# Journal Club Eastern Virginia Medical School
# Therapy Article

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**CITATION:** Moler FW, Silverstein FS, Holubkov R, et al. Therapeutic Hypothermia after Out-of-Hospital Cardiac Arrest in Children. N Engl J Med 2015;372:1898-908.

| I. **WHAT IS BEING STUDIED?** | |
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| 1. Study Objective | Efficacy of therapeutic hypothermia in improving 1 year survival with good neurobehavioral outcome for pediatric cardiac arrest patients |
| 2. Study Design | Randomized controlled trial, multi-center 38 PICU's US and Canada |
| 3. Inclusion Criteria | -Age >48 hrs, <18 years<br>-Cardiac arrest requiring chest compression for at least 2 minutes<br>-Mechanical ventilator dependent after ROSC |
| 4. Exclusion Criteria | -Inability to undergo randomization within 6 hrs after ROSC<br>-GCS-M 5-6<br>-Clinical team decides to withhold aggressive treatment<br>-Major trauma associated with the cardiac arrest<br>History of poor cognitive function prior to arrest |
| 5. Interventions Compared | Intervention: Therapeutic hypothermia – cooled to 33.0 C (range 32-34) for 48 hrs, then rewarmed over 16+ hrs to 36.8 C (36-37.5), and then actively kept at that temp for remainder of 120 hrs<br>Control: Therapeutic normothermia – actively kept at 36.8 C (36-37.5) for 120 hrs. |
| 6. Outcomes Evaluated | Primary: Survival at 12 months with "good neurobehavioral outcome" – defined as score >=70 on VABS-II.<br>Secondary: Survival at 12 months and change in neurobehavioral function (difference between baseline and 12-month |

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| | VABS-II assessment)<br>Tertiary: Global cognitive score, based on on-site neuropsychological testing<br>Safety: Blood-product use, infection, serious arrhythmias through 7 days, 28 day mortality |
| II. **Are the results of the study valid** | |
| 1. Was the assignment of patients randomized? | Yes – 1:1 ratio with permuted blocked stratified according to clinical center and age group (<2yrs, 2- <12yrs, >=12yrs) |
| 2. Was randomization concealed (blinded)? | Yes. The randomization process to a particular group was concealed. |
| 3. Were patients analyzed in the groups to which they were randomized? | Yes authors stated that they used an intention-to-treat analysis however– one in normothermia group was excluded because he received hypothermia tx; 3 in hypothermia group received no treatment. Here the authors did not explicitly state in they were included in the intention to treat analysis. |
| 4. Were patients in the treatment and control groups similar with respect to known prognostic factors? | Yes – similar demographics, medical histories and characteristics of cardiac arrest |
| III. **Did experimental and control groups retain a similar prognosis after the study started (answer the questions posed below)?** | |
| 1. Were patients aware of group allocation? | Unlikely given clinical state (intubated). Not specifically stated if parents were aware, but seems likely they were as patients would have been cool to the touch. |
| 2. Were clinicians aware of group allocation? | Yes. PICU providers were aware of treatment group as they were managing patients. |
| 3. Were outcome assessors aware of group allocation? | No – VABS-II collected by blinded telephone interviewer |
| 4. Was follow-up complete? | Mostly. 8/260 had 12 month f/u – 4 in hypothermia group and 4 in normothermia group had unknown vital status at 12mo, and 2 in normothermia group were alive but had unknown VABS-II status at 12 mo |

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| **IV. What were the results?**<br>Answer the questions posed below | |
| 1. How large was the treatment effect? (Difference between treatment and control group). | 12mo survival with VABS-II >=70: The Absolute Risk Reduction was 7.3% ( 19.5% exp. vs. 12.2% control) – but this was not statistically significant with P=0.14. (95% CI -1.5-16.1)<br><br>12mo survival: 9.1% Absolute risk reduction (38% exp. vs 29% control) (P=0.13) (95% CI -1.8-19.9)<br><br>Survival over time longer for hypothermia group: +30 days; 149 +/- 14 days vs 119 +/- 14 days, P=0.04 |
| 2. What was the estimated treatment effect at a 95% confidence interval? (Precision) | As above. Both CI's cross 1.0) 12mo survival with good neurobehavioral outcome: -1.5 – 16.1%<br><br>12 mo survival: -1.8 – 19.9% |
| V. **Will the results help me in caring for my patients? (Applicable?)** | |
| 1. Were the study patients similar to my patient? | Yes – pediatric population with similar demographics, received treatment available at CHKD |
| 2. Were all clinically important outcomes considered? | Yes I think so – good neurobehavioral outcomes is the main goal, and the safety parameters were also important and covered all major concerns I can think of |
| 3. Are the likely treatment benefits worth the potential harm and costs? | Given no statistically significant benefits, I think no. |

**Limitations:** A larger trial may have shown a clinical benefit, despite the lack of statistical difference in this trial.
Clinicians/researchers not blinded to treatment assignments
Longer survival time in hypothermia group may have been due to delayed prognostic assessment (not dead until warm and dead).
There are no clear guidelines for duration of hypothermia therapy – would a different protocol change outcomes?
**Clinical Bottom Line:** Therapeutic hypothermia, when compared to therapeutic normothermia, seems to have no benefit to children. It seems that control of fever,