



# ARTICLE OF THE MONTH

## Targeted Temperature Management for 48 vs 24 Hours and Neurologic Outcome After Out-of-Hospital Cardiac Arrest: A Randomized Clinical Trial

Kirkegaard H, Søreide E, de Haas I, Pettilä V, Taccone FS, Arus U, Storm C, Hassager C, Nielsen JF, Sørensen CA, Ilkjær S, Jeppesen AN, Grejs AM, Duez CHV, Hjort J, Larsen AI, Toome V, Tiainen M, Hästbacka J, Laitio T, Skrifvars MB.  
*JAMA*. 2017 Jul 25;318(4):341-350. doi:10.1001/jama.2017.8978.

Happy New Year! Welcome to the January 2018 installment of the SNACC Article of the Month! The article presented today is looking at the effects of targeted temperature management for an extended period of 48 hours on the neurologic outcome after out of hospital cardiac arrest. Dr Ines Koerner has been kind enough to share her invaluable perspective on this subject.

Ines Koerner is an anesthesiologist and neurointensivist who maintains an active translational neuroscience research program. She currently is an Associate Professor and Medical Director of the Neurosciences Intensive Care Unit at OHSU in Portland, Oregon. Her research on the role of microglia after stroke and cardiac arrest has received funding from the NIH and AHA. She serves on the SNACC Scientific and Research Committees and is a Co-Chair of the Special Interest Group for Critical Care and Perioperative Medicine.

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~ Nina Schloerker MD, Adrian Pichurko MD and Oana Maties MD

### Commentary

Ines Koerner, MD, PhD

Temperature control remains the single most effective intervention to improve neurologic outcome after cardiac arrest. This multicenter, randomized, pragmatic clinical trial tested whether prolonging hypothermia from 24 to 48 hours can further improve outcome in unconscious survivors of cardiac arrest. 355 patients who were admitted with a Glasgow Coma Scale score of less than eight after an out-of-hospital cardiac arrest (OHCA) of presumed cardiac origin to one of ten participating ICUs throughout Europe were randomized to receive targeted temperature management at  $33\pm 1^{\circ}\text{C}$  for 24 or 48 hours. Patients with both shockable and non-shockable initial rhythms were included, while patients with unwitnessed asystole were excluded from the trial. Withdrawal of life support was not allowed before 72 hours after rewarming, and followed a standardized assessment by a multidisciplinary team, similar to the protocol used in the 2013 Targeted Temperature Management (TTM) Trial by Nielsen *et al*. The primary endpoint in the Kirkegaard trial was favorable neurologic outcome at six months after

cardiac arrest, as assessed by a Cerebral Performance Categories (CPC) score of one or two, while six month mortality was a secondary endpoint. The study was powered to detect a 15% difference in the primary endpoint. 69% of patients in the 48-hour group versus 64% in the 24-hour group achieved a favorable outcome, while 27% of patients in the 48-hour group and 34% in the 24-hour group died. Neither difference was statistically significant. The rate of adverse events was high in both groups (97% versus 91%), with more early rewarming (6%) in the 48-hour group. ICU length-of-stay, but not hospital length-of-stay, was significantly longer in the 48-hour group. Given the absence of a significant outcome benefit, the trial does not support the use of prolonged hypothermia beyond 24 hours for unconscious survivors of OHCA.

The back-to-back publication of two multicenter studies by Bernard *et al.* (Australia) and the Hypothermia after Cardiac Arrest Study Group (Europe) in 2002 established that hypothermia to 33°C, instituted early after return of spontaneous circulation (ROSC), significantly improved survival and neurologic outcome in unconscious survivors of OHCA. This changed the field of resuscitation medicine and made hypothermia the accepted standard of care. Both studies were small, however, and enrolled highly selected patients with initial cardiac rhythms of ventricular fibrillation or ventricular tachycardia. The Targeted Temperature Management (TTM) trial, published in 2013, was much larger, enrolling 939 patients and including patients with initial non-shockable as well as shockable rhythms. It found that strict temperature control to 36°C for 24 hours afforded the same benefit for survival and functional outcome as more aggressive cooling to 33°C, changing the field yet again. TTM to 33-36°C for 24 hours for all unconscious survivors of OHCA has since been the accepted standard of care. Despite strong pre-clinical data that support a neuroprotective effect of hypothermia in a wide range of injury paradigms, comatose survivors of OHCA and newborns with hypoxic/ischemic injury are the only patient groups for whom a benefit of hypothermia could be established in clinical trials. In contrast, patients suffering from ischemic stroke, traumatic brain injury, or pediatric cardiac arrest, do not appear to benefit from hypothermia or TTM. The Kirkegaard study set out to further characterize the optimal dose of hypothermia for adult survivors of cardiac arrest.

While the Kirkegaard study may have been underpowered to detect small benefits of prolonged hypothermia, the most striking finding is the overall excellent outcome, with two thirds of enrolled patients achieving CPC scores of one or two (able to live independently and work full time or part time) at six months. This compares favorably to the TTM Trial published only four years earlier in 2013, in which only half (47%) of enrolled patients reached CPC scores of one or two at six months, independent of whether they were cooled to 33°C or 36°C. Similarly, mortality was low in the Kirkegaard trial, with one third (27% or 34%) of the patients dead at six months, while 47% versus 49% of patients died in the TTM Trial. In Bernard *et al.*'s initial hypothermia trial a decade earlier, only half of the patients in the hypothermia group had survived to hospital discharge. The fact that such large improvements in survival and neurological outcome have been achieved in 15 short years, independent of the dose or duration of hypothermia, emphasizes how much post-resuscitation intensive care has improved overall. High-quality, guideline-driven intensive care is widely accepted today. Similarly, guideline recommendations have improved pre-hospital care. Patients in the Kirkegaard study likely benefitted from impressively high rates of bystander CPR (87/84%), short time to ACLS (eight minutes from collapse) and a high rate of immediate coronary angiography (82/83%). Each of these interventions have been shown to improve survival and outcome after cardiac arrest. These excellent numbers can serve as benchmarks for future trials, and are excellent targets for institutions and communities aiming to improve their post-cardiac arrest care.

What does optimal care for a comatose survivor of cardiac arrest look like in 2017? Multidisciplinary, comprehensive post-arrest care should be provided in an intensive care unit, including early access to coronary angiography and percutaneous intervention when a cardiac cause of the arrest is suspected. Targeted temperature management should be used for all unconscious survivors of OHCA for the first 24 hours. 36°C is sufficient, but 33°C is not inferior. Likewise, prolonging the duration of TTM to 48 hours is not detrimental to survival and function. Prognostication and possible withdrawal of support should be delayed until 72 hours after rewarming, and accepted protocols should be used for prognostication, as suggested in the 2015 American Heart Association (AHA) guidelines. It seems unlikely that further refinement of TTM dose and duration will be able to produce survival benefits similar to those that have been achieved by guideline-compliant post-resuscitation care. More benefit may be gained by basic interventions, such as further increasing rates of bystander CPR through education, shortening times to defibrillation by increasing access to AEDs, and increasing rates of early coronary intervention by transporting survivors of OHCA to appropriate centers.