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Hypothermia vs Normothermia in Patients With Cardiac Arrest and Nonshockable Rhythm
A Meta-Analysis

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IMPORTANCE International guidelines recommend body temperature control below 37.8 °C in unconscious patients with out-of-hospital cardiac arrest (OHCA); however, a target temperature of 33 °C might lead to better outcomes when the initial rhythm is nonshockable.

OBJECTIVE To assess whether hypothermia at 33 °C increases survival and improves function when compared with controlled normothermia in unconscious adults resuscitated from OHCA with initial nonshockable rhythm.

DATA SOURCES Individual patient data meta-analysis of 2 multicenter, randomized clinical trials (Targeted Normothermia after Out-of-Hospital Cardiac Arrest [TTM2; NCT02908308] and HYPERION [NCT01994772]) with blinded outcome assessors. Unconscious patients with OHCA and an initial nonshockable rhythm were eligible for the final analysis.

STUDY SELECTION The study cohorts had similar inclusion and exclusion criteria. Patients were randomized to hypothermia (target temperature 33 °C) or normothermia (target temperature 36.5 to 37.7 °C), according to different study protocols, for at least 24 hours. Additional analyses of mortality and unfavorable functional outcome were performed according to age, sex, initial rhythm, presence or absence of shock on admission, time to return of spontaneous circulation, lactate levels on admission, and the cardiac arrest hospital prognosis score.

DATA EXTRACTION AND SYNTHESIS Only patients who experienced OHCA and had a nonshockable rhythm with all causes of cardiac arrest were included. Variables from the 2 studies were available from the original data sets and pooled into a unique database and analyzed. Clinical outcomes were harmonized into a single file, which was checked for accuracy of numbers, distributions, and categories. The last day of follow-up from arrest was recorded for each patient. Adjustment for primary outcome and functional outcome was performed using age, gender, time to return of spontaneous circulation, and bystander cardiopulmonary resuscitation.

MAIN OUTCOMES AND MEASURES The primary outcome was mortality at 3 months; secondary outcomes included unfavorable functional outcome at 3 to 6 months, defined as a Cerebral Performance Category score of 3 to 5.

RESULTS A total of 912 patients were included, 490 from the TTM2 trial and 422 from the HYPERION trial. Of those, 442 had been assigned to hypothermia (48.4%; mean age, 65.5 years; 287 males [64.9%]) and 470 to normothermia (51.6%; mean age, 65.6 years; 327 males [69.6%]); 571 patients had a first monitored rhythm of asystole (62.6%) and 503 a presumed noncardiac cause of arrest (55.2%). At 3 months, 354 of 442 patients in the hypothermia group (80.1%) and 386 of 470 patients in the normothermia group (82.1%) had died (relative risk [RR] with hypothermia, 1.04; 95% CI, 0.89-1.20; P = .63). On the last day of follow-up, 386 of 429 in the hypothermia group (90.0%) and 413 of 463 in the normothermia group (89.2%) had an unfavorable functional outcome (RR with hypothermia, 0.99; 95% CI, 0.87-1.15; P = .97). The association of hypothermia with death and functional outcome was consistent across the prespecified subgroups.

CONCLUSIONS AND RELEVANCE In this individual patient data meta-analysis, including unconscious survivors from OHCA with an initial nonshockable rhythm, hypothermia at 33 °C did not significantly improve survival or functional outcome.

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Editorial
Supplemental content

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The role of temperature management in treatment of postanoxic brain injury is uncertain. The Targeted Hypothermia vs Targeted Normothermia after Out-of-Hospital Cardiac Arrest (TTM2) trial showed that a therapeutic hypothermia at 33 °C did not reduce mortality or poor functional outcome in unconscious patients experiencing out-of-hospital cardiac arrest (OHCA), as compared with early treatment of fever (ie, core temperature 37.8 °C or higher).[1] In comparison with 2 landmark trials evaluating the same intervention,[2,3] the TTM2 trial included a much larger study cohort and was methodologically more robust; however, most patients had initial shockable rhythm and a cardiac arrest of presumed cardiac origin, thus, limiting the generalizability of these findings to other subgroups of cardiac arrest patients.

Recent guidelines recommended actively preventing fever for at least 72 hours in unconscious patients resuscitated after cardiac arrest; however, these guidelines also highlighted the absence of evidence to support or discourage temperature control at lower body temperatures in specific patient populations.[4] Patients with an initial nonshockable rhythm generally have prolonged resuscitation, more cardiovascular impairment and hypoxic brain injury on admission, and higher mortality rates.[5] Hypothermia at 33 °C was suggested to be of potential benefit in this setting.[6] In patients with an initial nonshockable rhythm, while the TTM2 study did not show any benefit on mortality or functional outcomes for hypothermia at 33 °C,[1] the HYPERION study[7] reported a significant increase in the proportion of cardiac arrest patients rhythm presenting with a favorable functional outcome when treated at 33 °C, as compared with targeted normothermia. These effects were more pronounced for patients with in-hospital cardiac arrest[8]; the OHCA population has not been evaluated specifically.

Therefore, we performed an individual patient data meta-analysis of the TTM2 and HYPERION trials[1,7] to assess whether hypothermia at 33 °C was associated with reduced mortality or probability of poor functional outcome in this patient population and to evaluate whether specific subgroups of patients may benefit or be harmed by such intervention.

Key Points

Question Is therapeutic hypothermia at 33 °C associated with reduced mortality and improved functional outcomes in unconscious patients experiencing out-of-hospital cardiac arrest presenting with an initial nonshockable rhythm?

Findings In this individual patient meta-analysis of 2 randomized clinical trials, the use of hypothermia at 33 °C was not associated with reductions in mortality or unfavorable functional outcome at 3 to 6 months when compared with controlled normothermia. The results were consistent in all prespecified subgroups; trial sequential analysis indicated futility for hypothermia on mortality and functional outcome.

Meaning In this meta-analysis, hypothermia did not improve survival or functional outcome in unconscious adults resuscitated from out-of-hospital cardiac arrest with an initial nonshockable rhythm.

Methods

Study Design

The design and results of the TTM2 (NCT02908308) and HYPERION (NCT01994772), 2 prospective, randomized, open-label trials, have been published previously.[1,7,9,10] Inclusion and exclusion criteria, as well description of the interventions for the 2 trials, are summarized in the eMethods and eTable 1 in Supplement 1. Both studies were conducted according to the requirements of the Declaration of Helsinki. This pooled individual participant analysis was not preplanned; a detailed protocol of the statistical analysis has been published online.[11]

Patient Selection and Study Outcomes

For the purpose of this study, only patients who experienced OHCA and had a nonshockable rhythm with all causes of cardiac arrest were included. Patients were followed up with for 6 months (TTM2) or 3 months (HYPERION).

The primary outcome in this pooled analysis was mortality at 3 months. The secondary outcome was unfavorable functional outcome. In the TTM2 study, functional outcome was assessed using the Glasgow Outcome Scale Extended (GOSE) via a structured interview.[1,9] An unfavorable functional outcome was defined as GOSE score of 1 to 4 at 6 months. In the HYPERION study, functional outcome was assessed using the Cerebral Performance Category (CPC) scale, defined as a CPC score of 3 to 5 at 3 months.[7,10] To facilitate the analysis, CPC was derived from GOSE before the analysis (eTable 2 in Supplement 1) from an independent statistician. Functional outcomes of the 2 studies were combined, despite the different follow-up time. Additional secondary outcomes were: (1) intensive care unit (ICU) length of stay; (2) the occurrence of arrhythmias (bradycardia, atrial fibrillation, ventricular fibrillation, or ventricular tachycardia), as defined in each study protocol; (3) the diagnosis of pneumonia, as defined in each study protocol; and (4) any serious bleeding, as defined in each study protocol. Additional exploratory outcomes included: time to death (survival data) for each participant from randomization until 3 months after randomization (ie, if death has not occurred, participants will be censored at this point) and the distribution of CPC score, with a specific reporting on CPC 1.

Data Collection

Variables from the 2 studies were available from the original data sets and pooled into a unique database and analyzed at the Hôpital Universitaire de Bruxelles (HUB) in Brussels, Belgium. Clinical outcomes were harmonized into a single file, which was checked for accuracy of numbers, distributions, and categories. Also, the last day of follow-up from arrest was recorded for each patient. Adjustment for primary outcome and functional outcome was performed using age, gender, time to return of spontaneous circulation (ROSC), and bystander cardiopulmonary resuscitation (CPR). The data were reported as relative risk (RR) and 95% CIs.

Additional analyses of mortality and unfavorable functional outcome were performed in the following subgroups: (1) age (65 years or younger or older than 65 years); (2) gender; (3) pulseless electrical activity (PEA) vs asystole; (4) cause of arrest (ie, cardiac vs others); (5) presence or absence of shock on admission (ie, as defined in each study); (6) time to ROSC (ie, 25 minutes or shorter or longer than 25 minutes); (7) lactate levels (separated in terciles); and (8) cardiac arrest hospital prognosis (CAHP) score (separated in low, medium, and high risk).

As the TTM2 study included patients with OHCA with presumed cardiac cause of arrest on admission, an independent investigator assessed the definite cause of arrest, and reclassified all patients as cardiac or noncardiac causes, before the present analysis. The initial proposal for CAHP analysis was based on tertiles, but this was changed according to a more accepted separation in different subgroups.[12] Also, according to an individual patient meta-analysis involving 2 large randomized clinical trials (RCTs) on temperature control after cardiac arrest,[13] the subgroup of bystander CPR was added after the publication of the statistical plan. Subgroup results are presented using forest plots.

Statistical Analysis

A detailed description of statistical analyses is provided in the eMethods in Supplement 1. All analyses were conducted according to the intention-to-treat principle. The analysis and discussion were primarily based on the primary outcome, so all tests of statistical significance (including subgroup analyses) were 2-sided with a type I error risk of 5%.[14] All regression analyses were adjusted for site to balance prognostic baseline characteristics across trial intervention groups. Significant interactions between trial interventions and site were also assessed. Dichotomized outcomes were presented as proportions of participants in each group with the event, as well as risk ratios with 95% CIs. Dichotomous outcomes were analyzed using multilevel mixed-effects generalized linear models using a log-link function with site as a random intercept using an exchangeable covariance matrix. Risk ratios and their 95% CIs were computed.

All randomized participants were included in the primary analysis. We anticipated that the proportion of missing values on primary and secondary outcomes was less than 5%. However, a secondary analysis considered using multiple imputation and/or present best-worst and worst-best case scenarios was performed.[15] Missing data for the secondary outcome were also handled with a multiple-imputation model; the imputations were performed using multivariate imputation by chained equations.[16]

Trial sequential analysis was performed on the primary and secondary outcomes to perform a post hoc sample size calculation to estimate the number of participants needed in a meta-analysis to detect or reject the intervention effect. Systematic assessment underlying statistical assumptions for all statistical analyses was performed.[14,15] For all regression analyses, both primary and secondary, major interactions between site and the intervention variable were tested. Assessment of whether deviance divided by the degrees of freedom was significantly greater than 1 (ie, relevant overdispersion) was performed. All the statistical analyses for this study were performed in R version 3.6.0 (R Foundation for Statistical Computing). *P* values are 2-tailed and values <.05 were considered statistically significant.

Results

Study Population

From November 2017 to January 2020 for TTM2 and from January 2014 through January 2018 for HYPERION, 2484 patients with OHCA were randomly assigned at 90 hospitals in Australia and New Zealand, Europe, and the US to the 2 intervention arms. Of those, a total of 912 patients (36.7%) were included in this analysis, 490 patients from the TTM2 trial (53.7%) and 422 patients from the HYPERION trial (46.3%) (eTable 3 in Supplement 1). Of those, 442 patients were assigned to the hypothermia and 470 patients to the normothermia group. Baseline characteristics are reported in **Table 1**; study groups were well balanced at baseline. On admission, motor Full Outline of Unresponsiveness median score on admission was 0 (IQR, 0 to 0) in the TTM2 study, while median Glasgow Coma Scale on admission was 3 (IQR, 3 to 3) in the HYPERION study. Most of patients had asystole as first monitored rhythm and a noncardiac cause of arrest. The temperature curves are shown in **Figure 1**.

Primary Outcome

Data on the primary outcome are reported in **Table 2**; mortality data were available for all patients. At 3 months, 354 of 442 patients in the hypothermia group (80.1%) and 386 of 470 patients in the normothermia group (82.1%) had died (RR with hypothermia, 1.04; 95% CI, 0.89-1.20; *P* = .63). The association of the temperature intervention with death at 3 months was consistent across all the prespecified subgroups (**Figure 2**A) and when assessed in a time-to-event analysis (hazard ratio in the hypothermia group, 1.05; 95% CI, 0.89-1.23 (**Figure 3**). The presence (RR with hypothermia, 1.02; 95% CI, 0.80-1.31; *P* = .83) or absence (RR with hypothermia, 1.03; 95% CI, 0.86-1.23; *P* = .74) of bystander CPR was not associated with statistical differences in the primary outcome (*P* for interaction = .98). The trial sequential analysis for mortality showed that the cumulative *z*-curve did not cross the trial sequential monitoring boundaries for benefit nor harm, but crossed the inner-wedge futility line (eFigure 1A in Supplement 1).

Secondary Outcomes

Functional outcome was available in 429 patients in the hypothermia (97.0%) and for 463 patients in the normothermia group (98.5%). On the last day of follow-up, 386 of 429 patients in the hypothermia group (90.0%) and 413 of 463 patients in the normothermia group (89.2%) had an unfavorable functional outcome (RR with hypothermia, 0.99; 95% CI, 0.87-1.15; *P* = .97). The association of the temperature intervention on functional outcome was consistent across the prespecified subgroups (Figure 2B). The presence (RR with hypothermia, 0.98; 95% CI, 0.76-1.23; *P* = .83) or absence (RR with hypothermia, 1.01; 95%

Table 1. Characteristics of the Intention-to-Treat Population at Randomization[a]

Characteristic	Hypothermia (n = 442)	Normothermia (n = 470)
Age, mean (SD), y	65.5 (13.0)	65.6 (13.7)
Sex, No. (%)		
Male	287 (64.9)	327 (69.6)
Female	155 (35.1)	143 (30.4)
Medical history, No. (%)		
Chronic heart disease	49 (11.5)[b]	51 (11.1)[c]
Arterial hypertension	170 (40.0)[b]	201 (43.6)[c]
Diabetes	102 (23.1)	102 (21.7)
Previous myocardial infarction	50 (11.8)[b]	60 (13.0)[c]
Charlson Comorbidity Index, median (IQR)	2.0 (1.0-4.0)	3.0 (1.0-4.0)
Characteristics of the cardiac arrest, No. (%)		
Location of arrest		
Home	100 (22.6)	150 (31.9)
Public place	308 (69.7)	294 (62.6)
Other	34 (7.7)	26 (5.5)
Bystander witnessed arrest	399 (90.5)[d]	444 (94.5)
Bystander CPR performed	278 (63.0)[d]	328 (69.9)
First monitored rhythm		
Asystole	277 (62.7)	294 (62.6)
PEA	133 (30.1)	132 (28.1)
Cause of arrest		
Cardiac	182 (41.2)	227 (48.3)
Others	260 (58.8)	243 (51.7)
Time from cardiac arrest to sustained ROSC, median (IQR), min[e]	27.0 (18.0-37.0)	25.0 (17.0-37.0)
Time from arrest to randomization, median (IQR), min	179.0 (127.2-227.8)	176.0 (126.2-233.0)
Clinical characteristics on admission		
Temperature on admission, median (IQR)	35.2 (34.3-36.1)	35.2 (34.4 - 36.0)
Arterial pH, mean (SD), pH	7.1 (0.2)	7.2 (0.2)
Serum lactate, mean (SD), mmol/L	7.3 (4.3)	7.4 (4.7)
Shock on admission, No. (%)	223 (50.5)	235 (50.0)
ST-elevation myocardial infarction, No. (%)	88 (19.9)	81 (17.2)
CAHP score, No. (%)		
Low risk	125 (30.4)[f]	147 (32.6)[g]
Medium risk	195 (47.4)[f]	202 (44.8)[g]
High risk	91 (22.1)[f]	102 (22.6)[g]

Abbreviations: CAHP, Cardiac Arrest Hospital Prognosis; CPR, cardiopulmonary resuscitation; PEA, pulseless electrical activity; ROSC, return of spontaneous circulation.

[a] Data are reported as count (%) or median (25th to 75th percentiles).

[b] n = 425.

[c] n = 461.

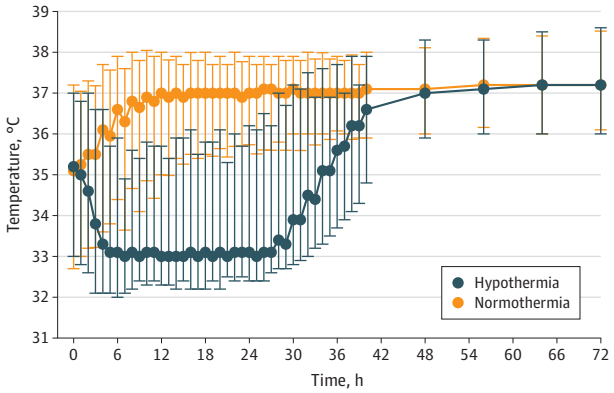
[d] n = 441.

[e] For unwitnessed arrest, the time to ROSC was calculated from the time of the emergency call.

[f] n = 411.

[g] n = 451.

Figure 1. Body Temperature Curves in the Hypothermia and Normothermia Groups for Patients in Whom a Core Temperature Was Recorded



Temperature curves show the median and 95% CIs of the observations are within the error bars.

CI, 0.85-1.19; P = .96) of bystander CPR was not associated with statistical differences in the occurrence of unfavorable functional outcome (P for interaction = 0.84). The trial sequential analysis for unfavorable functional outcome showed that the cumulative z-curve did not cross the trial sequential monitoring boundaries for benefit nor harm, but crossed the inner-wedge futility line (eFigure 1B in Supplement 1).

Best-worst, worst-best, and multiple imputation analyses indicated that missing data did not affect the results of the analyses of functional outcome (RR, 0.98; 95% CI, 0.85-1.13; P = .78; RR, 1.03; 95% CI, 0.89-1.18; P = .66; and RR, 0.99; 95% CI, 0.87-1.15; P = .98, respectively). There were no significant differences in the ICU length of stay and the proportion of patients with CPC 1 between groups. The distribution of CPC categories between groups is shown in eFigure 2 in Supplement 1.

Adverse Events

Prespecified adverse events are reported in Table 2. There were no significant differences in the occurrence of arrhythmias, bleeding, and pneumonia in the 2 groups.

Discussion

In this individual patient data meta-analysis of the TTM2 and HYPERION trials, hypothermia at 33 °C was not associated with improved survival or functional outcomes at 3 to 6 months for adult OHCA patients with an initial nonshockable rhythm when compared with targeted normothermia. Our study, along with recent systematic reviews that used traditional and bayesian meta-analyses,[17-19] suggests that the current type of temperature control used to induce and maintain hypothermia (ie, target of 33 °C; duration of the intervention of 24 to 40 hours; associated sedation), which has been used over the past 2 decades, does not provide the intended benefit, as shown in landmark trials.[2,3] Of note, the TTM2 and HYPERION studies are not comparable with previous trials,[2,3] as study cohorts were larger, more heterogenous (ie, different initial rhythms or different causes of

Table 2. Study Outcomes and Main Adverse Events

Outcome	No./total No. (%)		Risk ratio (95% CI)[a]	P value
	Hypothermia	Normothermia		
Primary outcome				
All-cause mortality at 3 mo	354/442 (80.1)	386/470 (82.1)	1.04 (0.89-1.18)	.63
Secondary outcome				
Unfavorable functional outcome at least at 3 mo	386/429 (90.0)	413/463 (89.2)	0.99 (0.87-1.15)	.97
ICU length of stay, d	4.0 (2.0-8.0)	4.0 (2.0-8.0)	NA	.73
CPC 1 at 3 mo	28/429 (6.5)	26/463 (5.6)	1.08 (0.81-1.37)	.58
Serious adverse events				
Arrhythmias	58/438 (13.2)	71/469 (15.1)	0.92 (0.74-1.11)	.44
Bleeding	27/438 (6.2)	21/469 (4.5)	1.18 (0.88-1.47)	.29
Pneumonia	104/304 (34.2)	103/354 (29.1)	1.13 (0.95-1.34)	.18

Abbreviations: ICU, intensive care unit; CPC, cerebral performance category; NA, not applicable.

[a] Adjusted risk ratio for mortality and unfavorable functional outcome analyses.

arrest), and with a more rigorous methodological structure (ie, lower risk of bias).[20] However, the TTM2 and HYPERION studies also presented significant differences in the study populations, including the proportion of patients with nonshockable rhythm, cardiac causes of arrest, the incidence and severity of shock upon admission, the methods to prevent fever in the normothermia group, and the location of the arrest. These differences prevented drawing more definitive conclusions regarding the association of hypothermia with measured outcomes in other subgroups of patients.[17-19] Our analysis had enhanced statistical power (ie, combination of raw data resulting in larger sample sizes and increased statistical power), improved data quality (ie, verification and standardization of data across studies), the possibility to assess time-to-event outcomes (ie, time to death), flexibility in modeling (ie, adjust for potential confounders at the individual patient level), and detailed subgroup analyses for a better understanding of treatment effect heterogeneity.

As such, this individual patient meta-analysis provides the best available evidence regarding the use of hypothermia in the management of OHCA patients with an initial nonshockable rhythm. Our subgroup analyses showed no association of hypothermia with improved outcomes in some populations of patients, such as those with a noncardiac cause of arrest (ie, mostly hypoxic/respiratory), prolonged resuscitation, absence of bystander CPR, and higher CAHP score, in whom previous studies suggested potential benefits.[7,13,21,22] Moreover, the trial sequential analysis revealed that the use of hypothermia in this population was associated with futility, ie, the inability of these clinical trials to achieve a statistically significant and/or clinically relevant difference from hypothermia. Hypothermia did not increase the frequency of pneumonia, arrhythmias, or hemorrhagic bleeding; however, although not statistically significant, there was still a potentially clinically important difference in the increased occurrence of pneumonia in patients treated with hypothermia. Moreover, the absence of a demonstrated increased risk of adverse events does not provide a sound justification for routine use of such intervention in patients with nonshockable rhythms who remain comatose after resuscitation from OHCA. Although some baseline nonsignificant imbalances in the groups were observed (ie, less cardiac arrest at home and cardiac causes of arrest in the hypothermia population), no interaction of location, and cause of arrest was observed on the effects of hypothermia on outcome.

Our study focused on the potential effects of 2 different temperature targets and did not investigate the role of other potential factors, such as duration, speed of achieving hypothermia or of rewarming, as the modality of temperature control, such as surface, endovascular or other cooling methods, on the effectiveness of such intervention.[23] Also, our findings do not provide evidence on the role of hypothermia in other specific populations of cardiac arrest patients, such as for in-hospital arrest, intra-arrest hypothermia, and the use of extra-corporeal membrane oxygenation.[7,24-26]

Limitations

These analyses have several limitations. First, other interventions, such as sedation, paralysis, and mechanical ventilation, were not standardized among patients and studies. Therefore, it remains unclear how such elements might have influenced overall outcomes. Also, differences in study design, baseline characteristics, and interventions across the 2 cohorts may have impacted the internal validity of the analyses, despite meticulous data abstraction. Second, the studies have different protocols to induce hypothermia or normothermia and did not have a control group without temperature management. The role of the quality of temperature control will be assessed in an ongoing study (NCT05564754), comparing fever management with or without a feedback-controlled device. Third, no additional data on cognitive function or longer follow-up evaluations were available. The CPC score is no longer recommended in the assessment of functional outcome for effectiveness trials conducted in cardiac arrest patients.[27] Fourth, some heterogeneity between studies might have influenced the robustness of our findings; however, no interaction on the effect of intervention was observed between the 2 trials. Fifth, outcome assessment was largely driven by nonsurvivors (ie, CPC 5); however, while CPC scores of 3 and 4 indicate neurologic impairments due to the initial anoxic injury, a CPC score of 5 or death is not necessarily related directly to brain damage and is also influenced by withdrawal of life sustaining therapies decisions. Sixth, we did not perform a systematic review of the literature to include all existing RCTs on this topic; a recent systematic review[17] identified 2 other

Figure 2. Subgroup Analysis of Death From Any Cause at 90 Days and of Unfavorable Functional Outcome Last Day of Follow-Up

A Death from any cause at 90 d

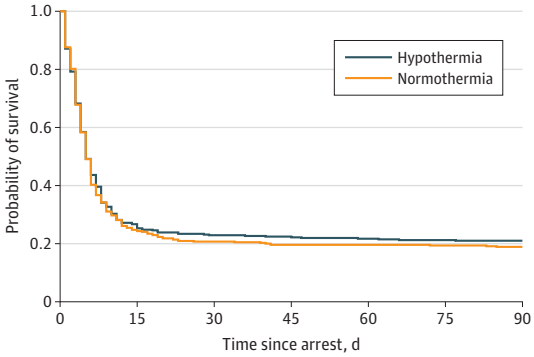
Variable	Hypothermia, No.		Normothermia, No.		Risk ratio (95% CI)	P value
	Died	Survived	Died	Survived		
Study						
HYPERION	182	29	181	30	1.01 (0.82-1.24)	
TTM	204	55	173	58	1.05 (0.86-1.29)	.76
Overall					1.04 (0.90-1.20)	
Age, y						
<65	154	43	141	45	1.03 (0.82-1.30)	
≥65	231	41	211	43	1.02 (0.85-1.23)	.95
Sex						
Female	125	18	126	29	1.08 (0.84-1.38)	
Male	261	66	228	59	1.01 (0.84-1.20)	.66
Location of arrest						
Public	268	52	275	67	1.04 (0.88-1.23)	
Other places	118	32	79	21	1.00 (0.75-1.33)	.79
Cause of arrest						
Other reasons	205	38	217	43	1.01 (0.83-1.22)	
Cardiac	181	46	137	45	1.06 (0.85-1.32)	.78
Time to ROSC, min						
<25	161	52	131	50	1.05 (0.83-1.32)	
≥25	225	32	223	38	1.03 (0.85-1.24)	.91
Shock						
No	187	48	167	52	1.04 (0.85-1.29)	
Yes	199	36	187	36	1.01 (0.83-1.23)	.82
First monitored rhythm						
Asystole	262	32	237	40	1.20 (0.66-2.19)	
PEA	96	36	100	33	1.04 (0.87-1.24)	.80
CAHP score						
Low	103	44	90	35	0.98 (0.74-1.30)	
Medium	172	30	160	35	1.05 (0.85-1.31)	.92
High	95	70	82	90	1.03 (0.76-1.38)	
Lactate level, mg/dL						
<42.3	99	45	91	43	1.01 (0.76-1.34)	
42.3-79.3	133	26	105	25	1.04 (0.80-1.34)	.99
>79.3	129	90	134	13	1.03 (0.81-1.31)	

B Unfavorable outcome at last day of follow-up

Variable	Hypothermia, No.		Normothermia, No.		Risk ratio (95% CI)	P value
	Unfavorable outcome	Favorable outcome	Unfavorable outcome	Favorable outcome		
Study						
HYPERION	194	17	199	12	0.97 (0.80-1.19)	
TTM	219	33	187	31	1.01 (0.83-1.23)	.79
Overall					1.00 (0.87-1.15)	
Age, y						
<65	166	29	156	23	0.98 (0.79-1.22)	
≥65	246	21	228	20	1.00 (0.84-1.20)	.86
Sex						
Female	132	80	141	11	1.02 (0.80-1.29)	
Male	281	42	245	32	0.98 (0.83-1.17)	.83
Location of arrest						
Public	286	30	301	30	1.00 (0.85-1.17)	
Other places	127	20	85	13	1.00 (0.76-1.31)	>.99
Cause of arrest						
Other reasons	219	19	233	18	0.99 (0.82-1.19)	
Cardiac	194	31	153	25	1.00 (0.81-1.24)	.93
Time to ROSC, min						
<25	176	32	151	26	0.99 (0.80-1.23)	
≥25	237	18	235	17	1.00 (0.83-1.19)	.97
Shock						
No	201	29	183	26	1.00 (0.82-1.22)	
Yes	212	21	203	17	0.99 (0.81-1.20)	.93
First monitored rhythm						
Asystole	275	17	256	16	0.81 (0.47-1.39)	
PEA	110	19	106	22	1.00 (0.84-1.19)	.73
CAHP score						
Low	112	31	104	19	0.93 (0.71-1.21)	
Medium	185	15	173	20	1.04 (0.85-1.28)	.80
High	99	30	85	30	1.00 (0.75-1.34)	
Lactate level, mg/dL						
<42.3	112	29	108	20	0.94 (0.72-1.23)	
42.3-79.3	142	15	112	15	1.03 (0.80-1.31)	.89
>79.3	133	40	138	50	1.01 (0.79-1.28)	

Relative risks are derived from a multilevel mixed-effects generalized linear models with trial site as a random intercept. The forest plot shows the relative risks for prespecified subgroups. The horizontal bars represent 95% CIs. CAHP indicates cardiac arrest hospital prognosis; PEA, pulseless electrical activity; ROSC, return on spontaneous circulation; TTM, Targeted Normothermia After Out-of-Hospital Cardiac Arrest.

Figure 3. Kaplan-Meier Estimates of the Probability of Survival Until 90 Days After Randomization Among Patients Assigned to Undergo Hypothermia or Normothermia



No. at risk

Hypothermia	419	93	89	84
Normothermia	449	97	91	88

Data are for the 912 patients included in the final analysis. Data were censored according to the last day of follow-up.

RCTs[28,29]; however, 1 had significant risks of bias[28] and both had a small number of patients (ie, 30 and 61, respectively) and used hypothermia devices (ie, helmet and hemofiltration) that are not recommended for temperature management. Lastly, the total sample size might still be relatively small for detecting clinically important differences between groups; however, taken together with the other available trials and the trial sequential analysis, it seems unlikely that conducting a future trial with larger sample size would lead to a different conclusion.

Conclusions

In this individual patient data meta-analysis including unconscious survivors resuscitated from OHCA with an initial nonshockable rhythm, hypothermia was not associated with improved survival and functional outcome, when compared to controlled normothermia. Trial sequential analysis indicated futility for hypothermia on mortality and functional outcome.

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