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Hypothermia versus normothermia in patients with cardiac arrest and shockable rhythm: a secondary analysis of the TTM-2 study

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Abstract

Background The aim of this study was to assess whether hypothermia increased survival and improved functional outcome when compared with normothermia in out-of-hospital cardiac arrest (OHCA) patients with similar characteristics than in previous randomized studies showing benefits for hypothermia.

Methods Post hoc analysis of a pragmatic, multicenter, randomized clinical trial (TTM-2, NCT02908308). In this analysis, the subset of patients included in the trial who had similar characteristics to patients included in one previous randomized trial and randomized to hypothermia at 33 °C or normothermia (i.e. target < 37.8 °C) were considered. The primary outcome was survival at 6 months; secondary outcomes included favorable functional outcome at 6 months, defined as a modified Rankin scale of 0–3. Time-to-death and the occurrence of adverse events were also reported.

Results From a total of 1891 included in the TTM-2 study, 600 (31.7%) were included in the analysis, 294 in the hypothermia and 306 in the normothermia group. At 6 months, 207 of the 294 patients (70.4%) in the hypothermia group and 220 of the 306 patients (71.8%) in the normothermia group had survived (relative risk with hypothermia, 0.96; 95% confidence interval [CI], 0.81 to 1.15; P = 0.71). Also, 198 of the 294 (67.3%) in the hypothermia group and 202 of the 306 (66.0%) in the normothermia group had a favorable functional outcome (relative risk with hypothermia, 1.03; 95% CI, 0.87 to 1.23; P = 0.79). There was a significant increase in the occurrence of arrythmias in the hypothermia group (62/294, 21.2%) when compared to the normothermia group (43/306, 14.1%—OR 1.49, 95% CI 1.05–2.14; p = 0.026).

Conclusions In this study, hypothermia at 33˚C did not improve survival or functional outcome in a subset of patients with similar cardiac arrest characteristics to patients in whom benefit from hypothermia was shown in prior studies.

Keywords Cardiac arrest, Shockable rhythm, Hypothermia, Outcome

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Introduction

The role of temperature control in the management of post-anoxic brain injury remains controversial. The Hypothermia versus Normothermia after Out-of-Hospital Cardiac Arrest (TTM-2) trial demonstrated that therapeutic hypothermia at 33 °C neither reduced mortality nor improved functional outcomes in unconscious patients who experienced out-of-hospital cardiac arrest (OHCA), in comparison to early fever avoidance (i.e., maintaining a core temperature < 37.8 °C) [1]. Recent guidelines advocate for the proactive fever prevention in unconscious patients who have been successfully resuscitated following a cardiac arrest, emphasizing a minimum duration of 72 h [2]. However, these guidelines acknowledge the absence of conclusive evidence either endorsing or discouraging management at lower body temperatures in specific patient subgroups.

Amongst patients initially presenting with a shockable rhythm, the TTM-2 study did not reveal any advantageous effects on mortality or functional outcomes associated with therapeutic hypothermia at 33 °C [1]. These patients typically have shorter resuscitation times, less cardiovascular compromise, less frequently severe hypoxic brain injury upon admission, and lower mortality rates compared to other patient subgroups [3]. However, in the Hypothermia after Cardiac Arrest (HACA) trial [4], only patients with witnessed OHCA, an initial shockable rhythm and other specific inclusion criteria were randomized; those who received hypothermia at 33 °C had better neurological outcome than controls. Moreover, in another small trial including patients with similar characteristics [5], hypothermia initiated using pre-hospital cooling was associated with improved functional outcome and survival when compared to normothermia. Whether these baseline characteristics might influence the impact of hypothermia on this subgroup of patients with shockable rhythm remains unknown.

In a study using data from the Swedish Intensive Care Registry covering a 6 year span and encompassing out-of-hospital cardiac arrest (OHCA) cases, therapeutic hypothermia at 33 °C did not demonstrate a statistically significant improvement in 6-month survival when compared to hypothermia at 36 °C (47.2% vs. 47.3%) [6]. Nevertheless, when the analysis was restricted to patients meeting the same criteria as those in the HACA trial, the use of hypothermia at 33 °C was associated with a significant increase in the proportion of survivors from 67.6 to 77.8%. Hence, the findings from the TTM-2 trial might not be representative of the subgroup of cardiac arrest patients resembling those in the HACA trial.

Accordingly, we conducted a secondary analysis of the TTM-2 trial to evaluate whether therapeutic hypothermia at 33 °C was linked to decreased likelihood of mortality and/or of adverse functional outcome in patients with similar baseline characteristics to those in the HACA trial.

Methods

Study design

We conducted a post hoc secondary analysis of the TTM-2 trial (NCT02908308), which was an international, multicenter randomized controlled trial comparing the effects of hypothermia at 33 °C versus maintaining normothermia (temperature < 37.8 °C) for 24 h; the methodology of this study was published in the original report of the trial [1]. This study adhered to the CONsolidated standards of reporting trials (CONSORT) reporting guidelines [7]. Main differences between the TTM-2 trial [1] and the HACA trial [4] have been described in Supplemental eTable 1. Ethical approvals were obtained from the coordinating center and, therefore, in each participating center, along with informed consent in accordance with local regulations. The analysis was conducted strictly following the principles of the Declaration of Helsinki and the Medical Research Involving Human Subjects Act. No additional ethical clearance was required for the execution of this analysis.

Patients' selection

For the purpose of this study, inclusion and exclusion criteria followed the HACA trial [2]. In particular, all inclusion criteria should be met, such as: a) Witnessed cardiac arrest; b) Ventricular fibrillation or non-perfusing ventricular tachycardia as the initial cardiac rhythm; c) Presumed cardiac origin of the arrest; d) Age of 18 to 75 years; e) Estimated interval of 5 to 15 min from the patient's collapse to the first attempt at resuscitation by emergency medical personnel; f) Interval of no more than 60 min from collapse to restoration of spontaneous circulation. Exclusion criteria were: a) Temperature below 30 °C on admission; b) Coma before the cardiac arrest due to the administration of drugs that depress the central nervous system; c) Pregnancy; d) Response to verbal commands after the return of spontaneous circulation and before randomization; e) Evidence of hypotension (mean arterial pressure < than 60 mm Hg) for more than 30 min after the return of spontaneous circulation (ROSC) and before randomization; f) Evidence of hypoxemia (arterial oxygen saturation < than 85%) for more than 15 min after ROSC and before randomization; g) a terminal illness that preceded the arrest; h) Factors that made participation in follow-up unlikely; i) Enrollment in another study; j) The occurrence of cardiac arrest after the arrival of emergency medical personnel; k) A known preexisting coagulopathy. Interventions in the study arms are described in the Supplemental Material. In the

TTM-2 trial, neurological prognostication was protocolized and followed the European Resuscitation Council guidelines. Also, decision of withdrawal of life sustaining therapies (WLST) was regulated and clearly documented in a structured and transparent approach.

Study outcomes

The primary outcome in this study was 6 month survival. Secondary outcome was the incidence of a favorable functional outcome at the 6 month follow-up, as defined by a modified Rankin Scale (mRS) score within the range of 0–3 [8]. The mRS was collected using a structured interview by a blinded and study-trained outcome assessor. The follow-up was mainly performed as a face-to-face meeting; however, whenever needed, alternative methods were allowed, including telephone interviews, or, in cases where patients had impaired cognitive capacity that hindered direct interviews, contact with the patient's next of kin. Additional endpoints included: a) time-to-death (survival data) for each participant from randomization until the last day of follow-up; b) the occurrence of arrhythmias (bradycardia, atrial fibrillation, ventricular fibrillation, or ventricular tachycardia), pneumonia, sepsis or any serious bleeding, as defined in the study protocol [1].

Data collection

Data collected included patients' demographic characteristics, pre-cardiac arrest comorbidities (including Charlson comorbidity index), location, timing, type and management of cardiac arrest, clinical presentation (presence of shock, ST-elevation myocardial infarction, STEMI) and clinical outcomes.

Statistical analysis

All analyses were conducted according to the intention-to-treat principle. All tests of statistical significance were two-sided with a type I error risk of 5%. Dichotomized outcomes were presented as proportions of participants in each group with the event, as well as risk ratios with 95% confidence intervals. All randomized participants were included in the primary analysis; no imputation for missing information on neurological outcome was performed. Adjustment for survival and favorable neurological outcome was performed using a multivariable logistic regression model including age, gender, participating site, time to ROSC and bystander CPR. A conventional test for an interaction effect was tested in a model containing the entire TTM-2 population with indicator variables for patients included in this analysis. This interaction model was designed to assess the "HACA-like population" as a conventional subgroup. The interaction test applied was the same as that used for the subgroups shown in the Forest plot of the main trial results [1]. The model includes a term for the randomization group, a term for identifying "HACA-like" patients, and an interaction term between the two. The reported p-value corresponds to the interaction term.

All the statistical analyses for this study were performed in R version 3.6.0 (R Foundation for Statistical Computing, Vienna, Austria). P-values are two-tailed and values < 0.05 were considered statistically significant.

Results

Study population

From November 2017 to January 2020, a total of 1861 participants with informed consent were included in the TTM-2 trial. Of those, 1228 (65.9%) did not fulfill all the inclusion criteria of the HACA trial and 33 were excluded because of persistent hypotension on admission (n = 26) or missing outcome data (n = 7) (Fig. 1). A total of 600 patients were included in the final analysis, 294 (49.0%) assigned to the hypothermia and 306 (51.0%) to the normothermia group. Baseline characteristics are reported in Table 1; study groups were well balanced at baseline. On admission, more than 80% had bystander CPR and the median time to ROSC was 22 min. The temperature curves by treatment group are shown in Fig. 2. A device to achieve the target temperature was used in 288 patients (98.0%) in the hypothermia group (187 with a surface device, 99 with an intravascular device and 2 with both) compared to 162 patients (52.9%; $p < 0.01$) in the normothermia group (103 with a surface device and 59 with an intravascular device).

Primary outcome

Data on the primary outcome are reported in Table 2. At 6 months, 207 of the 294 patients (70.4%) in the hypothermia group and 220 of the 306 patients (71.8%) in the normothermia group had survived (relative risk with hypothermia, relative risk with hypothermia, 0.96; 95% confidence interval [CI], 0.81 to 1.15; P = 0.71). The association of the temperature intervention with survival was consistent when assessed in a time-to-event analysis (Fig. 3). There was no interaction on survival between the entire cohort and the selected population for this study (p = 0.87). Adjusted analysis showed no significant differences between groups (OR 0.99, 95% CI 0.67–1.46, p = 0.96). Decision of withdrawal of life sustaining therapies according to the protocolized prognostication algorithm was applied in 68 (23.6%) patients in the hypothermia group and 61 (19.9%) in the normothermia group (p = 0.37).

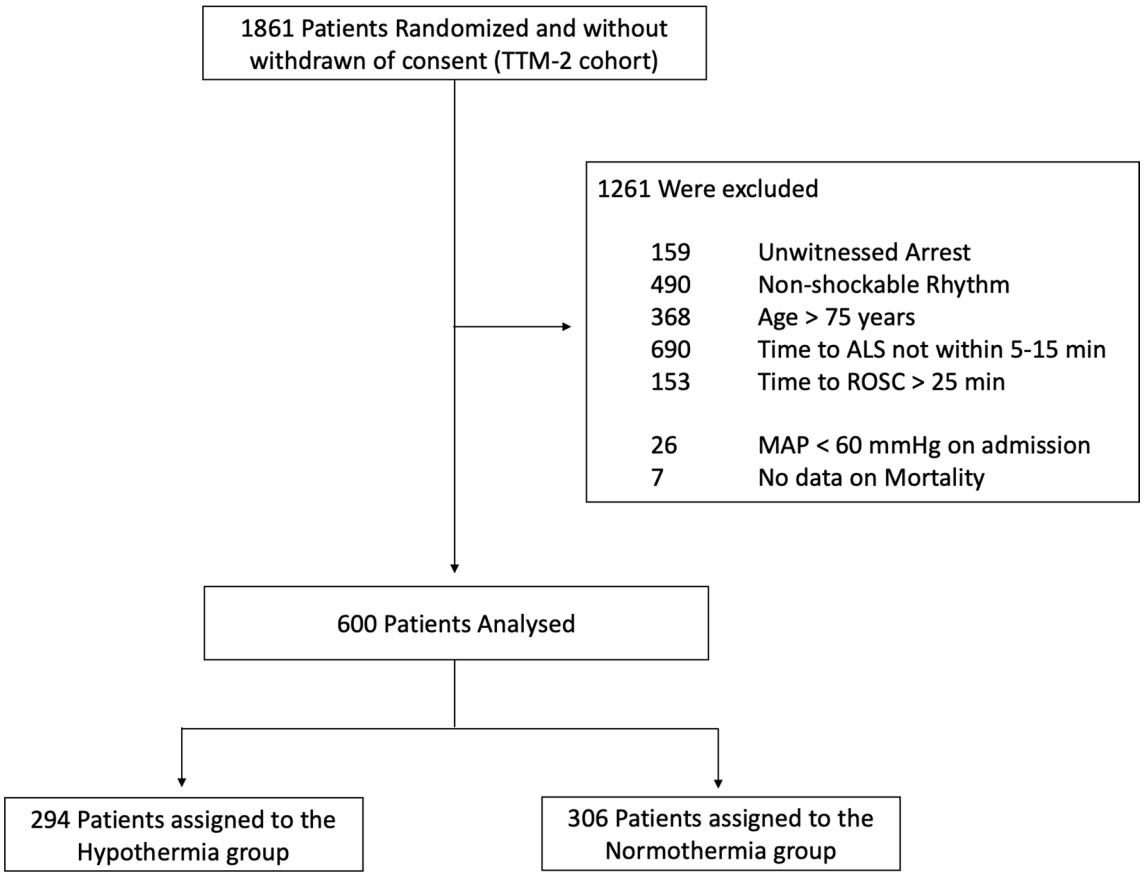

Fig. 1 Flow-chart of the study

Secondary outcomes

Data on the neurological outcome are reported in Table 2. At 6 months, 198 of the 294 (67.3%) in the hypothermia group and 202 of the 306 (66.0%) in the normothermia group had a favorable functional outcome (relative risk with hypothermia, 1.03; 95% CI, 0.87 to 1.23; P = 0.79). The distribution of mRS categories between groups is shown in Supplemental Fig. 1. There was no interaction on survival between the entire cohort and the selected population for this study (p = 0.75). Adjusted analysis showed no significant differences between group (OR 0.85, 95% CI 0.58–1.23, p = 0.39).

Adverse events

Prespecified adverse events are reported in Table 2. There was a significant increase in the occurrence of arrythmias in the hypothermia group (62/294, 21.2%) when compared to the normothermia group (43/306, 14.1%—OR 1.49, 95% CI 1.05–2.14; p = 0.026), while no significant differences in the occurrence of sepsis, bleeding, and pneumonia were observed in the two groups.

Discussion

In this secondary analysis of the TTM-2 trial, hypothermia at 33 °C was not associated with improved survival or functional outcomes at 6 months compared to controlled normothermia in adult OHCA patients with an initial shockable rhythm and similar inclusion/exclusion criteria as in previous studies showing benefits [4, 5]. Our study, along with recent systematic reviews and meta-analyses [9–11], suggested that the methods proposed to induce and maintain hypothermia (i.e., targeting 33 °C for 24 h with associated sedation and temperature-feedback devices), which have been in practice for the past two decades, do not provide the intended benefits in the same patient population that was evaluated in two landmarks studies [4, 5]. Importantly, we observed significant differences in patient characteristics, such as higher rates of bystander CPR and overall improved survival, in the TTM-2 trial when compared to others. These changes reflect the evolving approach to cardiac arrest management, both in terms of emergency response systems and advancements in intensive care management.

The disparities in inclusion and exclusion criteria between the TTM-2 study and its predecessors (i.e., a

Table 1 Characteristics of the intention to treat population at randomization. Data are reported as count (%), mean (SD) or median (25th-75th percentiles)

Characteristic	Hypothermia (n = 294)	Normothermia (n = 306)
Age – years mean (SD)	59.9 ± 11.9	58.3 ± 12.2
Male sex – no. (%)	250 (85.0)	263 (85.9)
Medical History		
Chronic heart disease—no. (%)	17 (6.0)	17 (5.8)
Arterial hypertension—no. (%)	106 (37.3)	87 (29.9)
Diabetes – no. (%)	51 (17.3)	39 (12.7)
Previous myocardial infarction – no. (%)	41 (14.4)	37 (12.7)
Charlson Comorbidity index – median (IQR)	2.0 [1.0—4.0]	3.0 [1.0—4.0]
Characteristics of the cardiac arrest		
Location of arrest		
- Home – no. (%)	146 (49.7)	151 (49.3)
- Public place – no. (%)	115 (39.1)	122 (39.9)
- Other – no. (%)	33 (11.2)	33 (10.8)
Bystander witnessed arrest – no. (%)	294 (100.0)	306 (100.0)
Bystander CPR performed – no. (%)	247 (84.0)	264 (86.3)
Epinephrine, mg – median (IQR)	1 (0–2)	1 (0–2)
Number of defibrillation—median (IQR)	3 (1–4)	3 (1–4)
First monitored rhythm		
VF – no. (%)	258 (87.8)	259 (84.6)
VT – no. (%)	36 (12.2)	47 (15.4)
Admission FOUR Motor Score of 0 – no. (%)	230 (84.6)	229 (82.7)
Time from cardiac arrest to ALS—minutes, mean (IQR)	9.4 ± 3.1	9.3 ± 2.9
Time from cardiac arrest to sustained ROSC – minutes, median (IQR)	22.0 [15.0—32.0]	22.0 [16.0—32.0]
Time from arrest to randomization – minutes, median (IQR)	102.9 ±42.1	103.1 ±41.9
Clinical characteristics on admission		
Temperature on admission – median (IQR)	35.2 [34.3—36.1]	35.2 [34.4—36.0]
Serum lactate—mmol/L, median (IQR)	4.1 (2.4–6.6)	4.0 (1.9–6.6)
Shock on admission—no. (%)	63 (21.4)	72 (23.5)
ST-elevation myocardial infarction—no. (%)	141 (48.6)	138 (45.4)
CAHP score—mean (SD)	129 ± 36	124 ± 37

CPR, Cardiopulmonary resuscitation; *GCS*, Glasgow Coma Scale; *CAHP*, Cardiac Arrest Hospital Prognosis; *FOUR*, Full Outline of UnResponsiveness; *ALS*, Advanced life support

higher rate of bystander CPR and potential heterogeneity in post-resuscitation care due to the multitude of recruiting centers in the TTM-2 trial) have led to varying interpretations of the evidence and divergent recommendations on temperature management from scientific societies. While the European Resuscitation Council (ERC) and the European Society of Intensive Care Medicine (ESICM) guidelines recommend early fever avoidance (i.e., maintaining a core temperature below 37.8 °C) for a minimum duration of 72 h, based primarily on findings from the TTM-2 trial [2] and systematic reviews [9–11], the American Heart Association (AHA) suggests that for the broader group of patients with in-hospital cardiac arrest (IHCA) or OHCA of non-cardiac origin, or with non-shockable rhythms, the benefit of temperature control between 33 and 37.5 °C remains unclear [12]. On the opposite, the European Society for Emergency Medicine (EUSEM) and the European Society of Anesthesiology and Intensive Care (ESAIC) advocated for the consideration of hypothermia within the range of 32–34 °C for a duration of 24 h in all adult patients following cardiac arrest, as promptly as possible [13], using findings from another meta-analysis [14]. Our analysis provides augmented statistical robustness to the available evidence, such as: a) A larger cohort of patients; b) The implementation of a standardized protocol for assessment of neurological prognosis and withdrawal of life-sustaining therapies and utilization of an independent outcome-assessor, thereby mitigating the risk of overestimating intervention effects [15]; c) A time from arrest

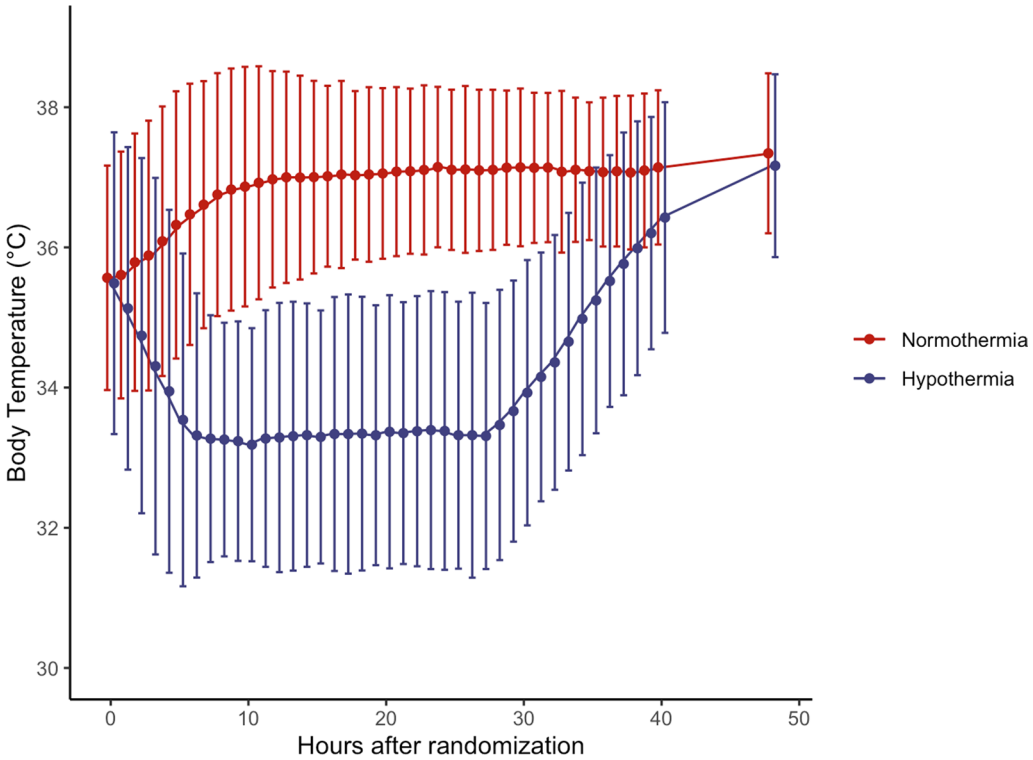

Fig. 2 Body temperature curves from randomization to 48 h in the hypothermia and normothermia groups for the patients in whom a core temperature was recorded. Temperature curves show the median and 95% of the observations are within the error bars

Table 2 Study outcomes and main adverse events

	Hypothermia	Normothermia	Risk Ratio	P Value
	no./total no. (%)		*(95%CI)*	
Primary outcome				
Survival at 6 months	207/294 (70.4)	220/306 (71.8)	0.96 (0.81 to 1.15)	0.71
Secondary outcome				
Favorable functional outcome at 6 months	198/294 (67.3)	202/304 (66.4)	1.03 (0.87 to 1.23)	0.79
Serious adverse events				
Arrhythmias	62/294 (21.2)	43/306 (14.1)	1.49 (1.05–2.14)	0.026
Bradycardia	19	10		
Ventricular fibrillation	16	8		
Atrial Fibrillation	8	13		
Others	19	12		
Bleeding	18/294 (6.1)	10/306 (3.3)	1.86 (0.89–4.14)	0.11
Pneumonia	126/294 (43.0)	117/306 (38.6)	1.11 (0.92–1.35)	0.27
Sepsis	24/294 (8.2)	29/306 (9.5)	0.86 (0.51–1.43)	0.66

ICU, Intensive Care Unit; *CPC*, Cerebral Performance Category

to hypothermia which is aligned with findings from prior investigations [4]; d) Enhanced control group management to prevent fever; e) A contemporary approach to cardiac arrest management, contrasting with previous studies in whom post-resuscitation care was not available yet.

How do we propose to explain the differences between the present analysis and the previous studies?

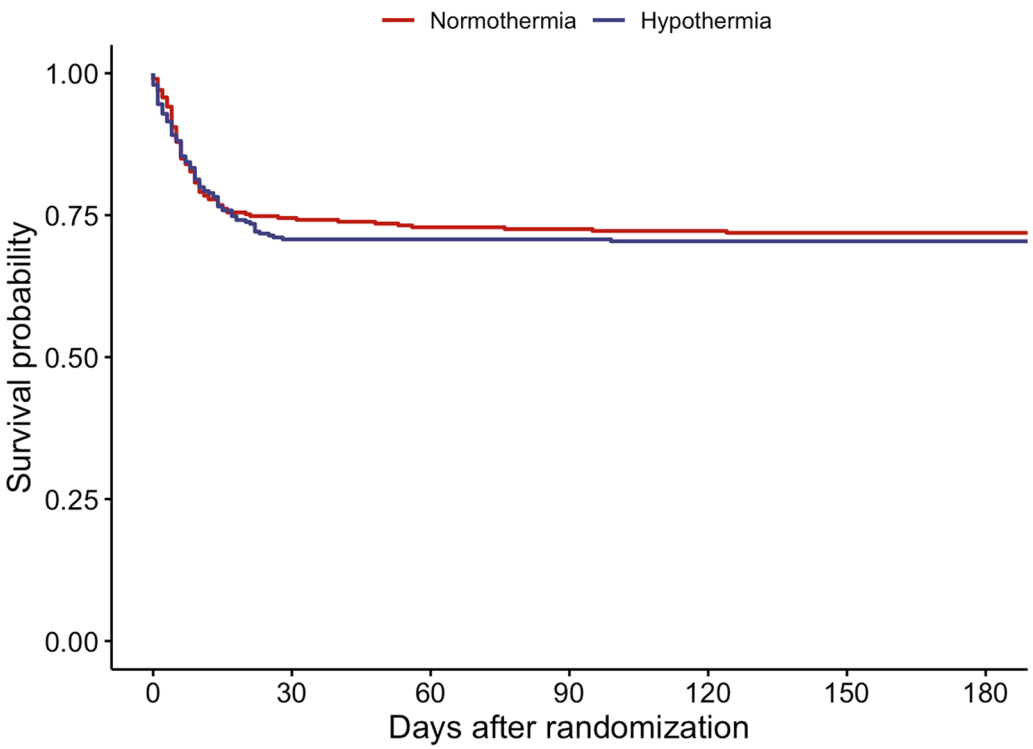

Fig. 3 Probability of survival at 90 days after randomization. Kaplan–Meier estimates of the probability of survival until 90 days after randomization among patients assigned to undergo hypothermia or normothermia. Data are for the 600 patients included in the final analysis. Data were censored according to the last day of follow-up. Hazard ratio for mortality in the hypothermia group = 1.06 (95%CI 0.79–1.43)

Firstly, the two initial RCTs [4, 5] had a smaller sample size and lower methodological quality, including both random and systematic errors, when compared to the TTM-2 trial. Secondly, the study using data from the Swedish Intensive Care Registry [6] was observational in nature, introducing a risk of confounding by indication. Thirdly, the overarching outcome of OHCA cases presenting with an initial shockable rhythm, along with selected characteristics, has demonstrated significant improvement over time. In a large national registry study [6], long-term favorable functional outcome was 77% in patients resembling those in the HACA trial, as opposed to the 49–55% range reported over 20 years ago [4, 5]. In the current investigation, a functional neurological recovery was observed in 67% of patients. This might have occurred because of advances in resuscitation techniques (i.e. high-quality chest compressions and early defibrillation), public awareness and training in CPR for early interventions, improved post-resuscitation care, including optimized hemodynamic and respiratory support, extensive research leading to a better understanding of cardiac arrest and the implementation of evidence-based practices [16–18]. Consequently, the potential additional benefits of hypothermia may have been attenuated by better clinical management of patients, notably those maintained at normothermia, where fever was diligently avoided. This stands in contrast to previous studies where control patients were slightly hyperthermic, potentially heightening the risk of exacerbated post-anoxic brain injury [19]. Fourthly, despite aligning with eligibility criteria akin to those of the HACA trial, the selected patient cohort could still manifest differences, thus introducing an indirect comparison bias. For example, the proportion of patients receiving bystander CPR surpassed 80% in the TTM-2 trial, compared to approximately 50% in earlier studies [4, 5]. Pooling data from larger clinical trials focusing on hypothermia post-cardiac arrest revealed that populations with lower bystander CPR rates exhibited greater benefit from hypothermia than those with elevated rates of bystander CPR [20]. However, in a secondary analysis of a randomized trial comparing hypothermia at 33 °C and 36 °C post-OHCA, neither the duration of no-flow nor the presence of bystander CPR displayed a significant interaction with hypothermia at 33 °C regarding neurological outcomes [21]. Furthermore, unlike a prior study [5], patients in the TTM-2 trial were enrolled after hospital admission, potentially reducing the neuroprotective effects of early exposure to hypothermia. However, pre-hospital

hypothermia, particularly using cold intravenous fluids, was linked to a shorter time to achieve the targeted temperature but, if anything, correlated with an increased risk of unfavorable outcomes [22]. Lastly, the methodologies employed in the TTM-2 study to induce hypothermia (i.e., surface or intravascular cooling devices with temperature-feedback mechanisms) markedly outperform devices utilized decades ago [23]. Therefore, inefficacies in cooling devices cannot elucidate the observed lack of benefits for hypothermia in the present study.

This study has several limitations that warrant acknowledgment. First, interventions such as sedation, paralysis, and mechanical ventilation were not standardized across patients, rendering comparisons with strategies employed in previous studies challenging. Second, we did not perform a trial sequential analysis including previous trials [4, 5] due to several methodological differences compared to the TTM-2 trial, which suggests a high probability of heterogeneity among the studies. Third, the findings from this analysis are specific to the participating countries, each with its own resuscitation and ICU systems, which may differ from those in other regions of the world. Finally, the overall sample size may still be relatively modest for detecting clinically significant differences between groups.

Conclusions

In this secondary analysis of the TTM-2 trial including unconscious survivors resuscitated from OHCA with an initial shockable rhythm and similar inclusion and exclusion criteria than the HACA trial, hypothermia was not associated with improved survival and functional outcome, when compared to controlled normothermia.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13054-024-05119-3.

Supplementary material 1

Author contributions

JD and NN had full access to all the data in the initial databases and had responsibility for the integrity of the data and the accuracy of the data analysis. All the authors provided substantial contributions to conception or design of the work, or the acquisition, analysis, or interpretation of data of the two randomized trials. FST, JD and NN wrote the first draft of the manuscript. All authors critically revised and approved the final version of the manuscript.

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Availability of data and materials

Data of this study will not be shared, because of restrictions due to ethical decisions.

Declarations

Ethics approval and consent to participate

The study was approved by the Ethics Committees of participating centers.

Competing interests

A Cariou, P Young, and T R Keeble reported receiving lecture fees from BD. FS Taccone received lecture fees from BD and ZOLL and is scientific advisor for Nihon Khoden, Neuroptics and Eurosets. C Robba received lectures fees from Integra, BD and Edwards. N Nielsen received lecture fees from Bard Medical and consulting fees from BrainCool. Other authors reported no potential conflict of interest relevant to this study.

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