
**Hypothermia vs. Normothermia after OHCA**

**Key Article**

*Dankiewicz J, et al. Hypothermia versus normothermia after out—of-hospital cardiac arrest. N Engl J Med. 2021; 384:2283-94.*

**Background**

- Current guidelines from the AHA recommend TTM as a Class I intervention for all adult patients who remain comatose or unable to follow commands following OHCA.
- These guidelines recommend a constant temperature between 32-36C and state it is reasonable to maintain TTM for 24 hours after reaching target temp.
- The evidence for this recommendation began with 2 trials published in NEJM in 2002 that demonstrated improved neurologic outcome if OHCA patients who had a shockable rhythm and were cooled to 33 C.
- The initial TTM trial in 2013 that compared TTM at 33 C with TTM at 36 C did not demonstrate a dose effect.
- More recently, the HYPERION trial (CCPEM October 2019 Episode) demonstrated improved neurologic outcome for patients with OHCA with a nonshockable rhythm and who received TTM to 33 C compared with TTM to 37 C.
- Despite these trials, the overall level of evidence supporting current recommendations is felt to be of low certainty.
- As fever may be a risk factor for poor neurologic outcome following OHCA, it is uncertain is there is a causal relationship.

**Objective**

- To assess the beneficial and harmful effects of hypothermia as compared with normothermia and early treatment of fever in patients after cardiac arrest.

**Study**

- International, investigator-initiated, superiority trial
- Performed in 61 centers in 14 countries
- Patients
    - Included
        - Adults ≥ 18 years of age
        - Admitted to the hospital after OHCA of a presumed cardiac or unknown cause
        - Any initial rhythm
        - More than 20 consecutive minutes of ROSC
        - Remained unconscious and unable to follow verbal commands
    - Excluded
        - Interval from ROSC to screening for enrollment > 180 minutes
        - Unwitnessed cardiac arrest with asystole as initial rhythm
        - Limitations in care

- Trial intervention period – 40 hours
- Randomized in 1:1 ratio
    - Hypothermia
        - Immediately cooled to 33 C (cold IVFs, surface device, or intravascular device)
        - Maintained for 28 hours
        - Rewarmed to 37 C in hourly increments
    - Normothermia
        - Maintain temperature of 37.5 C or less
        - If temperature reached > 37.8 C, cooling with surface or intravascular devices was initiated to target a temperature of 37.5 C
        - No active warming or cooling was initiated for patients who had a spontaneous temperature < 37.8 C
    - After the 40-hour intervention period, a temperature target of 36.5-37.7 C was maintained for 72 hours
- Neuroprognostication
    - Performed at 96 hours after randomization or later
    - Physician was unaware of intervention assignments
    - All decisions about withdrawal of care were at the discretion of the treating physician
- Primary Outcome
    - All-cause mortality at 6 months
- Secondary Outcomes
    - Poor functional outcome at 6 months (mRS of 4 to 6)
    - Number of days alive and out of the hospital until 180 days
    - Health-related quality of life
- Adverse Events
    - Pneumonia
    - Sepsis
    - Bleeding
    - Arrhythmia resulting in hemodynamic compromise
- Statistical Analysis
    - Investigators hypothesized that the incidence of death at 6 months would be lower in the hypothermia group
    - They estimated a sample size of 1862 patients needed to provide 90% power to detect a 15% relative reduction in death in the hypothermia group

**Results**

- 1861 patients included in the intention-to-treat population
    - Hypothermia Group: 930 patients
    - Normothermia Group: 931 patients
    - Baseline characteristics between the groups reasonably well balanced
- Hypothermia Group
    - Median time from start of intervention until a temp of 34 C was reached – 3 hours
    - 6% rewarmed before 40-hour intervention period completed due to cardiovascular instability and arrhythmias
    - 95% of patients received cooling with a device (70% surface, 30% intravascular)
- Normothermia Group
    - 46% of patients received cooling with a device (69% surface, 31% intravascular)

- Primary Outcome – All-cause mortality at 6 months
    - Hypothermia Group: 50%
    - Normothermia Group: 48%
    - RR with hypothermia 1.04 (95% CI 0.94 to 1.14; p=0.37)
    - Consistent across subgroups (gender, age, initial rhythm, shock present on admission)
- Secondary Outcome – Poor functional outcome at 6 months
    - Hypothermia Group: 55%
    - Normothermia Group: 55%
    - RR with hypothermia 1.00 (95% CI 0.92 to 1.09)
- Secondary Outcome – Health-related quality of life
    - Similar in both groups
- Adverse Events
    - Arrhythmias
        - Hypothermia Group: 24%
        - Normothermia Group: 17%
    - No difference in pneumonia, sepsis, or bleeding were observed

**Limitations**

- Elements of ICU care (sedation, paralysis, mechanical ventilation) included in the trial protocol many not be representative of common clinical practice
- Non-blinded
- No control group without TTM was included (almost 50% in the Normothermia Group had TTM applied to keep temp below target)
- Limited to OHCA – did not include IHCA patients

**Take Home Point**

- TTM to target a temperature of 33 C did not lower 6-month all-cause mortality in patients with OHCA compared to those treated with TTM to target normothermia.