Target temperature management after out-of-hospital cardiac arrest—a randomized, parallel-group, assessor-blinded clinical trial—rationale and design

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Background Experimental animal studies and previous randomized trials suggest an improvement in mortality and neurologic function with induced hypothermia after cardiac arrest. International guidelines advocate the use of a target temperature management of 32°C to 34°C for 12 to 24 hours after resuscitation from out-of-hospital cardiac arrest. A systematic review indicates that the evidence for recommending this intervention is inconclusive, and the GRADE level of evidence is low. Previous trials were small, with high risk of bias, evaluated select populations, and did not treat hyperthermia in the control groups. The optimal target temperature management strategy is not known.

Methods The TTM trial is an investigator-initiated, international, randomized, parallel-group, and assessor-blinded clinical trial designed to enroll at least 850 adult, unconscious patients resuscitated after out-of-hospital cardiac arrest of a presumed cardiac cause. The patients will be randomized to a target temperature management of either 33°C or 36°C after return of spontaneous circulation. In both groups, the intervention will last 36 hours. The primary outcome is all-cause mortality at maximal follow-up. The main secondary outcomes are the composite outcome of all-cause mortality and poor neurologic function (cerebral performance categories 3 and 4) at hospital discharge and at 180 days, cognitive status and quality of life at 180 days, assessment of safety and harm.

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Clinicaltrials.gov identifier: NCT01020916.

Submitted October 7, 2011; accepted January 5, 2012.

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0002-8703/$ - see front matter

doi:10.1016/j.ahj.2012.01.013

Discussion The TTM trial will investigate potential benefit and harm of 2 target temperature strategies, both avoiding hyperthermia in a large proportion of the out-of-hospital cardiac arrest population. (Am Heart J 2012;163:541-8.)

Background

Lowering of the body temperature is a promising intervention for improving survival and neurologic function after resuscitation from cardiac arrest. Animal experiments suggest that neuronal damage is diminished when hyperthermia and fever in the postresuscitation phase are prevented or counteracted, by achieving either normothermia or various degrees of hypothermia.[1,2] One randomized trial and 1 quasi-randomized trial suggest a benefit of hypothermia of 32°C to 34°C for 12 to 24 hours after return of spontaneous circulation (ROSC),[3,4] and international guidelines on postresuscitation care recommend this strategy.[5] However, recent reviews have emphasized that these recommendations are based on relatively weak evidence.[6,7]

A systematic review of trials comparing the effect of hypothermia with standard intensive care not using induced hypothermia after cardiac arrest was undertaken before designing the trial.[7]

Although the results of previous studies may favor hypothermia, the findings of this systematic review indicate that the evidence is inconclusive, associated with nonnegligible risks of systematic and random errors and low quality of evidence according to the GRADE classification, suggesting clinical equipoise.

Nevertheless, the published trials introduced temperature management in clinical practice, and observational studies indicate a possible detrimental effect of fever and hyperthermia. Hence, to create a relevant control intervention to definite hypothermia, we compare temperature management at 2 levels: 33°C versus 36°C.

Methods

The Target Temperature Management (TTM) trial was designed using data from the Hypothermia Network Registry[8] and was based on Good Clinical Practice and CONSORT guidelines.[9,10] The trial is registered at clinicaltrials.gov (NCT01020916). The full trial protocol is available at www.ttm-trial.org.

Trial design

The TTM trial is a multicenter, randomized, parallel-group, assessor-blinded, monitored, and investigator-initiated clinical trial, financed by noncommercial funding. The aim is to evaluate if there is a difference in mortality, neurologic function, and safety with a target temperature management at 33°C (TTM33) compared with 36°C (TTM36) following sustained ROSC (uninterrupted spontaneous circulation >20 minutes) after out-of-hospital cardiac arrest at maximal follow-up using a time-to-event analysis. The primary outcome is all-cause mortality at maximal follow-up, which will be at least 180 days. The secondary outcomes are a composite outcome of all-cause mortality and poor neurologic function (defined as cerebral performance categories [CPCs] 3-5) at hospital discharge and at 180 days, all-cause mortality at hospital discharge and at 180 days, neurologic function at hospital discharge and at 180 days, quality of life at 180 days, best neurologic outcome during the trial period, and safety measures. The trial period is divided into 5 phases; see Tables I and II.

Inclusion criteria

Adult patients (≥18 years) resuscitated from out-of-hospital cardiac arrest of a presumed cardiac cause, who are unconscious (Glasgow Coma Score [GCS] <8) after sustained ROSC are eligible for inclusion.

Exclusion criteria

The exclusion criteria are pregnancy, known bleeding diathesis (medically induced coagulopathy does not exclude a patient), suspected or confirmed acute intracranial bleeding or stroke, unwitnessed arrest with initial rhythm asystole, temperature <30°C on admission, limitations in therapy including do-not-resuscitate order, disease before the cardiac arrest making 180-day survival unlikely, known prearrest cerebral performance category (CPC) 3 or 4, >4 hours from ROSC to screening, persistent cardiogenic shock with a systolic blood pressure <80 mm Hg in spite of volume loading/vasopressors/inotropes or mechanical assistance.

Randomization

The patients are randomized 1:1 via a Web-based application using a center-stratified, block-permuted randomization scheme with varying block sizes.

Intervention

Patients in both groups are sedated, endotracheally intubated, and mechanically ventilated. Core body temperature is measured via a urinary catheter. Temperature is managed with either an external or an intravascular system. The intervention period is divided into 3 fixed periods, which will ensure that patients in both groups are receiving equal duration of intervention (including equal time on mandatory sedation and mechanical ventilation), allowing for comparability between groups. The periods are (*a*) achievement of target temperature (4 hours), (*b*) maintenance of target temperature (24 hours), and (*c*) rewarming to 37°C (8 hours) (Table II).

When the patient is randomized, immediate measures will be taken to achieve the allocated target temperature. For patients allocated to TTM36 and with an initial temperature <36°C, the body temperature will be allowed to passively reach 36°C before it is maintained at this level. At 28 hours after the start of intervention, the temperature management system is set to gradually raise the temperature to 37°C, with a rewarming

Table I. Trial flow chart

Phase 1 (hospital admission to start of intervention)	Patients with ROSC after OHCA present at the hospital and are admitted. The inclusion window is 220 min: ie, from 20 min after ROSC (defined as sustained ROSC) and to 240 min from ROSC. Patients are randomly assigned to intervention group. Baseline characteristics are obtained.
Phase 2	Phase 2 starts at the time of randomization. Intervention period (see Table II).
Phase 3 (from end of intervention period to 72 h after end of intervention period)	Sedation is stopped or tapered at 37°C. Continued normothermia of 37°C ± 0.5°C is aimed for until 72 h from cardiac arrest in both treatment groups. Extubation should be attempted at the earliest possible time during this phase if applicable and based on standard procedures for discontinuation of mechanical ventilation. Neurologic evaluation is performed by a blinded physician at 72 h or later after end of intervention period.
Phase 4 (72 h after end of intervention period to 28 d after OHCA)	Neurologic status, according to the CPC scale, and survival are evaluated every day in the intensive care unit and/or at days 1, 2, 3, 4, 5, 6, 7, 14, 21, and 28 and/or at hospital discharge, whichever comes first.
Phase 5 (day 28 to 180 days after OHCA)	Survival and neurologic status are evaluated on day 90 (telephone) and day 180 (outpatient clinic). Occupational therapists/research nurses blinded to the intervention allocation perform evaluation.

OHCA, Out-of-hospital cardiac arrest.

speed of 0.5°C per hour in both groups. After 36 hours, sedation is discontinued, and the patients are allowed to recover spontaneously. Sedation may be temporarily reintroduced to allow for mechanical ventilation until extubation is considered appropriate. Efforts are taken to control and achieve a body temperature of 37°C until 72 hours after cardiac arrest with antipyretic drugs and, if applicable, continued temperature management with devices. If a patient in the TTM33 group experiences life-threatening arrhythmias, uncontrolled bleeding, or any other intolerable untoward effect suspected to be caused by hypothermia, the target temperature will be titrated to a level where the symptoms are under control but maximally to 36°C.

Blinding

Because of the inherent logistic problems with blinding of temperature management, the immediate caregivers are unblinded. An external blinded physician evaluates the neurologic status for patients who are still unconscious 72 hours after the end of the intervention period. Patients and their legal representatives are only informed that the patient has received target temperature management, and no information of their group allocation during the trial or follow-up is given. Outcome assessors, statisticians performing the final data analyses, and the steering committee are blinded to the allocation.

Prognostication and limitations of life support

All patients are actively treated for a minimum of 72 hours after the intervention period (end of phase 3, see Table I). At this time point, an evaluation of neurologic prognosis for all unconscious patients is performed by a physician blinded for treatment allocation who will make a recommendation concerning further life-sustaining treatment. Life-supporting therapy is delivered according to standard practice and at the discretion of the treating physicians. The neurologic evaluation is based on a clinical neurologic examination (including GCS motor score [GCS-M] and pupillary and corneal reflexes), somatosensory evoked potentials (SSEPs) and electroencephalogram (EEG).

Findings allowing for discontinuation of life support are the following:

1. Brain death;
2. Early myoclonus status* (<24 hours from sustained ROSC) and bilateral absence of N20 peak on somatosensory evoked potentials (SSEP) after the intervention period;
3. Seventy-two hours after end of intervention period: GCS-M 1-2 and bilateral absence of N20 peak on SSEP performed 48 to 72 hours after the end of the intervention period, or later; and
4. Seventy-two hours after end of intervention period: A treatment refractory status epilepticus# and GCS-M 1-2.

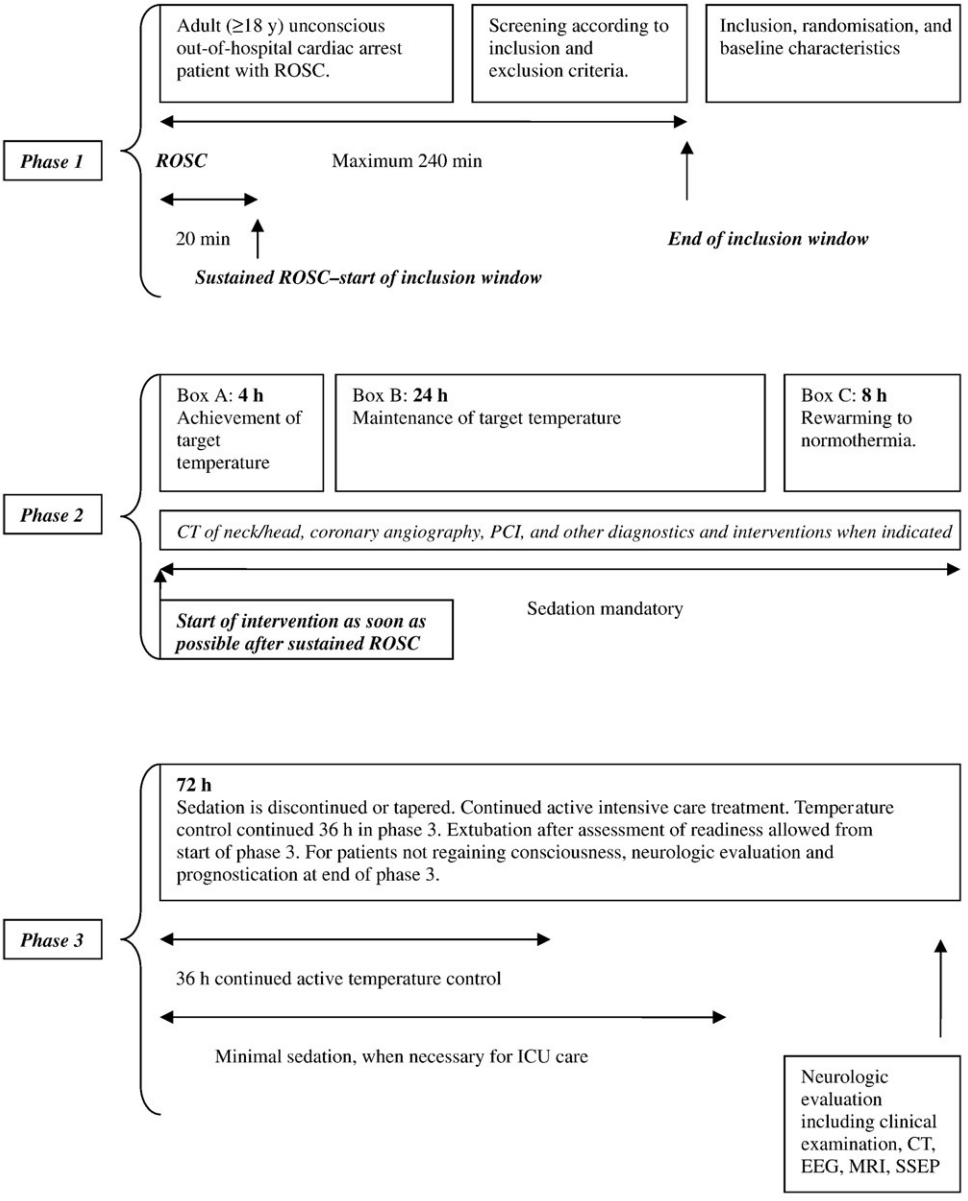
Comatose patients with GCS-M 1 or 2 at 72 hours after the intervention period who have retained N20 peak on the SSEP or in hospitals where SSEP is not available should be reexamined daily and the withdrawal of intensive care considered if GCS does not improve and metabolic and pharmacologic causes have been ruled out.

Ethical reasons to withdraw life support before 72 hours after the intervention period may include presentation of previously

* Generalized myoclonic seizures in face and extremities and continuous for a minimum of 30 minutes.

Status epilepticus defined by EEG as sequences (>10 seconds) of repetitive epileptiform discharges with an amplitude >50 μV and a medium frequency ≥1 Hz, constituting >50% of a 30-minute period in a patient with or without clinical manifestations. *Refractory treatment* is defined as unresponsive to propofol, midazolam, or thiopental for at least 24 hours in combination with at least 1 intravenous antiepileptic substance (including valproate and/or fos-Phenytoin) in adequate dose for at least 24 hours. Free use of further antiepileptic substances and combinations at the discretion of the attending physician.

Table II. Detailed flow chart of phases 1 to 3



CT, Computed tomography; *ICU*, intensive care unit; *MRI*, magnetic resonance imaging; *PCI*, percutaneous coronary intervention.

unknown information about end-stage cancer or refractory shock with concomitant multiorgan failure. Any reasons for withdrawal of life support will be recorded.

Follow-up

At 90 days, an assessor-blinded follow-up of mortality and neurologic function is undertaken. At 180 days, surviving patients are summoned to a follow-up meeting for evaluation of neurologic function and quality of life. Final population mortality will be evaluated at the end of the trial, using mortality at maximal follow-up.

Outcome measures

Efficacy variables are survival from national databases and/or hospital records, neurologic function, and quality of life according to the CPC scale,[11] modified Rankin Scale (mRS),[12] Mini Mental State Examination (MMSE),[13] Informant Questionnaire on Cognitive Decline in the Elderly,[14] Short-Form-36,[15] and 2 questions: (1) "In the last 2 weeks, did you require help from another person for your every day activities?" (If yes, "Is this a new situation following the heart arrest?") and (2) "Do you feel that you have made a complete mental recovery after your heart arrest?"[16]

Table III. Adverse events collected during days 1 to 7 in the intensive care unit

Bleeding: Bleeding from nose, gastrointestinal tract, oral cavity, genitals, insertion sites, intramuscular, etc
Major bleeding: Uncontrolled bleeding (>1 U of blood/10 kg/1 h), bleeding causing fatality; symptomatic bleeding in critical organ, eg, intracranial, intraspinal, intraocular, intraarticular, pericardial; other bleeding: gastrointestinal, tracheal, oral cavity, nose, genital, insertion sites, other bleeding with hemoglobin fall >50 g/L (3.1 mmol/L) and required >2 U of transfused blood
Infection: Severe sepsis, septic shock, pneumonia, etc
Renal impairment: Need for CRRT or IHD
Electrolyte disorders: Hypokalemia (<3.0 mmol/L), hypophosphatemia (<0.7 mmol/L), hypomagnesemia (<0.7 mmol/L)
Metabolic disorders: Sustained hyperglycemia (>10 mmol/L >4 h), hypoglycemia (<3.0 mmol/L)
Arrhythmia: VF, VT, tachycardia >130/min, bradycardia <40/min, atrial flutter, atrial fibrillation, need for pacing, circulatory collapse mandating CPR
Seizures: Tonic-clonic, myoclonic, electrographic status epilepticus
Clinical significant shivering
Elevated body temperature (cumulated duration of >38°C)
Other adverse event potentially associated to intervention? Specify.

CRRT, Continuous renal replacement therapy; *IHD*, intermittent hemodialysis; *VF*, ventricular fibrillation; *VT*, ventricular tachycardia; *CPR*, cardiopulmonary resuscitation.

Good neurologic function is categorized as:

1. Survivors with good outcome defined by mRS ≤3
2. Survivors with good outcome defined by CPC ≤2
3. Survivors with complete recovery defined by: MMSE ≥27 (or ≥19 on MMSE-Adult Lifestyle Functioning Interview by telephone interview), modified Informant Questionnaire on Cognitive Decline in the Elderly ≤78, answer "No" to question 1a or "No" to question 1b, answer "Yes" to question 2.

Adverse events

Adverse events are recorded daily during phases 2 and 3 following the items in Table III and reported according to the CONSORT Statement.[17]

Statistics

Outcome measures will be analyzed for all randomized patients in the intention-to-treat analysis, which will be the primary result of the trial. According to guidelines for analyses of randomized clinical trials,[9] univariate analyses will be carried out for all outcome measures. The primary outcome of mortality will be analyzed after a minimum of 180 days of follow-up with Cox regression analysis, and the primary analysis will be an unadjusted univariate analysis for the effect of intervention. The secondary analysis will be a multivariate Cox regression analysis adjusting for design variables: time to ROSC, age, initial rhythm, gender, and cardiogenic shock at admission. All intervention effect estimates will be given with 95% CIs and a 2-tailed type 1 error (α) <.05 will be considered significant. Potential post hoc analyses will be specified as such.

Sample size

According to the trial sequential analysis (TSA)[7,18] based on the published randomized controlled trials, there is an information gap of 555 patients between the accrued information size and the required information size (Figure 1). Of all the published trials included in the TSA, none is of low risk of bias, probably making the TSA overly optimistic.

If we find no statistically significant differences between the intervention groups, we have to be confident that this is a finding with a reasonably high reliability, that the trial is powered to detect a difference if it is present, and that otherwise true effects may be so small that they are of less clinical significance. The TTM trial will, therefore, aim for 950 patients to be randomized to detect or reject a hazard ratio reduction of 20% with a power of 90% and a type 1 error of 5% equivalent to a prolongation of the median survival with 1 month in either intervention group. The sample size of 950 participants is estimated assuming 24 months of accrual and a follow-up of 6 months of the last randomized patient. However, because of consideration of funding and human resources, the trial may have to be stopped when 850 patients have been randomized if the accrual of 950 participants seems to extend substantially beyond the 31st of December 2012. With 850 participants, the TTM trial will be able to show a hazard ratio reduction of 20% with a slight reduction of the power to 87%.

Data Monitoring Committee and interim analysis

An independent Data Safety Monitoring Committee (DSMC) is established to evaluate safety and efficacy during the trial and at 1 scheduled interim analysis. This interim analysis will take place when half of the patients have been followed up for 90 days, according to the Haybittle-Peto rule (a P value of .001).[19] Alternatively, the Lan-DeMets group sequential monitoring boundaries will be used, with the possibility to analyze whenever the DSMC requires.[20] Based on these guidelines, the DSMC could advise the steering committee to continue, stop, or pause the trial.

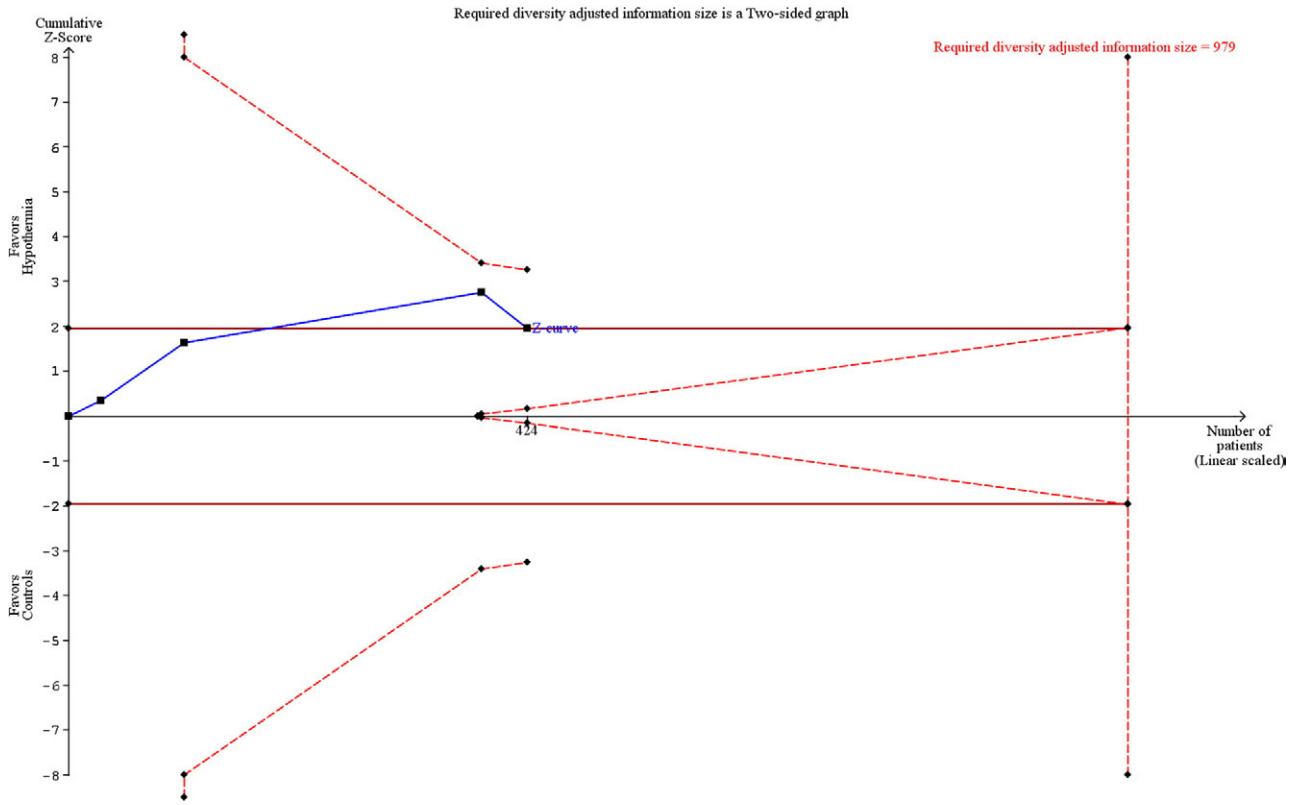
Trial status and timeline

The first patient was randomized mid November 2010, and trial sites have been added gradually. As of December 2011, 319 patients have been recruited. We anticipate that the last 180-day follow-up will be performed in mid 2013.

Discussion

From animal experimental data, we know that the beneficial effect of targeted temperature management after cerebral ischemia may be substantial, but the current body of evidence in man is prone to high risk of bias, is not fully relevant for the general cardiac arrest population, and still has a substantial information gap before an effect may be established. However, the trials already published have had high impact, and hypothermia and avoidance of fever have been introduced as core elements of post–cardiac arrest care in guidelines worldwide. As a consequence, the implementation of temperature management has overthrown the therapeutic nihilism that previously prevailed in the cardiac arrest

Figure 1



Trial sequential analysis. Trial sequential analysis for a relative risk reduction of all-cause mortality of 16% of hypothermia after cardiac arrest in 4 trials reporting mortality. A diversity-adjusted information size of 979 participants using a diversity of 23%. α = .05 2-Sided and β = .20 (power, 80%) and a required diversity adjusted information size of 979, based on a relative risk reduction of mortality of 16% suggested by a random-effects meta-analysis of all trials. The cumulative z-curve is constructed using a random-effects model, as nonignorable heterogeneity was present with a diversity D^2 = 23% (I^2 = 20%). The z-curve (blue) nearly touches the traditional boundary (P = .051) but does not cross the trial sequential monitoring boundaries for benefit or futility indicating lack of firm evidence for a beneficial effect of 16% relative risk reduction of the intervention when the analysis is adjusted for repetitive testing on accumulating data. There is insufficient information to reject or detect an intervention effect of 16% relative risk reduction (adjusted 95% CI for repetitive testing and sparse data: 0.62 - 1.13) of all-cause mortality, as the required information size is not yet reached. The information gap may be 555 patients (424-979).

population. Concomitantly, active standardized intensive care including coronary reperfusion has been emphasized in this patient group, which may have equivalent or even more beneficial effects.

When designing a new randomized trial for temperature management in post–cardiac arrest care, the influence from previous trials, clinical guidelines, and current clinical practice had to be taken into consideration. We wanted to address problems of bias, power, generalizability, and underreporting of adverse events in earlier trials without overly challenging modern intensive care's zeal to avoid fever.

Regarding temperature management, there are 2 questions to address: first, is induced hypothermia to 33°C superior to intensive care without any temperature management often associated with fever, and second, is induced hypothermia to 33°C superior to avoiding fever? The trials so far have, not conclusively, addressed the first question, and the results of our systematic review, in fact, establish clinical equipoise. However, with the novel clinical focus on temperature management and considering experimental and observational findings suggesting that hyperthermia may be detrimental after brain damage,[1,21] we concluded that a trial with no temperature management in the control group, as in previous trials, would be unfeasible. We, therefore, decided on a trial design with 2 active intervention arms, each with strict temperature control, with broad inclusion criteria increasing the generalizability of the results, with a thorough reporting of adverse events and with a design minimizing the risk of systematic errors.

Besides the issue of temperature management and fever in control groups, the previous trials were highly selective regarding study populations. Therefore, we have designed a pragmatic trial with wide inclusion criteria, excluding only patients with a definite pessimistic prognosis. With the inclusion of patients resuscitated after cardiac arrest of a cardiac cause with any initial cardiac rhythm (except patients with unwitnessed arrests with initial rhythm asystole), we will strengthen the generalizability of the results.[22]

The design of the TTM trial tries to address some areas of concern for a trial in the cardiac arrest population, to avoid possible systematic errors. Neurologic prognostication and how to decide on limitations of life support are strictly defined in the protocol to avoid self-fulfilling outcomes. Moreover, we have chosen a bias-limited primary outcome with all-cause mortality at maximal follow-up. With stratification for center, we match the inevitable hospital effect based on case mix, therapeutic traditions, and clinical performance.

Earlier trials used a composite primary outcome of mortality and neurologic function.[23-25] We believe that mortality is a more suitable outcome, not only in being less prone to bias, but also because the trajectory of neurologic recovery is hard to define and probably of a much longer duration than previously estimated. Discharge from hospital is far too early[26] and even 6 months may not be sufficient; for a person to be able to recover, survival is a prerequisite. Moreover, earlier trials showed that more randomized patients were needed to power for mortality than for the composite outcome of mortality and neurologic function; hence, our secondary outcome of neurologic function will gain power when we calculate our sample size on mortality. Finally, we avoid the imminent risks of competing outcomes.[27] To strengthen the secondary outcome measures, we perform more thorough neurologic examinations than ever performed in a cardiac arrest trial, with focus on many aspects of cognitive dysfunction, in addition to the well-established and Utstein-recommended CPC scale.[28]

The TTM trial will increase the total number of cardiac arrest patients randomized for temperature management by almost 200%, but nevertheless, the trial may still be underpowered to detect smaller relative risk reductions than the a priori anticipated 20%. However, failure to demonstrate a statistically significant difference between the 2 interventions would at worst equate to an undemonstrated potential median increase in survival of <1 month.

In case of a beneficial effect of a target temperature of 33°C, the implementation of induced hypothermia, as recommended in current guidelines, will be founded on solid evidence. If the findings are in favor of a target temperature of 36°C, we may have to challenge the concept of *temperature management* per se and consider if strict normothermia is superior to intensive care without temperature management. With a neutral result, we may have to accept the possibility of undisclosed small but clinically significant effects, both for benefit or harm on mortality and neurologic outcome. However, a neutral result of the TTM trial most probably will stimulate future trials to investigate the optimal target temperature after cardiac arrest in even larger trials, rather than suggest succumbing to previous treatment traditions.

Conclusions

To further investigate the evidence for temperature management of patients with out-of-hospital cardiac arrest, a trial comparing 2 different target temperature levels, each avoiding hyperthermia, is of paramount importance. We believe that the pragmatic trial design and the protocol that is in accordance with current clinical practice will support the validity of the TTM trial. We anticipate that the results of this trial will apply to a general population admitted to hospital for intensive care after out-of-hospital cardiac arrest.

Acknowledgements

This trial is supported by grants from The Swedish Heart and Lung Foundation, AFA Insurance Foundation, the Swedish National Health System (ALF), the County Council of Skåne, the Stig and Ragna Gorthon Foundation, Thure Carlsson Foundation, Segerfalk Foundation, and the Gyllenstierna-Krapperup Foundation, all in Sweden.

Disclosures

None of the authors declare any conflicts of interest.

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