



Targeted hypothermia versus targeted Normothermia after out-of-hospital cardiac arrest (TTM2): A randomized clinical trial—Rationale and design

Josef Dankiewicz,^a Tobias Cronberg,^b Gisela Lilja,^b Janus Christian Jakobsen,^c Jan Bělohávek,^d Clifton Callaway,^e Alain Cariou,^f Glenn Eastwood,^g David Erlinge,^a Jan Hovdenes,^y Michael Joannidis,^h Hans Kirkegaard,ⁱ Michael Kuiper,^j Helena Levin,^k Matt P. G. Morgan,^l Alistair D Nichol,^m Per Nordberg,ⁿ Mauro Oddo,^o Paolo Pelosi,^p Christian Rylander,^q Manoj Saxena,^r Christian Storm,^s Fabio Taccone,^t Susann Ullén,^u Matthew P. Wise,^l Paul Young,^v Hans Friberg,^w and Niklas Nielsen,^x *Lund, Stockholm, Gothenburg, Sweden; Copenhagen, Aarhus N, Denmark; Prague, Czech Republic; PA, MD, USA; Paris, France; Heidelberg, Melbourne, Sydney, Australia; Innsbruck, Austria; Leeuwarden, Netherlands; Cardiff, United Kingdom; Genoa, Italy; Brussels, Belgium; and Wellington, New Zealand*

Background Less than 500 participants have been included in randomized trials comparing hypothermia with regular care for out-of-hospital cardiac arrest patients, and many of these trials were small and at a high risk of bias. Consequently, the accrued data on this potentially beneficial intervention resembles that of a drug following small phase II trials. A large confirmatory trial is therefore warranted.

Methods The TTM2-trial is an international, multicenter, parallel group, investigator-initiated, randomized, superiority trial in which a target temperature of 33°C after cardiac arrest will be compared with a strategy to maintain normothermia and early treatment of fever ($\geq 37.8^\circ\text{C}$). Participants will be randomized within 3 hours of return of spontaneous circulation with the intervention period lasting 40 hours in both groups. Sedation will be mandatory for all patients throughout the intervention period. The clinical team involved with direct patient care will not be blinded to allocation group due to the inherent difficulty in blinding the intervention. Prognosticators, outcome-assessors, the steering group, the trial coordinating team, and trial statistician will be blinded.

The primary outcome will be all-cause mortality at 180 days after randomization. We estimate a 55% mortality in the control group. To detect an absolute risk reduction of 7.5% with an alpha of 0.05 and 90% power, 1900 participants will be enrolled. The main secondary neurological outcome will be poor functional outcome (modified Rankin Scale 4–6) at 180 days after arrest.

Discussion The TTM2-trial will compare hypothermia to 33°C with normothermia and early treatment of fever ($\geq 37.8^\circ\text{C}$) after out-of-hospital cardiac arrest. (Am Heart J 2019;217:23-31.)

From the ^aLund University, Skåne University Hospital, Department of Clinical Sciences, Cardiology, Lund, Sweden, ^bLund University, Skåne University Hospital, Department of Clinical Sciences, Neurology, Lund, Sweden, ^cThe Copenhagen Trial Unit, Centre for Clinical Intervention Research, Copenhagen University Hospital, Copenhagen, Denmark, ^d2nd Department of Medicine, First Faculty of Medicine, Charles University in Prague and General University Hospital, Prague, Czech Republic, ^eDepartment of Emergency Medicine, University of Pittsburgh, Pittsburgh, PA, USA, ^fMedical Intensive Care Unit, Cochin University Hospital (APHP) and Paris Descartes University, Paris, France, ^gDepartment of Intensive Care, Austin Hospital, Heidelberg, Australia, ^hDivision of Intensive Care and Emergency Medicine, Department of Internal Medicine, Medical University Innsbruck, Austria, ⁱResearch Center for Emergency Medicine, Department of Clinical Medicine, Aarhus University Hospital and Aarhus University, Aarhus N, Denmark, ^jDepartment of Intensive Care, Medical Center Leeuwarden, Leeuwarden, Netherlands, ^kDepartment of Research & Education, Lund University and Skåne University Hospital, ^lAdult Critical Care, University Hospital of Wales, Cardiff, United Kingdom, ^mUniversity College Dublin- Clinical Research Centre, St Vincent's University Hospital Dublin, Ireland; ⁿAustralian and New Zealand Intensive Care-Research Centre, Monash University, Melbourne, Australia and ^oDept of Critical Care, Alfred Hospital, Melbourne, Australia, ^pSection of Cardiology, Stockholm, South General Hospital, Stockholm, Sweden, ^qDepartment of Intensive Care Medicine, Centre Hospitalier Universitaire Vaudois (CHUV)-University Hospital, University of Lausanne, Faculty of Biology and Medicine, ^rDepartment of Surgical Sciences and Integrated Diagnostics, San Martino Policlinico Hospital, IRCCS on Oncology, University of Genoa, Genoa, Italy, ^sDepartment of Anesthesiology and Intensive Care Medicine, Institute of Clinical Sciences,

Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden, ^tDivision of Critical Care and Trauma, George Institute for Global Health, Intensive Care Unit, St George Hospital, Sydney, Australia, ^uDepartment of Nephrology and Medical Intensive Care, Charité - Universitätsmedizin Berlin, Germany and Division of Neuroscience Critical Care, Department of Anesthesiology and Critical Care Medicine, Johns Hopkins University School of Medicine, Baltimore, MD, USA, ^vDepartment of Intensive Care, Erasme University Hospital, Université Libre de Bruxelles (ULB), Brussels, Belgium, ^wClinical Studies Sweden, Skåne University Hospital, Lund, Sweden, ^xMedical Research Institute of New Zealand, Wellington, New Zealand, ^yLund University, Skåne University Hospital, Department of Clinical Sciences, Anesthesia & Intensive care, Lund, Sweden, ^zLund University, Helsingborg Hospital, Department of Clinical Sciences Lund, Anesthesia & Intensive care, Lund, Sweden, and ^{aa}Department of Anesthesia and Intensive Care, Oslo University Hospital, Rikshospitalet, Oslo, Norway.

RCT# NCT03114033

Submitted November 22, 2018; accepted June 19, 2019.

Reprint requests: Dr. Josef Dankiewicz.

E-mail: josef.dankiewicz@med.lu.se

0002-8703

© 2019 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

<https://doi.org/10.1016/j.ahj.2019.06.012>

Background

To date, targeted temperature management (TTM) is the only neuroprotective intervention after resuscitation from cardiac arrest that is recommended by guidelines. When studied in animals, interventions to lower the body temperature during cardiopulmonary arrest (intra-ischemic cooling) appear to attenuate brain damage and improve survival.^{1,2} Cooling induced after the cardiac arrest (post-ischemic cooling) with a delayed onset might also be beneficial.^{3,4} In dogs, delayed post-ischemic cooling was less effective than immediate hypothermia after defibrillation.⁵

In humans, post-arrest hypothermia has shown favorable results in one randomized trial and one quasi-randomized trial. These two trials reported improved neurological outcome at 6 months^{6,7} and one suggested improved survival.⁶ Outcomes from two smaller randomized trials have also been published.^{8,9}

In total, less than 500 participants have been included in randomized trials comparing hypothermia with regular care. In a systematic review by our group, these trials were assessed as having a high risk of bias.¹⁰ Consequently we believe that the accrued evidence supporting the clinical use of hypothermia after adult cardiac arrest resembles that of a drug following small phase-II trials. This is also reflected by the level of evidence found in current guidelines in which TTM is recommended, based on *low*-quality evidence for patients with an initial shockable rhythm and based on *very low*-quality evidence for patients with an initial non-shockable rhythm.^{11,12} Guidelines further recommend maintaining a constant temperature of between 32°C and 36°C for those patients in whom temperature control is used, based on the results of the TTM-trial (TTM1) which showed no difference between a target temperature of 33°C compared with 36°C.¹³

In line with the drug trial comparison, there is a need for a large confirmatory trial on hypothermia for treatment of comatose cardiac arrest survivors, similar to a phase-III drug trial. To address this evidence gap we have designed the TTM2-trial, to compare hypothermia with a control group targeting normothermia with early treatment of fever.

To ensure that the TTM2 trial is warranted, on 26th September 2018 we searched for trials assessing the effects of hypothermia after out-of-hospital cardiac arrest in PubMed. We found no new randomized trials comparing hypothermia with normothermia since our prior meta-analysis.¹⁰ Our conclusion was that the evidence supporting hypothermia over normothermia is of low quality thus remains unchanged. A different conclusion was found by an independent group in a Cochrane meta-analysis 2016, which judged the overall quality of the included studies to be at a higher level. However, only three studies, with a total of 383 participants, were included in the assessment of the effects of hypothermia compared with no hypothermia on risk of death, and random error was not assessed.¹⁴

Methods

Trial design

The TTM2-trial protocol was designed according to SPIRIT guidelines and the trial will be reported according to the CONSORT guidelines¹⁵. It is registered at clinicaltrials.gov (NCT02908308). The full trial protocol is available at www.ttm2trial.org.

The TTM2-trial is an international, multicenter, parallel group, investigator-initiated, randomized, superiority trial in which a target temperature of 33°C after cardiac arrest will be compared with a target of normothermia with early treatment of fever ($\geq 37.8^\circ\text{C}$). As a pragmatic measure, general intensive care management will be according to standard practice at participating hospitals and multiple temperature management devices will be allowed. A pragmatic approach will also be taken to inclusion, by further minimizing exclusion criteria compared to the TTM1-trial.¹⁶

Rapid cooling in the hypothermia group will be achieved by means of cold fluids and cooling devices (intravascular/body-surface/nasal/esophageal). A closed loop surface or intravascular cooling system will be used to maintain the target temperature. In the normothermia arm the aim will be to maintain normothermia using conservative measures (eg, exposure, lowering of ambient temperature and cold fluids). For participants who develop a temperature of 37.8°C (trigger), a device will be used and set at 37.5°C for the remainder of the intervention period. At 28 hours after randomization the participants in the hypothermia group will be rewarmed over 12 hours. Participants who remain unconscious will be assessed according to a conservative protocol based on the European Resuscitation Council (ERC)'s recommendations for neurological prognostication after cardiac arrest. Follow-up and outcome assessment will be performed at 30 days, 6 and 24 months after cardiac arrest.

Inclusion criteria

The trial population will be adults (18 years of age or older) who experience a cardiac arrest of a presumed cardiac or unknown cause with stable return of spontaneous circulation (20 minutes with signs of circulation without the need for chest compressions) and who are unconscious (FOUR score motor response < 4 and does not obey verbal commands). Participants should also be eligible for intensive care without limitations (eg, absence of a 'do not resuscitate' order or a decision not to escalate care) to be included in the trial. Screening should be performed as soon as possible, but no later than 180 minutes after return of spontaneous circulation (ROSC). The inclusion window will thus be 160 minutes (180 min minus 20 min of sustained ROSC).

Table I. Trial phases

Time	Hypothermia	Normothermia
ROSC and 20 minutes of spontaneous circulation	Sustained ROSC	
Sustained ROSC + max 160 minutes	Inclusion window: screening and randomization as soon as possible.	
0 h	RANDOMIZATION	
0 h – 28 h	1. Rapid cooling to $\leq 33.0^{\circ}\text{C}$ (device may be set to 32.0°C to increase speed of cooling)	Device started if temperature $\geq 37.8^{\circ}\text{C}$ (device set at 37.5°C)
28 h – 40 h	2. Maintenance at 33.0°C (device set at 33.0°C)	
40 h – 72 h	Rewarming ($1/3^{\circ}\text{C}$ per hour)	
	Sedation is discontinued or tapered according to clinical state.	
	If device used, continued active temperature control in normothermic range ($36.5\text{--}37.7^{\circ}\text{C}$), unless awake and extubated	
96 h	Prognostication	

All times are in reference to the time of randomization which will be considered time 0. ROSC, Return of spontaneous circulation.

Exclusion criteria

Exclusion criteria will be pregnancy, known or suspected intracranial bleeding, an unwitnessed arrest with an initial rhythm of asystole, and an admission temperature $<30^{\circ}\text{C}$. Patients for whom extracorporeal membrane oxygenation (ECMO) is started prior to ROSC will also be excluded, as will those who have severe chronic obstructive pulmonary disorder (COPD) with home oxygen therapy (Table II).

Randomization

Randomization will be performed by a healthcare professional in the emergency department, in the angiography suite or in the intensive care unit via web-based application using permuted blocks with varying size, stratified by site. For those participants who are co-enrolled in the TAME-trial, randomization will also be stratified according to group allocation in the TAME-trial (2×2 factorial allocation).

Intervention

The intervention period will commence immediately after randomization. Participants allocated to hypothermia at 33.0°C , will be cooled as rapidly as possible with available cooling equipment including an intravascular or surface closed-loop device to 33.0°C . Local protocols should emphasize speed of cooling. However, we recognize that cooling speed may vary between centers as the choice of the main temperature management device will be at the discretion of the treating physician. Both surface and intravascular devices will be allowed, although they must be approved and include feedback-control. Upon reaching this first temperature goal a maintenance phase will commence, which will end 28 hours after randomization. During the maintenance phase the target temperature will be 33.0°C . The

maintenance phase will be followed by rewarming at $\frac{1}{3}^{\circ}\text{C}/\text{hour}$ for 12 hours (See Table I).

In the normothermia group the participants' temperature trajectory will be followed, and the aim will be to keep a temperature below or at 37.5°C . If conservative and pharmacological measures are insufficient and the temperature reaches 37.8°C , cooling with a device will be initiated with the device set at 37.5°C to ensure normothermia. Participants in whom active temperature management is initiated will be kept at 37.5°C until 40 hours after randomization. If the participant's body temperature spontaneously is below 37.5°C there will be no active warming.

In both groups, active rewarming will only be allowed, but not mandated, if the initial temperature is between 30.0°C and 32.9°C . In this case active rewarming with a device may be performed, at the discretion of the treating physician until the temperature reaches 33.0°C , at which point active rewarming should cease. Active rewarming in this range should be considered a safety measure to avoid arrhythmias associated with a temperature below 32°C .

Measurements of temperature during the intervention will be performed using a bladder probe. If a bladder probe is unfeasible or unreliable; esophageal or intravascular temperature probes will be used.

Participants in both groups will be sedated, mechanically ventilated and hemodynamically supported throughout the intervention period of 40 hours. Short-acting drugs are recommended for sedation and analgesia and should be titrated to achieve a Richmond Agitation-Sedation Scale (RASS) of at least minus 4 (deep sedation).

Shivering will be treated according to a protocol, with both allocation arms receiving prophylactic acetaminophen/paracetamol. This drug may be withheld at the

Table II. Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Adult (18 years or older)	Pregnancy
Out-of-hospital arrest of cardiac or unknown cause.	Known or suspected intracranial bleeding
Stable ROSC (20 minutes without the need for chest compressions)	Extracorporeal membrane oxygenation required before ROSC
Unconscious (FOUR motor score <4 and does not obey verbal commands)	Initial body temperature <30°C
Eligible for intensive care without restrictions	Severe chronic obstructive pulmonary disorder (COPD) with home oxygen therapy. Unwitnessed cardiac arrest with an initial rhythm of asystole

discretion of the treating physician if there is a contraindication to acetaminophen/paracetamol administration (eg, hypersensitivity or liver failure). The goal will be to maintain a score of 0 or 1 on the bedside shivering assessment scale (BSAS).¹⁷

Blinding

The clinical team responsible for the participant (physicians, nurses and others) and involved with direct patient care will not be blinded to allocation group due to the inherent difficulty in blinding the intervention. Measures will be taken to ensure that the information about allocation will not disseminate beyond the immediate group of caregivers responsible for patient care. A blinded physician will evaluate the patient at 96 hours after randomization and make a statement on neurological prognosis.

The intensive care physician will not be allowed to share any information regarding temperature allocation group. Participants, their legal representatives, and family will only be informed that the patient has received a temperature intervention. Health personnel responsible for outcome assessment at follow-up will be blinded to the allocation of the intervention. The steering group, author group, statisticians and the trial coordinating team will be blinded to group allocation. The two intervention groups will be coded as “A” and “B”. Two manuscripts will be written: one assuming that “A” is the experimental group and “B” is the control group—and one assuming the opposite. Both manuscripts will be approved by the author group before the code is broken. Group analyses of variables that might unblind the randomization (ie, potassium, lactate, heart rate) will not be allowed before the manuscripts have been completed.

Prognostication and withdrawal of life-sustaining therapies

Withdrawal of life-sustaining therapies (WLST) based on a presumed poor neurological prognosis should not be

performed before prognostication. However, should further life-sustaining therapies be deemed unethical due to irreversible organ failure, a medical comorbidity or other reasons, life-sustaining therapies may be withdrawn prior to the time point of protocolized prognostication, in which case the reason will be recorded. WLST for participants in whom brain death is established will be defined as death, rather than withdrawal of life-sustaining therapies.

Prognostication will be performed on all participants still in the ICU at 96 hours after randomization. The prognostication will be based on the ERC and European Society for Intensive Care Medicine recommendations^{12,34} and performed at approximately 96 h after randomization, but may be delayed due to practical reasons (such as weekend or national holiday). Efforts will be made to sufficiently delay prognostication to ensure that any lingering effects of sedative agents will not affect the assessment.

The physician performing the prognostication will be a neurologist, intensivist or other specialist experienced in neuroprognostication after cardiac arrest and who has not been otherwise involved in patient care. The prognosticator will be blinded for group allocation, but not for relevant clinical data. Prognostication and the potential decision to withdraw active life-sustaining therapies are closely related but will be considered separate entities.

The result of the prognostication will be categorized as “YES” or “NO”, based on the answer to the question “Does this patient fulfil the TTM2-trial criteria for a likely poor neurological outcome?”. This assessment will be recorded and communicated to the treating clinician.

Any decision to withdraw active life support will be made by the treating physicians, together with the patient's relatives or legal surrogates, as required by local legislation. In making this decision the treating physician may use the information from the prognostication together with all other relevant information about the patient. The blinded external physician will not make any recommendation on limitations in care.

TTM2 criteria for a likely poor neurological prognosis

In the TTM2 trial the prognosis is considered *likely poor* if criteria A, B and C are all fulfilled.

- Confounding factors such as severe metabolic derangement and lingering sedation has been ruled out.
- The patient has no response or a stereotypic extensor response to bilateral central and peripheral painful stimulation at ≥ 96 hours after randomization.
- At least two of the below mentioned signs of a poor prognosis are present:

- C.1. Bilateral absence of pupillary and corneal reflexes at 96 h after cardiac arrest or later
- C.2. A prospectively documented early (within 48 hours). status myoclonus (continuous and generalized myoclonus persisting for at least 30 min
- C.3. A highly malignant EEG-pattern according to the TTM2 definition without reactivity to sound and painful stimulation.¹⁸
- C.4. CT brain with signs of global ischemic injury, such as: generalized edema with reduced gray/white matter differentiation and sulcal effacement or MRI-brain with signs of global, diffuse, or bilateral multifocal ischemic lesions.
- C.5. Serial serum-NSE samples consistently higher than locally established levels associated with a poor outcome
- C.6. Bilaterally Absent SSEP N20-responses more than 48 hours after randomization.

Follow-up

At 30 days after randomization, a blinded outcome assessor will perform the first follow-up. For those participants who have been discharged, this follow-up will be performed by telephone. But for some participants, this will take place face-to-face in hospital. At 6 months and at 24 months, participants will be invited to a face-to-face follow-up visit for a detailed evaluation of neurological function, cognitive function, quality-of-life, and participation in society, including return to work.

Outcome measures

The primary outcome measure will be all-cause mortality. Secondary outcome measures will be: the proportion of participants with a poor functional outcome according to the modified Rankin Scale (mRS), number of days alive and outside hospital, health-related quality of Life (HRQoL) using EQ-5D-5 L, and survival assessed as time-to-death. All outcomes (except time-to-death) will be assessed at 6 months after randomization. These outcomes follow international recommendations of the recently published Core Outcome Set for Cardiac Arrest trials (COSCA).¹⁹

The mRS is a hierarchical rating scale consisting of seven categories (0–6) to reflect overall functional recovery. There is strong evidence that the mRS has good psychometric properties and is a valid instrument to assess functional outcome related to neurological disability.^{20,21} The mRS has also been used in a number of cardiac arrest trials to evaluate neurological outcome.¹⁹ Problems with inter-rater reliability for the mRS have been described, but may be less problematic if using the dichotomization of good and

poor. Poor functional outcome in TTM2 will be defined as mRS 4–6. Inter-rater reliability is also increased if there is a structured approach to scoring, and training, which will be provided within the trial. The choice of the mRS as the main neurological assessment in the trial is based on the recommendations by COSCA and increased granularity, especially in the range of no-mild symptoms, compared to the CPC-scale.²²

HRQoL will be assessed by the EQ-5D-5 L,²¹ a well-known generic health survey used to assess patient-reported health. Psychometric properties for the EQ-5D-5 L have been found superior to the earlier EQ-5D-3 L.²³ EQ-5D-5 L consists of five questions/dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) and a VAS scale of overall self-reported health. Responsiveness to change has not yet been described for the EQ-5D-5 L, but the EQ-5D-3 L demonstrates evidence of responsiveness, although primarily in situations with large clinical improvement.

Adverse events

Adverse events, defined as “any untoward medical occurrence in a clinical trial subject” will not be reported in this trial. Participants will, because of the circumstances of their admission be monitored and treated for a vast number of untoward medical occurrences, and this is considered standard care.

The incidence of a number of pre-defined serious adverse events will be reported (Table III). In addition to the pre-defined events, investigators will also report any unexpected serious adverse event.

Statistics

A detailed statistical analysis plan will be submitted for publication before the last participant is included in the trial. Our primary conclusions will be based on the results of the primary outcome. Outcome measures will be analyzed for all randomized participants in the intention-to-treat (ITT) analysis, which will be the primary result of the trial. Per-protocol analyses may be considered if important deviations from the protocol compromise the validity of the ITT analysis. Main results will be presented with adjustment for site (as a random effect) and enrolment in TAME-trial. The primary outcome will be analyzed as a binary variable (alive versus dead) at 6 months using mixed model logistic regression. Functional outcome will be evaluated by dichotomizing the modified Rankin scale (0-3 vs 4-6) and using mixed model logistic regression. Survival data will be analyzed using Cox regression.

The secondary outcome HRQoL will be presented as the difference in EQ5D-5 L VAS-score and this outcome will be analyzed using mixed model linear regression.

Table III. Definition of specific serious adverse events

Serious adverse event	Definition
Pneumonia	Pragmatic modification (due to TTM) of the CPIS score; ²⁴ increased or purulent tracheal secretions, new or progressive radiographic infiltrate and a decreased P/F-ratio should all be present.
Sepsis and septic shock	According to the 3rd international consensus definitions for sepsis and septic shock. ²⁵
Bradycardia	Requiring pacing
Moderate or severe bleeding	According to the GUSTO criteria. ²⁶
Device related skin complications	Blistering or skin necrosis in areas covered by surface device.
Arrhythmia	Resulting in hemodynamic compromise (for example: VF and VT)

TTM, Targeted temperature management; CPIS, Clinical Pulmonary Infection Score; P/F-ratio, ratio of arterial oxygen partial pressure to fractional inspired oxygen, GUSTO, Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries, VF, ventricular fibrillation; VT, ventricular tachycardia.

Days alive outside hospital will be analyzed using the van Elteren test. Time-to-death will be analyzed using Cox regression. Reporting on secondary outcomes will be limited to point estimates of treatment effects and confidence intervals. Pre-defined subgroup analysis will be performed based on age, sex, presence of bystander CPR, initial rhythm, time to ROSC, and circulatory state at admission.

Sample size

Based on the results of the TTM1-trial and information in the international cardiac arrest registry, (INTCAR) we estimate a mortality of approximately 55% in the control group (normothermia group).²⁷ Using an absolute risk reduction of 7.5% as the anticipated intervention effect of hypothermia, an acceptable alpha of 5%, and an acceptable beta of 10%, 931 participants are required in each group. The sample size calculation corresponds to a relative risk reduction (RRR) of 13.6% and a number needed to treat (NNT) of 14.^{6,7} To allow for a possible loss to follow-up we will recruit 1900 participants; loss to follow up was minimal in our previous trial.¹³

Power calculations for the secondary outcomes are estimated to ensure the validity of including the studied parameters, but they are not adjusted for multiplicity. With 931 participants per group, the functional outcome measure (dichotomized mRS) has a power of 90% to detect a relative risk of 0.86 based on a poor outcome (mRS 4–6) in 55% of cases in the control group. For the secondary outcome survival, we estimate a power of >90% based on the survival estimates mentioned above. Health-related quality of life will be reported for survivors. We estimate a power of 85% to detect a difference in five points on the VAS-

scale, based on a mean value of 70 in the control group and a standard deviation of 25 points. The secondary outcome “days alive outside hospital” has an estimated power of 89%, based on simulations where 8% of deaths occur outside hospital.

Data monitoring committee and interim analysis

There will be an independent Data Safety Monitoring Committee (DSMC) arranging an independent statistician to conduct blinded interim analysis. The DSMC will be able to request unblinding of data if they find it necessary. The DSMC will be provided with data on survival and safety parameters continuously during the conduct of the trial and can initiate analysis at any time they request. Lan-DeMets group sequential monitoring boundaries will be used to adjust thresholds for statistical significance according to the accrued sample size.²⁸ The DSMC may stop or pause the trial if:

- Group difference in the primary outcome measure is found in the interim analysis according to pre-defined stopping rules.
- Group difference in serious adverse events is found in the interim analysis.
- Results from other trials show benefit or harm with one of the allocation arms.

Trial status and timeline

Randomization commenced in November 2017, and trial sites have been added gradually. We anticipate that the last six-month follow-up will be performed in 2021. Results of the primary and secondary outcomes at 6 months will be reported in the initial publication. Explorative outcomes and results from the 24-month follow-up will be reported separately.

Co-enrolment in the TAME trial

The Targeted Therapeutic Mild Hypercapnia After Resuscitated Cardiac Arrest: A Phase III Multi-Centre Randomized Controlled Trial (TAME trial) (NCT03114033) aims to determine whether targeted therapeutic mild hypercapnia improves neurological outcome at 6 months compared to standard care and targeted normocapnia. Co-enrolment in this trial will be allowed, and encouraged for sites participating in the TTM2-trial.²⁹ However, the option to participate in only the TTM2-trial will be retained for sites that are not willing, or able to co-enroll. We consider co-enrolment in TTM2 and TAME as an effective utilization of research resources. A difficulty with co-enrolment is the potential for an interaction between the interventions. However, data analysis from the TTM1-trial shows no interaction between temperature and pCO₂ with regard to major

outcomes.³⁰ Considering the paucity of basic science studying the combination of hypothermia and hypercapnia, we acknowledge the possibility that a biological interaction might be identified. As randomization will be stratified to achieve a two-by-two factorial design, any differences in primary or secondary outcomes will become evident to the data safety monitoring committee which will monitor both trials. An assessment of the interaction term will also be performed in the final analyses.

Data from the Australian New Zealand Intensive Care Society Adult Patient Database suggest a large variation of carbon dioxide tension among survivors of cardiac arrest.³¹ We therefore do not anticipate a significant effect on external validity, although a possible consequence of enrolment might be a lower incidence of hypocapnia. As temperature measurements are not affected by the TAME intervention and stratification will be performed, we do not believe that internal validity will be compromised.

Funding

The trial is supported by grants from: The Swedish Research Council (Vetenskapsrådet), The Swedish Heart-Lung Foundation, Stig and Ragna Gorthon Foundation and the Knutsson Foundation, the Skåne University Hospital Foundations, the Gyllenstierna-Krapperup Foundation, and governmental funding of clinical research within the Swedish National Health System. The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the manuscript, and its final contents.

Discussion

The evidence for hypothermia in a broad context is conflicting. Clinical trials in various areas of brain damage indicate both benefit and harm.^{32,33} Theoretical rationale exists and currently hypothermia is the only clinical strategy aiming for neuroprotection for cardiac arrest victims. Specifically, in adults with cardiac arrest with shockable rhythms low quality evidence indicate benefit of 33°C and moderate quality evidence indicate no difference between 33°C and 36°C. The recent TTM1-trial has had a significant influence on the new ILCOR, AHA and ERC statements and guidelines for 2015,^{11,34} which have adopted the view that different temperature targets provide similar clinical results. The recommended temperature range has also been changed to include 36°C. Most importantly, however, is that the overall evidence level for temperature management after out-of-hospital cardiac arrest has been changed to low to very-low, in line with our conclusion from the meta-analyses performed in 2010.¹⁰

Internationally, many hospitals and regions have already changed strategy in favor of TTM at 36°C, reasoning that a less invasive and easier administrated

temperature strategy yielding the same clinical results is preferable. Some hospitals however remain at 33°C based on earlier evidence while others, motivated by a lack of robust evidence, do not use temperature management at all.³⁵⁻³⁷ Recent studies have shown a trend towards an increased mortality and an increased incidence of fever since 2014, when many hospitals changed their target temperature to 36°C. No causal links have been identified, but this has increased the uncertainty about optimal temperature targets.^{38,39}

Based on the above, and the knowledge gaps indicated in international guidelines, it is reasonable to assess whether rapidly administered hypothermia to a low target level is beneficial, and to define subgroups, where the intervention effect can be studied. At the same time, it is important to clarify if early treatment of fever (easier, less costly and less invasive than the 36°C-arm in the TTM1-trial) is sufficient to achieve a good functional outcome.

Rationale for early treatment of fever

Fever has been proposed as a risk factor for death after Cardiac arrest (CA) although it still remains an open question if it is a causative risk factor. Zeiner and colleagues showed an increase in the odds of a poor neurological outcome for each degree in peak temperature higher than 37°C, within 48 h of arrest.⁴⁰ However, a body temperature above 37°C can occur due to individual or diurnal variation. When temperature is measured in a large population it appears that 37°C has no special significance to human thermometry.^{41,42} It therefore seems reasonable to apply a less strict definition of fever than >37.0°C. At the other end of the spectrum, it could be argued that it would be problematic to allow temperatures up to 38.3°C (A level usually employed in the definition of fever of unknown origin) even if this is based on no or very low quality evidence.⁴³

This trial will employ normothermia-targeted temperature management in the control arm, with 37.8°C as a trigger for active temperature management with a feedback device. Although any temperature cut-off is arbitrary, the choice of this value is motivated by the following.

- Diagrammatic data from the HACA-trial⁶ suggests a median temperature between 37.5°C and 37.8°C among participants in the control arm of the trial. If a similar distribution is assumed in the current trial a substantial number of participants will not require a device, thus making temperature management considerably less labor and resource intense.
- 37.7°C has been proposed as the upper limit of normal body temperature in healthy adults.^{41,44} Employing active fever control for any patient who exceeds this

temperature therefore constitutes an aggressive approach to fever control.

- Temperature fluctuations are unavoidable. In the TTM1-trial, the measured temperature among participants allocated to TTM at 36°C had a standard deviation of approximately 0.5°C. Assuming a similar variation around 37.5°C (for patients in whom active temperature management is used), few patients would become unequivocally febrile with temperatures above 38.3°C.)

Strengths and limitations

Strengths of the TTM2-trial include a large sample size with a reasonable absolute risk reduction, when compared to other interventions used in the ICU. An international collaboration, including different health-care settings and broad inclusion criteria vouch for a representative group of participants. A further strength is the blinding of outcome assessors, prognosticators, the steering group, author group, statisticians, and the trial coordinating team – and our choice of outcomes that are both patient-centered and clinically important. We deliberately designed the assessment of neurological prognosis and the approach to withdrawal of care to be more conservative compared to current international guidelines which we also consider a major strength.

The primary limitation of our trial is the choice of control intervention. There is a no clear evidence of causality between fever and poor neurological outcomes, but observational data have shown an association.⁴⁰ While a total laissez-faire attitude to temperature in the control group would be a benefit from a methodological point of view, we have chosen to include an intervention of fever-control. This decision is based on earlier observational data and uncertainty about how control group temperature management was conducted in prior trials.^{6,7} From a practical stand point fever-control is also an intervention acceptable to clinicians who are strong proponents of hypothermia, which makes global recruitment feasible. Active fever prevention was studied in a recent trial on brain injury due to trauma,⁴⁵ but fever-control is largely unstudied, and its clinical effects are uncertain which needs to be taken into consideration when the results of the trial are to be interpreted.

Another important limitation of the trial is the compromise between the study of effectiveness of hypothermia and a pragmatic design. The true effect of hypothermia might be underestimated as the control group includes a temperature intervention, at the same time the pragmatic aspect of the trial is limited by mandated sedation in both allocation groups. Another drawback of a pragmatic design is a potential heterogeneous intervention effect, depending on the mode of cooling, and hence different speeds of cooling.

Conclusion

A large confirmatory trial is needed to investigate the effectiveness of hypothermia after out-of-hospital cardiac arrest. To study the use of a temperature management strategy that does not mandate a device in all cases is also necessary. We believe that a pragmatic trial with a clear separation in temperature between groups is the best option. Considering the international collaboration and broad inclusion criteria we expect the results of the TTM2-trial to be broadly applicable to the care of survivors of cardiac arrest treated in the intensive care setting.

Disclosure

Dr. Cariou reports personal fees from Bard, outside the submitted work; Dr. Morgan reports personal fees from BD Bard for teaching use of surface cooling devices, outside the submitted work; Dr. Friberg reports receiving lecture fees from Bard and consulting fees from QuickCool, outside the submitted work; Dr. Storm reports personal fees from BD BARD, personal fees from BD BARD, personal fees from ZOLL GmbH, personal fees from Braincool Inc, personal fees from Xenios, personal fees from Philips, outside the submitted work; Dr. Young reports personal fees from Bard Medical, outside the submitted work.

References

1. Busto R, Dietrich DW, Globus M, et al. Small Differences in Intraischemic Brain Temperature Critically Determine the Extent of Ischemic Neuronal Injury. *Journal of Cerebral Blood Flow & Metabolism* 1987;7(6):729-38.
2. Sterz F, Safar P, Tisherman S, et al. Mild hypothermic cardiopulmonary resuscitation improves outcome after prolonged cardiac arrest in dogs. *Crit Care Med* 1991;19(3):379-89.
3. Borismoller F, Smith ML, Siesjo BK. Effects of Hypothermia on Ischemic Brain-Damage - a Comparison between Preischemic and Postischemic Cooling. *Neuroscience Research Communications* 1989;5(2): 87-94.
4. Colbourne F, Corbett D. Delayed postischemic hypothermia: a six month survival study using behavioral and histological assessments of neuroprotection. *J Neurosci* 1995;15(11):7250-60.
5. Kuboyama K, Safar P, Radovsky A, et al. Delay in cooling negates the beneficial effect of mild resuscitative cerebral hypothermia after cardiac arrest in dogs: a prospective, randomized study. *Crit Care Med* 1993;21(9):1348-58.
6. Hypothermia after Cardiac Arrest Study G. Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. *N Engl J Med* 2002;346(8):549-56.
7. Bernard SA, Gray TW, Buist MD, et al. Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. *N Engl J Med* 2002;346(8):557-63.
8. Hachimi-Idrissi S, Corne L, Ebinger G, et al. Mild hypothermia induced by a helmet device: a clinical feasibility study. *Resuscitation* 2001;51(3):275-81.

9. Laurent I, Adrie C, Vinsonneau C, et al. High-volume hemofiltration after out-of-hospital cardiac arrest: a randomized study. *J Am Coll Cardiol* 2005;46(3):432-7.
10. Nielsen N, Friberg H, Gluud C, et al. Hypothermia after cardiac arrest should be further evaluated—a systematic review of randomised trials with meta-analysis and trial sequential analysis. *Int J Cardiol* 2011;151(3):333-41.
11. Nolan JP, Soar J, Cariou A, Cronberg T, Moulart VRR, Deakin CD, et al. European Resuscitation Council and European Society of Intensive Care Medicine Guidelines for Post-resuscitation Care 2015: Section 5 of the European Resuscitation Council Guidelines for Resuscitation 2015. *Resuscitation* 2015;95:202–222.
12. Atkins D, Best D, Briss PA, et al. Grading quality of evidence and strength of recommendations. *BMJ* 2004;328(7454):1490.
13. 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.
14. Arrich J, Holzer M, Havel C, et al. Hypothermia for neuroprotection in adults after cardiopulmonary resuscitation. *Cochrane Database Syst Rev* 2016(2), CD004128.
15. Schulz KF, Altman DG, Moher D, et al. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. *BMJ* 2010;340:c332.
16. Nielsen N, Wetterslev J, al-Sabaie N, et al. Target Temperature Management after out-of-hospital cardiac arrest—a randomized, parallel-group, assessor-blinded clinical trial—rationale and design. *Am Heart J* 2012;163(4):541-8.
17. Badjatia N, Strongilis E, Gordon E, et al. Metabolic impact of shivering during therapeutic temperature modulation: the Bedside Shivering Assessment Scale. *Stroke* 2008;39(12):3242-7.
18. Westhall E, Rossetti AO, van Rootselaar AF, et al. Standardized EEG interpretation accurately predicts prognosis after cardiac arrest. *Neurology* 2016;86(16):1482-90.
19. Haywood K, Whitehead L, Nadkarni VM, et al. COSCA (Core Outcome Set for Cardiac Arrest) in adults: an advisory statement from the International Liaison Committee on Resuscitation. *Circulation* 2018;137(22):e783-801.
20. Banks JL, Marotta CA. Outcomes validity and reliability of the modified Rankin scale: implications for stroke clinical trials: a literature review and synthesis. *Stroke* 2007;38(3):1091-6.
21. van Swieten JC, Koudstaal PJ, Visser MC, et al. Interobserver agreement for the assessment of handicap in stroke patients. *Stroke; a journal of cerebral circulation* 1988;19(5):604-7.
22. Jennett B, Bond M. Assessment of outcome after severe brain damage. *Lancet* 1975;1(7905):480-4.
23. Janssen MF, Pickard AS, Golicki D, et al. Measurement properties of the EQ-5D-5L compared to the EQ-5D-3L across eight patient groups: a multi-country study. *Qual Life Res* 2013;22(7):1717-27.
24. Schurink CA, Van Nieuwenhoven CA, Jacobs JA, et al. Clinical pulmonary infection score for ventilator-associated pneumonia: accuracy and inter-observer variability. *Intensive Care Med* 2004;30(2):217-24.
25. Singer M, Deutschman CS, Seymour CW, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA* 2016;315(8):801-10.
26. Gusto-investigators. An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. *N Engl J Med* 1993;329(10):673-82.
27. Nielsen N, Hovdenes J, Nilsson F, et al. Outcome, timing and adverse events in therapeutic hypothermia after out-of-hospital cardiac arrest. *Acta Anaesthesiol Scand* 2009;53(7):926-34.
28. Gordon Lan KK, Demets DL. Discrete sequential boundaries for clinical trials. *Biometrika* 1983;70(3):659-63.
29. Parke RL, McGuinness S, Eastwood GM, et al. Co-enrolment for the TAME and TTM-2 trials: the cerebral option. *Crit Care Resusc* 2017;19(2):99-100.
30. Ebner F, Harmon MBA, Aneman A, et al. Carbon dioxide dynamics in relation to neurological outcome in resuscitated out-of-hospital cardiac arrest patients: an exploratory Target Temperature Management Trial substudy. *Crit Care* 2018;22(1):196.
31. Schneider AG, Eastwood GM, Bellomo R, et al. Arterial carbon dioxide tension and outcome in patients admitted to the intensive care unit after cardiac arrest. *Resuscitation* 2013;84(7):927-34.
32. Gluckman PD, Wyatt JS, Azzopardi D, et al. Selective head cooling with mild systemic hypothermia after neonatal encephalopathy: multicentre randomised trial. *Lancet* 2005;365(9460):663-70.
33. Andrews PJ, Harris BA, Murray GD. Hypothermia for Intracranial Hypertension after Traumatic Brain Injury. *N Engl J Med* 2016;374(14):1385.
34. Callaway CW, Donnino MW, Fink EL, et al. Part 8: Post-Cardiac Arrest Care: 2015 American Heart Association Guidelines Update for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation* 2015;132(18 Suppl 2):S465-82.
35. Deye N, Vincent F, Michel P, et al. Changes in cardiac arrest patients' temperature management after the 2013 "TTM" trial: results from an international survey. *Ann Intensive Care* 2016;6(1):4.
36. Ford AH, Clark T, Reynolds EC, et al. Management of cardiac arrest survivors in UK intensive care units: a survey of practice. *J Intensive Care Soc* 2016;17(2):117-21.
37. Storm C, Nee J, Sunde K, et al. A survey on general and temperature management of post cardiac arrest patients in large teaching and university hospitals in 14 European countries-The SPAME trial results. *Resuscitation* 2017;116:84-90.
38. Bradley SM, Liu W, McNally B, et al. Temporal trends in the use of therapeutic hypothermia for out-of-hospital cardiac arrest. *JAMA Netw Open* 2018;1(7), e184511.
39. Salter R, Bailey M, Bellomo R, et al. Changes in temperature management of cardiac arrest patients following publication of the Target Temperature Management Trial. *Crit Care Med* 2018;46(11):1722-30.
40. Zeiner A, Holzer M, Sterz F, et al. Hyperthermia after cardiac arrest is associated with an unfavorable neurologic outcome. *Arch Intern Med* 2001;161(16):2007-12.
41. Mackowiak PA, Wasserman SS, Levine MM. A critical appraisal of 98.6 degrees F, the upper limit of the normal body temperature, and other legacies of Carl Reinhold August Wunderlich. *JAMA* 1992;268(12):1578-80.
42. Sund-Levander M, Forsberg C, Wahren LK. Normal oral, rectal, tympanic and axillary body temperature in adult men and women: a systematic literature review. *Scand J Caring Sci* 2002;16(2):122-8.
43. Petersdorf RG, Beeson PB. Fever of unexplained origin: report on 100 cases. *Medicine (Baltimore)* 1961;40:1-30.
44. Obermeyer Z, Samra JK, Mullainathan S. Individual differences in normal body temperature: longitudinal big data analysis of patient records. *BMJ* 2017;359, j5468.
45. Cooper DJ, Nichol AD, Bailey M, et al. Effect of early sustained prophylactic hypothermia on neurologic outcomes among patients with severe traumatic brain injury: The POLAR Randomized Clinical Trial. *JAMA* 2018;221:1-20.