ORIGINAL ARTICLE

Hypothermia versus Normothermia after Out-of-Hospital Cardiac Arrest

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ABSTRACT

BACKGROUND

Targeted temperature management is recommended for patients after cardiac arrest, but the supporting evidence is of low certainty.

METHODS

In an open-label trial with blinded assessment of outcomes, we randomly assigned 1900 adults with coma who had had an out-of-hospital cardiac arrest of presumed cardiac or unknown cause to undergo targeted hypothermia at 33 C, followed by controlled rewarming, or targeted normothermia with early treatment of fever (body temperature, ≥37.8 C). The primary outcome was death from any cause at 6 months. Secondary outcomes included functional outcome at 6 months as assessed with the modified Rankin scale. Prespecified subgroups were defined according to sex, age, initial cardiac rhythm, time to return of spontaneous circulation, and presence or absence of shock on admission. Prespecified adverse events were pneumonia, sepsis, bleeding, arrhythmia resulting in hemodynamic compromise, and skin complications related to the temperature management device.

RESULTS

A total of 1850 patients were evaluated for the primary outcome. At 6 months, 465 of 925 patients (50%) in the hypothermia group had died, as compared with 446 of 925 (48%) in the normothermia group (relative risk with hypothermia, 1.04; 95% confidence interval [CI], 0.94 to 1.14; P=0.37). Of the 1747 patients in whom the functional outcome was assessed, 488 of 881 (55%) in the hypothermia group had moderately severe disability or worse (modified Rankin scale score ≥4), as compared with 479 of 866 (55%) in the normothermia group (relative risk with hypothermia, 1.00; 95% CI, 0.92 to 1.09). Outcomes were consistent in the prespecified subgroups. Arrhythmia resulting in hemodynamic compromise was more common in the hypothermia group than in the normothermia group (24% vs. 17%, P<0.001). The incidence of other adverse events did not differ significantly between the two groups.

CONCLUSIONS

In patients with coma after out-of-hospital cardiac arrest, targeted hypothermia did not lead to a lower incidence of death by 6 months than targeted normothermia. (Funded by the Swedish Research Council and others; TTM2 ClinicalTrials.gov number, NCT02908308.)

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*A complete list of TTM2 Trial Investigators is provided in the Supplementary Appendix, available at NEJM.org.

N Engl J Med 2021;384:2283-94.
DOI: 10.1056/NEJMoa2100591
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International guidelines recommend targeted temperature management to prevent hypoxicñischemic brain damage in patients with coma after cardiac arrest.[1,2] The evidence to support these recommendations originated in trials involving patients who had been resuscitated from out-of-hospital cardiac arrest of a presumed cardiac cause and shockable initial rhythms.[3,4] These trials suggested an increased survival and improved neurologic outcome in patients who underwent hypothermia at 33 C. A recent trial involving patients who had cardiac arrest with nonshockable rhythm showed better neurologic outcomes with targeted hypothermia at 33 C than with targeted normothermia at 37 C.[5] Trials comparing the level of targeted temperature management (33 C or 36 C) and the duration of this management (24 hours or 48 hours) have not indicated a dose effect.[6,7]

Although guidelines strongly recommend targeted temperature management with a constant target between 32 C and 36 C, they also state that the overall evidence is of low certainty. A systematic review that included a meta-analysis and trial sequential analysis indicated that the available trials had high risks of bias and random errors.[8]

Fever has been proposed as a risk factor for an unfavorable neurologic outcome after cardiac arrest, although it is unknown whether there is a causal and modifiable relationship.[9] Accordingly, we conducted the randomized Targeted Hypothermia versus Targeted Normothermia after Out-of-Hospital Cardiac Arrest (TTM2) trial to assess the beneficial and harmful effects of hypothermia as compared with normothermia and early treatment of fever in patients after cardiac arrest. We hypothesized that at 6 months, the incidence of death would be lower in the hypothermia group than in the normothermia group.

Methods

Trial Design

The design of this international, investigator-initiated superiority trial and its statistical analysis plan have been published previously.[10,11] The protocol (available with the full text of this article at NEJM.org) was approved by the ethics committees in each participating country. Written informed consent was waived, deferred, or obtained from a legal surrogate, depending on the circumstances, and was obtained from each patient who regained mental capacity. An independent data and safety monitoring committee reviewed the data and performed one prespecified, blinded interim analysis. Additional details on the trial design, including investigator responsibilities, are described in the Supplementary Appendix, available at NEJM.org. There was no commercial funding for the trial.

Patients

We consecutively screened adults (≥18 years of age) who had been admitted to the hospital after out-of-hospital cardiac arrest of a presumed cardiac or unknown cause, irrespective of the initial rhythm. All the patients were unconscious and not able to obey verbal commands (score of <4 on the Full Outline of Unresponsiveness [FOUR] scale,[12] which ranges from 0 to 4, with higher scores indicating better motor function) and did not have a verbal response to pain. Eligible patients had more than 20 consecutive minutes of spontaneous circulation after resuscitation.[13] The main exclusion criteria were an interval from return of spontaneous circulation to screening of more than 180 minutes, unwitnessed cardiac arrest with asystole as the initial rhythm, and limitations in care. Detailed inclusion and exclusion criteria are provided in the Supplementary Appendix.

Randomization and Blinding

After eligibility screening, patients were randomly assigned in a 1:1 ratio to undergo hypothermia or normothermia. Randomization was performed with the use of a Web-based system involving permuted blocks of varying sizes and was stratified according to trial site and coenrollment in the Targeted Therapeutic Mild Hypercapnia after Resuscitated Cardiac Arrest (TAME) trial (ClinicalTrials.gov number, NCT03114033).

Health professionals caring for the trial patients were aware of the trial-group assignments because of inherent problems with blinding body temperature. The physicians assessing neurologic prognosis, assessors of functional outcome, and study administrators were unaware of the trial-group assignments. During the analysis

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phase, the statisticians and authors were unaware of the trial-group assignments, which were identified as Y and Z. A manuscript was written for each scenario before the randomization code was broken.[14]

TRIAL INTERVENTION

The intervention period of 40 hours began at the time of randomization. Patients who were assigned to undergo hypothermia were immediately cooled with a surface or intravascular temperature-management device to a target temperature of 33 C. This target was maintained until 28 hours after randomization, followed by rewarming to 37 C in hourly increments of one third of a degree. In the normothermia group, the aim was to maintain a temperature of 37.5 C or less. If conservative and pharmacologic measures were insufficient and the body temperature reached 37.8 C or higher, cooling with a surface or intravascular temperature-management device was initiated with a target temperature of 37.5 C. No active warming or cooling was provided for patients in the normothermia group who had a spontaneous body temperature below 37.8 C. Sedation was mandated in both groups until the end of the intervention period. After the intervention period, a normothermic target (36.5 C to 37.7 C) was maintained until 72 hours after randomization in patients who remained sedated or comatose. Details of the trial interventions are provided in the Supplementary Appendix.

ASSESSMENT OF NEUROLOGIC PROGNOSIS AND WITHDRAWAL OF LIFE SUPPORT

At 96 hours after randomization or later, a physician who was unaware of the intervention assignments performed a neurologic assessment of patients who remained in the intensive care unit (ICU). The physician assessed whether the criteria for a likely poor neurologic outcome were present.

All decisions about withdrawal of life-sustaining therapy were at the discretion of the treating physician, guided by the protocol. After assessment of neurologic prognosis, withdrawal of life-sustaining therapies due to a presumed poor neurologic prognosis was allowed. (Details regarding the neurologic evaluation are provided in the Supplementary Appendix.)

PRIMARY AND SECONDARY OUTCOMES

The primary outcome was death from any cause at 6 months. The main secondary outcome was a poor functional outcome at 6 months, defined as a score of 4 to 6 on the modified Rankin scale.[15,16] Scores on the modified Rankin scale range from 0 to 6, with 0 representing no symptoms, 1 no clinically significant disability, 2 slight disability, 3 moderate disability, 4 moderately severe disability, 5 severe disability, and 6 death. A trained outcome assessor used a structured questionnaire to evaluate the patient s condition. The functional score was determined after face-to-face or telephone interviews with patients, relatives, and health care providers.[17]

If a structured assessment could not be completed, a binary assessment based on all available data (including medical records) was performed; functional outcome was classified as good or poor on the basis of a dichotomized modified Rankin scale (a score of 0 to 3 or 4 to 6). This post hoc approach was used because of the restrictions imposed during the coronavirus disease 2019 pandemic.

Other secondary outcomes were the number of days the patient was alive and out of the hospital until day 180, survival determined in a time-to-death analysis, and health-related quality of life, which was assessed with the use of the visual-analogue scale on the European Quality of Lifeñ5-Dimensionñ5-Level questionnaire (EQ-5D-5L), which ranges from 0 to 100, with higher scores indicating better health status as assessed by the patient.[15] Verification of trial data and the outcome measures are described in the Supplementary Appendix.

ADVERSE EVENTS

Prespecified adverse events were pneumonia, sepsis, bleeding, arrhythmia resulting in hemodynamic compromise, and skin complications related to the device used for targeted temperature management. Definitions of these adverse events are provided in the Supplementary Appendix.

STATISTICAL ANALYSIS

We estimated that a sample of 1862 patients would provide 90% power to detect a relative reduction of 15% in the risk of death in the hypothermia group, as compared with the normo-

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

Characteristic	Hypothermia (N=930)	Normothermia (N=931)
Demographic characteristics		
Age yr	64±13	63±14
Male sex no. (%)	742 (80)	735 (79)
Medical history		
Hypertension no. (%)	345 (37)	298 (32)
Diabetes no. (%)	173 (19)	167 (18)
Myocardial infarction no. (%)	139 (15)	154 (17)
PCI no. (%)	130 (14)	140 (15)
Coronary-artery bypass grafting no. (%)	73 (8)	76 (8)
Heart failure no. (%)	90 (10)	93 (10)
NYHA III or IV heart failure no./total no. (%)	20/906 (2)	23/904 (3)
Median Charlson comorbidity index (IQR)á	3 (2 4)	3 (1 4)
Characteristics of the cardiac arrest no. (%)		
Location at cardiac arrest		
Place of residence	487 (52)	491 (53)
Public place	338 (36)	320 (34)
Other	105 (11)	120 (13)
Bystander-witnessed cardiac arrest	850 (91)	852 (92)
Bystander-performed CPR	759 (82)	728 (78)
First monitored rhythm no. (%)		
Shockable rhythm	671 (72)	700 (75)
Ventricular fibrillation	576 (62)	585 (63)
Nonperfusing ventricular tachycardia	31 (3)	29 (3)
ROSC after bystander-initiated defibrillation	24 (3)	41 (4)
Unknown rhythm, shock administered	40 (4)	45 (5)
Nonshockable rhythm	259 (28)	231 (25)
Pulseless electrical activity	117 (13)	113 (12)
Asystole	124 (13)	100 (11)
Unknown rhythm, no shock administered	18 (2)	18 (2)
Median time from cardiac arrest to sustained ROSC (IQR) min	25 (16 40)	25 (17 40)
Median time from cardiac arrest to randomization min (IQR)	136 (103 170)	133 (99 173)
Clinical characteristics on admission		
Tympanic temperature C	35.3±1.1	35.4±1.1
FOUR motor score‖	0	0
Bilateral corneal reflexes present no./total no. (%)	168/511 (33)	194/537 (36)
Bilateral pupillary reflexes present no./total no. (%)	535/761 (70)	529/776 (68)
Arterial pH**	7.2±0.2	7.2±0.2
Arterial lactate level mmol/liter	5.9±4.4	5.8±4.2
Shock no. (%)áá	261 (28)	275 (30)
ST-segment elevation myocardial infarction no./total no. (%)	379/918 (41)	370/921 (40)

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Table 1. (Continued.)

* Plus minus values are means ±SD. CPR denotes cardiopulmonary resuscitation, IQR interquartile range, PCI percutaneous coronary intervention, and ROSC return of spontaneous circulation.
New York Heart Association (NYHA) heart failure class was not assessed in 51 patients (24 in the hypothermia group and 27 in the normothermia group) who had a history of heart failure.
á On the Charlson comorbidity index, each comorbidity category is weighted from 1 to 6 on the basis of adjusted risk of death or resource use, and the sum of the weights produces the score. A score of 0 indicates an absence of known coexisting conditions, and higher scores indicate higher risks of death and greater resource use.
For unwitnessed cardiac arrests, the time to ROSC was calculated from the time of the emergency call.
Tympanic temperature was assessed in 1559 patients.
‖ Full Outline of Unresponsiveness (FOUR) motor scores range from 0 to 4, with higher scores indicating better motor function. The FOUR motor score was assessed in 1696 patients.
** Arterial pH was measured in 1829 patients.
The arterial lactate level was measured in 1781 patients.
áá Shock at admission was defined as a systolic blood pressure of less than 90 mm Hg for more than 30 minutes or end-organ hypoperfusion (cool arms and legs, urine output <30 ml per hour, and heart rate <60 beats per minute).

thermia group, at a two-sided alpha level of 0.05 (absolute risk reduction of 7.5 percentage points). The estimated relative risk was based on results from earlier trials of hypothermia for cardiac arrest.[10] To allow for loss to follow-up and withdrawn consent, a sample size of 1900 was chosen.

The principal trial analyses were performed in the intention-to-treat population, defined as all randomly assigned patients except those for whom consent was withdrawn. Dichotomous outcomes, including the primary analysis, were assessed with the use of a mixed-effects generalized linear model with a logit link with adjustment for stratification variables and were reported as population-level (marginal) relative risks derived by G-computation. Analysis of survival data was performed with Cox regression. For all regression analyses, we tested for an interaction effect between group assignment and assignment in the TAME trial. We made no assumptions regarding the pattern of missing data, which were handled according to the statistical analysis plan.[11,18] A P value of less than 0.05 was considered to indicate statistical significance for the primary outcome. Secondary outcomes are presented with 95% confidence intervals and were not adjusted for multiplicity. All analyses were performed with the use of R: A Language and Environment for Statistical Computing.[19]

RESULTS

PATIENTS

A total of 1900 patients were enrolled between November 2017 and January 2020. Consent could not be obtained or was withdrawn in 37 patients, and 2 patients underwent randomization twice, resulting in an intention-to-treat population of 1861, of whom 930 were assigned to the hypothermia group and 931 to the normothermia group (Fig. S1 in the Supplementary Appendix). Baseline characteristics are reported in Table 1. Details regarding procedures and administered drugs, assessment of neurologic prognosis, withdrawal of life-sustaining therapy, length of ICU and hospital stay, and data regarding coenrollment in the TAME trial are provided in Tables S1 through S6 and Figures S2 and S3.

TEMPERATURE INTERVENTION

The temperature curves are shown in Figure 1. In the hypothermia group, the median time from the start of the intervention until a temperature of 34 C was reached was 3 hours. In this group, 53 of 930 patients (6%) were rewarmed before 40 hours after randomization, as allowed by the protocol, primarily because of cardiovascular instability and arrhythmias (Table S7). A total of 882 of 930 patients (95%) in the hypothermia group and 428 of 931 patients (46%) in the normothermia group received cooling with a device. Among patients who received cooling, the types of devices used in each treatment group were similar (70% surface and 30% intravascular in the hypothermia group and 69% surface and 31% intravascular in the normothermia group). In the hypothermia group, the reasons for not receiving cooling with a device were intracranial hemorrhage, early death, early awakening, hemodynamic instability, and referral for cardiac surgery, whereas the main reason in the normothermia group was not reaching the threshold

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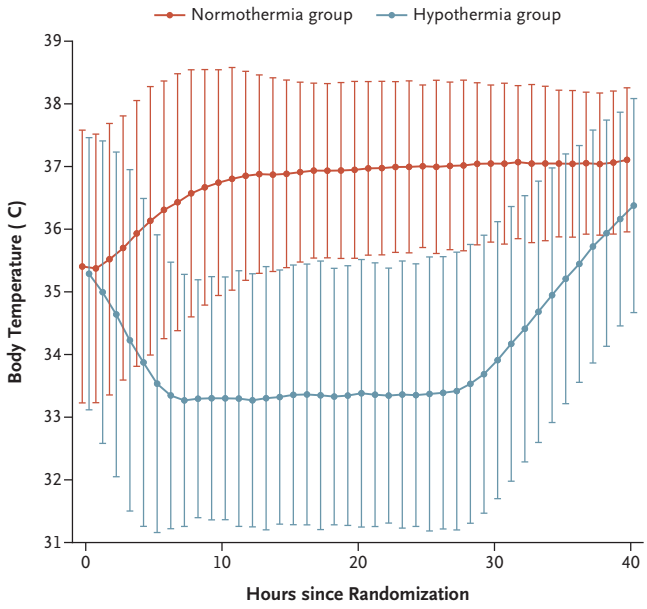

Figure 1. Body Temperature during the Intervention Period.

Shown are body-temperature curves in the hypothermia and normothermia groups for the patients in whom a bladder temperature was recorded. The median number of temperature recordings was 38 in both the hypothermia group and the normothermia group, out of 41 possible recordings. The temperature curves show the means, and the I bars indicate ±2 SD (95% of the observations are within the error bars). The median time from cardiac arrest to randomization in the trial was 135 minutes.

for fever. Additional data regarding temperatures and shivering are available in Figures S4 through S7 and Table S8.

PRIMARY AND SECONDARY OUTCOMES

Data on the primary outcome were missing for 11 patients (5 in the hypothermia group and 6 in the normothermia group) of 1861 patients overall (<1%). At 6 months, 465 of 925 patients (50%) in the hypothermia group and 446 of 925 patients (48%) in the normothermia group had died (relative risk with hypothermia, 1.04; 95% confidence interval [CI], 0.94 to 1.14; P=0.37). The effect of the temperature intervention on death at 6 months was consistent across the prespecified subgroups (Fig. 2A) and when assessed in a time-to-event analysis (hazard ratio in the hypothermia group, 1.08; 95% CI, 0.95 to 1.23) (Fig. 3).

Functional outcome was assessed according to the modified Rankin scale in 1747 of 1861 patients (94%) (Fig. S8). A structured assessment was performed in a face-to-face interview (72%), by phone (23%), or by proxy interview (5%). In addition, functional outcome was classified only as good or poor on the basis of telephone interviews with relatives and health care providers and on the basis of medical records in 37 of 930 patients (4%) in the hypothermia group and 45 of 931 patients (5%) in the normothermia group. In total, functional outcome was assessed in 1829 of 1861 patients (98%).

At 6 months, 488 of 881 patients (55%) in the hypothermia group and 479 of 866 patients (55%) in the normothermia group had a modified Rankin scale score of 4 to 6 (relative risk with hypothermia, 1.00; 95% CI, 0.92 to 1.09). In the binary assessment of functional outcome, 495 of 918 patients (54%) in the hypothermia group and 493 of 911 patients (54%) in the normothermia group had a poor functional outcome (relative risk in the hypothermia group, 1.00; 95% CI, 0.91 to 1.08). The effect of the temperature intervention on functional outcome was consistent across the prespecified subgroups (Fig. 2B).

Health-related quality of life as assessed with the use of the EQ-5D-5L visual-analogue scale was similar in the hypothermia and normothermia groups, regardless of whether the patients who died were included (with the score on the EQ-5D-5L visual-analogue scale set to 0) or only those who survived were assessed (mean between-group difference in patients who survived to 6 months, −0.8 points; 95% CI, −3.6 to 2.0) (Table S9). The distribution of days when the patients were alive and out of the hospital was similar in the two groups (Fig. S9).

Bestñworst and worstñbest analyses indicated that missing data did not have the potential to affect the results of the analyses of both death from any cause and functional outcome (Table S10). Additional sensitivity analyses are reported in Table S11. There were no significant interactions between group assignments in the current trial and assignments in the TAME trial for any of the outcomes (range of P for interaction, 0.58 to 0.94) (Table S12).

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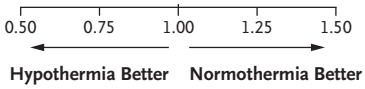
A Death at 6 Months

Subgroup	Hypothermia	Normothermia	Relative Risk of Death (95% CI)
	no. of patients		
All patients	925	925	1.04 (0.94 1.14)
Sex			
Male	738	729	1.03 (0.92 1.15)
Female	187	196	1.10 (0.94 1.29)
Age			
<65 yr	421	457	0.99 (0.83 1.18)
≥65 yr	504	468	1.04 (0.94 1.15)
Time to ROSC from cardiac arrest			
<25 min	419	416	1.09 (0.91 1.33)
≥25 min	506	509	1.02 (0.92 1.12)
Initial rhythm			
Nonshockable	259	231	1.04 (0.94 1.14)
Shockable	666	694	1.00 (0.87 1.15)
Shock on admission			
Not present	665	651	1.07 (0.95 1.23)
Present	260	274	1.01 (0.89 1.15)



B Modified Rankin Scale Score of 4 6 at 6 Months

Subgroup	Hypothermia	Normothermia	Relative Risk of Score of 4 6 (95% CI)
	no. of patients		
All patients	881	866	1.00 (0.92 1.09)
Sex			
Male	701	679	1.00 (0.90 1.10)
Female	180	187	1.03 (0.90 1.19)
Age			
<65 yr	391	429	0.94 (0.79 1.10)
≥65 yr	490	437	1.01 (0.92 1.10)
Time to ROSC from cardiac arrest			
<25 min	395	389	1.04 (0.87 1.24)
≥25 min	486	477	0.98 (0.90 1.07)
Initial rhythm			
Nonshockable	252	218	1.00 (0.93 1.08)
Shockable	629	648	0.96 (0.84 1.08)
Shock on admission			
Not present	629	606	1.03 (0.92 1.16)
Present	252	260	0.97 (0.86 1.08)

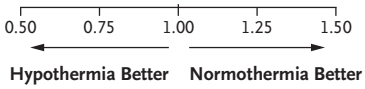


Figure 2. Subgroup Analysis of Death from Any Cause and the Modified Rankin Scale Score at 6 Months.

Shown are the results of the analyses of the primary outcome (death from any cause at 6 months) (Panel A) and of the secondary outcome of a score of 4 to 6 on the modified Rankin scale (Panel B) in prespecified subgroups. Modified Rankin scale scores range from 0 to 6, with 0 representing no symptoms, 1 no clinically significant disability, 2 slight disability, 3 moderate disability, 4 moderately severe disability, 5 severe disability, and 6 death. Relative risks are derived from a stratified generalized linear model with trial site as a random intercept. The forest plot shows the relative risks for five prespecified subgroups. The horizontal bars represent 95% confidence intervals. The events are the total events 6 months after randomization. For unwitnessed cardiac arrests, the time until a return of spontaneous circulation (ROSC) was calculated from the time of the emergency call. Shock on admission was defined as a systolic blood pressure of less than 90 mm Hg for more than 30 minutes or end-organ hypoperfusion (cool arms and legs, urine output <30 ml per hour, and heart rate <60 beats per minute).

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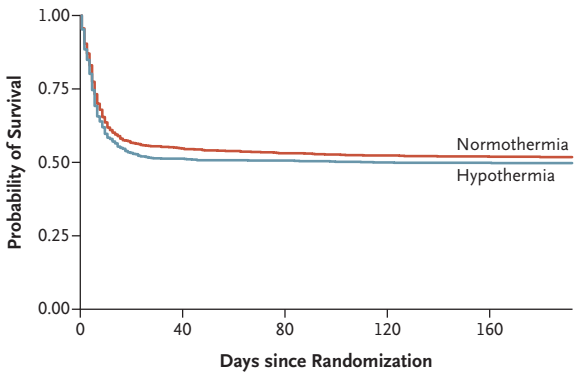

No. at Risk					
Normothermia	925	506	491	484	480
Hypothermia	925	474	468	462	461

Figure 3. Probability of Survival until 180 Days after Randomization.
Shown are Kaplan Meier estimates of the probability of survival until 180 days after randomization among patients assigned to undergo hypothermia or normothermia. Data are for the 1850 patients for whom survival status (including time of death) was available. Data were censored according to the last day of follow-up.

ADVERSE EVENTS

Prespecified adverse events are reported in Table 2. Arrhythmias resulting in hemodynamic compromise were more common in the hypothermia group than in the normothermia group (in 24% vs. 17%; P<0.001). There were no significant differences in other prespecified adverse events. Two unexpected serious, possibly intervention-related adverse events occurred in each group: an intravascular deviceñrelated thrombosis in one patient in the hypothermia group and two patients in the normothermia group, and bradycardia with worsening hemodynamic function in one patient in the hypothermia group (see the Supplementary Appendix).

DISCUSSION

In this randomized trial, we compared hypothermia with normothermia in patients with coma who had been resuscitated after out-of-hospital cardiac arrest of a presumed cardiac or unknown cause. There was no significant difference between the two groups with respect to death and poor functional outcome at 6 months. The distribution of scores on the modified Rankin scale between the groups was similar, as was health-related quality of life. The results were consistent in the analysis of survival and in prespecified subgroups.

Our results contrast with findings of practice-changing trials published in 2002 in which a benefit of hypothermia was reported.[3,4] Since then, there have been changes in standards of intensive care that may have influenced intervention effects.[20,21] Other explanations would be a lower risk of bias in the current trial[22] and a lower risk of random error with a sample size that was five times the combined enrollment of the earlier trials.[23,24] Although the patient population we studied differed somewhat from those in previous trials, our subgroup analyses indicate that different eligibility criteria are unlikely to explain the discordance.

Our findings are consistent with those of a recent trial in which hypothermia at 33 C, as compared with normothermia at 37 C, in patients with nonshockable rhythms was not shown to reduce mortality.[5] That trial indicated that hypothermia may improve functional outcomes, but this finding was based on a small number of events and was not replicated in the subgroup of patients with initial nonshockable rhythm in our trial.

The results of the current trial are broadly consistent with the results of our previous TTM (Target Temperature Management 33 C versus 36 C after Out-of-Hospital Cardiac Arrest) trial.[6] The combined results of the two trials imply a low likelihood of any meaningful clinical improvement with hypothermia as compared with normothermia, since 36 C may be considered to be the lower boundary of normothermia.

It is physiologically plausible that the interval between a cardiac event and the initiation of hypothermia is related to potential benefits of the intervention, a hypothesis that is supported by experiments in animals.[25] In our trial, patients were cooled at a similar or faster rate than that in most previous trials.[3,5-7] Since all participating sites in our trial had previous experience with the use of hypothermia, and a large percentage of the patients in our trial underwent randomization at cardiac arrest centers, the cooling rates we observed were probably faster than those that are feasible in current clinical practice.

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Table 2. Outcomes and Adverse Events.

Outcome or Event	Hypothermia (N=930)	Normothermia (N=931)	Relative Risk (95% CI)*	P Value
Primary outcome: death from any cause at 6 mo no./total no. (%)	465/925 (50)	446/925 (48)	1.04 (0.94 1.14)	0.37
Main secondary outcome no./total no. (%)				
Score of 4 6 on modified Rankin scale at 6-mo follow-up	488/881 (55)	479/866 (55)	1.00 (0.92 1.09)	
Poor functional outcome at 6 moá	495/918 (54)	493/911 (54)	1.00 (0.91 1.08)	
Score on modified Rankin scale at 6-mo follow-up no./total no. (%)				
0	140/881 (16)	148/866 (17)		
1	87/881 (10)	80/866 (9)		
2	132/881 (15)	127/866 (15)		
3	34/881 (4)	32/866 (4)		
4	16/881 (2)	20/866 (2)		
5	7/881 (1)	13/866 (2)		
6	465/881 (53)	446/866 (52)		
Serious adverse events no./total no. (%)				
Arrhythmia resulting in hemodynamic compromise	222/927 (24)	152/921 (16)	1.45 (1.21 1.75)	<0.001
Bleeding	44/927 (5)	46/922 (5)	0.95 (0.63 1.42)	0.81
Skin complication related to device used for targeted temperature management	10/927 (1)	5/922 (<1)	1.99 (0.71 6.37)	0.21
Pneumonia	330/927 (36)	322/921 (35)	1.02 (0.90 1.15)	0.75
Sepsis	99/926 (11)	83/922 (9)	1.19 (0.90 1.57)	0.23

* The relative risks of death from any cause, a modified Rankin scale score of 4 to 6, and poor neurologic function at 6 months were adjusted for the stratification variables. The relative risks of serious adverse events were adjusted for coenrollment status in the Targeted Therapeutic Mild Hypercapnia after Resuscitated Cardiac Arrest (TAME) trial, but not for site. The relative risks of skin complications related to the device used for targeted temperature management were unadjusted. The widths of the confidence intervals have not been adjusted for multiple testing, so the intervals should not be used to infer definitive differences between the groups.
Scores on the modified Rankin scale range from 0 to 6, with 0 representing no symptoms, 1 no clinically significant disability, 2 slight disability, 3 moderate disability, 4 moderately severe disability, 5 severe disability, and 6 death. These results are based on data from a structured interview
á These results are based on all available data..

Hypothermia did not increase the frequency of pneumonia, sepsis, or bleeding, but arrhythmias causing hemodynamic compromise were more common in the hypothermia group than in the normothermia group. Possible reasons for this include electrolyte disturbances, fluid status, and a temperature effect on cardiac myocytes.[26]

Our trial has several limitations. First, to isolate the effect of hypothermia, both trial groups were treated similarly, except for the temperature intervention. Elements of standard care in the ICU, such as sedation, paralysis, and mechanical ventilation, were therefore included in the trial protocol in a form that was not necessarily representative of clinical practice. It is unclear what influence these elements had on the outcomes. The trial also included a conservative protocol for assessment of neurologic prognosis and guidance for withdrawal of life support, which may have influenced outcomes. Second, staff members in the ICU were aware of the assigned target temperature during the ICU stay. We aimed to minimize this problem by using outcomes with a low risk of bias, outcome assessors who were unaware of the trial-group

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assignments, and a conservative protocol for determination of the neurologic prognosis and withdrawal of life-supporting therapies. During the analysis and writing process, the investigators, statisticians, and authors were unaware of the temperature-group assignments, and writing of the manuscript was performed in duplicate, with the groups interchanged. Third, since we did not include a control group without temperature management, this trial leaves a knowledge gap regarding whether any temperature management is better than no temperature management. Nonetheless, actual temperatures in the normothermia group were broadly similar to those recorded in the control group of the Hypothermia after Cardiac Arrest trial, in which no temperature management was used.[3] As compared with that trial, about half the patients in the normothermia group in our trial were cooled with a device. Whether this type of fever control is of benefit must be addressed in a separate trial. Fourth, concomitant care, except for sedation and prognostication, was not part of the protocol and was left to the discretion of participating hospitals. However, sites were instructed to treat the groups similarly, and the stratification for participating hospitals should have balanced intersite differences. Fifth, the trial was limited to out-of-hospital cardiac arrest of a presumed cardiac or unknown cause, so the results are not fully applicable to other presentations of cardiac arrest. However, a lack of cerebral perfusion is the primary cause of hypoxicñ ischemic encephalopathy in cardiac arrest, regardless of where the event occurs or the cause of arrest. Finally, one fifth of the patients were also enrolled in the TAME trial. We did not anticipate any between-trial interaction, an expectation that was supported by our analyses, although such comparisons were probably underpowered.

Our results were consistent across the objective outcome of death from any cause, the clinician-reported functional outcome (as measured on the modified Rankin scale), and patient-reported health-related quality of life (as measured on the EQ-5D-5L visual-analogue scale). The large sample size, broad eligibility criteria, and numerous hospitals and countries represented in this trial increase the generalizability.

Patients with coma after out-of-hospital cardiac arrest who were treated with hypothermia did not have a lower incidence of death at 6 months than those who were treated with normothermia.

Supported by independent research grants from nonprofit or governmental agencies (the Swedish Research Council [Vetenskapsr det], Swedish HeartñLung Foundation, Stig and Ragna Gorthon Foundation, Knutsson Foundation, Laerdal Foundation, Hans-Gabriel and Alice Trolle-Wachtmeister Foundation for Medical Research, and Regional Research Support in Region Sk ne) and by governmental funding of clinical research within the Swedish National Health Service.

Dr. Oddo reports receiving advisory board fees from Neuroptics; Dr. Cariou, receiving lecture fees from Bard Medical; Dr. Saxena, receiving consulting fees from Bard Medical; Dr. Young, receiving lecture fees from Bard Medical; Dr. Storm, receiving lecture fees and travel support from Bard Medical and consulting fees from BrainCool, Pfizer, Sedana Medical, and Xenios; Dr. Taccone, receiving grant support from Bard Medical and ZOLL Medical; Dr. Callaway, holding patent US7269454B2 on methods and devices to guide therapy for ventricular fibrillation with waveform analysis, patent WO2016168181A1 on identification of non-ST elevation ischemic events on electrocardiography, and patent US6438419B1 on a method and apparatus using a scaling exponent for selective defibrillation; Dr. Morgan, receiving fees for coordinating an educational workshop from Bard Medical; Dr. Nichol, receiving grant support, paid to University College Dublin, from AM Pharma and grant support, paid to Monash University, from Baxter Healthcare; Dr. Chew, receiving lecture fees from Edwards Lifesciences; Dr. Levis, receiving donated supplies from Prytime Medical Devices; Dr. Keeble, receiving travel support from Zoll Circulation; Dr. Leithner, receiving lecture fees, paid to Charit Universit tzmedizin, from Bard Medical and ZOLL Medical; Dr. Friberg, receiving fees for academic advising from TEQCool; and Dr. Nielsen, receiving lecture fees from Bard Medical and consulting fees from BrainCool. No other potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

We thank the trial patients, their relatives, and clinical and research staff at all the trial sites; Audrey Shearer and colleagues at Spiral Software; Richard Frobell, Kristina K ll n, Ulf Malmqvist, Kathy Rowan, David Harrison, Paul Mouncey, Manu Shankar-Hari, Duncan Young, Karolina Palm r, and Viktor Hultqvist; and the TAME trial group.

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