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Targeted Temperature Management After Cardiac Arrest Finding the Right Dose for Critical Care Interventions

Clifton W. Callaway, MD, PhD

Many clinical trials in critically ill patients do not detect important differences in outcomes between groups receiving different treatments. The trial by Kirkegaard et al¹ in this issue of *JAMA* compared 24 hours vs 48 hours of targeted temperature management (TTM) with cooling to 33°C among



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355 patients who were comatose after out-of-hospital cardiac arrest. The investigators found **no significant difference in favorable functional neurologic outcome** (defined as Cerebral Performance Categories score of 1 or 2) at 6 months for patients treated for **24 hours** (n = 176; 64% with favorable outcome) vs **48 hours** (n = 175; 69% with favorable outcome) (difference, 5%; 95% CI, -5% to 14.8%). This absence of a dose-effect relationship could cast doubt on the efficacy of TTM, but it also should prompt examination of the core assumptions of dose-finding trials in resuscitation.

Targeted temperature management changed post-cardiac arrest care. For decades, survival of patients with restoration of pulses after cardiac arrest did not change. In 2002, **2 trials randomized 352 patients** after out-of-hospital cardiac arrest and reported **improved survival** and **functional recovery** with a package of care that included mild hypothermia (32°C-34°C for 12 or 24 hours) compared with care with **no hypothermia**.^{2,3} Implementation of therapeutic hypothermia, which came to be known as TTM, improved outcomes in many locales,⁴ but outcomes worsened with lower adherence to TTM.⁵ Most institutions adopted the temperatures (32°C-34°C) and duration (**usually 24 hours**) used in these early trials.⁶ However, **no clinical data** existed on the **optimal depth, timing, or duration** of hypothermia. In other words, what was the optimum dose of TTM?

No particular depth of hypothermia is clearly superior for TTM. In a **recent systematic review**, **no superiority** was iden-

tified for various temperatures from **32°C to 36°C**.⁷ The largest trial reported similar excellent outcomes for 939 patients after out-of-hospital cardiac arrest who were randomized to TTM at **33°C or at 36°C**.⁸

More **rapid initiation** of TTM is **not** clearly **superior**. Six trials found **no difference** in outcomes for 2379 patients after out-of-hospital cardiac arrest who were randomized to very early, prehospital initiation of hypothermia (**<1 hour** after arrest) vs later, in-hospital initiation of hypothermia (**1-4 hours after arrest**).⁹ Observational studies of hundreds of nonrandomized patients who received TTM have found **no consistent relationship** between **time-to-target temperature** and **outcome** with early (**<4-6 hours**) initiation.¹⁰ Preclinical data suggest that TTM initiated **after 4 hours** is **no different** from **non-TTM** treatment.¹¹ In the trial by Kirkegaard et al,¹ patients had prompt initiation of TTM (<2 hours) and reached **target temperature at around 5 hours**. The investigators also found **no differential effect of TTM duration** among patients who reached target temperature **within 4 hours** after arrest.

Is any **duration** of hypothermia superior? A systematic review found no interventional clinical data to answer this question.⁷ Yet in one preclinical study, 48 hours of hypothermia was superior to 24 hours of hypothermia for reducing neuronal degeneration.¹¹ It is thus biologically plausible that longer periods of hypothermia may be clinically beneficial. The clinical trial by Kirkegaard et al¹ is the first to explore whether longer durations of TTM improve patient outcomes. This pragmatic trial also made a reasonable assumption that doubling the usual duration of hypothermia to 48 hours was a sufficient dose escalation to detect any signal of benefit while minimizing adverse effects from very prolonged hypothermia.

This trial has many excellent features in its design and conduct.^{1,12} Participating centers enrolled more than 98% of

eligible patients following cardiac arrest, patients were randomized individually, treating teams were unaware of allocation until randomization, only 1 individual was lost to follow-up, and **more than 80% of patients had prompt coronary angiography**. Although it was not possible to blind treating teams to the intervention, assessors for 6-month outcomes were blinded to treatment allocation. In addition, this trial directly addressed the potential bias from withdrawal of life support by providing independent clinicians to conduct multimodal prognostic assessment at least 72 hours after cardiac arrest. This approach has been used in one other large trial,⁸ and it should become more standard in all trials of post-cardiac arrest care.

Size is the principal limitation of the trial by Kirkegaard et al.¹ With 355 patients, the study was **powered to detect a 15% absolute difference** in favorable survival between the intervention groups. However, **very few interventions in medicine are that potent**, and this effect **size is comparable to the original effect of adding TTM to postarrest care.**^{2,3,7} It is very unlikely that different doses of TTM would affect outcomes as much as the presence or absence of TTM. Nevertheless, **this trial does exclude (with 95% CIs) the possibilities that 48 hours of TTM results in a more than 5% decrease in good outcome or a more than 14.8% increase in good outcome.** These bounds can guide the design of future trials.

Does the absence of an effect in this trial indicate that duration of TTM does not matter? Combined with the absence of a clearly superior target temperature or a clearly better time of initiation, these data **may indicate that dose of TTM does not matter.** Alternatively, this trial provides information to help inform the design of other dose-finding trials in resuscitation.

First, **power calculations should be realistic** and try to detect clinically important effects. This **trial cannot exclude a 5% or 10% difference in good outcome**, and such a difference **might alter practice.** Trials with **binary outcomes** will almost **always** require **thousands of participants** to detect such differences. A systematic review of trials in cardiac arrest from 1994-2014 found only 11 trials that randomized more than 1000 individuals.¹³ **Continuous** measures of outcome **rather than dichotomous** outcome measures might **reduce** the required **sample sizes.**

Second, trials must consider whether **ancillary care** for individual patients overwhelms any intervention effect. Because a team constantly attends to critically ill patients, additional effort might be exerted to improve outcomes for patients allocated to a less efficacious intervention. This influence of medical care will bias the trial toward no difference between groups. Measuring as many ancillary treatments as possible may detect this effect, but there will still be unmeasured confounders given the complexity of intensive care. Regimenting all ancillary care sometimes may be unethical and will al-

ways be very expensive. Furthermore, the influence of ancillary care will be greatest in critical care research involving situations in which treating teams constantly adjust therapy, such as duration of ventilator support or dosage of vasoactive drugs. **Large pragmatic trials are most prone to bias from medical beneficence**, and they may represent a **false economy for testing critical care interventions.**

Third, dose-finding trials should **not assume** that there is an **optimum fixed dose** for the **entire population.** Analogy to other critical care interventions illustrates how this assumption may be conceptually flawed. For example, in determining the **optimal dose of norepinephrine for shock**, patients might be randomly assigned to different fixed rates (0.04 µg/kg/min vs 0.1 µg/kg/min), fixed durations (24 hours vs 72 hours), or fixed onsets (immediately on recognition of shock vs within 6 hours of shock.). This approach might identify regimens that are lethal or dangerous, but it would be **irrelevant to guiding** actual use of a **drug that is titrated to individual response.** An example of a **more relevant** trial design would be random assignment to **different target blood pressures** to which **norepinephrine dose is titrated.**¹⁴

Fourth, what are **potential targets** for titration of TTM? Many basic laboratory experiments have explored how hypothermia reduces molecular events leading to cell death.¹⁵ At a more macroscopic level, hypothermia reduces brain edema, lowers intracranial pressure, reduces frequency of seizures, and lowers brain metabolic need.¹⁶ Intervening with these latter effects may reduce secondary brain injury. Clinicians could titrate temperature to a particular goal based on the response of the patient. For example, a patient with cerebral edema might be maintained at a lower temperature until intracranial pressure is controlled, then rewarmed slowly as long as pressure does not increase.¹⁷ While case series show **effects of temperature on individual patient physiology**, no trials have compared fixed vs titrated doses of TTM.

In summary, the trial by Kirkegaard et al¹ **excludes** the possibility that **48 hours of TTM** results in outcomes that are **15% better** or **5% worse** than **24 hours of TTM** for **good outcomes** in patients after out-of-hospital cardiac arrest. However, **absence of a superior duration of TTM for the whole population** does **not exclude** the possibility that **titration of TTM duration might benefit an individual.** Together with other trials, the available data suggest that the benefit from a package of care including TTM is resilient to implementation with a **range of target temperatures (32°C-36°C), onsets (0-6 hours), and durations (12-48 hours).** Perhaps the dose-effect relationship is flat across a wide range of these doses, or perhaps trials are biased to not detect individual differences. Advancement in resuscitation requires identification of appropriate targets or monitors to guide titration of postarrest care to individual response. Advances may also require more sophisticated trial designs.

ARTICLE INFORMATION

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Conflict of Interest Disclosures: The author has completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Callaway reports serving as a volunteer for the American Heart Association Emergency

Cardiovascular Care Committee, and his institution received research funding from the National Institutes of Health (grants U10 NS080371; UL1TR001856; R01HL133818; UH2HL125163; K12HL109068; U01HL077871).

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Interventions to Improve Infant Safe Sleep Practices

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In 2013, there were nearly 3500 deaths among infants from sudden infant death syndrome (SIDS) and other sleep-related events (eg, accidental suffocation) in the United States.¹ Although the



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cause of SIDS is unknown, several modifiable risk factors have been identified, including prone and side sleep position, bed sharing, and use of potentially hazardous soft bedding in the sleep environment. SIDS rates declined by more than 50% following the Back to Sleep campaign in the 1990s,² but since then, rates of sudden unexpected infant deaths have declined less rapidly^{1,3} and SIDS remains the leading cause of post-neonatal mortality in the United States.¹

To improve infant care practices and ultimately reduce SIDS and other sleep-related infant deaths, innovative strategies that educate caregivers about safe sleep and encourage them to adopt recommended infant safe sleep practices need to be developed³ and their effectiveness evaluated. Effective interventions could be scaled up to reach populations at highest risk and ultimately reduce infant mortality.

A key component to developing effective evidence-based strategies to promote safe sleep is understanding caregivers' barriers to adopting recommendations. Examples of barriers are caregiver concerns about choking risk if an infant is

placed supine for sleep⁴ or perceived discomfort if the infant is not placed in a warm and soft environment with blankets and pillows.⁵ With an understanding of the barriers, interventions can be developed to counteract them.

In this issue of *JAMA*, the Social Media and Risk-Reduction Training (SMART) randomized clinical trial evaluated 2 such strategies: a nursing quality improvement (NQI) intervention provided postpartum teaching and modeling to mothers during the postpartum hospital stay, and a mobile health (mHealth) intervention delivered tailored email or text messages and videos to mothers up to 60 days after giving birth.⁶ The safe sleep interventions encouraged supine sleep position, room sharing without bed sharing, not using soft bedding in the sleep environment, and pacifier use when placing the infant to sleep for naps and at bedtime. In addition, the safe sleep mHealth messaging aimed to counteract barriers that can limit use of safe sleep practices. Control interventions substituted breastfeeding for safe sleep practices.

Sixteen US hospitals were selected from a nationally representative sample of 32 hospitals with more than 100 deliveries annually, based on their history of successful recruitment for the Study of Attitudes and Factors Effecting Infant Care Practices (SAFE) study.⁷ Hospitals were randomly assigned to 1 of 4 intervention combinations: breastfeeding NQI

Targeted Temperature Management for 48 vs 24 Hours and Neurologic Outcome After Out-of-Hospital Cardiac Arrest

A Randomized Clinical Trial

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IMPORTANCE International resuscitation guidelines recommend targeted temperature management (TTM) at 33°C to 36°C in unconscious patients with out-of-hospital cardiac arrest for at least 24 hours, but the optimal duration of TTM is uncertain.

OBJECTIVE To determine whether TTM at 33°C for 48 hours results in better neurologic outcomes compared with currently recommended, standard, 24-hour TTM.

DESIGN, SETTING, AND PARTICIPANTS This was an international, investigator-initiated, blinded-outcome-assessor, parallel, pragmatic, multicenter, randomized clinical superiority trial in 10 intensive care units (ICUs) at 10 university hospitals in 6 European countries. Three hundred fifty-five adult, unconscious patients with out-of-hospital cardiac arrest were enrolled from February 16, 2013, to June 1, 2016, with final follow-up on December 27, 2016.

INTERVENTIONS Patients were randomized to TTM (33 ± 1°C) for 48 hours (n = 176) or 24 hours (n = 179), followed by gradual rewarming of 0.5°C per hour until reaching 37°C.

MAIN OUTCOMES AND MEASURES The primary outcome was 6-month neurologic outcome, with a Cerebral Performance Categories (CPC) score of 1 or 2 used to define favorable outcome. Secondary outcomes included 6-month mortality, including time to death, the occurrence of adverse events, and intensive care unit resource use.

RESULTS In 355 patients who were randomized (mean age, 60 years; 295 [83%] men), 351 (99%) completed the trial. More patients in the 48-hour group had a favorable outcome, but this was not statistically significant. Six-month mortality was not different between the groups. Adverse events were more common in the 48-hour group than in the 24-hour group. There was no significant difference in the time to mortality (hazard ratio, 0.79; 95% CI, 0.54-1.15; *P* = .22). The median length of ICU stay (151 vs 117 hours; *P* < .001), but not hospital stay (11 vs 12 days; *P* = .50), was longer in the 48-hour group than in the 24-hour group.

	No. (%) of Patients		Difference, % (95% CI)	RR (95% CI)	<i>P</i> Value
	48-Hour Group (n = 175)	24-Hour Group (n = 176)			
Primary outcome: CPC score of 1 or 2 at 6 mo	120 (69)	112 (64)	4.9 (−5 to 14.8)	1.08 (0.93 to 1.25)	.33
Secondary outcomes					
Mortality at 6 mo	48 (27)	60 (34)	−6.5 (−16.1 to 3.1)	0.81 (0.59 to 1.11)	.19
Any adverse event	169 (97)	161 (91)	5.6 (0.6 to 10.6)	1.06 (1.01 to 1.12)	.03

CONCLUSIONS AND RELEVANCE In unconscious survivors from out-of-hospital cardiac arrest admitted to the ICU, targeted temperature management at 33°C for 48 hours did not significantly improve 6-month neurologic outcome compared with targeted temperature management at 33°C for 24 hours. However, the study may have had limited power to detect clinically important differences, and further research may be warranted.

TRIAL REGISTRATION clinicaltrials.gov Identifier: [NCT01689077](https://clinicaltrials.gov/ct2/show/study/NCT01689077)

JAMA. 2017;318(4):341-350. doi:10.1001/jama.2017.8978

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+ Supplemental content

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Short- and long-term outcomes in unconscious patients admitted to the intensive care unit (ICU) after out-of-hospital cardiac arrest are characterized by prognostic uncertainty and a high risk of death and neurologic deficit.¹ To improve the chance of survival and neurologic recovery, international guidelines recommend use of targeted temperature management (TTM), together with urgent coronary angiography and percutaneous coronary intervention when appropriate, and delayed multimodal prognostication before withdrawal of care.²

The results of the TTM trial (Target Temperature Management 33°C versus 36°C After Out-of-Hospital Cardiac Arrest)³ showed that TTM to 36°C had benefits similar to those of TTM to 33°C, but the optimal duration of cooling is still under debate.²⁻⁴ Current recommendations state that the patient's temperature should be kept at a target of 32°C to 36°C for at least 24 hours.^{2,4} This recommended duration was based on the results of the 2 largest randomized clinical trials on TTM conducted with adult patients with out-of-hospital cardiac arrest, which used 24 hours of cooling.^{3,5} Nevertheless, in some units, longer cooling periods (up to 72 hours) were not uncommon,^{6,7} and for newborns with anoxic-asphyxia brain injury, cooling periods of 72 hours were considered standard practice.^{8,9} Animal studies have also suggested a potential benefit of prolonged cooling,^{10,11} but for adults with out-of-hospital cardiac arrest, this approach is currently supported only by retrospective data from small cohort studies.^{12,13}

Because of this specific knowledge gap,⁴ this clinical trial was designed to compare long-term neurologic outcomes in patients managed with 48-hour TTM at 33°C compared with the standard 24-hour duration.

Methods

Study Design

The Time-differentiated Therapeutic Hypothermia trial was an investigator-initiated, blinded-outcome-assessor, parallel, pragmatic, multicenter, randomized clinical trial conducted in 10 European ICUs. The study protocol (Supplement 1) was approved by the ethics committee in each participating center or country (list of ethical approvals available in Supplement 2). The study was conducted according to the requirements of the Declaration of Helsinki; written informed consent was obtained from the next of kin or a legal surrogate before randomization, and from each patient who regained mental capacity, according to local ethical approval. An independent data and safety monitoring committee performed predefined blinded interim analyses when 175 patients had been included, evaluating only safety issues and mortality at 6 months. Accuracy of collected study data was monitored by the principal investigator (see Supplement 2) or a person nominated within the study group.

Patients

All patients admitted to the ICU after an out-of-hospital cardiac arrest of presumed cardiac origin were screened for

Key Points

Question Does targeted temperature management at 33°C for 48 hours result in better neurologic outcome compared with standard 24-hour targeted temperature management in unconscious patients with out-of-hospital cardiac arrest?

Findings In this randomized clinical trial enrolling 355 adults with out-of-hospital cardiac arrest, there was no significant difference in favorable neurologic outcome at 6 months for those treated for 48 hours (69%) vs 24 hours (64%) (difference, 5%).

Meaning Prolonged targeted temperature management at 33°C did not result in better neurologic outcome; however, the study may have had limited power to detect clinically important differences, and further research may be warranted.

eligibility, with the inclusion criteria older than 17 years and younger than 80 years, sustained return of spontaneous circulation for more than 20 consecutive minutes, and Glasgow Coma Scale score less than 8.¹⁴ Patients with shockable and nonshockable rhythms were eligible; patients with unwitnessed asystole were excluded. A full description of the exclusion criteria is available in Supplement 2. Randomization had to take place within the first 23 hours after a core temperature less than or equal to 34°C had been reached.

Randomization and Blinding

After screening for eligibility, patients were randomly assigned in a 1:1 ratio to 1 of the 2 study groups, using a web-based central randomization procedure provided by the Department of Clinical Medicine, Aarhus University, Denmark (Figure 1). Randomization was carried out within strata defined by study site, age (<60 vs ≥60 years), and initial rhythm (shockable or not), using blinded randomly permuted block sizes of 6, 4, and 2. Medical personnel caring for the study patients, research staff entering data into the electronic case report form, and relatives were aware of group assignments.

Neurologic prognostication and decisions about withdrawal of treatment were made by medical personnel independent of the research team. Physicians and health personnel assessing 6-month functional outcomes and the statisticians were unaware of the study group assignments. During the analysis phase, the 2 study groups were identified as group 1 and group 2, and the results were incorporated in a final report by the writing group before data were unblinded.

Intervention

Patients were randomized to TTM at 33°C (±1°C) for 24 or 48 hours. Surface and invasive cooling methods were allowed, including boluses of intravenous cold fluids for induction of TTM (4°C). The aim was to reach target temperature as fast as possible. Temperature was measured in the bladder, rectum, or esophagus, or with intravascular probes according to local practices. Timing of the 24- or 48-hour duration started from the first point at which the core temperature

was 34°C or lower. At the end of the 24- or 48-hour period, rewarming was performed at a maximal rate of 0.5°C/h until a core temperature of 37°C was reached. Sedation was used in both groups until rewarming was complete. The trial protocol included recommendations on supportive treatment, including the use of vasopressors, mechanical ventilation, and blood pressure targets.

In patients with severe bleeding, life-threatening arrhythmias, or refractory low cardiac output, cooling could be prematurely stopped and the temperature increased to 36°C to 37°C by the treating physicians, independent of the research team. These patients were analyzed in their assigned treatment group in a modified intention-to-treat analysis, but excluded from the per-protocol analysis.

Neurologic Prognostication

All centers agreed to provide active treatment until 72 hours after normothermia, with the exception of patients with brain death or refractory shock with multiple organ dysfunctions. Patients who remained unconscious despite cessation of sedation were assessed according to trial protocol recommendations (Supplement 1) with a combination of neurologic examination, electroencephalography, somatosensory-evoked potentials, computed tomography, and magnetic resonance imaging of the brain according to the decision of the attending physicians. Decisions to withdraw life-supporting therapy were made by a multidisciplinary team according to protocol recommendations and local practice, and were recorded in the electronic case report form.

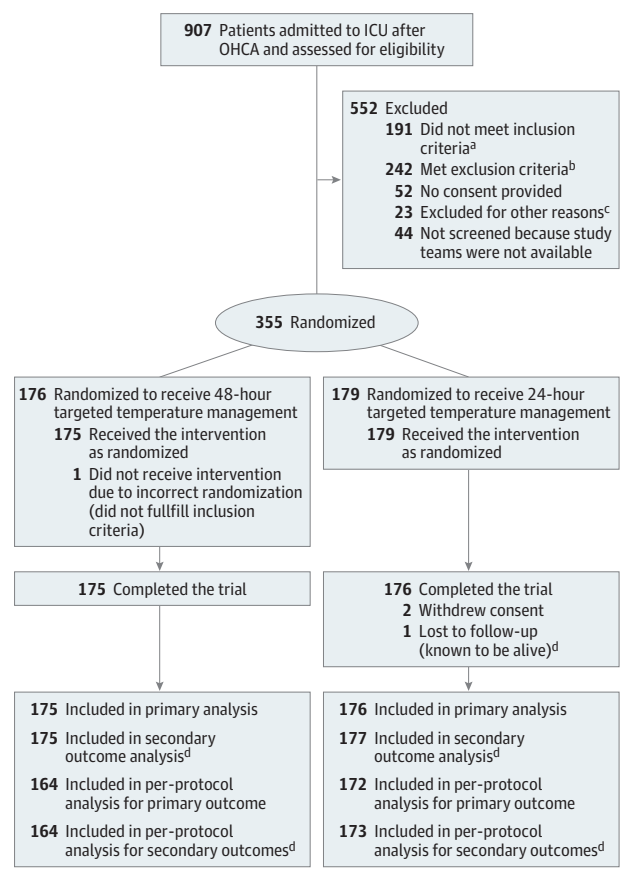
Adverse Events and Hospital Stay

Adverse events data were collected throughout the hospital stay, including the occurrence of a new cerebral abnormality (including seizures), hypotension, cardiac arrhythmia, gastrointestinal feeding intolerance, renal failure, infections (in particular, pneumonia), and bleeding (including need for transfusion) (Supplement 1 and 2). Time receiving ventilator assistance (time to extubation) was collected, as well as length of stay in the ICU and in the hospital and the use of medical procedures (ie, tracheostomy, echocardiography, gastroscopy, and computed tomography scan).

Follow-up and Outcome

All surviving patients were followed up until 6 months after enrollment. The primary outcome, neurologic outcome at 6 months after the cardiac arrest, was defined by and based on the Cerebral Performance Categories score: 1, alert, able to work and lead a normal life; 2, moderate cerebral disability and sufficient cerebral function for part-time work; 3, severe cerebral disability, dependent on others, and impaired brain function; 4, coma and vegetative state; and 5, dead or certified brain dead. A Cerebral Performance Categories score of 1 or 2 was considered a favorable neurologic outcome.^{15,16} Assessors blinded to the treatment allocation performed the assessment during a telephone or person-to-person interview. The main secondary outcomes were 6-month mortality and time to death. Cause of death

Figure 1. Screened, Excluded, and Included Patients in the Study of Targeted Temperature Management



OHCA indicates out-of-hospital cardiac arrest; ICU, intensive care unit; ROSC, return of spontaneous circulation.

^a Reasons for not meeting inclusion (eligibility) criteria were as follows: not cardiac OHCA (n=75), age (n=53), Glasgow Coma Scale score >8 (n=49), and no stable ROSC (n=14).

^b Exclusion criteria met were as follows: estimated time from collapse to ROSC >60 min (n=40), cardiac arrest with presumed noncardiac cause (eg, trauma, aorta dissection, intracerebral disease, massive bleeding, hanging, or hypoxemia) (n=63), in-hospital cardiac arrest (n=6), terminal disease or do-not-resuscitate order (n=15), severe coagulopathy (anticoagulant therapy, including thrombolysis, was not an exclusion criteria) (n=8), unwitnessed OHCA with asystole as first rhythm (n=21), time from cardiac arrest to initiation of cooling >240 min (n=19), neurologic disease with cognitive impairment (n=8), persistent cardiogenic shock, systolic blood pressure <80 mm Hg despite vasoactive treatment, or aortic balloon pump intervention (n=46), suspected or confirmed acute intracerebral bleeding (n=9), suspected or confirmed acute stroke (n=6), and acute coronary artery bypass surgery (n=1).

^c Other reasons for exclusion were as follows: patient died before enrollment (n=10), other interventional study precluding co-enrollment (n=5), patients transferred to other ICU because of bed availability (n=5), and patient not native to country of treatment, rendering follow-up difficult or impossible (n=3).

^d The patient lost to follow-up was known to be alive and was included in the survival analyses, but could not be included in the primary analyses due to lack of primary outcome data.

was reported as multiple organ dysfunction, brain death, withdrawal of life-supporting treatment, and other or undetermined reasons.

Statistical Analyses

For 80% power (2-sided $P = .05$) to show an absolute difference of 15% (50% vs 65%), a sample size of 338 patients was required. The choice of 15% as detectable difference was based on the effect sizes observed in the original TTM studies from 2002 and on observational data.^{5,17,18} The expected outcome of 50% was estimated according to the percentage of patients with good outcome in the 2 randomized studies from 2002, 49% and 55%, and supported by registry data.¹⁹ To account for potential loss to follow-up, sample size was inflated by 5% to 355 participants. No adjustment was made to the sample size analysis to account for the preplanned interim safety analysis. A modified intention-to-treat analysis (including all randomized patients who initiated the intervention and did not withdraw their consent)²⁰ was undertaken in accordance with the protocol (Supplement 1) and the previously published analysis plan²¹ by an independent statistician blinded to treatment allocation. An additional per-protocol analysis was also conducted, excluding patients in whom cooling was terminated earlier than scheduled.

Categorical data were compared with χ^2 tests for equal proportion (or Fisher exact test), t test for normally distributed data, and Wilcoxon test otherwise. Results are presented as numbers (percentages), means (SD), and medians (interquartile range [IQR]), as appropriate. Binomial outcomes are presented as proportions (95% CIs), with group comparisons presented as unadjusted differences (95% CIs) and as both unadjusted and adjusted relative risks (95% CIs), which were derived from Poisson regression with robust error variance.²²

Unadjusted and adjusted 6-month survival analyses were performed with Cox proportional hazards regression, with results reported as hazard ratios. Survival time is presented with Kaplan-Meier curves and was compared between groups by using the log-rank test, with proportionality assumptions verified with Schoenfeld residuals. Resource usage variables were log transformed, with unadjusted and adjusted analysis performed by using mixed hierarchic linear modeling, with results presented as geometric means, ratios of geometric means, and Hodges-Lehmann differences between medians, each with 95% CIs. Multivariable analyses were performed by adjusting for a priori-defined covariates (trial site, age, sex, initial cardiac arrest rhythm, time to return of spontaneous circulation, and bystander-initiated life support), with patients nested within site and site treated as a random effect. Second subgroup analyses were performed on the following predefined subgroups: age (<60 or ≥ 60 years), cardiac rhythm (shockable or not shockable), time to return of spontaneous circulation (<25 or ≥ 25 minutes), bystander-initiated life support (performed or not performed), method of cooling (invasive or noninvasive), time from return of spontaneous circulation to target temperature (<240 or ≥ 240 minutes), out-of-hospital cardiac arrest score (<20 or ≥ 20 points),²³ and the site with the highest number of recruited patients compared with the other sites. Subgroup results are presented as a forest plot, with heterogeneity among subgroups determined by fitting an interaction between treatment and subgroup.

Temperatures during the first 24 hours of TTM and from completion of TTM (after 24 or 48 hours) to normothermia (37°C) were analyzed with repeated-measures analysis of variance, with pairwise post hoc comparisons performed by using t tests. Because multiple comparisons were considered, in the absence of any post hoc adjustment of the significance level, secondary outcomes should be considered as hypothesis generating and interpreted as exploratory. Because the number of missing values for primary and secondary outcomes and for variables needed for the adjusted analysis was minimal, no imputation was performed.

All analyses were conducted with SAS version 9.4 and SPSS version 22.0. A 2-sided $P < .05$ was used to indicate statistical significance.

Results

Patients

Between February 2013 and June 2016, all patients with out-of-hospital cardiac arrest ($n = 907$) who were admitted to a participating ICU were screened; 716 met the inclusion criteria. Of these patients, 361 had at least 1 exclusion criterion so that 355 patients were randomized, 176 to the 48-hour TTM group and 179 to the 24-hour TTM group. The population in the modified intention-to-treat primary outcome analysis included 175 patients in the 48-hour group and 176 in the 24-hour group (Figure 1). One patient was lost to follow-up but was known to be alive and therefore included in the mortality analysis. Baseline characteristics were comparable between groups (Table 1).

Intervention

The mean body temperature at ICU admission was 35°C (SD, 1.1°C) in the 48-hour group and 34.9°C (SD, 1.0°C) in the 24-hour group. Invasive cooling with an intravascular catheter was the most common cooling method ($n = 218$ [62%]), with no significant differences between groups (Table 2). Time from return of spontaneous circulation to target temperature was shorter in the 48-hour group than in the 24-hour group (281 [IQR, 217-360] vs 320 [IQR 241-410] minutes; $P = .01$). After achievement of the target temperature ($\leq 34^\circ\text{C}$), there were no significant differences in body temperature between groups until 24 hours (mean, 33.0°C [SD, 0.5°C] in the 24-hour group and 33.1°C [SD, 0.5°C] in the 48-hour group; $P = .66$) (Figure 2). The intervention was stopped early in 11 patients in the 48-hour group (6%) and 3 patients (2%) in the 24-hour group (Table 2). The rewarming rate did not differ significantly between the 2 groups (0.4°C [SD, 0.2°C] per hour in the 24-hour group and 0.3°C [SD, 0.2°C] per hour in the 48-hour group; $P = .07$) (Table 2). Temperatures were significantly lower in the 48-hour group at 60 hours but not at 72 hours from when the target temperature was achieved (Table 2). ICU parameters in regard to other aspects of care were similar between groups during the first 24 hours (eTable 2 in Supplement 2). During the intervention, the majority of patients were sedated with propofol ($n = 305$) and remifentanyl ($n = 164$). Midazolam ($n = 46$) and fentanyl

Table 1. Baseline and Prerandomization Characteristics of the Intention-to-Treat Population

	No. (%) of Patients	
	48-Hour Group (n = 175)	24-Hour Group (n = 176)
Demographic characteristics		
Age, mean (SD), y	61 (12)	60 (12)
Male sex	144 (82.3)	148 (84.1)
Weight, mean (SD), kg ^a	86 (17)	86 (16)
Neurologic function before arrest		
Normal, CPC score 1	172 (98)	169 (96)
Some disability, CPC score 2	3 (2)	7 (4)
Medical history		
Previous myocardial infarction	28 (16)	26 (15)
Previous PCI or CABG	29 (17)	26 (15)
Previous cardiac arrest	0	3 (2)
Chronic heart failure (NYHA class IV)	5 (3)	13 (7)
Chronic obstructive pulmonary disease	13 (7)	11 (6)
Liver cirrhosis	3 (2)	0
Chronic renal failure with dialysis	1 (<1)	1 (<1)
Diabetes mellitus	35 (20)	28 (16)
Immunosuppression	2 (<1)	1 (<1)
Previous stroke	11 (6)	14 (8)
Cardiac arrest location		
Home	89 (51)	102 (58)
Public place	70 (40)	66 (38)
Other out-of-hospital	16 (9)	8 (5)
Arrest witnessed		
Bystander	153 (87)	147 (84)
Emergency medical services	7 (4)	15 (9)
Unwitnessed ^b	15 (9)	14 (8)
Resuscitation factors		
Bystander-initiated CPR	147 (84)	144 (82)
Shockable rhythm	160 (91)	152 (86)
AED used	38 (22)	43 (24)
Time to basic life support, median (IQR), min ^a	1 (0-2)	1 (0-2)
Time to advanced life support, median (IQR), min ^c	8 (5-11)	8 (5-11)
Time to return of spontaneous circulation, median (IQR) ^d	20 (15-30)	21 (16-27)
Mechanical chest compression used	43 (25)	47 (27)
Out-of-hospital treatment		
Epinephrine	110 (63)	109 (62)
Amiodarone	79 (45)	68 (39)
Immediate interventional cardiology		
Coronary angiography	146 (83)	144 (82)
Percutaneous coronary intervention	76 (43)	69 (39)
Clinical status on ICU admission		
Receiving mechanical ventilation at ICU admission	175 (100)	176 (100)
Glasgow Coma Scale score, median (IQR) ^e	3 (3-3)	3 (3-3)
Time from ICU admission to randomization, median (IQR), h	15.2 (5.9-19.9)	15 (7.5-19.5)
Temperature, mean (SD), °C ^f	35 (1.1)	34.9 (1.0)
Mean arterial blood pressure, mean (SD), mm Hg ^g	82 (21)	80 (18)
Lactate, median (IQR), mg/dL ^c	23.4 (12.6-40.5)	24.3 (13.5-45.9)
Creatinine, mean (SD), mg/dL	1.2 (0.7)	1.2 (0.4)
pH, mean (SD)	7.27 (0.10)	7.27 (0.10)
Pao ₂ , median (IQR), mm Hg	118 (91-183)	120 (90-176)
Paco ₂ , mean (SD), mm Hg	46 (10)	45 (10)

Abbreviations: AED, automated external defibrillator; CABG, coronary artery bypass grafting; CPC, Cerebral Performance Categories (1, alert, able to work and lead a normal life; 2, moderate cerebral disability and sufficient cerebral function for part-time work; 3, severe cerebral disability, dependent on others, and impaired brain function; 4, coma and/or vegetative state; and 5, dead or certified brain dead); CPR, cardiopulmonary resuscitation; ICU, intensive care unit; IQR, interquartile range; NYHA, New York Heart Association; PCI, percutaneous coronary intervention.

^a Data missing for 1 patient. In some cases, the weight was estimated and not measured.

^b When the cardiac arrest was unwitnessed, intervals were calculated from the time of the call to emergency medical services.

^c Data missing for 2 patients.

^d Data missing for 3 patients.

^e Untestable because of sedation in 105 patients.

^f Data missing for 8 patients.

^g Data missing for 4 patients.

Table 2. Timing, Methods, and Results of the Cooling Intervention With Included Protocol Violations

	48-Hour Group (n = 175)	24-Hour Group (n = 176)	P Value
Time to intervention, median (IQR), min			
Time from ROSC to start of TTM ^a	102 (47-174)	112 (33-185)	.92
Time from ROSC to achievement of target temperature ^b	281 (217-360)	320 (241-404)	.01
TTM methods used, No. (%)			
Surface cooling ^c	75 (43)	81 (46)	.55
Invasive cooling catheter ^c	114 (65)	104 (59)	.24
Cold fluid bolus	65 (37)	58 (33)	.41
Rewarming, mean (SD)			
Rate, °C/h	0.3 (0.2)	0.4 (0.2)	.08
Rewarming duration, h	10 (4)	10 (3)	.65
Protocol violations			
Rewarmed to 36°C or above before scheduled time (protocol violations), No. (%)	11 (6.3)	3 (1.7)	.03
Bradycardia or conduction disturbance	3	0	
Arrhythmia	3	0	
Refractory cardiac arrest	1	0	
Circulatory shock	2	0	
Excessive sedation requirement	1	0	
Brain death	0	2	
Equipment problem	1	0	
Unspecified	0	1	
Temperatures after TTM, mean (SD), °C			
60 h from target temperature	37.0 (1.0)	37.2 (0.6)	.02
72 h from target temperature	37.2 (0.8)	37.4 (0.7)	.16

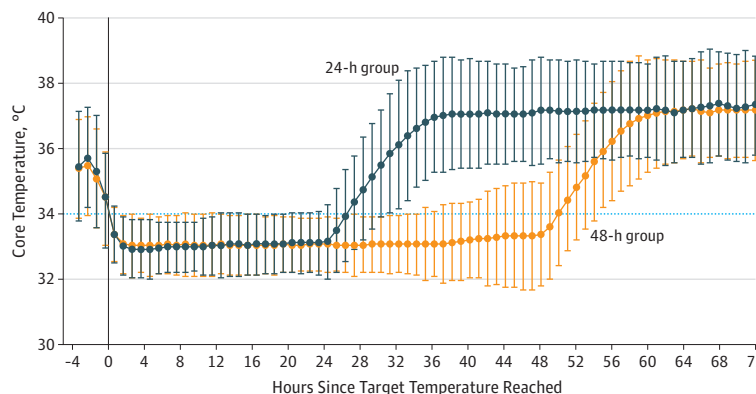
Abbreviations: IQR, interquartile range; ROSC, return of spontaneous circulation; TTM, targeted temperature management.

^a Data missing for 72 patients. Exact time was impossible to determine because of pre-ICU start of cooling.

^b Data missing for 5 patients.

^c Some units used both surface and invasive cooling.

Figure 2. Core Temperature of the Intervention Groups



Temperatures in the study groups until 72 hours after achieving target temperature ($\leq 34^{\circ}\text{C}$ [dotted horizontal line]), with T0 defined as the time target temperature was reached. Temperature data were available for 347 of 352 patients and were recorded with variable frequency (median, 188; interquartile range, 61-798) during the depicted period, with no statistically significant difference in frequency between groups ($P = .15$). Values are presented as mean ± 2 SDs.

(n = 89) were also used in a minority of patients. Infusion of neuromuscular-blocking drugs was used in 61 patients.

Outcomes

Six-month neurologic outcome was available for 351 patients (Figure 1); 120 of 175 patients in the 48-hour group (69%; 95% CI, 62%-75%) and 112 of 176 in the 24-hour group (64%; 95% CI, 56%-71%) had a favorable neurologic outcome (absolute difference, 4.9%; 95% CI, -5% to 14.8%; relative risk, 1.08; 95% CI, 0.93-1.25; $P = .33$) (Table 3). Similar results were obtained in the adjusted and the per-protocol analyses (eTable 2 in Supplement 2). The lack of a significant effect of TTM dura-

tion on neurologic outcome was consistent across all pre-defined subgroups (eFigure 1 in Supplement 2).

Mortality at 6 months was 27% (95% CI, 21%-34%) in the 48-hour group and 34% (95% CI, 27%-41%) in the 24-hour group (difference, -6.5%; 95% CI, -16.1% to 3.1%; relative risk, 0.81; 95% CI, 0.59-1.11; $P = .19$). The median follow-up time was 184 days (IQR, 33-196 days) in the 48-hour group and 181 days (IQR, 15-193 days) in the 24-hour group ($P = .43$). There were no significant differences in time to death overall or in the adjusted and per-protocol analyses (Figure 3 and eTable 2 in Supplement 2). There were no differences in the other pre-specified primary and secondary outcomes between groups,

Table 3. Primary and Secondary Outcomes After Targeted Temperature Management

	48-Hour Group (n = 175)	24-Hour Group (n = 176)	Difference, % (95% CI)	Relative Risk or Ratio of Geometric Means (95% CI)	P Value
Primary outcome, No. (%)					
CPC score of 1 or 2 at 6 mo ^a	120 (69)	112 (64)	4.9 (−5 to 14.8)	1.08 (0.93 to 1.25)	.33
Secondary outcomes, No. (%)					
ICU mortality	26 (15)	30 (17)	−2.1 (−9.7 to 5.5)	0.88 (0.54 to 1.42)	.59
Hospital mortality	40 (23)	44 (25)	−2 (−10.9 to 6.9)	0.92 (0.63 to 1.34)	.66
Mortality at 6 mo	48 (27)	60 (34)	−6.5 (−16.1 to 3.1)	0.81 (0.59 to 1.11)	.19
Adverse events, No. (%)					
Any adverse event	169 (97)	161 (91)	5.6 (0.6 to 10.6)	1.06 (1.01 to 1.12)	.03
Pneumonia	86 (49)	76 (43)	6.2 (−4.2 to 16.6)	1.14 (0.91 to 1.44)	.24
Any bleeding	17 (10)	23 (13)	−3.3 (−9.9 to 3.3)	0.75 (0.41 to 1.35)	.33
Resource use, median (IQR)					
Time receiving mechanical ventilation, h ^{b,c}	120 (99 to 146)	87 (72 to 106)	26 (16 to 36)	1.37 (1.19 to 1.59)	<.001
Survivors, h	121 (98 to 149)	85 (69 to 105)	28 (18 to 38)	1.41 (1.22 to 1.64)	<.001
Nonsurvivors, h	107 (71 to 163)	151 (89 to 256)	−79 (−205 to 48)	0.71 (0.37 to 1.37)	.35
ICU length of stay, h ^c	151 (127 to 178)	117 (99 to 138)	28 (15 to 41)	1.3 (1.14 to 1.47) ^c	<.001
Survivors, h	184 (141 to 240)	134 (103 to 175)	30 (17 to 44)	1.37 (1.22 to 1.54)	<.001
Nonsurvivors, h	92 (66 to 129)	88 (64 to 121)	9 (−25 to 44)	1.04 (0.66 to 1.64)	.86
Hospital length of stay, d ^c	11.1 (9.3 to 13.3)	11.8 (9.9 to 14.1)	−0.85 (−2.6 to 0.9)	0.94 (0.79 to 1.11)	.50
Survivors, d	15.9 (12.6 to 20)	17.2 (13.7 to 21.6)	−1.15 (−3.1 to 0.8)	0.93 (0.8 to 1.06)	.28
Nonsurvivors, d	5.1 (3.6 to 7.1)	5.3 (3.8 to 7.5)	0 (−1.9 to 1.9)	0.95 (0.64 to 1.41)	.79

The relative risks are unadjusted. The *P* values are from the results of χ^2 analysis of categorical data from a nonparametric comparison of continuous data. CPC indicates Cerebral Performance Categories; ICU, intensive care unit; IQR, interquartile range.

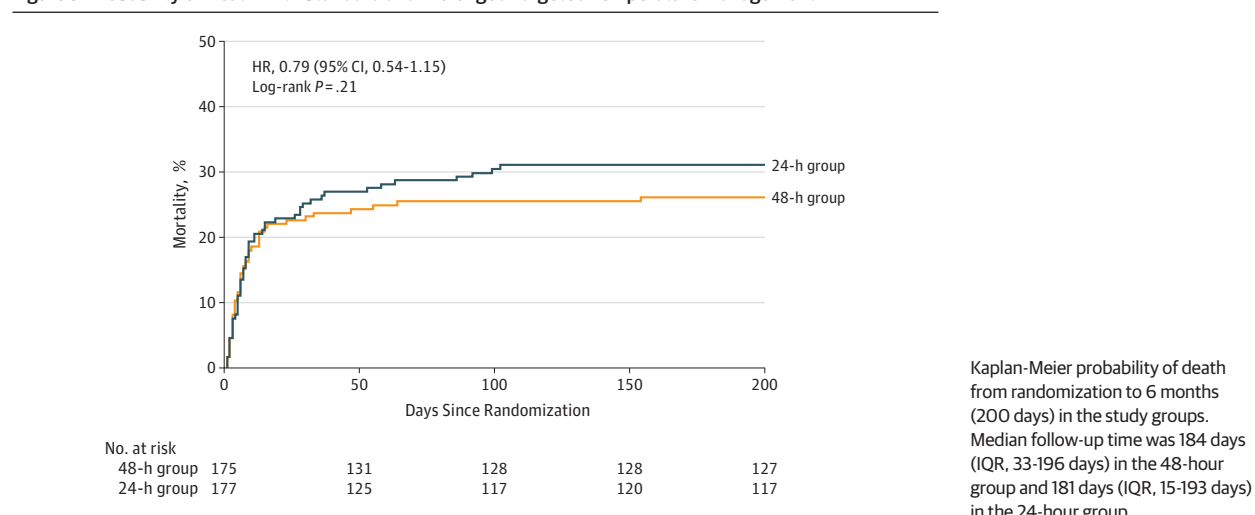
^a In the 24-hour group, 100% equals 176 because 1 patient was alive but lost to follow-up. CPC score: 1, alert, able to work and lead a normal life; 2, moderate cerebral disability and sufficient cerebral function for part-time work; 3, severe

cerebral disability, dependent on others, and impaired brain function; 4, coma and vegetative state; 5, dead or certified brain dead.

^b Time calculated as time to extubation.

^c Comparison of the geometric means between groups. Difference was calculated with the Hodges-Lehmann estimator.

Figure 3. Probability of Death With Standard and Prolonged Targeted Temperature Management.



ie, Cerebral Performance Categories scores at hospital discharge, 3 months, and 6 months, or in the level of consciousness at 3 days from the arrest (eTable 3 in Supplement 2). Causes of death were comparable in the 2 groups, and there were no significant differences in the number of patients for whom life-supporting treatment was withdrawn for cerebral reasons (eTable 4 in Supplement 2).

Adverse Events

The proportion of patients with 1 or more adverse events was significantly higher in the 48-hour group (97%) than in the 24-hour group (91%) (difference, 5.6%; 95% CI, 0.6%-10.6%; relative risk, 1.06; 95% CI, 1.01-1.12; *P* = .04) (Table 3). Significantly more patients had hypotension in the 48-hour group than in the 24-hour group (62% vs 49%; *P* = .013) (eTable 6 in

Supplement 2). There were no significant differences in the rates of pneumonia or bleeding between the groups; however, severe bleeding was more common in the 24-hour than in the 48-hour group (4% vs 1%; $P = .03$).

Resource Use

The median ICU length of stay was longer in the 48-hour than in the 24-hour group (151 hours [IQR, 127-178 hours] vs 117 hours [IQR, 99-138 hours]; $P < .001$), but there was no significant difference in hospital length of stay (Table 2). There were no significant differences between groups in the use of mechanical assist devices, tracheostomy, echocardiography, gastroscopy, or other operative procedures. Four patients in the 48-hour group had coronary artery bypass grafting compared with none in the 24-hour group (eTable 6 in Supplement 2).

Discussion

In this pragmatic, international, multicenter, randomized clinical trial, 48-hour TTM at 33°C was compared with standard 24-hour TTM in comatose patients admitted to the ICU after an out-of-hospital cardiac arrest of presumed cardiac origin. There were no significant differences between groups in the rates of favorable neurologic outcome or survival at 6-month follow-up. Patients who received TTM for 48 hours had a higher incidence of adverse events and a longer ICU length of stay. These results were consistent across predefined subgroups and after adjustment for prerandomization characteristics. However, the study may have had limited power to detect clinically important differences.

Current resuscitation guidelines recommend TTM at 33°C to 36°C for at least 24 hours.^{2,4} Previous studies have focused on the concept of cooling^{5,17} and on which core temperature should be targeted,³ but not on duration. The overall survival rate and proportion of patients with good neurologic outcome at 6 months were higher than in previous TTM studies, and higher than anticipated when sample size calculation^{5,17} was performed. Although general improvements in out-of-hospital and in-hospital care over time may partly explain this observation, differences between the current study population and those of previous studies may also be important. For example, the rate of bystander cardiopulmonary resuscitation and use of automated external defibrillators were higher in the current study than in previous randomized clinical trials and observational studies.^{3,5,17,24} Furthermore, compared with the TTM trial,³ patients in the current study were younger and more frequently had a shockable rhythm, as well as slightly shorter times from cardiac arrest to return of spontaneous circulation. A high percentage of patients also had immediate interventional cardiac procedures (coronary angiography or percutaneous coronary intervention), factors known to influence outcome after out-of-hospital cardiac arrest.¹ Nevertheless, the current study included comatose patients after an anoxic injury, which is the population in whom TTM appeared to be effective in previous trials,^{3,5,17} supporting that findings in the current study are likely to be generalizable.

Duration of TTM in the prolonged-cooling group was set to 48 hours. There is no scientific evidence that specifically supports 48 hours or other durations longer than 24 hours. The 48-hour period was selected to balance a clear augmentation of “cooling dose” against an expected prolonged ICU stay and the risk of more adverse events.

In this study, adverse event rates may appear high but are comparable to those of previous trials on TTM at 33°C.^{3,5} More patients were rewarmed to 36°C before conclusion of the intervention in the 48-hour group compared with the 24-hour group, but overall rewarming rates and causes were similar to those of a previous study.³ Furthermore, the higher rate of rewarming and adverse effects was expected, given the longer treatment. Although 48-hour TTM was associated with slightly more adverse events than 24-hour TTM, most of them were mild and did not appear to affect neurologic outcome. In neonates with hypoxic-ischemic brain injury, TTM at 33°C for 72 hours is standard practice^{8,9}; prolonged cooling for 120 hours in one trial resulted in significant harm.⁸ Unlike the findings of one observational study,¹³ the 48-hour group had no increased risk of severe arrhythmias or pneumonia, which are known complications with TTM.^{25,26}

This study has several strengths. It is a multicenter study and has clear recommendations for interventions. Both invasive and noninvasive cooling methods were allowed, which represents current management and thus increases the generalizability of the findings. Because TTM affects neurologic prognostication and some patients regain consciousness long after the initial anoxic injury, a multimodal prognostication approach was used to avoid self-fulfilling outcome with withdrawing of life-sustaining treatment.²⁷ Finally, the initial intensive care management was similar between groups. The majority of patients underwent electroencephalography, somatosensory-evoked potential, or cerebral computed tomography scan as part of this multimodal approach, with no significant differences between groups.

Limitations

This study also has several limitations. Sample size calculation using a 15% absolute difference in the primary outcome may have increased the risk of a type II error. The protocol was, however, written before the publication of the TTM study.³ The assumed treatment effect was comparable to that in the original TTM trials^{5,17} and also appeared supported by observational data.^{5,8,18,28} Recent randomized clinical trials on the effect of TTM in adults after status epilepticus, in children after cardiac arrest, and in neonates after asphyxia used similar effect sizes, with an assumed improvement of 10% to 15% in the intervention group (at 33°C) compared with controls.^{8,28,29} Although this study did not find a statistically significant difference between treatment groups, the 95% CIs around the difference (−5% to 14.8%) indicate that a true difference between groups is unlikely to lie outside this range. The 5% higher rate of 6-month favorable neurologic outcome in the prolonged-cooling group could represent a clinically meaningful difference. A trial to confirm or reject such a 5% absolute difference in good neurologic outcome between groups would, according to the unadjusted differences,

require a much larger study with approximately 3000 patients. In addition, as in other studies,^{3,23} it was not possible to blind the ICU staff to the treatment group. The 6-month evaluation was, however, carried out by research personnel from outside the ICU. In most of the countries participating in the trial, ethical requirements did not allow allocation to the study before consent from a legal surrogate. This may have introduced bias toward exclusion of some patients otherwise eligible on admission to the ICU. The presence or absence of brain stem reflexes on admission to the ICU was not collected, and therefore imbalances between treatment groups in regard to these important components cannot be excluded. Finally, as in other studies of patients with cardiac arrest, good neurologic outcome was defined as a Cerebral Performance Categories score of 1 or 2, which may

be considered a rather crude measure of neurologic outcome. Therefore, this study cannot provide definitive conclusions about the potential effects of the studied intervention on other patient outcomes, such as quality of life or more refined measures of cognitive function.

Conclusions

In unconscious survivors from out-of-hospital cardiac arrest who were admitted to the ICU, TTM for 48 hours did not significantly improve 6-month neurologic outcome compared with TTM for 24 hours. However, the study may have had limited power to detect clinically important differences, and further research may be warranted.

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Accepted for Publication: June 23, 2017.

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Statistical analysis: Skrifvars.

Obtained funding: Kirkegaard.

Administrative, technical, or material support: Kirkegaard, Hjort, Jeppesen, Grejs, Duez.

Study supervision: Kirkegaard.

Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

Dr Taccone reports receiving lecture fees from Bard. Dr Storm reports receiving remuneration for presentations, travel costs, and partial technical or material support from Philips, C. R. Bard, Zoll, Medivance, Covidien, and Nonin Medical and a grant from the German Heart Foundation. Dr Jeppesen reports receiving grants from Aarhus University Research Foundation, Research Center for Emergency Medicine, Danish Heart Foundation, Aase og Ejnar Danielsens Foundation, Dr Sofus Carl Emil Friis and Olga Doris Friis Foundation, Kathrine and Vigo Skovgaards Foundation, and "Fonden til lægevidenskabens fremme." Dr Grejs reports receiving grants from Central Denmark Region, Aarhus University Hospital, the Danish Society of Anaesthesiology and Intensive Care Medicine, the Scandinavian Society of Anaesthesiology and Intensive Care Medicine, Foundation of 1870, Aase and Ejnar Danielsens foundation, Lily Benthine Lund's Foundation, Foundation of 1.6.1978, Raimond and Dagmar Ringgaard-Bohn's Foundation, the Danish Heart Association, and the Classenske Fideicommiss Book and Software Scholarship. Dr Skrifvars reports receiving research funding from GE Healthcare and lecture fees from Covidien, Orion Pharma, Astellas, and Axis Shield Diagnostics.

Funding/Support: The study was funded by independent research grants from The Danish Heart Foundation, The Laerdal Foundation,

The Scandinavian Society of Anaesthesiology and Intensive Care Medicine, The Danish Society of Anaesthesiology and Intensive Care Medicine, The Augustinus Foundation, Finska Lakaresällskapet, and Medicinska Understödsforeningen Liv och Halsa och Stiftelsen Dorothea Olivia, Karl Walter och Jarl Walter Perklens minne.

Role of the Funder/Sponsor: The funders had no role in the design and conduct of the study; collection, management, analyses, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Additional Contributions: Study investigators are listed in Supplement 2. **Independent Statistician:** Michael Bailey, PhD, Australian and New Zealand Intensive Care Research Centre, School of Public Health and Preventive Medicine, Monash University, Melbourne, Australia. **Data and Safety Monitoring Committee:** Anders Perner, MD, PhD (Chair), University of Copenhagen, Denmark; Michael F. Haney, MD, PhD, Umeå University, Umeå, Sweden; Risto O. Roine, MD, PhD, Turku University, Turku, Finland; and Kjetil Sunde, MD, PhD, Oslo University, Oslo, Norway.

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