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Therapeutic hypothermia after out-of-hospital cardiac arrest in children

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ORIGINAL ARTICLE

Therapeutic Hypothermia after Out-of-Hospital Cardiac Arrest in Children

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ABSTRACT

BACKGROUND

Therapeutic hypothermia is recommended for comatose adults after witnessed out-of-hospital cardiac arrest, but data about this intervention in children are limited.

METHODS

We conducted this trial of two targeted temperature interventions at 38 children's hospitals involving children who remained unconscious after out-of-hospital cardiac arrest. Within 6 hours after the return of circulation, comatose patients who were older than 2 days and younger than 18 years of age were randomly assigned to therapeutic hypothermia (target temperature, 33.0°C) or therapeutic normothermia (target temperature, 36.8°C). The primary efficacy outcome, survival at 12 months after cardiac arrest with a Vineland Adaptive Behavior Scales, second edition (VABS-II), score of 70 or higher (on a scale from 20 to 160, with higher scores indicating better function), was evaluated among patients with a VABS-II score of at least 70 before cardiac arrest.

RESULTS

A total of 295 patients underwent randomization. Among the 260 patients with data that could be evaluated and who had a VABS-II score of at least 70 before cardiac arrest, there was no significant difference in the primary outcome between the hypothermia group and the normothermia group (20% vs. 12%; relative likelihood, 1.54; 95% confidence interval [CI], 0.86 to 2.76; P=0.14). Among all the patients with data that could be evaluated, the change in the VABS-II score from baseline to 12 months was not significantly different (P=0.13) and 1-year survival was similar (38% in the hypothermia group vs. 29% in the normothermia group; relative likelihood, 1.29; 95% CI, 0.93 to 1.79; P=0.13). The groups had similar incidences of infection and serious arrhythmias, as well as similar use of blood products and 28-day mortality.

CONCLUSIONS

In comatose children who survived out-of-hospital cardiac arrest, therapeutic hypothermia, as compared with therapeutic normothermia, did not confer a significant benefit in survival with a good functional outcome at 1 year. (Funded by the National Heart, Lung, and Blood Institute and others; THAPCA-OH ClinicalTrials.gov number, NCT00878644.)

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Out-of-hospital cardiac arrest in children often results in death or in poor long-term functional outcome in survivors.[1-3] In 2002, two trials involving adults showed that therapeutic hypothermia improved neurologic outcomes in comatose survivors after out-of-hospital cardiac arrest with ventricular fibrillation or ventricular tachycardia.[4,5] International guidelines recommend therapeutic hypothermia for adults with out-of-hospital cardiac arrest who have similar characteristics.[6,7] Recently, another trial involving adults after out-of-hospital cardiac arrest showed that therapeutic hypothermia with the use of a target temperature of 33°C, as compared with actively maintained therapeutic normothermia (36°C), did not improve outcomes.[8] The fundamental difference between this recent trial and the earlier 2002 trials was the active intervention to prevent fever in the comparison group of patients who were treated with normothermia.[4,5,8]

Published results of randomized trials of therapeutic hypothermia in children after out-of-hospital cardiac arrest are lacking.[9] In observational studies, therapeutic hypothermia has not been associated with improved outcomes in children after cardiac arrest.[10-12] Moreover, one trial involving pediatric patients with traumatic brain injury showed a trend toward increased mortality in the hypothermia group.[13] There are significant differences between adult and pediatric populations with out-of-hospital cardiac arrest, and results cannot be generalized between age groups.[14] We report results of the Therapeutic Hypothermia after Pediatric Cardiac Arrest Out-of-Hospital (THAPCA-OH) trial, which compared the efficacy of therapeutic hypothermia (target temperature, 33.0°C) with that of therapeutic normothermia (target temperature, 36.8°C).[15,16]

METHODS

STUDY DESIGN AND OVERSIGHT

This randomized clinical trial, which was conducted in pediatric intensive care units (ICUs) at 38 children's hospitals in the United States and Canada, involved children who were admitted after out-of-hospital cardiac arrest. The rationale, study design, outcome selection process, protocol summary, and 12-month pilot vanguard phase have been described previously.[15-17]

The trial was funded by the National Heart, Lung, and Blood Institute (NHLBI). The protocol was designed by the first, third, and last authors. The institutional review board at each participating site and the data coordinating center at the University of Utah (see the Supplementary Appendix, available with the full text of this article at NEJM.org) approved the protocol and informed-consent documents.

The site research coordinators listed in the Supplementary Appendix collected all the data, and statisticians at the data coordinating center performed all the analyses. Details of site training, data management, and site monitoring are provided in the Supplementary Appendix. An independent data and safety monitoring board that was appointed by the NHLBI conducted interim safety and efficacy analyses.[18] All the authors vouch for the accuracy and completeness of the submitted data, the third and last authors vouch for the data management and statistical analyses, and all the authors vouch for the fidelity of this report to the study protocol, which is available at NEJM.org.

PATIENT POPULATION

Children older than 48 hours and younger than 18 years of age were eligible for inclusion in the study if they had a cardiac arrest requiring chest compressions for at least 2 minutes and remained dependent on mechanical ventilation after the return of circulation. Major exclusion criteria were the inability to undergo randomization for any reason within 6 hours after the return of circulation, a score of 5 or 6 on the Glasgow Coma Scale motor-response subscale (on which scores range from 1 to 6, with lower scores indicating reduced levels of function), the decision by the clinical team to withhold aggressive treatment, and major trauma associated with the cardiac arrest. A full listing of the exclusion criteria is provided in the Supplementary Appendix. Written informed consent from a parent or legal guardian was obtained for each participant.

RANDOMIZATION AND INTERVENTION

Eligible patients were randomly assigned in a 1:1 ratio to either therapeutic hypothermia or therapeutic normothermia. Randomization was performed with the use of permuted blocks stratified according to clinical center and age at entry (<2 years, 2 to <12 years, and ≥12 years).

Targeted temperature management was actively maintained for 120 hours in each group.

Children who were assigned to therapeutic hypothermia were pharmacologically paralyzed and sedated, and a Blanketrol III temperature management unit (Cincinnati Sub-Zero) was used, with blankets applied anteriorly and posteriorly, to achieve and maintain a core temperature of 33.0°C (range, 32.0 to 34.0) for 48 hours. The children were then rewarmed over a period of 16 hours or longer to a target temperature of 36.8°C (range, 36.0 to 37.5); this temperature was actively maintained throughout the remainder of the 120-hour intervention period. Children who were randomly assigned to therapeutic normothermia received identical care except that the core temperature was actively maintained with the cooling unit at 36.8°C (range, 36.0 to 37.5) for 120 hours.

Dual monitoring of the central temperature (esophageal, rectal, or bladder temperature) and an automatic mode on the temperature management unit were used for all the patients. The probe connected to the cooling unit was designated to be the primary probe; the other probe was connected to the bedside monitor for safety backup. In three patients who received extracorporeal membrane oxygenation (ECMO) at the time of randomization, ECMO was used for temperature control. All other aspects of clinical care were determined by the clinical teams.

OUTCOMES

The primary outcome was survival with a good neurobehavioral outcome at 12 months of follow-up. A good neurobehavioral outcome was defined as an age-corrected standard score of 70 or higher on a scale of 20 to 160 on the Vineland Adaptive Behavior Scales, second edition (VABS-II).[19] The VABS-II has an age-corrected mean score of 100 and a standard deviation of 15; higher scores indicate better function. The VABS-II data were collected centrally at the Kennedy Krieger Institute by means of telephone interviews conducted by a trained interviewer who was unaware of the treatment assignments.

As prespecified in the trial protocol, enrolled children whose reported VABS-II scores were less than 70 before cardiac arrest (on the basis of data from a standardized caregiver questionnaire completed by a parent or guardian at each site within 24 hours after randomization) were not included in the primary efficacy analysis.

Figure 1 (facing page). Enrollment, Randomization, and Treatment.

Scores on the Glasgow Coma Scale (GCS) motor-response subscale range from 1 to 6, with lower scores indicating reduced levels of function. Scores on the Pediatric Overall Performance Category (POPC) and Pediatric Cerebral Performance Category (PCPC) scales range from 1 to 6, with lower scores indicating less disability. Scores on the Vineland Adaptive Behavior Scales, second edition (VABS-II), range from 20 to 160, with higher scores indicating better function. CNS denotes central nervous system, ICU intensive care unit, ITT intention to treat, and THAPCA Therapeutic Hypothermia after Pediatric Cardiac Arrest.

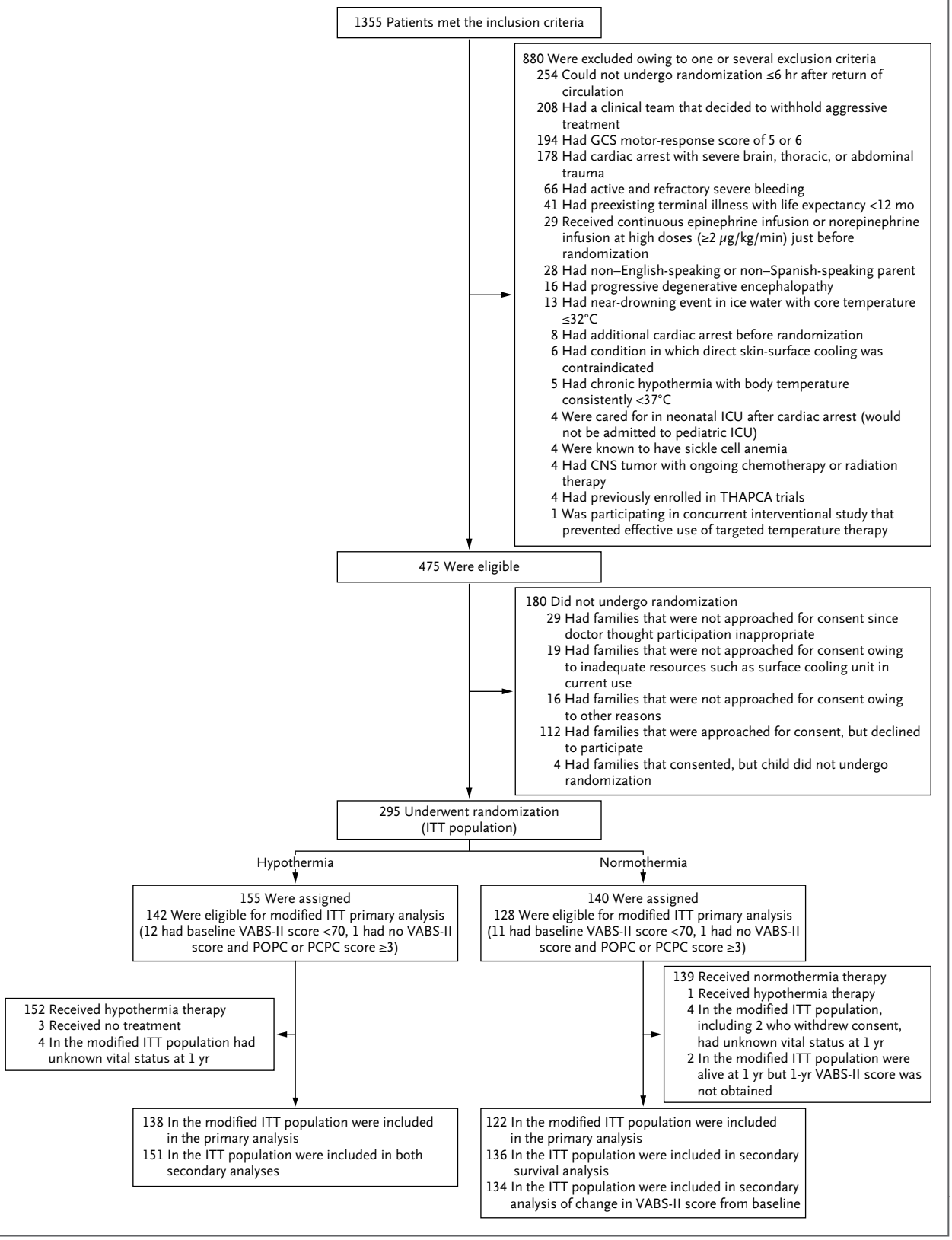
Patients for whom no baseline VABS-II score was available were considered to be eligible for the primary analysis if the baseline Pediatric Overall Performance Category (POPC) and Pediatric Cerebral Performance Category (PCPC) scores[20] were in the normal or mild disability category.[17,21] Both scales range from 1 to 6, with lower scores indicating less disability; patients with scores of either 1 or 2 on both scales were eligible for the primary analysis.

Secondary outcomes were survival 12 months after cardiac arrest and change in neurobehavioral function, measured as the difference between the baseline level before cardiac arrest and the 12-month measurement on the VABS-II. For the latter, patients who had died and patients with the lowest possible VABS-II score were assigned the worst possible outcomes, regardless of baseline function.

A global cognitive score that was based on results of on-site neuropsychological testing was a tertiary outcome (see the Supplementary Appendix). Safety outcomes included the incidences of blood-product use, infection, and serious arrhythmias through 7 days and 28-day mortality. Details of the methods used for the assessment of outcomes are provided in the Supplementary Appendix.

STATISTICAL ANALYSIS

The target sample size was calculated on the basis of an absolute effect size of 15 to 20%, with an estimated primary outcome rate of 15 to 35% in the normothermia group. Assuming that 5% of the patients would be excluded owing to a baseline neurologic deficit and that 5% of patients would be lost to follow-up, we estimated that 276 patients would need to be enrolled to



provide the study with 85% power to detect a 20% treatment effect.

The efficacy analysis for the primary outcome was performed with the use of a prespecified modified intention-to-treat approach, excluding children with poor neurobehavioral function before cardiac arrest, as noted above. Secondary efficacy outcomes were analyzed in all the children. Safety analyses were performed according to the treatment received in treated patients only. The primary outcome and 12-month mortality were compared between the treatment groups with the use of a Cochran–Mantel–Haenszel test stratified according to age category.

The change in the VABS-II score was analyzed with the use of van Elteren's modification of the Mann–Whitney test,[22] with stratification according to age category, treatment of death as the worst outcome, and treatment of the lowest possible VABS-II score at 1 year as the second worst outcome. An alpha level of 0.05 was set for the primary analysis, and an alpha level of 0.025 was set for each of the two formal secondary analyses, with two-sided tests used in all instances. The probability of survival to 1 year was evaluated by comparing survival curves over time between treatment groups with the use of a log-rank test stratified according to age category. All analyses were performed with the use of SAS software, version 9.3 (SAS Institute).

RESULTS

PATIENTS

Between September 1, 2009, and December 31, 2012, we identified 1355 patients who were screened for eligibility and met the trial inclusion criteria (Fig. 1). Of these patients, 475 were eli-

Table 1. Baseline Characteristics of the Patients before Randomization.*

Characteristic	Hypothermia Group (N=155)	Normothermia Group (N=140)
Demographic characteristics		
Age — yr		
Median	2.1	1.6
Interquartile range	0.6–10.1	0.4–7.0
Age category — no. (%)		
<2 yr	76 (49)	73 (52)
2 to <12 yr	48 (31)	45 (32)
≥12 yr	31 (20)	22 (16)
Male sex — no. (%)	102 (66)	94 (67)
Medical history — no. (%)		
No preexisting medical condition	81 (52)	71 (51)
Preexisting medical condition		
Lung or airway disease	33 (21)	34 (24)
Neurologic condition	30 (19)	19 (14)
Gastrointestinal disorder	19 (12)	22 (16)
Prenatal condition	15 (10)	22 (16)
Congenital heart disease	14 (9)	21 (15)
Other	34 (22)	37 (26)
Characteristics of the cardiac arrest		
Primary cause of the cardiac arrest — no. (%)		
Respiratory event	111 (72)	102 (73)
Cardiovascular event	14 (9)	18 (13)
Other	11 (7)	4 (3)
Unknown	19 (12)	16 (11)
Bystander witnessed cardiac arrest — no./total no. (%)	58/145 (40)	51/136 (38)
Bystander performed CPR — no./total no. (%)	101/149 (68)	85/134 (63)

Table 1. (Continued.)

Characteristic	Hypothermia Group (N=155)	Normothermia Group (N=140)
Initial rhythm noted by EMS or hospital — no. (%)		
Asystole	85 (55)	87 (62)
Bradycardia	9 (6)	10 (7)
Pulseless electrical activity	25 (16)	18 (13)
Ventricular fibrillation or tachycardia	14 (9)	9 (6)
Unknown	22 (14)	16 (11)
Time from cardiac arrest to CPR in 82 patients — min		
Median	3.0	2.0
Interquartile range	0.0–7.0	0.0–8.0
Duration of CPR in 186 patients — min		
Median	23.0	28.0
Interquartile range	15.0–35.0	19.0–45.0
First hospital patient arrived at was the study hospital — no. (%)	45 (29)	43 (31)
Chest compressions still required at time of arrival at first hospital — no./total no. (%)	97/152 (64)	100/137 (73)
No. of doses of epinephrine		
Administered by EMS in 270 patients†		
Median	2.0	1.0
Interquartile range	0.0–3.0	0.0–2.0
Administered at hospital in 289 patients†		
Median	1.0	2.0
Interquartile range	0.0–3.0	0.0–4.0
All doses administered by EMS and at hospital in 265 patients		
Median	3.0	3.0
Interquartile range	2.0–4.5	2.0–5.0

* CPR denotes cardiopulmonary resuscitation, and EMS emergency medical services.
† $P<0.05$ for the comparison between the two groups.

gible to enroll in the study. The families of 411 of these patients were approached for consent, 299 families consented, and 295 patients underwent randomization at 36 sites in the United States and Canada (2 sites did not enroll any patients). Of the patients who underwent randomization to targeted temperature management, 155 were assigned to therapeutic hypothermia and 140 were assigned to therapeutic normothermia. A total of 3 patients who were assigned to therapeutic hypothermia did not receive an intervention, and 1 patient assigned to therapeutic normothermia received hypothermia therapy.

Of the 295 patients who underwent randomization, 13 in the hypothermia group and 12 in the normothermia group were ineligible for the primary outcome analysis owing to baseline VABS-II scores that were less than 70, or POPC or PCPC scores that were 3 or higher. At 12 months, vital status was not known in 4 patients in each group, and 2 additional surviving children in the normothermia group did not undergo VABS-II testing (Fig. 1). Therefore, 260 patients had data that could be evaluated for the primary outcome.

CHARACTERISTICS AT BASELINE AND TEMPERATURE INTERVENTION

The characteristics of the patients in the hypothermia group and those in the normothermia group were similar at baseline (Table 1, and Table S1 in the Supplementary Appendix). The median age of the patients was 2 years; two thirds of the patients were male. Bystanders witnessed the cardiac arrest in 39% of the patients and per-

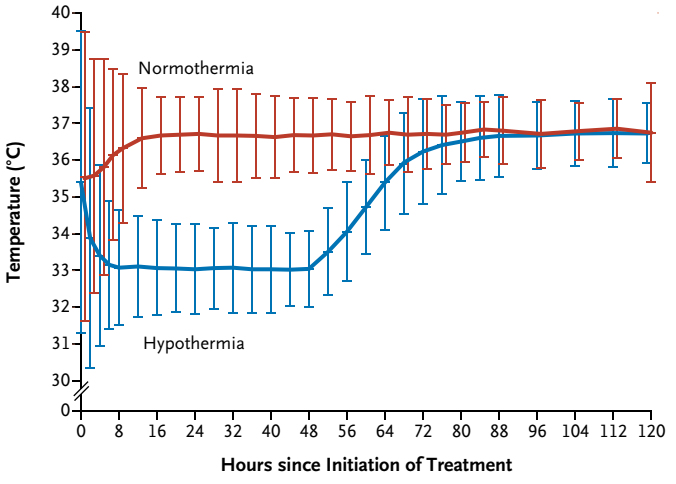


Figure 2. Temperature of Patients during 120 Hours of Targeted Temperature Management, According to Treatment Group.

The temperature curves show the means of all primary temperature readings within each time interval (for example, all primary temperature readings from 22 to 26 hours after the initiation of treatment are counted in the category "24 hours since initiation of treatment"). The I bars indicate ±2 SD from the mean temperature within each time interval. Time points for normothermia are slightly shifted to prevent overlap. Temperatures recorded after early termination of treatment are not included in this analysis.

formed cardiopulmonary resuscitation in 66% of them. The initial rhythm was ventricular fibrillation or ventricular tachycardia in 8% of the patients. Baseline functional status based on the VABS-II, PCPC, and POPC scores is shown in Table S2 in the Supplementary Appendix.

The median time from the return of circulation to the initiation of treatment was 5.9 hours (interquartile range, 5.2 to 6.7) in the hypothermia group and 5.8 hours (interquartile range, 5.0 to 6.4) in the normothermia group. Figure 2 shows the primary central (core) temperatures recorded for the two groups. Additional information regarding temperature control is provided in the Supplementary Appendix.

OUTCOMES

The proportion of survivors with VABS-II scores of 70 or more at 12 months was not significantly different between the two groups (20% in the hypothermia group vs. 12% in the normothermia group; relative likelihood, 1.54; 95% confidence interval [CI], 0.86 to 2.76; P=0.14) (Table 2). Sensitivity analyses, including a per-protocol analysis and analyses with imputation of missing data, did not alter the primary-outcome result (see the Supplementary Appendix).

The secondary outcome of change in the VABS-II score from baseline to 12 months also did not differ significantly between the two groups (P=0.13). The overall proportion of patients with 12-month VABS-II scores that did not decrease by more than 15 points (1 SD) of their baseline measurements was similar in the hypothermia group and the normothermia group (14% and 13%) (Table 2).

Mortality among all patients who underwent randomization and whose vital status was known (287 of 295 patients [97%]) was assessed at 12 months. Survival at 1 year did not differ significantly between the groups (38% in the hypothermia group vs. 29% in the normothermia group; relative likelihood, 1.29; 95% CI, 0.93 to 1.79; P=0.13) (Table 2). Survival over time was significantly longer with therapeutic hypothermia than with therapeutic normothermia (mean survival, 149±14 days vs. 119±14 days; P=0.04 for the comparison of survival between the two treatment groups by means of the log-rank test) (Fig. S1 in the Supplementary Appendix). The primary cause of death was brain death or withdrawal of life-sustaining therapy owing to a poor neurologic prognosis in the majority of patients in the two groups (82% of the patients in the hypothermia group and 79% of the patients in the normothermia group) (Table S3 in the Supplementary Appendix).

Data on global cognitive functioning in survivors are shown in Table S4 in the Supplementary Appendix. Results of the Early Learning Composite score from the Mullen Scales of Early Learning[23] did not differ significantly between the survivors in the hypothermia group and those in the normothermia group; there were also no significant between-group differences in the IQ score[24] distributions on the Wechsler Abbreviated Scale of Intelligence or in the combined categories from both the Mullen and the Wechsler tests.

SAFETY

The incidences of infection, bleeding, and serious arrhythmias within 7 days after randomization were similar in the 153 patients who received hypothermia therapy and the 139 who received normothermia therapy (Table 3). Mortality at 28 days was also not significantly different in the two groups (57% in the hypothermia group vs.

Table 2. Primary and Secondary Outcomes.*

Outcome	Hypothermia Group	Normothermia Group	Risk Difference	Relative Likelihood (95% CI)	P Value
	no./total no. (%)		*percentage points (95% CI)*		
Primary outcome					
Alive with VABS-II score ≥70 at 1 yr	27/138 (20)	15/122 (12)	7.3 (–1.5 to 16.1)	1.54 (0.86 to 2.76)	0.14†
Detailed supportive analysis					0.14‡
Death	87/138 (63)	88/122 (72)			
Disability					
Profound§	16/138 (12)	11/122 (9)			
Moderate-to-severe¶	8/138 (6)	8/122 (7)			
Good functional status‖	27/138 (20)	15/122 (12)			
Secondary outcomes					
Alive at 1 yr	57/151 (38)	39/136 (29)	9.1 (–1.8 to 19.9)	1.29 (0.93 to 1.79)	0.13†
1-yr change in VABS-II score from baseline					0.13**
Death	94/151 (62)	97/134 (72)			
Lowest possible VABS-II score	6/151 (4)	1/134 (1)			
Decrease in VABS-II score					
>30 points	19/151 (13)	15/134 (11)			
16–30 points	11/151 (7)	4/134 (3)			
≤15 points or improved	21/151 (14)	17/134 (13)			

* The primary outcome was evaluated in patients with a baseline Vineland Adaptive Behavior Scales, second edition (VABS-II), score of 70 or higher at 12 months (scores on the VABS-II range from 20 to 160, with higher scores indicating better function). The secondary outcomes were evaluated in all patients with available data. Denominators reported are for patients whose outcomes were known. CI denotes confidence interval.
† The P value was calculated by means of the Cochran–Mantel–Haenszel test, with adjustment for age category.
‡ The P value was calculated by means of the Mann–Whitney test on the basis of the 1-year continuous VABS-II score, stratified according to age category. Deceased patients and those with the lowest possible VABS-II score were assigned ranks of –2000 and –1000, respectively (i.e., the worst possible scores).
§ Profound disability was defined as a VABS-II score of less than 45 or the lowest possible score.
¶ Moderate-to-severe disability was defined as a VABS-II score of 45 to 69.
‖ Good functional status was defined as a VABS-II score of 70 or higher.
** The P value was calculated by means of the Mann–Whitney test on the basis of the continuous change in VABS-II score, stratified according to age category. Deceased patients and those with the lowest possible VABS-II score were assigned ranks of –2000 and –1000, respectively (i.e., the worst possible scores).

67% in the normothermia group, P=0.08). Additional data regarding adverse events are provided in Table S5 in the Supplementary Appendix. Hypokalemia and thrombocytopenia occurred more frequently in the hypothermia group, and renal-replacement therapy was used more often in the normothermia group.

DISCUSSION

The THAPCA-OH trial evaluated the efficacy of therapeutic hypothermia (targeted temperature management at 33.0°C) and therapeutic normothermia (targeted temperature management at 36.8°C) to improve outcomes after out-of-hospital cardiac arrest in children. There was no significant between-group difference in the primary outcome of survival with a good neurobehavioral outcome (VABS-II composite score of ≥70) at 12 months. The secondary outcome, the change in the VABS-II score from baseline to 1 year, did not differ between the groups; the proportion of children with VABS-II scores that decreased no more than 15 points (1 SD) from their baseline scores was similar in the two groups. All-cause mortality at 1 year also did not differ significantly between the two groups, although survival analysis through 365 days showed a significant difference in survival time in favor of therapeutic hypothermia.

Table 3. Safety Outcomes within 7 Days after Randomization and 28-Day Mortality.

Outcome	Hypothermia Group (N=153)	Normothermia Group (N=139)	P Value*
Blood-product use — no./total no. (%)			
Any	83/153 (54)	74/138 (54)	0.92
Type			
Cryoprecipitate	13/153 (8)	12/137 (9)	0.94
Fresh-frozen plasma	50/153 (33)	41/138 (30)	0.59
Packed red cells or whole blood	65/153 (42)	59/137 (43)	0.92
Platelets	19/153 (12)	12/137 (9)	0.32
Arrhythmias — no./total no. (%)			
Serious	17/153 (11)	13/137 (9)	0.66
Type			
Asystole	6/153 (4)	5/137 (4)	0.91
Atrial (supraventricular tachycardia, atrial flutter, junctional ectopic tachycardia)	4/153 (3)	2/137 (1)	0.53
Pulseless electrical activity	1/153 (1)	0/137	0.53
Ventricular (sustained ventricular tachycardia >30 sec, ventricular fibrillation, torsades)	5/153 (3)	5/137 (4)	0.86
Other	7/153 (5)	2/137 (1)	0.14
Culture-proven infections			
Any — no./total no. (%)	70/153 (46)	54/137 (39)	0.28
No. of infections	109	76	
No. of days at risk	978	765	
Rate of infections/100 days (95% CI)†	11.1 (9.2–13.4)	9.9 (7.8–12.4)	0.46†
All-cause mortality 28 days — no./total no. (%)	87/153 (57)	93/139 (67)	0.08

* P values for all comparisons, except where noted, are two-sided mid-P values, based on an exact likelihood-ratio test.
† Confidence intervals are exact two-sided 95% confidence intervals, and the P value is based on an exact test of homogeneity of event rates between the hypothermia group and the normothermia group, assuming that event data follow Poisson distributions.

One important potential limitation of the trial is that, on the basis of the observed confidence limits for treatment differences, a potentially important clinical benefit cannot be ruled out despite the lack of a significant difference in the primary outcome measure. A larger trial might have detected or rejected a smaller intervention effect. Indeed, there was a significant difference in survival time with therapeutic hypothermia, although this was a secondary outcome measure.

Other trial limitations should also be noted. Caregivers and research staff in the ICU could not be unaware of the treatment assignments of the patients, although the primary outcome assessments were blinded. We could not rule out the possibility of earlier death or determination by clinical teams of futility in the normothermia group. Patients in the hypothermia group may have survived longer because prognostic assessments were delayed until normothermia was achieved. For logistical reasons, we did not conduct a preclinical trial site phase-in or use only high-enrolling sites; such strategies have been suggested in other hypothermia trials.[13,25-28]

Our overall findings are consistent with those of a previous clinical trial investigating the efficacy of therapeutic hypothermia (target temperature, 33°C) versus therapeutic normothermia (target temperature, 36°C) in adult survivors of out-of-hospital cardiac arrest.[8] In contrast to the earlier trials,[4,5] in the recent trial involving adults, fever was prevented in the normothermia group through an active intervention similar to that in our normothermia group.[8] The duration of temperature control, however, was much longer in our trial (120 hours vs. 36 hours). Moreover, the characteristics of our population of

children with out-of-hospital cardiac arrest differed markedly from the population of adults with out-of-hospital cardiac arrest, as expected. The leading cause of cardiac arrest was a respiratory condition in 72% of our patients, as compared with a presumed cardiac cause in all patients in the recent trial involving adults.[8] Our trial also had a much lower proportion of patients with shockable rhythms (8% vs. 80%).[8]

One possible explanation for the difference between the early trials of therapeutic hypothermia and the more recent studies is that controlled normothermia (which was used in the more recent trials) may be beneficial in patients with cardiac arrest. Fever commonly occurs after hypoxic–ischemic brain injury.[3,29-31] Initial trials of therapeutic hypothermia for neonatal asphyxial encephalopathy and adult cardiac arrest did not prevent fever in control groups.[4,32-34] A recent trial of cooling versus normal temperature control in neonatal patients at high risk for neurologic injury who were receiving ECMO support showed no difference in outcome or adverse effects.[35] Studies of the usefulness of therapeutic hypothermia for traumatic brain injury in children have not shown efficacy,[36] and one showed a trend toward higher mortality.[13]

Unanswered questions remain concerning the potential role of targeted temperature management in children after cardiac arrest. Alternative durations of therapeutic hypothermia temperature control (longer or shorter), different depths of temperature control (higher or lower), and a different therapeutic window for initiating therapeutic hypothermia (shorter) are modifications that might be considered for future study. Modification of inclusion and exclusion criteria and a combination of targeted temperature management with neuroprotective agents might also be considered in future trials of treatment involving children after cardiac arrest.[37] We are currently evaluating targeted temperature management in children after in-hospital cardiac arrest (ClinicalTrials.gov number, NCT00880087); this represents a pathophysiologically distinct population, and the efficacy of the interventions may differ.[38]

In conclusion, in comatose children who survive of out-of-hospital cardiac arrest, therapeutic hypothermia, as compared with therapeutic normothermia, did not confer a significant benefit with respect to survival with good functional outcome at 1 year. Survival at 12 months did not differ significantly between the treatment groups.

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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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