ORIGINAL ARTICLE

Targeted Temperature Management at 33°C versus 36°C after Cardiac Arrest

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ABSTRACT

BACKGROUND

Unconscious survivors of out-of-hospital cardiac arrest have a high risk of death or poor neurologic function. Therapeutic hypothermia is recommended by international guidelines, but the supporting evidence is limited, and the target temperature associated with the best outcome is unknown. Our objective was to compare two target temperatures, both intended to prevent fever.

METHODS

In an international trial, we randomly assigned 950 unconscious adults after out-of-hospital cardiac arrest of presumed cardiac cause to targeted temperature management at either 33°C or 36°C. The primary outcome was all-cause mortality through the end of the trial. Secondary outcomes included a composite of poor neurologic function or death at 180 days, as evaluated with the Cerebral Performance Category (CPC) scale and the modified Rankin scale.

RESULTS

In total, 939 patients were included in the primary analysis. At the end of the trial, 50% of the patients in the 33°C group (235 of 473 patients) had died, as compared with 48% of the patients in the 36°C group (225 of 466 patients) (hazard ratio with a temperature of 33°C, 1.06; 95% confidence interval [CI], 0.89 to 1.28; P=0.51). At the 180-day follow-up, 54% of the patients in the 33°C group had died or had poor neurologic function according to the CPC, as compared with 52% of patients in the 36°C group (risk ratio, 1.02; 95% CI, 0.88 to 1.16; P=0.78). In the analysis using the modified Rankin scale, the comparable rate was 52% in both groups (risk ratio, 1.01; 95% CI, 0.89 to 1.14; P=0.87). The results of analyses adjusted for known prognostic factors were similar.

CONCLUSIONS

In unconscious survivors of out-of-hospital cardiac arrest of presumed cardiac cause, hypothermia at a targeted temperature of 33°C did not confer a benefit as compared with a targeted temperature of 36°C. (Funded by the Swedish Heart–Lung Foundation and others; TTM ClinicalTrials.gov number, NCT01020916.)

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Unconscious patients admitted to critical care units after out-of-hospital cardiac arrest are at high risk for death, and neurologic deficits are common among those who survive.[1] Two previous trials, involving patients who remained unconscious after resuscitation from cardiac arrest (of presumed cardiac cause, with an initial shockable rhythm), compared therapeutic hypothermia (32°C to 34°C for 12 to 24 hours) with standard treatment. These trials showed a significant improvement in neurologic function[2,3] and survival[3] with therapeutic hypothermia.

Therapeutic hypothermia (also called targeted temperature management) is now recommended in international resuscitation guidelines, and its use has been extended to cardiac arrest of other causes and with other presenting rhythms as well as to the in-hospital setting.[4] Although a Cochrane review supports these guidelines,[5] some investigators have suggested a need for additional trials to confirm or refute the current treatment strategy.[6-8] Furthermore, one trial showed that fever developed in many patients in the standard-treatment group.[3] It is therefore unclear whether the reported treatment effect was due to hypothermia or to the prevention of fever, which is associated with a poor outcome.[9-11] We conducted a trial to investigate the benefits and harms of two targeted temperature regimens, both intended to prevent fever, in a broader population of patients with cardiac arrest than previously studied.

Methods

Trial Design

The Target Temperature Management 33°C versus 36°C after Out-of-Hospital Cardiac Arrest (TTM) trial was a randomized clinical trial recruiting patients in 36 intensive care units (ICUs) in Europe and Australia. The rationale for and design of the trial, as well as the statistical analysis plan, have been published previously.[12,13] The protocol (available with the full text of this article at NEJM.org) was approved by the ethics committees in each participating country and institution. An independent data and safety monitoring committee reviewed the data and performed one prespecified, blinded interim analysis. The steering group (see the Supplementary Appendix, available at NEJM.org) vouches for the accuracy and completeness of the data and analysis and for the adherence of this report to the trial protocol.

Patients

We consecutively screened patients 18 years of age or older who were unconscious (a score of <8 on the Glasgow Coma Scale [on which scores range from 3 to 15, with lower scores indicating reduced levels of consciousness]) on admission to the hospital after out-of-hospital cardiac arrest of presumed cardiac cause, irrespective of the initial rhythm. Eligible patients had more than 20 consecutive minutes of spontaneous circulation after resuscitation.[14] The main exclusion criteria were an interval from the return of spontaneous circulation to screening of more than 240 minutes, unwitnessed arrest with asystole as the initial rhythm, suspected or known acute intracranial hemorrhage or stroke, and a body temperature of less than 30°C. A full list of exclusion criteria is provided in the Supplementary Appendix. In accordance with national requirements and the principles of the Declaration of Helsinki, written informed consent was waived, delayed, or obtained from a legal surrogate, depending on the circumstances, and was obtained from each patient who regained mental capacity.[15]

Randomization and Trial Intervention

After being screened for eligibility, patients were randomly assigned in a 1:1 ratio to targeted temperature management with a target body temperature of either 33°C or 36°C. Randomization was performed centrally with the use of a computer-generated assignment sequence. Intervention assignments were made in permuted blocks of varying size and were stratified according to site.

Health care professionals caring for the trial patients were aware of the intervention assignments because of inherent problems with blinding of body temperature. Physicians performing neurologic prognostication, assessors of neurologic follow-up and final outcome, study administrators, statisticians, and the authors were unaware of the intervention assignments. During the analysis phase, the intervention groups were identified only as 0 and 1, and the manuscript was written and approved by all the authors before the randomization code was broken.[16]

The intervention period of 36 hours commenced at the time of randomization. Sedation was mandated in both groups until the end of the intervention period. The goal was to achieve the assigned temperature as rapidly as possible with the use of ice-cold fluids, ice packs, and intravascular or surface temperature-management

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devices at the discretion of the sites. Details of the trial interventions, including the management of an initial body temperature below the assigned target, are provided in the Supplementary Appendix.

After 28 hours, gradual rewarming to 37°C in hourly increments of 0.5°C was commenced in both groups. At 36 hours, mandatory sedation was discontinued or tapered. After the intervention period, the intention was to maintain the body temperature for unconscious patients below 37.5°C until 72 hours after the cardiac arrest, with the use of fever-control measures at the discretion of the sites.

NEUROLOGIC PROGNOSTICATION AND WITHDRAWAL OF LIFE-SUSTAINING THERAPIES

A physician who was unaware of the intervention assignments performed a neurologic evaluation 72 hours after the end of the intervention for patients who remained unconscious and issued a recommendation for the continuation or withdrawal of therapy. The trial protocol established prespecified criteria for withdrawal of life-sustaining therapy[12] (see the Supplementary Appendix). All clinical decisions remained at the discretion of the treating team.

FOLLOW-UP AND OUTCOMES

All surviving patients were followed until 180 days after the enrollment of the last patient. The primary outcome was all-cause mortality through the end of the trial. The main secondary outcome was a composite of poor neurologic function or death, defined as a Cerebral Performance Category[17,18] (CPC) of 3 to 5 and a score of 4 to 6 on the modified Rankin scale,[19,20] at or around 180 days. The CPC scale ranges from 1 to 5, with 1 representing good cerebral performance or minor disability, 2 moderate disability, 3 severe disability, 4 coma or vegetative state, and 5 brain death. 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. Mortality at 180 days and individual neurologic scores were also analyzed separately. Other secondary outcomes were the CPC at discharge from the ICU and from the hospital and the best (numerically lowest) reported CPC during the trial period. Predefined serious adverse events[21] were recorded up to day 7 in the ICU. Data collection and verification for all trial data and for the outcome measures are described in the Supplementary Appendix.

STATISTICAL ANALYSIS

We estimated that a sample of 900 patients would provide 90% power to detect a 20% reduction in the hazard ratio for death in the 33°C group as compared with the 36°C group, at a two-sided alpha level of 0.05. Alternatively, to detect a relative risk reduction of 20%, with the assumption of a mortality of 44% in the 33°C group versus 55% in the 36°C group, a sample of 850 patients would be needed. On the basis of these assumptions, a sample of 950 patients was chosen, to allow for a loss to follow-up of 50 patients.

The principal trial analyses were performed in the modified intention-to-treat population, defined as all randomly assigned patients except those withdrawing consent for use of all trial data and those not fulfilling inclusion criteria and never receiving the intervention.[22] Additional analyses were performed in the intention-to-treat population, which included all randomly assigned patients except those withdrawing consent, and in the per-protocol population, which excluded patients with one or more major protocol violations (listed in the Supplementary Appendix).

The Wilcoxon signed-rank test was used to compare distributions of continuous outcome measures. Kaplan–Meier survival curves were compared between the intervention groups with the use of the log-rank test. Relative risks were compared with the use of Cochran–Mantel–Haenszel statistics. Trends were assessed with the use of the Cochran–Armitage test. Logistic-regression and Cox analyses were performed as appropriate, with adjustment for site and for five baseline variables: age, sex, presence or absence of shockable rhythm, presence or absence of circulatory shock on admission, and the time from cardiac arrest (or from the emergency call for unwitnessed cardiac arrests) to the return of spontaneous circulation. Odds ratios were converted to relative risks.[23] All primary analyses were adjusted for site.[24] Temperature data were analyzed with the use of a mixed model with repeated measures. The effect of time was modeled with the use of a polynomial; the use of compound symmetry and first-order autoregressive covariance structures was compared, and the better-fitting model was used. SAS software, version 9.3, and SPSS software, version 17.1, were used for all analyses. All tests were two-sided

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Table 1. Characteristics of the Modified Intention-to-Treat Population before Randomization.*

Characteristic	33°C Group (N=473)	36°C Group (N=466)
Demographic characteristics		
Age — yr	64±12	64±13
Male sex — no. (%)	393 (83)	368 (79)
Medical history — no. (%)		
Chronic heart failure	32 (7)	29 (6)
Previous AMI	107 (23)	86 (18)
Ischemic heart disease	145 (31)	115 (25)
Previous cardiac arrhythmia	87 (18)	79 (17)
Arterial hypertension	193 (41)	181 (39)
Previous TIA or stroke	35 (7)	38 (8)
Diabetes mellitus	61 (13)	80 (17)
Asthma or COPD	48 (10)	49 (11)
Previous percutaneous coronary intervention	58 (12)	50 (11)
Previous coronary-artery bypass grafting	47 (10)	42 (9)
Characteristics of the cardiac arrest		
Location of cardiac arrest — no. (%)†		
Place of residence	245 (52)	255 (55)
Public place	197 (42)	188 (40)
Other	31 (7)	22 (5)
Bystander witnessed cardiac arrest — no. (%)	420 (89)	418 (90)
Bystander performed CPR — no. (%)	344 (73)	339 (73)
First monitored rhythm — no. (%)†		
Shockable rhythm	375 (79)	377 (81)
Ventricular fibrillation	349 (74)	356 (77)
Nonperfusing ventricular tachycardia	12 (3)	12 (3)
Unknown rhythm but responsive to shock	5 (1)	5 (1)
Perfusing rhythm after bystander-initiated defibrillation	9 (2)	4 (1)
Asystole	59 (12)	54 (12)
Pulseless electrical activity	37 (8)	28 (6)
Unknown first rhythm, not responsive to shock or not shocked	2 (<0.5)	6 (1)
Time from cardiac arrest to event — min‡		
Start of basic life support		
Median	1	1
Interquartile range	0–2	0–2
Start of advanced life support		
Median	10	9
Interquartile range	6–13	5–13
Return of spontaneous circulation		
Median	25	25
Interquartile range	18–40	16–40

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Table 1. (Continued.)

Characteristic	33°C Group (N=473)	36°C Group (N=466)
Clinical characteristics on admission		
First measured body temperature — °C	35.2±1.3	35.3±1.1
Glasgow Coma Scale score§		
Median	3	3
Interquartile range	3–4	3–4
Corneal reflex present — no./total no. (%)	264/407 (65)	258/392 (66)
Pupillary reflex present — no./total no. (%)	344/460 (75)	363/458 (79)
Serum pH	7.2±0.2	7.2±0.2
Serum lactate — mmol/liter	6.7±4.5	6.7±4.5
Circulatory shock — no. (%)¶	70 (15)	67 (14)
ST-segment elevation myocardial infarction — no. (%)	190 (40)	194 (42)

* Plus–minus values are means ±SD. P>0.05 for all comparisons. AMI denotes acute myocardial infarction, COPD chronic obstructive pulmonary disease, CPR cardiopulmonary resuscitation, and TIA transient ischemic attack.
† In the 36°C group, data for location of cardiac arrest and first monitored rhythm were missing for one patient.
‡ For unwitnessed arrests, intervals were calculated from the time of the emergency call.
§ Scores on the Glasgow Coma Scale range from 3 to 15, with lower scores indicating reduced levels of consciousness. The distribution of Glasgow Coma Scale motor scores is provided in Table S1 in the Supplementary Appendix.
¶ Circulatory shock was defined as a systolic blood pressure of less than 90 mm Hg for more than 30 minutes or end-organ hypoperfusion (cool extremities, a urine output of <30 ml per hour, and a heart rate of <60 beats per minute).

and adjusted for multiple comparisons. A P value of 0.05 or less was considered to indicate statistical significance.

RESULTS

PATIENTS

A total of 950 patients were enrolled between November 2010 and January 2013; of these patients, 476 were randomly assigned to the 33°C group and 474 to the 36°C group. The modified intention-to-treat population (the primary-analysis population) consisted of 473 patients assigned to 33°C and 466 assigned to 36°C (Fig. S1 in the Supplementary Appendix). The two groups had similar prerandomization characteristics (Table 1). Glasgow Coma Scale scores on admission, cardiovascular Sequential Organ Failure Assessment scores, and details of diagnostic procedures, interventions, and the use of health services are provided in Tables S1, S2, and S3, respectively, in the Supplementary Appendix.

TEMPERATURE INTERVENTION

The mean values of the initial recorded body temperature (tympanic) were 35.2°C and 35.3°C in the 33°C and 36°C groups, respectively. Temperature was managed with an intravascular cooling catheter in 24% of patients and with a surface cooling system in 76% of patients in both groups. The temperature curves are depicted in Figure 1 (P<0.001 for separation of the curves). Three patients in the 33°C group and four in the 36°C group did not receive the assigned intervention (Table S4 in the Supplementary Appendix). Sixteen patients assigned to the 33°C group were rewarmed before reaching the intended time point of 28 hours after randomization, at the discretion of the treating physician and as allowed by the protocol (Table S5 in the Supplementary Appendix). Additional information regarding shivering and fever is available in the Supplementary Appendix.

WITHDRAWAL OF LIFE-SUSTAINING THERAPY

During the first 7 days of hospitalization, life-sustaining therapy was withdrawn in 247 patients (132 in the 33°C group and 115 in the 36°C group). Reasons for withdrawal of life-sustaining therapy included brain death, multiorgan failure, and ethical concerns (Table S7 in the Supplementary Appendix). A protocol-defined approach to neu-

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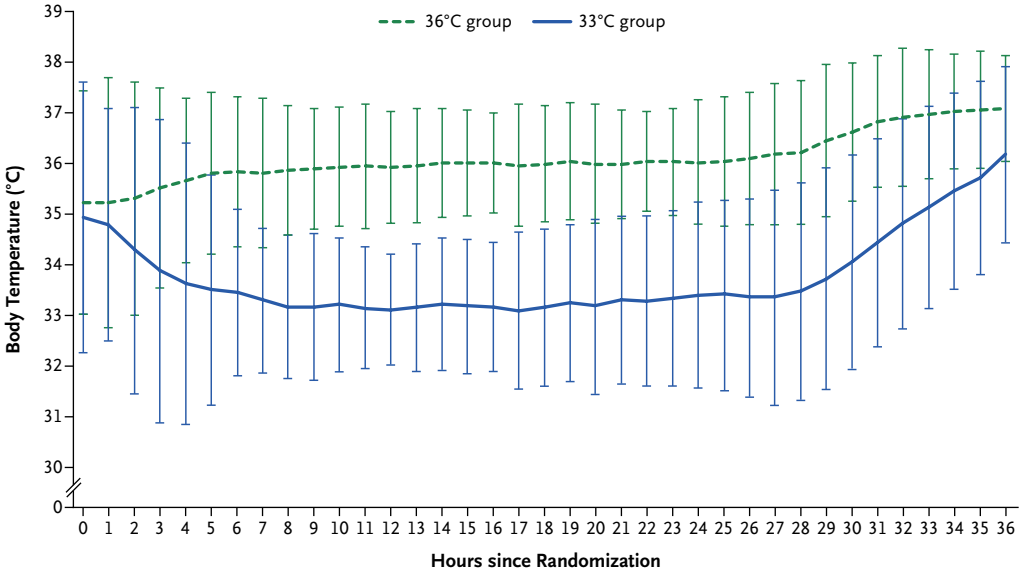

Figure 1. Body Temperature during the Intervention Period.

Shown are body-temperature curves in the 33°C and 36°C groups for the 860 patients in whom a bladder temperature was recorded. In the remaining 79 patients, the temperature was recorded with an intravascular or esophageal probe, with a similar temperature profile (data not shown). Rewarming was commenced at 28 hours after randomization. The temperature curves display the means, and the I bars indicate ±2 SD (95% of the observations are within the error bars).

Table 2. Outcomes.

Outcome	33°C Group	36°C Group	Hazard Ratio or Risk Ratio (95% CI)*	P Value
	no./total no. (%)			
Primary outcome: deaths at end of trial	235/473 (50)	225/466 (48)	1.06 (0.89–1.28)	0.51
Secondary outcomes				
Neurologic function at follow-up†				
CPC of 3–5	251/469 (54)	242/464 (52)	1.02 (0.88–1.16)	0.78
Modified Rankin scale score of 4–6	245/469 (52)	239/464 (52)	1.01 (0.89–1.14)	0.87
Deaths at 180 days	226/473 (48)	220/466 (47)	1.01 (0.87–1.15)	0.92

* The hazard ratio is shown for the primary outcome, and risk ratios are shown for the secondary outcomes. CI denotes confidence interval.

† The neurologic follow-up was specified in the protocol to be performed at 180 days ±2 weeks, but the time to follow-up was in some cases several weeks longer for logistic reasons. The Cerebral Performance Category (CPC) scale ranges from 1 to 5, with 1 representing good cerebral performance or minor disability, 2 moderate cerebral disability (function is sufficient for independent activities of daily life), 3 severe cerebral disability, 4 coma or vegetative state, and 5 brain death. Scores on the modified Rankin scale range from 0 to 6, with 0 representing no symptoms, 1 no clinically significant disability despite some symptoms, 2 slight disability (patient is able to look after own affairs without assistance), 3 moderate disability (patient requires some help but is able to walk unassisted), 4 moderately severe disability (patient is unable to attend to own bodily needs), 5 severe disability (patient is bedridden), and 6 death.

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rologic prognostication was used to make recommendations regarding the continuation or withdrawal of life-sustaining therapy (Table S8 in the Supplementary Appendix).

FOLLOW-UP AND OUTCOMES

Follow-up was obtained by means of a face-to-face interview with the patient (for 86% of patients), a structured telephone interview with the patient (6%), a telephone call to the patient or a relative (5%), or a telephone call to a proxy provider of information (i.e., a staff member of a nursing home or a general practitioner) (3%). The last follow-up assessment was performed on July 9, 2013. The mean period of follow-up for all patients was 256 days.

At the end of the trial, 235 of 473 patients in the 33°C group (50%) and 225 of 466 patients in the 36°C group (48%) had died (hazard ratio in the 33°C group, 1.06; 95% confidence interval [CI], 0.89 to 1.28; P=0.51) (Table 2 and Fig. 2). The groups did not differ significantly with respect to the composite outcome of death or poor neurologic function at 180 days with the use of either the CPC or the modified Rankin scale score (risk ratio for a CPC of 3 to 5 in the 33°C group, 1.02; 95% CI, 0.88 to 1.16; P=0.78; and risk ratio for a score of 4 to 6 on the modified Rankin scale in the 33°C group, 1.01; 95% CI, 0.89 to 1.14; P=0.87) (Table 2). The neurologic scores on both scales are shown in Table 3 and in Table S9 in the Supplementary Appendix. There were no significant differences in the distribution of CPCs or modified Rankin scale scores between the two groups (P=0.85 and P=0.67 for trend, respectively). With the use of the best reported CPC during the trial (Table 3), the relative risk of death or poor neurologic function in the 33°C group was 1.04 (95% CI, 0.89 to 1.17; P=0.67).

Similar results were obtained in adjusted analyses and in the intention-to-treat and per-protocol populations (see the Supplementary Appendix, including Tables S10 and S11). The effect of the intervention was consistent across predefined subgroups (Fig. S2 in the Supplementary Appendix).

One or more serious adverse events occurred in 439 of 472 patients in the 33°C group (93%) as compared with 417 of 464 patients in the 36°C group (90%) (risk ratio, 1.03; 95% CI, 1.00 to 1.08; P=0.09). Hypokalemia was more frequent in the 33°C group (19%, vs. 13% in the 36°C group, P=0.02). For the full list of serious adverse events, see Table S12 in the Supplementary Appendix. The presumed causes of death as assessed by the trial investigators were similar in the two groups (Table S13 in the Supplementary Appendix).

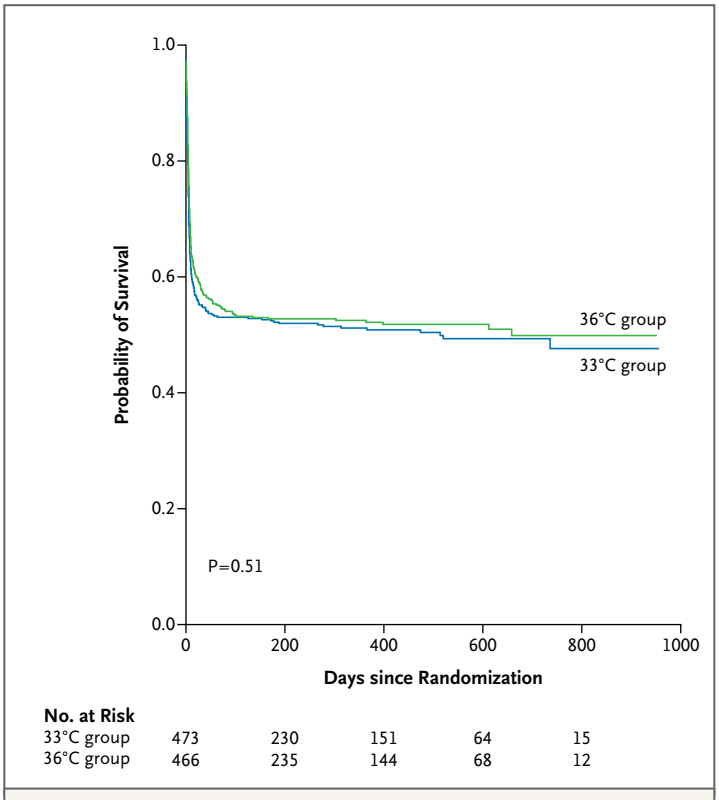

Figure 2. Probability of Survival through the End of the Trial.

Shown are Kaplan–Meier estimates of the probability of survival for patients assigned to a target temperature of either 33°C or 36°C and the number of patients at risk at each time point. The P value was calculated by means of Cox regression, with the effect of the intervention adjusted for the stratification variable of study site.

DISCUSSION

In this international, multicenter, randomized trial, we compared a target body temperature of 33°C with one of 36°C in patients who had been resuscitated after out-of-hospital cardiac arrest of presumed cardiac cause. There were no significant differences between the two groups in overall mortality at the end of the trial or in the composite of poor neurologic function or death at 180 days. The results were consistent in six predefined subgroups. We did not find any harm with a targeted temperature of 33°C as compared

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Table 3. Neurologic Scores.*

Variable	33°C Group	36°C Group
CPC at follow-up†		
Total no. of patients	469	464
Category — no. (%)		
1	195 (42)	183 (39)
2	23 (5)	39 (8)
3	17 (4)	20 (4)
4	6 (1)	2 (0.5)
5	228 (49)	220 (47)
P value for trend	0.85	
Best, or lowest numerical, CPC during trial		
Total no. of patients	472	466
Category — no. (%)		
1	209 (44)	205 (44)
2	25 (5)	41 (9)
3	37 (8)	37 (8)
4	201 (43)	183 (39)
5	NA	NA
P value for trend	0.89	
Modified Rankin scale score at follow-up†		
Total no. of patients	469	464
Score — no. (%)		
0	88 (19)	89 (19)
1	69 (15)	83 (18)
2	50 (11)	34 (7)
3	17 (4)	19 (4)
4	8 (2)	11 (2)
5	9 (2)	8 (2)
6	228 (49)	220 (47)
P value for trend	0.67	

* P values for trend were calculated with the use of the Cochran–Armitage test. NA denotes not applicable.
† The neurologic follow-up was specified in the protocol to be at 180±14 days, but the time to follow-up was in some cases several weeks longer for logistic reasons.

with 36°C. However, it is worth recognizing that for all outcomes, none of the point estimates were in the direction of a benefit for the 33°C group. On the basis of these results, decisions about which temperature to target after out-of-hospital cardiac arrest require careful consideration.

After publication of the seminal trials of therapeutic hypothermia after cardiac arrest,[2,3] this approach was recommended in international guidelines,[4] despite arguments by some investigators that the evidence was weak, owing to the risk of bias and small samples.[6,25] The subsequent debate has focused on two issues. The first issue is whether therapeutic hypothermia should be extended to patients outside the originally described populations.[26-28] It may be reasoned that the potential benefits of temperature management on brain injury due to circulatory arrest would be the same irrespective of the cause of arrest. However, whole-body hypothermia influences all organ systems, and any potential benefit should be balanced against possible side effects.[29] The population of patients with cardiac arrest is heterogeneous, and the potential risks and benefits of temperature intervention may not be the same across subgroups. The second issue is the most beneficial target temperature for therapeutic hypothermia.[30] The recommended temperature of 32° to 34°C has been extrapolated from experiments in animals[31,32]; however, similar results have been observed with milder cooling.[33]

A difference between our trial and earlier trials[2,3] is that we did not allow the natural trajectory of temperature evolution in either group; we actively controlled the temperature during the intervention period and aimed to prevent fever during the first 3 days after cardiac arrest. We enrolled patients with out-of-hospital arrests of presumed cardiac cause, in line with enrollment in earlier trials, but our sample was larger and we had fewer exclusion criteria, with approximately 20% of participants having nonshockable rhythms. Other published studies involving patients with cardiac arrest who were admitted to the ICU have shown baseline characteristics and mortality that are in keeping with our findings, supporting the generalizability of our results.[34-38]

Our trial had several limitations. First, ICU staff members were aware of the assigned target temperature during the stay in the ICU. We aimed to minimize this problem by using robust outcomes and blinded outcome assessment. We also applied rigorous guidelines for neurologic prognostication and end-of-life decisions. Second, in one country, ethical approval required written consent from a legal surrogate before randomization, resulting in exclusion of a substantial proportion of eligible patients. Third, we do not have detailed data on the dose and type of sedation or the use of neuromuscular blocking agents. However, the sites were instructed to

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treat the groups similarly, and surrogate markers (e.g., the presence of shivering and the number of days that sedation affected neurologic evaluation) did not differ between groups.

The mortality in both groups in our trial may be lower than that in the control group of the Hypothermia after Cardiac Arrest trial.[3] These two trials are not easily comparable with respect to study populations. Furthermore, prehospital and critical care management have changed during the past decade.[36,39] Nevertheless, it is important to acknowledge that there may be a clinically relevant benefit of controlling the body temperature at 36°C, instead of allowing fever to develop in patients who have been resuscitated after cardiac arrest.[9]

In conclusion, our trial does not provide evidence that targeting a body temperature of 33°C confers any benefit for unconscious patients admitted to the hospital after out-of-hospital cardiac arrest, as compared with targeting a body temperature of 36°C.

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

APPENDIX

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