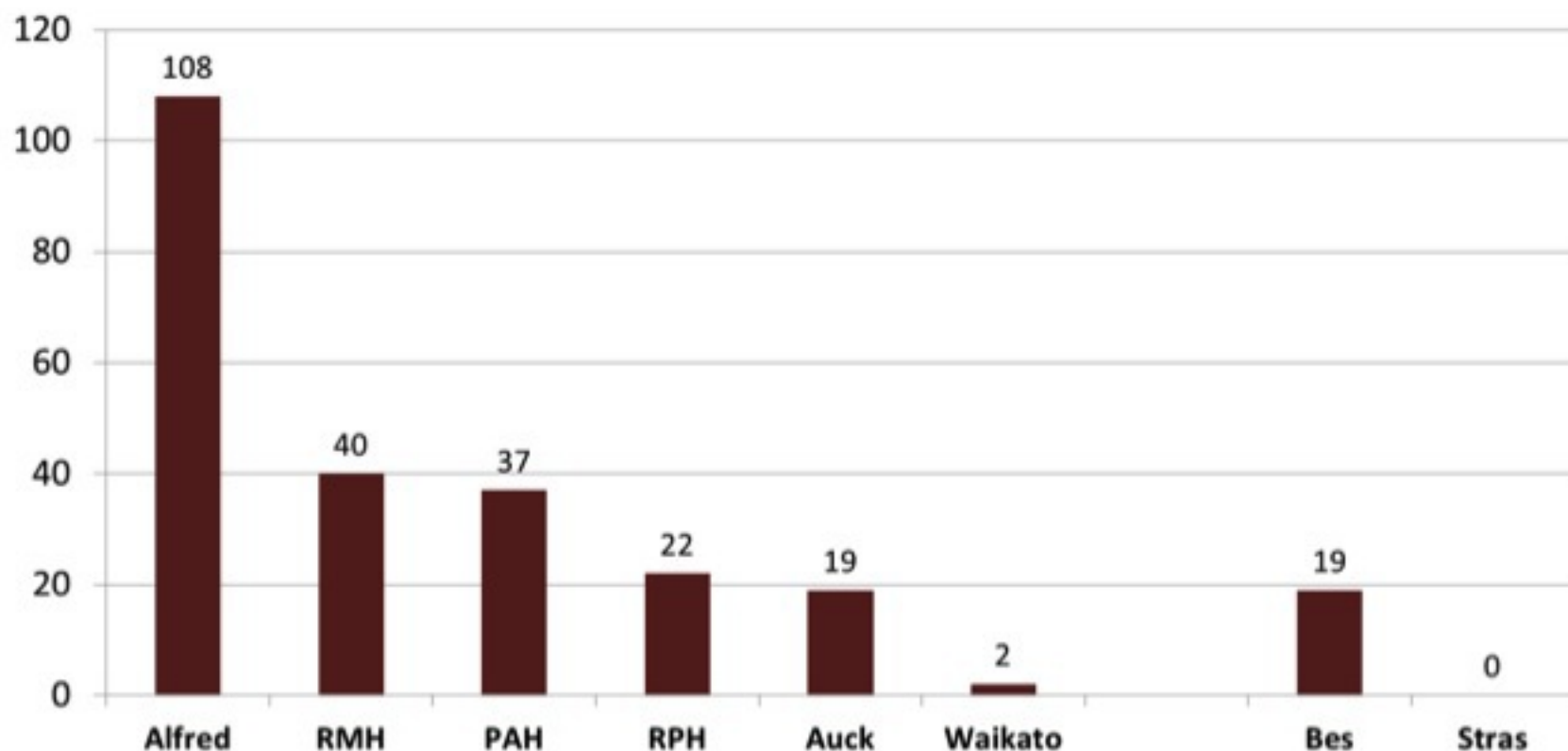


# The POLAR trial



# The POLAR trial

**Recruitment by hospital admission**



# Summary

- Therapeutic hypothermia commonly used
  - Most commonly in response to ICP rise
- Evidence is not strong
  - There is reasonable rationale
  - There is a 'signal' trend in the evidence
- The POLAR trial may help
  - No single trial ever provides all of the answers
  - In danger of failing to recruit enough patients



Thank you   
St John  
first to care

[Tony.Smith@stjohn.org.nz](mailto:Tony.Smith@stjohn.org.nz)