

December 2013 Tucson Pulmonary Journal Club: Hypothermia

Nielsen N, Wetterslev J, Cronberg T, et al. Targeted temperature management at 33°C versus 36°C after cardiac arrest. *N Engl J Med.* 2013;369(23):2197-206.

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Therapeutic hypothermia is recommended by international resuscitation guidelines for unconscious patients who regain spontaneous circulation after cardiac arrest (1). Two randomized controlled trials in 2002 demonstrated that mild therapeutic hypothermia significantly improved neurologic outcomes and survival among patients who experienced cardiac arrests due to an initial shockable rhythm (2,3). However, the optimal temperature target for therapeutic hypothermia has yet to be determined.

The Target Temperature Management (TTM-36) study was an international randomized control trial that investigated the benefits and harms of two temperature targets, 33°C and 36°C, among 950 participants who experienced out-of-hospital cardiac arrest. Participants were randomly assigned to receive 24 hours of therapeutic hypothermia at a temperature of 33°C or 36°C. The primary outcome was all-cause mortality through the end of the trial (180 days after the last participant was enrolled). Secondary outcomes included a composite of poor neurologic function or death at 180 days using both the Cerebral Performance Category (CPC) scale and the modified Rankin scale. Participants 18 years of age or older who were unconscious and had a score <8 on the Glasgow Coma on admission following out-of-hospital cardiac arrest were eligible. Eligible patients had more than 20 consecutive minutes of spontaneous circulation after resuscitation. The main exclusion criteria were an interval from the return of spontaneous circulation to screening of more than 240 minutes, unwitnessed arrest with asystole as the initial rhythm, suspected or known acute intracranial hemorrhage or stroke, and a body temperature of less than 30°C.

At the end of the trial, there was no significant difference in the number of deaths between the two groups (hazard ratio in the 33°C group, 1.06; 95% confidence interval, 0.89 to 1.28; P = 0.51). No significant difference was found with respect to composite outcome of poor neurologic function or death at 180 days with the use of either the CPC or the modified Rankin scale score. The results were consistent in six predefined subgroups. No significant harm was found with targeted temperature of 33°C as compared to 36°C.

TTM-36 failed to demonstrate post-arrest therapeutic hypothermia at 33°C to be superior to post-arrest therapeutic hypothermia of 36°C. Post-arrest therapeutic hypothermia at 33°C was not associated with any additional harm either. TTM-36 provides evidence that lowering temperature below 36°C does not yield additional clinical benefit among patients surviving out-of-hospital cardiac arrest. Given that the current treatment standard is 33°C, a non-inferiority design would have provided stronger evidence to support the safety of a higher temperature target (36°C).

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References

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2. Bernard SA, Gray TW, Buist MD, Jones BM, Silvester W, Gutteridge G, Smith K. Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. *N Engl J Med*. 2002;346(8):557-63. [\[CrossRef\]](#) [\[PubMed\]](#)
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