Background and Overview

Article Title/Citation:
Mild Therapeutic Hypothermia to Improve Neurologic Outcome after Cardiac Arrest. Nielsen et al. NEJM 2013;369:2197-206

Study objectives/purpose: (and research hypothesis if applicable)
To investigate the benefits and risks of two temperature regimens both intended to prevent fever in a broader population of cardiac arrest patients.

Brief Background: (why issue is important, summary of previous literature)
Fever as confounder in control groups of previous studies.

Methods

Study design and Methodology: (type of trial, Randomization, blinding, Controls, study groups, Length of study, etc.)
Randomized multicentre outcome-assessor blinded controlled study.

Patient selection and Enrollment: (inclusion/Exclusion criteria, sample Size etc.)
36 ICU’s, age >18, OHCA, sustained ROSC, GCS <8

Interventions: (if applicable)
Cooling to 33 or 36C for 36 hrs, fever control for 72 hrs

Outcome measures/Endpoints:
All cause mortality at 180d, secondary outcomes of neurologic performance.

Statistical analysis:
Logistic- regression and Cox analyses were performed as appropriate, with adjustment for site and for five baseline variables: age, sex, presence or absence of shockable rhythm, presence or absence of circulatory shock on admission, and the time from cardiac arrest.

Results
Enrollment & Baseline Characteristics: Well matched.
Summary of primary & secondary outcomes: (including subgroup analysis etc. include both efficacy and safety parameters)

No difference in primary or secondary outcomes between groups. Only significant adverse event was hypokalemia in 33C group.

Pertinent figures/diagrams:

![Kaplan-Meier Survival Curve](image)

**Figure 2. Probability of Survival through the End of the Trial.**
Shown are Kaplan-Meier estimates of the probability of survival for patients assigned to a target temperature of either 33°C or 36°C and the number of patients at risk at each time point. The P value was calculated by means of Cox regression, with the effect of the intervention adjusted for the stratification variable of study site.

Author’s Discussion and Conclusions

Brief summary of Authors’ main discussion points:

1. Did the authors honestly state their hypothesis? Were they an unbiased group?
2. Unblinded treating physicians ultimately had power to withdraw care – did this influence mortality results?
3. Did this study demonstrate equivalence between 33C and 36C or fail to demonstrate a difference?
4. Although no overall adverse events occurred with 33°C, patients receiving this target appeared to die earlier d/t refractory shock – does this provide impetus to use a non-inferior 36°C target?
5. Was the study adequately powered? Should the primary outcome (and power analysis) have been neurologic outcome rather than mortality?

**Author’s conclusions:**
In conclusion, our trial does not provide evidence that targeting a body temperature of 33°C confers any benefit for unconscious patients admitted to the hospital after out-of-hospital cardiac arrest, as compared with targeting a body temperature of 36°C.

**Your Discussion and Conclusions**

**Study strengths:**
Scientific rationale, broadly applicable inclusion criteria, similar baseline characteristics, standardized neurologic prognostication, predefined and controlled for confounding variables.

**Study limits, weaknesses, Potentials for bias:**
The study was powered to detect a rather large difference between groups (akin to previous landmark trials that arguably compared very cool to very warm). A smaller treatment effect may have been missed (type II error). However, no trends in the present analysis compellingly support this concern.

**Applicability & impact:**
This study has led many (including Bernard himself) to adopt a 36°C TTM approach to post arrest care. Our regional protocols should weigh the results of this trial.

**Additional thoughts/Comments:**
This is the largest, most rigorous and inclusive study regarding post arrest temperature management to date. It provides compelling evidence that a 36 degree, 28 hour target with active temperature control for 72 hours is a reasonable alternative to the current 32-34°C standard of care.

**Conclusions and Recommendations:**
At minimum – this study provides a strong argument to actively control temperature in patients with all initial rhythms (apart from unwitnessed asystole) for a duration of 72 hours. A more modest target of 36°C is strongly supported by the current medical literature.