EDITORIAL

Temperature Management and Modern Post–Cardiac Arrest Care

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Modern cardiopulmonary resuscitation (CPR) began in 1960, when clinicians translated observations about external chest compressions from the laboratory to patients.[1] CPR increased survival for patients who had cardiopulmonary collapse outside of the operating room from none to a few. Incremental improvements in the survivorship from CPR occurred as more persons were trained in CPR and as defibrillators became portable and were deployed in more locations. Unfortunately, a cascade of brain injury begins within minutes after cardiac arrest, with the consequence that most patients who had return of cardiac activity did not survive to leave the hospital or did so in a neurologically devastated state. In the early 2000s, overall survival after cardiac arrest outside the hospital remained about 7 to 8%.[2] About one quarter of patients regained pulses after CPR, and about one third of the patients with those initial successes survived hospitalization.

The devastating effects of post-CPR brain injury stimulated decades of investigation into the pathophysiology of, and potential treatments for, global brain ischemia. Because cardiac arrest is an unpredictable emergency, clinically useful treatments for post-CPR brain injury must work not just as pretreatments but even when initiated after CPR or after restoration of circulation. To date, the only intervention robustly meeting these specifications is mild reduction of body temperature (from 37°C to between 32 and 35°C) for at least 5 hours after restoration of circulation.[3]

In 2002, two randomized, controlled trials showed that induction of mild hypothermia for 12 or 24 hours increased survival and improved neurologic outcomes for very select patients with out-of-hospital cardiac arrest.[4,5] Induced hypothermia after cardiac arrest gained widespread use and is now advocated by international guidelines.[6] Implementation of induced hypothermia increased survival, even when applied to less selected cohorts of patients than studied in the original trials.[7]

A new randomized trial now reported in the *Journal* by Nielsen et al.[8] questions whether lower temperatures actually benefit patients after cardiac arrest. When 939 patients with return of spontaneous circulation after CPR were assigned to targeted temperature management at either 33°C or 36°C after cardiac arrest, survival (51%) and a good neurologic outcome (47 to 48%) did not differ significantly between groups. This superbly executed study is more than twice the size of the original trials combined (which enrolled a total of 352 patients) and was conducted with meticulous attention to modern intensive care. The overall conclusion that there is no significant difference between a near-normal temperature (36°C) and induced hypothermia (33°C) seems to contradict the previous trials and implementation studies.

One of the greatest innovations in this trial is adoption of a protocol for withdrawal of life-sustaining treatment. Almost all prior studies of post–cardiac arrest care are tainted by the fact that the most common cause of death is withdrawal of life support because of perceived poor neurologic prognosis. This confounder is problematic in trials because there are almost no certain methods to establish long-term prognosis. The current authors have clearly delineated their approach for the 26% of patients who had withdrawal of care before hospital discharge.

There are multiple possible explanations for the absence of benefit from lower temperatures in patients with cardiac arrest. The population was less select than in previous trials, including

patients with shockable rhythms and those with nonshockable rhythms. There has been evolution of intensive care over the past decade, and improvements in patient care may have reduced the potential incremental benefits of a single intervention. In addition, illness severity varies greatly among patients with cardiac arrest, and there may be subgroups of patients who do benefit from induced hypothermia but who were not designated in advance. Particularly if the degree or duration of hypothermia must be adjusted to match the severity of brain injury, the benefits to a subgroup may be missed in a trial of one regimen of hypothermia for all comers.

One interpretation of these results is that they reinforce the importance of controlling temperature, even while they question whether 33°C is the best temperature. For example, many patients in the "normothermia" group of the older trials actually became hyperthermic,[4,5] which is deleterious.[9,10] The exceptional rates of good outcomes in both the 33°C and 36°C groups in the present trial may reflect the active prevention of hyperthermia. Whatever the mechanisms, it seems clear that we should not regress to a pre-2002 style of care that does not manage temperature at all.

Perhaps the most important message to take from this trial is that modern, aggressive care that includes attention to temperature works, making survival more likely than death when a patient is hospitalized after CPR. In contrast to a decade ago, one half instead of one third of patients with return of spontaneous circulation after CPR can expect to survive hospitalization. Few medical situations have enjoyed such absolute improvement over the same time period. Future studies can continue to refine protocols, define subgroups that benefit from individual therapies, and clarify how to best adjust temperature or other interventions to each patient's illness.

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

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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

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

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

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-

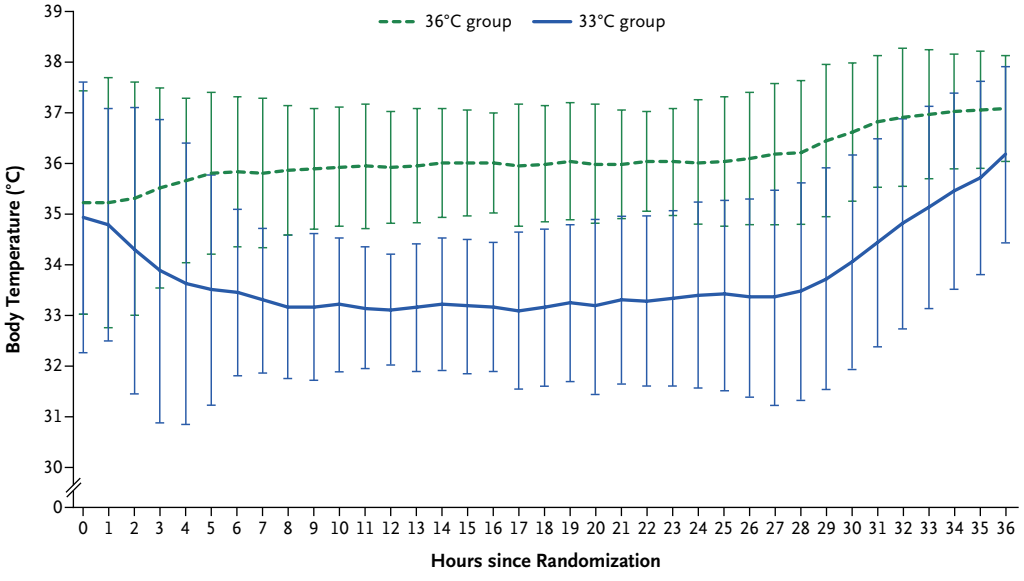

Figure 1. Body Temperature during the Intervention Period.

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.

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).

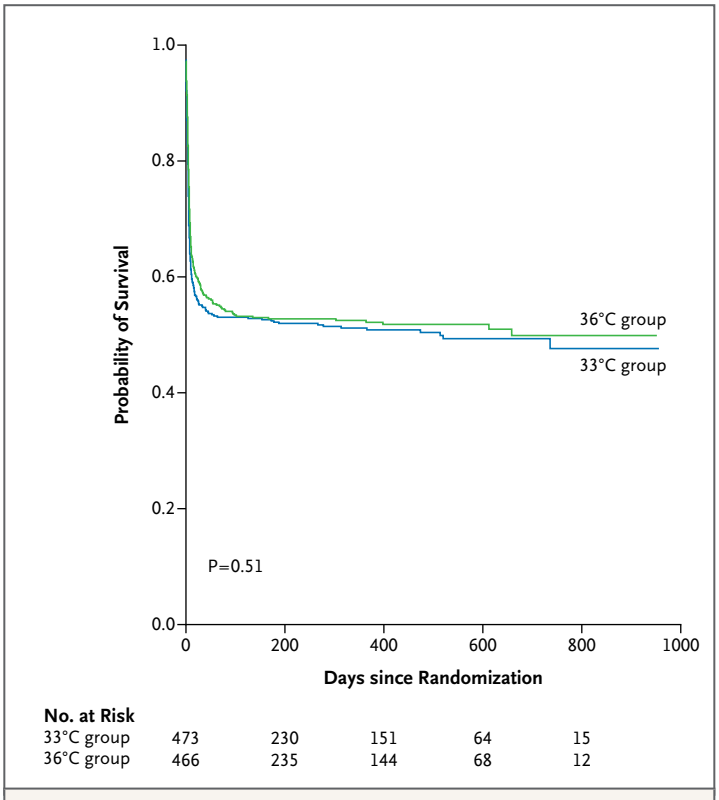

Figure 2. Probability of Survival through the End of the Trial.

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

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

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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forms of technology to ensure the safest delivery of the intervention.

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Since publication of their article, the authors report no further potential conflict of interest.

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Targeted Temperature Management after Cardiac Arrest

TO THE EDITOR: Nielsen and coauthors (Dec. 5 issue)[1] show the importance of avoiding hyperthermia in patients who have had a cardiac arrest. However, if the clinical objective is to improve the neurologic outcome, it is important to define the expected neurologic outcome in individual patients. Studies have shown that the severity of neuronal lesions is dependent on the delay in initiation of cooling after reperfusion.[2]

In the article by Nielsen et al., the studied patients had a median return of spontaneous circulation of 25 minutes, with a wide interquartile range of 18 to 40 in the hypothermic group and 16 to 40 in the normothermic group. In prolonged cardiac arrest, we do not expect that a reduction of neurologic metabolism by hypothermia will have a real effect on already damaged structures.

We should not conclude, on the basis of this trial, that hypothermia is simply an antihyperthermic strategy. Not all cardiac arrests are equal in terms of the time to return of spontaneous circulation. We should identify the subgroups of patients who can benefit from this form of therapy.

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TO THE EDITOR: Nielsen et al. confirm that fever should be avoided in resuscitated patients. However, several unanswered questions remain before abandoning therapeutic hypothermia in patients after cardiac arrest. One key issue is the potential benefit of early cooling initiated during cardiopulmonary resuscitation (CPR).

Pathophysiological mechanisms[1] as well as experimental data suggest a benefit of early cooling, with intra-arrest cooling clearly superior to postresuscitation cooling.[2] Thus, when moving from very early cooling in the experimental setting to several hours of delay in clinical practice, we might miss the time window for the greatest effectiveness of hypothermia.[3]

Transnasal evaporative cooling can be induced in field conditions during CPR.[4] The method induces continuous cooling, primarily to the brain, without the hemodynamic side effects recently seen with cold saline. Ongoing and future studies may add important knowledge to this field of research.[5]

Nielsen et al. permitted a time to initiate cooling of 4 hours. We suggest that this time window may be crucial to influence outcome.

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TO THE EDITOR: The study by Nielsen et al. revealed no significant difference between hypothermic and near-normothermic treatment groups in patients after cardiac arrest and CPR in terms of their survival and neurologic outcome. This striking finding contradicts the previous understanding of the benefits of this form of therapy, and the next question seems to be whether there is any need to induce hypothermia in these patients.

However, the neurologic evaluation in Nielsen et al. was based on the Cerebral Performance Category (CPC) scale and a modified Rankin scale. These are simple tests devised for assessing patients' independent daily living and are inadequate for assessing cognitive prognosis, when mild cognitive impairment is a real concern in survivors of cardiac arrest.[1-3] Thus, the findings of Nielsen et al. should not lead to changes in practice before the long-term prognosis of hypothermic versus near-normothermic treatments and the patients' recovery of cognitive function are investigated by means of recent advancements in neurologic assessment.[4] We ask for more clarification on this topic, which has to precede the decision to "drop the old habit" that may have brought a great deal of benefits to numerous patients during the past decade.

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TO THE EDITOR: Data from the study by Nielsen et al. showing that maintaining temperature at 33°C and at 36°C have similar benefits in comatose survivors of cardiac arrest originate from patients with an impressively short time to CPR and a higher percentage of bystander-initiated CPR (73%) than in previous clinical trials (49 to 58%).[1,2] Thus, whether such results could be widely applied to communities with a longer time to resuscitation remains to be clarified. Moreover, both midazolam and propofol provide additional neuroprotective effects[3]; however, doses of agents used were not specifically recorded. Finally, no specific guidelines for management of the postresuscitation syndrome were provided, yet it is known that early hemodynamic optimization may improve neurologic outcome after cardiac arrest.[4] Because patients in the 33°C group more frequently had severe cardiovascular impairment than those in the 36°C group (76% vs. 70% on day 2 and 67% vs. 54% on day 3), inadequate organ perfusion may account for potentially harmful effects of a lower target temperature; this was suggested by the higher proportion of deaths before prognostication from cardiac

causes or multiple organ failure observed in the 33°C group.

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DOI: 10.1056/NEJMc1401250

TO THE EDITOR: The large, randomized trial by Nielsen et al. showed no significant difference in survival between two strategies of targeted temperature management (33°C vs. 36°C) in comatose survivors of out-of-hospital cardiac arrest and therefore cast doubt on the results of earlier trials that evaluated induced hypothermia in this population. The investigators are to be commended for their rigorous trial with concurrent high rates of coronary angiography and structured, deferred approaches to prognostication and withdrawal of care. Before abandoning 33°C as a treatment target, we should consider whether the benefit of this strategy may have been attenuated in this trial.

First, patients in the current study underwent randomization up to 4 hours after cardiac arrest and had a further 4 hours to achieve mean temperatures below 34°C.[1] A briefer time to the target temperature after cardiac arrest[2] or in patients with ST-segment elevation myocardial infarction[3] may be required to modify reperfusion injury. Second, patients were sedated for 36 hours. Although details were not provided, it is plausible that sedation with propofol may have attenuated the effect of temperature management on the reduction of reperfusion injury.[4,5]

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DOI: 10.1056/NEJMc1401250

TO THE EDITOR: Nielsen and collaborators report that therapeutic hypothermia (33°C) conferred no outcome benefits after cardiac arrest, as compared with strict fever control. This directly contradicts the findings of two randomized, controlled trials previously published in the *Journal* and other data supporting the use of therapeutic hypothermia after hypoxemic injury.[1-3] How do we explain this? Should current guidelines be changed? The current study is large and well conducted but has potential limitations. One is a rapid rate of rewarming, from 33°C to 36°C in 6 hours — a much faster rate than in previous trials. Rapid warming is harmful and can negate the benefits of therapeutic hypothermia.[4,5] In addition, were all consecutive patients with cardiac arrest and return of spontaneous circulation screened for this study, or did physicians preassess potential eligibility? Participating centers routinely used therapeutic hypothermia before this study and continued to treat nonstudy patients with it. Physicians could have subconsciously selected patients with potential benefit for "routine" therapeutic hypothermia rather than refer for screening. The study enrolled an average of only one patient per center per month, possibly indicating preselection.

These results could be misconstrued to advocate abandoning temperature management after cardiac arrest altogether. We agree with the au-

thors that the question should be what temperature to maintain, not whether temperature control is needed.

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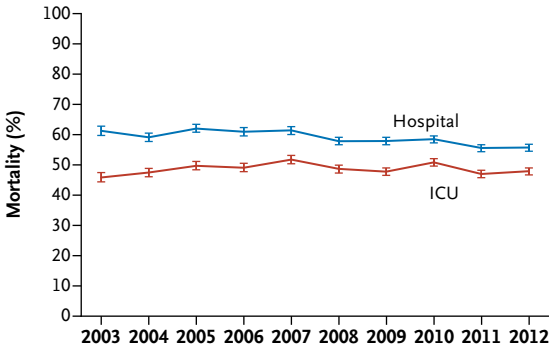
DOI: 10.1056/NEJMc1401250

TO THE EDITOR: With regard to the editorial accompanying the article by Nielsen and colleagues: we reflect on a key assertion that, "In contrast to a decade ago, one half instead of one third of patients with return of spontaneous circulation after CPR can expect to survive hospitalization."[1] In fact, in 2002, the Hypothermia after Cardiac Arrest Study Group[2] reported a hospital mortality of 43% (119 of 275 participants). The investigators participating in the Target Temperature Management 33°C versus 36°C after Out-of-Hospital Cardiac Arrest (TTM) trial now report a nearly identical hospital mortality of 44% (411 of 939 participants).

Using the Australian and New Zealand Intensive Care Society Adult Patient Database (ANZICS APD), which includes data on more than 1.4 million intensive care unit (ICU) admissions and more than 17,000 cardiac arrests, we determined the hospital mortality among patients with out-of-hospital cardiac arrest in Australia and New Zealand from 2003 to 2012. We found a hospital mortality of 61% in 2003 and 56% in 2012 and an ICU mortality of 46% in 2003 and 48% in 2012 (Fig. 1). These findings and those mentioned above indicate that hospital mortality in Australia and New Zealand and in the European trial sites has not improved over time. Investigators must now seek new therapeutic interventions that protect the brain and improve mortality and neurologic outcomes after out-of-hospital cardiac arrest.[3]



	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
No. of Hospital Deaths	665	752	852	802	863	905	947	1041	1017	1019
No. of ICU Deaths	489	592	676	644	711	733	774	888	851	872

Figure 1. Hospital and ICU Mortality, 2003–2012.
Shown are hospital and ICU mortality among patients with cardiac arrest who were admitted to ICUs in Australia and New Zealand between 2003 and 2012. I bars indicate 95% confidence intervals. Data are from the Australian and New Zealand Intensive Care Society Adult Patient Database.

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No potential conflict of interest relevant to this letter was reported.

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DOI: 10.1056/NEJMc1401250

DR. NIELSEN AND COLLEAGUES REPLY: Perchiazzi et al., Nordberg et al., and Stub suggest that a delay in the initiation of temperature management might influence outcome. The window of 240 minutes from return of spontaneous circulation to randomization was based on a study of data from the Hypothermia Network Registry, in which there was no association between time to the initiation of temperature management and 6-month neurologic outcome.[1] Other large observational studies have given similar signals.[2] Data from a recent randomized trial showed that early initiation of temperature management does not improve outcome.[3] Intra-arrest cooling is, however, compelling, and we look forward to results from ongoing trials.

Perchiazzi et al. call for subgroup analyses to elucidate which patients might benefit from one of the interventions. The forest plot in Figure S2 in the Supplementary Appendix (available with the full text of our article at NEJM.org) indicates a homogeneous intervention effect in five predefined subgroups. Further multivariate analysis may give signals in any direction, but we would not recommend basing practice on inferences that at best could be hypothesis-generating.

Oh and colleagues ask for more detailed neurologic assessment at follow-up, and we agree that the CPC scale and the modified Rankin scale represent crude measures. However, the CPC scale was used in trials introducing temperature management in clinical practice. Data from more detailed assessment were collected but have not yet been published.[4] Survival being the primary outcome, it is important to acknowledge that the TTM trial was not powered to conclusively assess these measures.

Taccone and Dell'Anna comment on the high rate of bystander-initiated CPR in the TTM trial. During the past decade, there has been a continuous rise in bystander-initiated CPR, with positive consequences on overall outcome.[5] The time to bystander-initiated CPR is naturally relevant only for patients receiving such help and should be short. The time to bystander-initiated CPR was, to our knowledge, not reported in earlier trials on temperature management.

In response to Varon and Polderman: we confirm that sites consecutively screened all patients meeting inclusion criteria and randomly assigned every patient not meeting exclusion criteria. The baseline characteristics, active care (60% early angiography and 40% coronary intervention), and survival rates strongly contradict a selection of patients with a presumed poor outcome.

Whether goal-directed changes in post–cardiac arrest care, sedatives, or the rewarming rate influence outcome is to our knowledge unknown and remains to be investigated in future randomized clinical trials.

We disagree that our trial showed a benefit of avoiding fever; to do so, a no-intervention group would have been necessary. That said, we definitely would not advocate abandoning any temperature management on the basis of the results of the TTM trial.

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Since publication of their article, the authors report no further potential conflict of interest.

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DOI: 10.1056/NEJMc1401250

THE EDITORIALISTS REPLY: The data from ANZICS APD are a welcome addition to the longitudinal data on survival after cardiac arrest. We urge three points of caution regarding interpretation of these data. First, we wonder whether partici-

pating ICUs adopted the use of a standard care plan including temperature management soon after the seminal articles,[1,2] making the excellent survival rates depicted in this graph representative of the "temperature-management era." Second, the relevant comparison group for baseline survival from the Hypothermia after Cardiac Arrest Study Group trial[1] is the control group, which received no regimented care with respect to temperature management. Although control patients were highly selected from a group with a high likelihood of survival, hospital mortality was 50% (69 of 138 patients), substantially higher than the hospital mortality of 44% (411 of 939 patients) in the TTM trial involving less selected patients. Third, if the ANZICS APD includes patients admitted to the ICU, it may not capture deaths that occur in the emergency department or during pre-ICU procedures. Despite this limitation, we do appreciate a modest decline in hospital deaths over the decade from more than 60% to its current level.

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Since publication of their editorial, the authors report no further potential conflict of interest.

1. The Hypothermia after Cardiac Arrest Study Group. Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. N Engl J Med 2002;346:549-56. [Erratum, N Engl J Med 2002;346:1756.]
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DOI: 10.1056/NEJMc1401250

BMI and Mortality among Adults with Incident Type 2 Diabetes

TO THE EDITOR: Tobias et al. (Jan. 16 issue)[1] found no evidence of lower mortality among obese patients with incident type 2 diabetes, as compared with their normal-weight counterparts. An "obesity paradox" (i.e., an association between obesity and reduced mortality) had been reported, in particular in patient populations with a short survival time, whereas obesity by its nature is a risk factor for increased long-term mortality. Our earlier results show that short follow-up and the advanced age of populations with chronic diseases are major limitations of such studies: over short periods, a high body-mass index (BMI) was not associated with increased mortality among patients with end-stage renal disease, but it was also not associated with increased mortality in the general population of equal age.[2] Moreover, different underlying causes of the disease and coexisting illnesses impede a valid comparison between patients with a high BMI and those with a low BMI. Because of these limitations, it is not possible to translate such observations into causal interpretations — for example, to advise a high body weight in these patients. The findings by Tobias et al. are a timely reminder of the many biases that need to be taken into account before a causal interpretation of population data is possible.

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No potential conflict of interest relevant to this letter was reported.

1. Tobias DK, Pan A, Jackson CL, et al. Body-mass index and mortality among adults with incident type 2 diabetes. N Engl J Med 2014;370:233-44.
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TO THE EDITOR: Although Carnethon et al.[1] found a better prognosis in obese patients with type 2 diabetes as compared with patients of "normal" weight, Tobias and colleagues did not find an obesity paradox. They explained that prior analyses were limited by short follow-up, a small number of deaths, and a lack of data on smoking or undiagnosed diseases.

We are concerned, however, that neither study mentioned above accounted for fitness, especially because obese but fit persons with type 2 diabetes have a considerably better prognosis

Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Nielsen N, Wetterslev J, Cronberg T, et al. Targeted temperature management at 33°C versus 36°C after cardiac arrest. N Engl J Med 2013. DOI: 10.1056/NEJMoa1310519

Supplementary appendix

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SUPPLEMENTARY METHODS

Inclusion and exclusion criteria

Inclusion criteria

1. Age ≥18 years.

2. Out of hospital cardiac arrest of presumed cardiac cause.

3. Sustained return of spontaneous circulation (ROSC)[#].

4. Unconsciousness (GCS <8) (patients not able to obey verbal commands) after sustained ROSC.

[#]Sustained ROSC: Sustained ROSC is when chest compressions have been not required for 20 consecutive minutes and signs of circulation persist

Exclusion criteria

1. Obvious or suspected pregnancy

2. Known bleeding diathesis (medically induced coagulopathy (e.g. warfarin, clopidogrel) does not exclude the patient).

3. Suspected or confirmed acute intracranial bleeding

4. Suspected or confirmed acute stroke

5. Unwitnessed cardiac arrest with initial rhythm asystole

6. Known limitations in therapy and Do Not Resuscitate-order

7. Known disease making 180 days survival unlikely

8. Known pre-arrest Cerebral Performance Category 3 or 4

9. >4 hours (240 minutes) from ROSC to screening

10. Systolic blood pressure <80 mm Hg in spite of fluid loading/vasopressor and/or inotropic medication/intra aortic balloon pump[#]

14. Temperature on admission <30°C.

If the systolic blood pressure (SBP) was recovering during the inclusion window (220 minutes) the patient could be included. The standard definition of shock did not preclude inclusion: A systolic blood pressure<90mmHg for >30min or end-organ hypoperfusion (cool extremities, urine output<30ml/hour, heart rate <60 beats/min).

Neurological prognostication

All patients in the trial were actively treated until a minimum 72 hours after the intervention period, i.e. 108 hours after start of treatment (end of phase 3), when neurological evaluation was done on patients not regaining consciousness. Exceptions from this rule were 1) patients with myoclonus status[#] in the first 24 hours after admission and a bilateral absence of N20-peak on median nerve somatosensory evoked potentials (SSEP), 2) patients who became brain dead due to cerebral herniation and 3) because of ethical reasons described below. External blinded physicians evaluated the patient at the end of phase 3 and made a statement on neurological prognosis. At that time-point, limitations in and withdrawal of therapy could be instituted by the treating physicians. The neurological evaluation was based on clinical neurological examination (including Glasgow Coma Scale (GCS), pupillary and corneal reflexes), SSEP and electroencephalogram (EEG). Biomarkers for brain damage were not used for operational prognostication.

Findings allowing for discontinuation of active intensive care:

- Brain death due to cerebral herniation.
- Severe myoclonus status[#] in the first 24 hours after admission and a bilateral absence of N20-peak on median nerve SSEP.
- Minimum 72 hours after the intervention period: persisting coma with a Glasgow Motor Score 1-2 and bilateral absence of N20-peak on median nerve SSEP.
- Minimum 72 hours after the end of the intervention period: persisting coma with a Glasgow Motor Score 1-2 and a treatment refractory status epilepticus*.

Generalized myoclonic convulsions in face and extremities and continuous for a minimum of 30 min.

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

Patients with Glasgow Motor Score 1-2 at 72 hours or later after the end of the intervention period who had retained N20-peak on the SSEP, or patients in hospitals where SSEP was not available, were re-examined daily and the limitations/withdrawal of intensive care considered if GCS-Motor did not improve and metabolic and pharmacological affection was ruled out. Recommendations and decisions on life sustaining treatment were recorded.
Active treatment could be withdrawn prior to 72 hours after the intervention period for ethical reasons (for instance: previously unknown information about disseminated end-stage cancer or refractory shock with end-stage multiorgan failure). However assumptions of a poor neurological function were not allowed be the sole reason for withdrawal of active treatment prior to 72 h after the intervention period (exception: brain death and early myoclonus status including a negative SSEP).

Details of the intervention

The intervention period of 36 hours commenced at the time of randomization. All patients were sedated, with sedation mandated in both groups until the end of the intervention period. The choices of sedatives, analgesics and neuromuscular blocking agents were at the discretion of the treating physician. Core body temperature was measured with a temperature probe in the urinary bladder, or with an esophageal or intravascular probe in patients with low urinary output.

The goal of the intervention was to achieve the allocated temperature as rapidly as possible using ice-cold fluids, ice-packs, and intravascular or surface temperature management devices at the discretion of the site. Patients with an initial body temperature between 30°C and 33°C were actively rewarmed to 33°C at a maximum rate of 0.5°C per hour in both groups. For patients allocated to the 36°C group, passive rewarming to 36°C was mandated in the range from 33°C to 36°C, after which controlled temperature management was commenced and continued throughout the intervention period. After 28 hours gradual rewarming to 37°C by 0.5°C per hour 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 post-cardiac arrest, using fever control measures at the discretion of the sites. Concomitant intensive care, cardiological and neurological treatment followed standard practice.

Data collection and verification

Data for the primary outcome measure were obtained from national- or hospital registries, or from contacting patients, relatives, and general practitioners. Data for the neurological evaluation at 180-day follow up were obtained from an in-hospital visit, a visit of a trial investigator at the patients' residence or from telephone contact with patients, relatives, or general practitioners. The remaining secondary outcomes were obtained from direct observations during the hospital stay or from hospital registries. The primary outcome, temperature data, and eligibility criteria were verified source data in all patients. Pre-randomization characteristics, adverse events, and the secondary outcomes were verified with a random sample of at least 20% of the patients.

SUPPLEMENTARY RESULTS

Shivering and fever

There was no statistically significant difference between the two trial groups in the reported number of patients with shivering: 141 patients (30%) in the 33°C group and 156 (34%) patients in the 36°C group, P=0.20. The number of hours per day with a temperature >38°C on days 3 through 7 was similar in the 33°C group and the 36°C group (median 1, interquartile range 0-4 in both groups; P=0.77). The highest recorded temperature and the hours of temperature above 38°C on days 2 to 4 are depicted in the Supplementary Appendix, Table S6.

Adjusted analyses, specific analysis populations, and subgroup analyses

Similar results were obtained in the unadjusted analyses, and the analyses adjusted for stratification and design covariates (see Supplementary Appendix Tables S10 and S11). The effect of the intervention did not depend significantly on the binary variables defined by sex, age > 65 years, presence of initial shockable rhythm, time from cardiac arrest to return of spontaneous circulation above 25 minutes, and presence of shock at admission (Supplementary Appendix Figure S2).

The results for the primary outcome were also similar for the intention-to-treat and the per-protocol analysis populations. In the intention-to-treat analysis, there were 236 deaths in 475 patients (50%) in the 33°C group and 228 deaths in 471 patients (48%) in the 36°C group. In the per-protocol analysis, there were 235 deaths in 472 patients (50%) in the 33°C group and 224 deaths in 464 patients (48%) in the 36°C group.

SUPPLEMENTARY FIGURES AND TABLES

Figure S1. CONSORT flow chart

Assessment, randomization, analysis populations, and follow-up of the patients in the TTM trial.

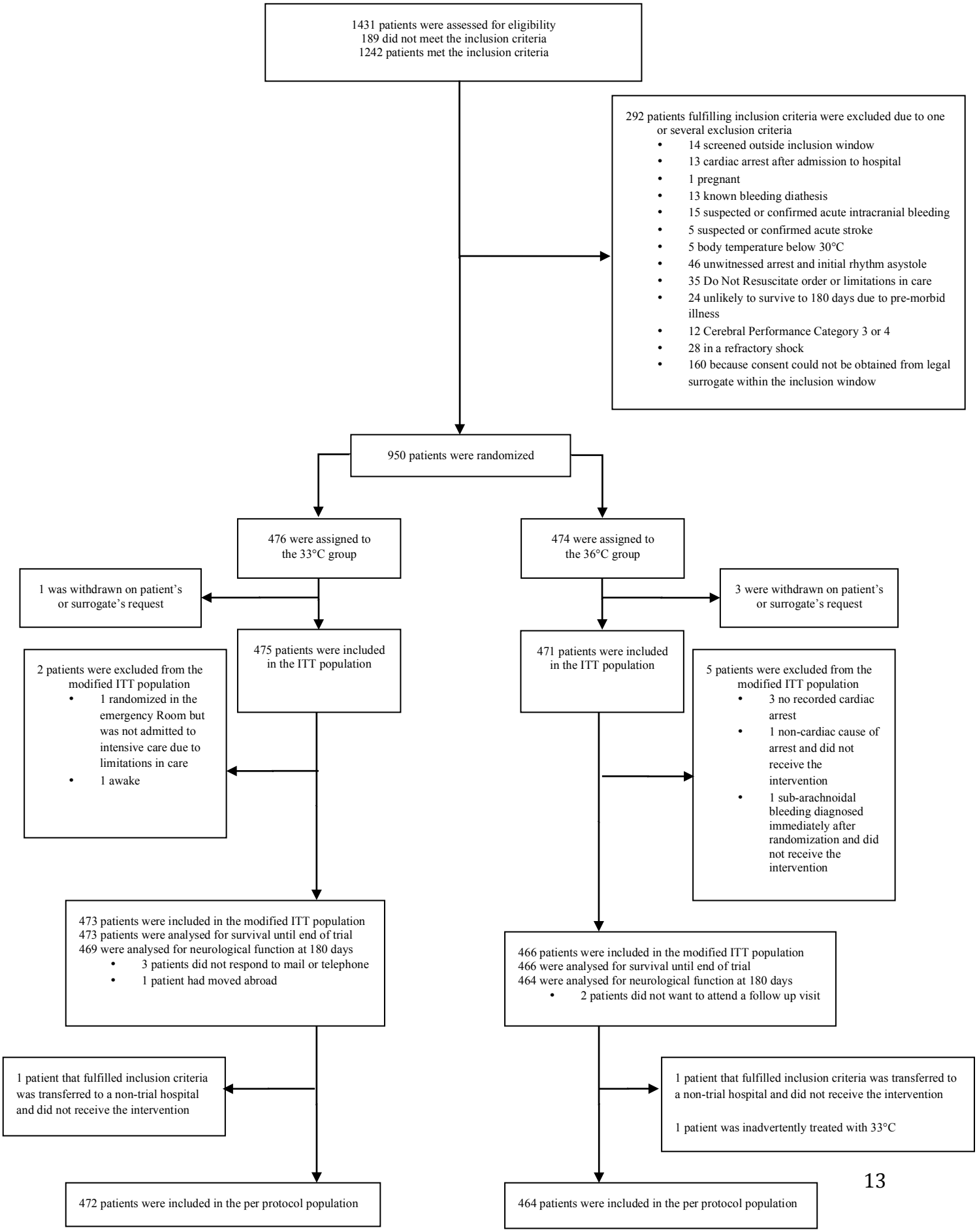

Figure S2. Hazard ratio of death, according to subgroup

The forest plot shows the hazard ratios for six predefined subgroups. The horizontal bars represent 95% confidence intervals. The events are the total events at end of trial. P values are for the tests of subgroup heterogeneity (tests of interactions). ROSC denotes return of spontaneous circulation. For unwitnessed cardiac arrests the time to ROSC was calculated form time of emergency call. Shock at admission was defined as a systolic blood pressure<90mmHg for >30min or end-organ hypoperfusion (cool extremities, urine output<30ml/hour, heart rate <60 beats/min).

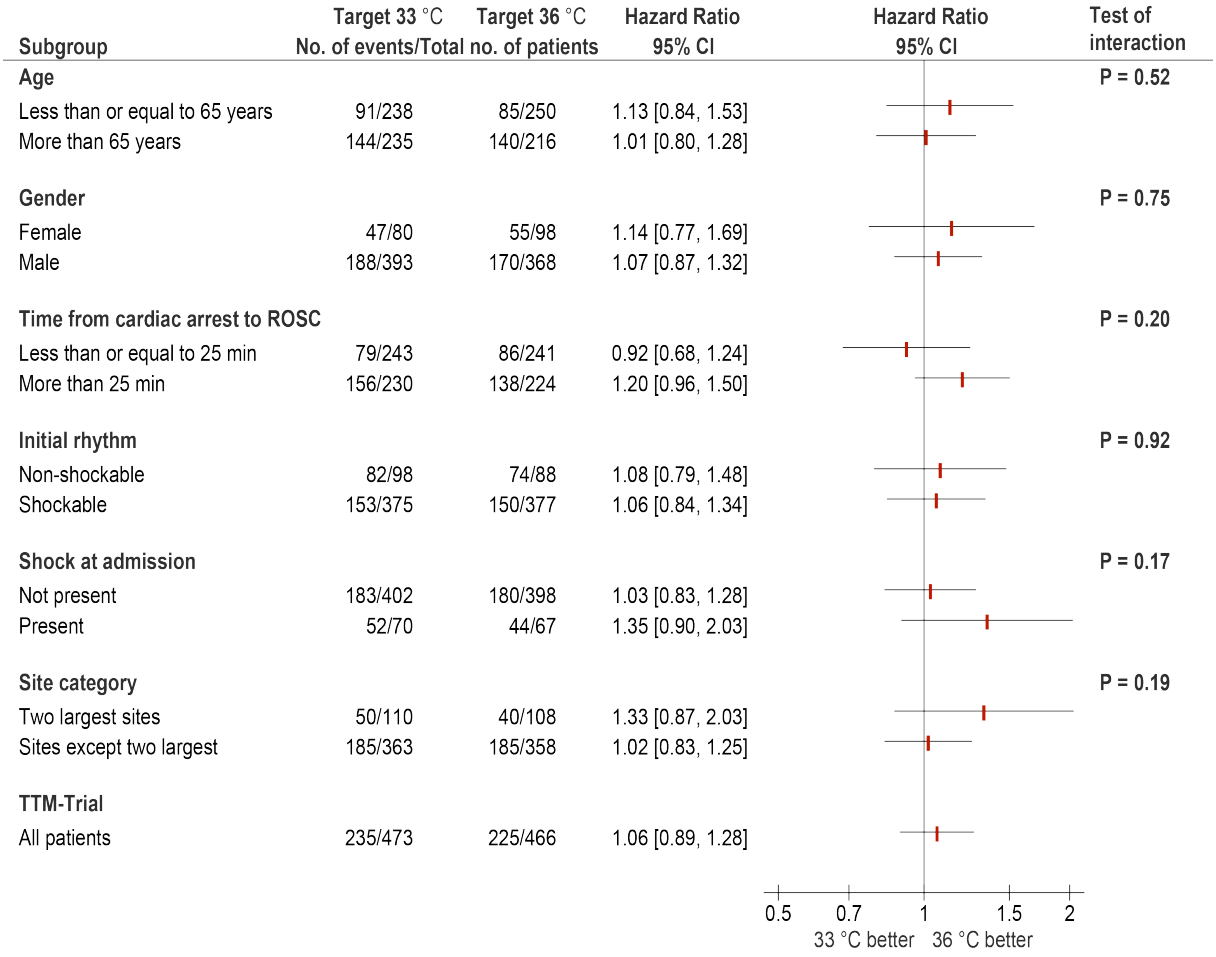

Table S1. Glasgow Coma Scale scores on admission

Table S1. **Glasgow Coma Scale Motor score on admission***			
	33°C	36°C	Total
Total no. patients	473	466	939
GCS-M no. (%)			
GCS-M 1	248 (52)	243 (52)	491
GCS-M 2	23 (5)	16 (3)	39
GCS-M 3	25 (5)	20 (4)	45
GCS-M 4	30 (6)	32 (7)	62
GCS-M 5	12 (3)	12 (3)	23
Sedation affecting GCS evaluation**	130 (27)	139 (30)	269
Missing	5 (1)	4 (1)	9

*GCS denotes Glasgow Coma Scale, GCS-M denotes GCS-motor.
**The patients that were sedated were mainly from tertiary hospitals with extended transfer from the scene of cardiac arrest. The evaluation of unconsciousness for randomization was based on the pre-sedation value (not reported here). The patients that were sedated on admission had similar proportions of initial rhythms and time from cardiac arrest to ROSC as the full cohort.

Table S2. Cardiovascular Sequential Organ Failure Assessment (SOFA) score

Table S2. **Cardiovascular component of Sequential Organ Failure Assessment score Day 1 to 3***						
	Day 1		Day 2		Day 3	
	33°C	36°C	33°C	36°C	33°C	36°C
Observations	466	454	450	434	428	421
SOFA-C						
0	55 (12)	65 (14)	41 (9)	70 (16)	65 (15)	113 (27)
1	47 (10)	41 (9)	11(2)	20 (5)	23 (5)	33 (8)
2	59 (13)	45 (10)	52 (12)	43 (10)	53 (12)	45 (11)
3	142 (30)	145 (32)	155 (34)	151 (35)	114 (27)	123 (29)
4	163 (35)	158 (35)	191 (42)	150 (35)	173 (40)	107 (25)

*SOFA denotes Sequential Organ Failure Assessment, SOFA-C denotes the cardiovascular subcomponent of the SOFA score. SOFA-C=0 No need for inotrope or vasopressor, mean arterial pressure (MAP) > 70mmHg, SOFA-C =1 MAP < 70mmHg, SOFA-C=2 any dose of dobutamine or dopamine <5 μg/kg/minute, SOFA-C=3 dopamine 5-15 μg/kg/minute or epinephrine or nor-epinephrine <0.1 μg/kg/minute, SOFA-C=4 dopamine >15 μg/kg/minute or epinephrine or nor-epinephrine >0.1 μg/kg/minute.

Table S3. Diagnostic procedures, interventions and service utilization

Table S3. **Diagnostic procedures, interventions and service utilization***			
	33°C	36°C	Total
	473	466	939
On admission no. (%)			
CT	150 (32)	165 (35)	315 (34)
Diagnostic procedures during ICU-stay no. (%)			
CT	174 (38)	182 (39)	356 (38)
MRI	18 (4)	17 (4)	35 (4)
EEG	205 (43)	184 (39)	389 (41)
SSEP	107 (23)	91 (19)	198 (21)
Interventions during ICU-stay no. (%)			
Coronary angiography	299 (63)	289 (62)	588 (63)
PCI	198 (42)	212 (45)	410 (44)
CABG	5 (1)	5 (1)	10 (1)
Thrombolysis	10 (2)	10 (2)	20 (2)
Time to intervention			
Hours from CA to angiography median [IQR]	2 [2-3]	2 [2-3]	2 [2-3]
Hours from CA to PCI median [IQR]	2 [2-3]	2 [2-3]	2 [2-3]
Mechanical ventilation** Days receiving mechanical ventilation/days in ICU median [IQR]	0.83 [0.67-1.00]	0.76 [0.60-1.00]	0.80 [0.60-1.00]
Sedation Days with sedation affecting neurological evaluation median [IQR]	2 [2-3]	2 [1-3]	2 [1-3]
Mechanical circulatory assist IABP no. (%)	78 (16)	62 (13)	140 (15)
Length of stay Hours from CA to ICU discharge median [IQR]	124 [71-201]	117 [74-190]	120 [73-195]
Days from CA to hospital discharge, median [IQR]	14 [8-24]	13 [8-24]	14 [8-24]

* CT denotes computed tomography of the head, MRI-magnetic resonance imaging of the head, EEG-electroencephalogram, SSEP-somatosensory evoked potentials, PCI-percutaneous coronary intervention, CABG-coronary artery bypass grafting, CA-cardiac arrest, ICU-intensive care unit, IABP-intra aortic balloon pump, IQR-interquartile range.
**There were no significant differences between the groups except for days receiving mechanical ventilation/days in ICU (P=0.006).

Table S4. Protocol violations and no intervention received

Table S4. **Protocol violations and no intervention received**		
	33°C	36°C
Transfer to another hospital*	1	1
Received the wrong intervention*	0	1
Died before start of intervention**,†	1	1
Fulfilled inclusion criteria but never received intervention†	1	1

*Excluded from the modified intention to treat population; included in the per protocol population.
**Died immediately after randomization.
†Included in the modified intention to treat population and in the per protocol population.

Table S5. Reasons for early rewarming

Table S5. **Reasons for early rewarming in the 33°C-group**	
Reason	**No.**
Arrhythmia (severe bradycardia, recurrent ventricular fibrillation, brady-tachy arrhythmia)	6
Severe circulatory instability	4
Bleeding	2
Uncontrolled lactate rise	2
Urgent coronary artery bypass grafting	1
No reason specified	1

Table S6. Development of fever

Table S6. **Development of fever in the intervention groups day 2-4***						
	Day 2		Day 3		Day 4	
Observations no.	898		865		765	
	33°C	36°C	33°C	36°C	33°C	36°C
Hours of temperature>38°C median [IQR]	0 [0-0]	0 [0-0]	0 [0-1]	0 [0-1]	0 [0-3]	0 [0-3]
Highest recorded temperature °C	36,0 (±1,5)	37,2 (±0.7)	37,7 (±0,5)	37,8 (±0,6)	37,8 (±0,6)	37,9 (±0,7)

*Cumulated hours above a body temperature of 38°C and highest recorded body temperature day 2-4 for patients in the intensive care unit. Trial sites were asked to actively treat fever until at least 72 hours after cardiac arrest. IQR denotes interquartile range. Plus-minus values are mean± standard deviation.

Table S7. Reasons for withdrawal of life sustaining therapy

Table S7. **Withdrawal of life sustaining therapy day 1-7***							
	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Total WLST no.	18	27	40	38	40	46	38
Brain dead	1	5	5	4	3	0	0
Neurological reasons	0	4	12	17	22	33	15
MOF and hemodynamic failure	23	32	31	25	13	5	6
Comorbidity	3	6	7	5	4	0	3
Ethical reason	2	5	7	14	10	13	4

*Withdrawal of life sustaining therapy of any reason (WLST) day 1 to 7 in the ICU. More than one reason could be registered for each patient. MOF denotes multi organ failure. Brain death was defined as having fulfilled criteria of brain death as per individual countries legislation. Neurological reasons were as defined in the trial protocol and above in this document. The risk of having a decision of withdrawal within the first 10 days did not differ between the groups: Hazard Ratio = 1.11 95%; CI 0.88-1.40, P=0.38. Median time to WLST of any reason was 5 days (interquartile range (IQR) 2-8) in the 33°C-group and 5 days (IQR 3-7) in the 36°C-group, (P=0.78)

Table S8. Neurological prognostication

Table S8. **Neurological prognostication***			
	33°C	36°C	Total
Total no.	473	466	939
Prognostication performed no. (%)	172 (36)	148 (32)	320 (34)
Recommendation no. (%)			
Continue care	65 (38)	52 (35)	117 (37)
Do not escalate	32 (19)	24 (16)	56 (17)
Withdraw care	73 (42)	71 (48)	144 (45)
Recommendation not recorded	2	1	3
Hours from CA to prognostication median (IQR)	117 (93-137)	119 (94-141)	118 (93-140)
Prognostication not performed no. (%)	16 (3)	15 (3)	31 (3)
Reasons no.			
No reason	2	2	4
Transfer to other hospital	7	10	17
Ongoing sedation	4	2	6
WLST due to ethical reasons	1	1	2
Ongoing multi organ failure	2	0	2
Died before prognostication no. (%)	76 (16)	62 (13)	138 (15)
Presumed cause of death no. (%)			
Cardiac/hemodynamic cause	36 (47)	27 (43)	63 (46)
Multi organ failure	19 (25)	12 (19)	31 (22)
Cerebral cause	21 (28)	23 (37)	44 (32)
WLST of patients who died before reported prognostication no. (%)	48 (63 %)	42 (68 %)	90 (65 %)
Regained consciousness before prognostication no. (%)**	209 (44 %)	241 (52 %)	450 (48 %)

*WLST denotes withdrawal of life sustaining therapy for any reason, CA-cardiac arrest, IQR-interquartile range. Neurological prognostication by a physician blinded to the intervention, was undertaken 72 hours after the end of the intervention period or later, except in cases of brain death and early generalized myoclonic seizures with bilaterally absent N20 waves on somatosensory evoked potentials, when an earlier prognostication could be performed. WLST was allowed in these cases and also due to ethical and medical reasons previously described.[1,2] For more details on reasons for WLST see Table S6.

**There were no statistical differences in the variables in this table between the groups except for the number of patients that regained consciousness before prognostication (P=0.03).

Table S9. Cerebral Performance Category at ICU and hospital discharge

Table S9. **Neurological scores at ICU and hospital discharge***				
Category no. (%)	**CPC ICU discharge**§		**CPC Hospital discharge**§	
	33°C	36°C	33°C	36°C
CPC 1	61 (13)	79 (17)	133 (28)	143 (31)
CPC 2	120 (25)	111 (24)	74 (16)	69 (15)
CPC 3	65 (14)	78 (17)	39 (8)	36 (8)
CPC 4	61 (13)	54 (12)	19 (4)	14 (3)
CPC 5	166 (36)	144 (31)	208 (44)	203 (44)
Total	473	466	473	465

* CPC denotes cerebral performance category
§ CPC 1: Good cerebral performance, may have mild deficits, 2: Moderate cerebral disability, sufficient for independent activities of daily life, 3: Severe cerebral disability, 4: coma or vegetative state, 5: dead.[3,4]

Table S10. Adjusted analyses I

Table S10. **Adjusted analyses I***						
Adjusting covariates	**Mortality end-of-trial**		**CPC score > 2 follow-up†**		**mRS score> 3 follow-up††**	
	HR with 95% CI and n	P value	RR[§§] with 95% CI and n	P value	RR† with 95% CI and n	P value
None	1.08(0.90-1.29) n=939	0.43	1.03 (0.90-1.17) n=933	0.67	1.02 (0.89-1.16) n=933	0.82
Site (primary analyses)	1.06 (0.89-1.28) n=939	0.51	1.02 (0.88-1.16) n=933	0.78	1.01 (0.89 to 1.14) n=933	0.87
Site + design variables[**]	1.14 (0.94-1.37) n=937	0.18	0.97 (0.68-1.27) n=932	0.65	0.96 (0.81-1.11) n=932	0.58
Site category[§]	1.07 (0.89-1.29) n=939	0.45	1.03 (0.90-1.17) n=933	0.67	1.01 (0.89-1.14) n=933	0.82
Site category[§] + design variables[**]	1.13 (0.94-1.35) n=937	0.21	0.99 (0.83-1.15) n=932	0.85	0.97 (0.83 to 1.12) n=932	0.71

*Hazard ratio (HR) and relative risk (RR) of a poor neurological outcome and death between the two intervention groups (36°C-group is reference group) and 95% confidence interval (CI) without and with adjusting covariates

**Effect of intervention (36°C-group is reference group) on survival, on the indicator that the Cerebral Performance Category (CPC) score threshold of 2 has been exceeded, and on the indicator that the modified Rankin Scale (mRS) score threshold of 3 has been exceeded. The design variables include age, gender, shockable first rhythm, duration/min of cardiac arrest, and shock at admission

§The site categories include the category comprising the patients from the two sites with the highest number of patients treated (from the modified intention-to-treat population) and the category comprising the rest of the patients (from the modified intention-to-treat population)

§§In the adjusted analyses logistic regression analyses were used and the odds ratio estimate (OR) and its 95% CI were transformed to estimated relative risk (RR) using the equation RR = OR/((1-P)+OR*P) where P is the observed risk of death in the reference group (36°C)[5]

†CPC 1: Good cerebral performance, may have mild deficits, 2: Moderate cerebral disability, sufficient for independent activities of daily life, 3: Severe cerebral disability, 4: coma or vegetative state, 5: dead.[3,4]

††mRS 0: mRS 0: no symptoms, 1: no significant disability despite symptoms, 2: slight disability, able to look after own affairs without assistance, 3: moderate disability, requires some help, but able to walk unassisted, 4: moderately severe disability, unable to attend own bodily needs, 5: severe disability, bedridden, 6: dead.[6]

Table S11. Adjusted analyses II

Table S11. **Adjusted analyses II***				
	Mortality 180 days		**Best CPC**	
Adjusting covariates	Relative risk (RR) † 95% CI and n	P value	Relative risk (RR) † 95% CI and n	P value
None	1.01 (0.94-1.08) n=939	0.92	1.03 (0.91-1.17) n=938	0.63
Site	1.01 (0.87-1.14) n=939	0.92	1.04 (0.89 to 1.17) n=938	0.67
Site + design covariates**	0.95 (0.79-1.11) n=937	0.74	0.99 (0.83-1.15) n=936	0.89
Site category§	1.01 (0.88-1.15) n=939	0.86	1.04 (0.90-1.17) n=938	0.62
Site category + design covariates§**	0.96 (0.81-1.13) n=938	0.66	0.99 (0.84-1.14)	0.89

*Relative risk (RR) of death and the best reported Cerebral Performance Category (CPC) threshold of 2 has been exceeded between the two intervention groups (36°C-group is reference group) and 95% confidence interval (CI) without and with adjusting covariates

**The design variables include age, gender, shockable first rhythm, duration/min of cardiac arrest, and shock at admission

§The site categories include the category comprising the patients from the two sites with the highest number of patients treated (from the modified intention-to-treat population) and the category comprising the rest of the patients (from the modified intention-to-treat population)

†In the adjusted analyses logistic regression analyses were used and the odds ratio estimate (OR) and its 95% CI were transformed to estimated relative risk (RR) using the equation RR = OR/((1-P)+OR*P) where P is the observed risk of death in the reference group (36°C)[5]

Table S12. Serious adverse events

*Serious adverse events collected during day 1-7 when the patient was in the intensive care unit. CA denotes cardiac arrest, CPR-cardiopulmonary resuscitation

Table S12. **Serious adverse events excluding death***			
Serious adverse event no. (%)	**Occurrence of event during stay in ICU**		
(Denominator 'n=xxx' in parenthesis)	33°C	36°C	P value
Seizures			
Myoclonic seizures (n=923)	128 (28)	101 (23)	0.13
Tonic-clonic seizures (n=934)	36 (7.7)	34 (7.3)	0.85
Bleeding			
Uncontrolled bleeding (n=916)	10 (2.2)	6 (1.3)	0.45
Intracranial bleeding (n=902)	2 (0.4)	7 (1.5)	0.09
Intraspinal bleeding (n=906)	0 (0.0)	1 (0.2)	0.49
Intraocular bleeding (n=904)	0 (0.0)	1 (0.2)	0.49
Intraarticular bleeding (n=902)	0 (0.0)	1 (0.1)	0.49
Pericardial bleeding (n=886)	4 (0.9)	5 (1.1)	0.75
Gastro-intestinal bleeding (n=906)	25 (5.4)	23 (5.1)	0.84
Tracheal bleeding (n=907)	16 (3.5)	16 (3.6)	0.93
Oral cavity bleeding (n=906)	31 (6.8)	30 (6.7)	0.97
Nose bleeding (n=904)	26 (5.7)	25 (5.6)	0.96
Genital bleeding (n=896)	8 (1.8)	6 (1.3)	0.81
Bleeding from insertion sites (n=901)	42 (9.2)	27 (6.1)	0.076
Infection			
Pneumonia (n=932)	245 (52)	214 (46)	0.089
Severe sepsis (n=925)	46 (10)	46 (10)	0.92
Septic shock (n=922)	22 (4.8)	25 (5.4)	0.63
Other serious infection (n=923)	10 (2.2)	13 (2.8)	0.52
Arrhythmia			
Atrial fibrillation (n=929)	123 (26)	130 (28)	0.51
Atrial flutter (n=923)	17 (3.6)	19 (4.2)	0.68
Tachycardia (n=924)	65 (14)	71 (16)	0.49
Bradycardia needing pacing (n=922)	24 (5.2)	29 (6.4)	0.43
Ventricular tachycardia (n=922)	86 (18)	70 (15)	0.21
Ventricular fibrillation (n=921)	39 (8.4)	34 (7.4)	0.59
Recurrent CA mandating CPR (n=913)	42 (9.1)	46 (10)	0.60
Electrolyte and metabolic disorder			
Hypokalemia (n=911)	86 (19)	60 (13)	0.018
Hypomagnesemia (n=674)	73 (22)	60 (18)	0.20
Hypophosphatemia (n=710)	153 (44)	138 (38)	0.13
Hypoglycemia (n=905)	25 (5.5)	22 (4.9)	0.68
Renal replacement therapy (n=917)	49 (11)	42 (9.1)	0.44
Any of the above events (n=936)	439 (93)	417 (90)	0.086

Table S13. Presumed cause of death

Table S13. **Presumed cause of death***		
	33°C	36°C
Total patients no.	473	466
Dead no. (% of dead) (% of total patients no.)	235 (100) (50)	225 (100) (48)
Cause of death		
Cardiovascular	58 (25) (12)	53 (23) (11)
Cerebral	131 (56) (28)	135 (60) (29)
MOF	31 (13) (7)	26 (11) (6)
Other or undetermined	15 (6) (3)	11 (5) (2)

* The cause of death was based on clinical judgment by the investigators and is not based on results from autopsies. MOF denotes multi organ failure.

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