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ORIGINAL ARTICLE

Therapeutic Hypothermia after In-Hospital Cardiac Arrest in Children

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ABSTRACT

BACKGROUND

Targeted temperature management is recommended for comatose adults and children after out-of-hospital cardiac arrest; however, data on temperature management after in-hospital cardiac arrest are limited.

METHODS

In a trial conducted at 37 children's hospitals, we compared two temperature interventions in children who had had in-hospital cardiac arrest. Within 6 hours after the return of circulation, comatose children older than 48 hours 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 score of 70 or higher on the Vineland Adaptive Behavior Scales, second edition (VABS-II, on which scores range from 20 to 160, with higher scores indicating better function), was evaluated among patients who had had a VABS-II score of at least 70 before the cardiac arrest.

RESULTS

The trial was terminated because of futility after 329 patients had undergone randomization. Among the 257 patients who had a VABS-II score of at least 70 before cardiac arrest and who could be evaluated, the rate of the primary efficacy outcome did not differ significantly between the hypothermia group and the normothermia group (36% [48 of 133 patients] and 39% [48 of 124 patients], respectively; relative risk, 0.92; 95% confidence interval [CI], 0.67 to 1.27; P=0.63). Among 317 patients who could be evaluated for change in neurobehavioral function, the change in VABS-II score from baseline to 12 months did not differ significantly between the groups (P=0.70). Among 327 patients who could be evaluated for 1-year survival, the rate of 1-year survival did not differ significantly between the hypothermia group and the normothermia group (49% [81 of 166 patients] and 46% [74 of 161 patients], respectively; relative risk, 1.07; 95% CI, 0.85 to 1.34; P=0.56). The incidences of blood-product use, infection, and serious adverse events, as well as 28-day mortality, did not differ significantly between groups.

CONCLUSIONS

Among comatose children who survived in-hospital cardiac arrest, therapeutic hypothermia, as compared with therapeutic normothermia, did not confer a significant benefit in survival with a favorable functional outcome at 1 year. (Funded by the National Heart, Lung, and Blood Institute; THAPCA-IH ClinicalTrials.gov number, NCT00880087.)

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*A complete list of the Therapeutic Hypothermia after Pediatric Cardiac Arrest (THAPCA) trial investigators is provided in the Supplementary Appendix, available at NEJM.org.

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THERAPEUTIC HYPOTHERMIA FOR COMATOSE adults who have had an out-of-hospital cardiac arrest was recommended on the basis of results of clinical trials reported in 2002.[1-3] More recent trials have shown that fever prevention with therapeutic normothermia is equally efficacious as therapeutic hypothermia in adult and pediatric populations.[4,5] Current guidelines recommend either hypothermia or normothermia for temperature management after out-of-hospital cardiac arrest in adults and children.[6,7]

In-hospital cardiac arrest in children commonly results in death or in a poor long-term functional outcome in survivors; however, outcomes in the in-hospital setting are significantly better than those in the out-of-hospital setting.[8,9] Furthermore, in-hospital outcomes are improving.[10,11] Published results of clinical trials of therapeutic hypothermia versus therapeutic normothermia in adults and children who have had an in-hospital cardiac arrest are lacking. Two retrospective studies involving cohorts of children who had in-hospital or out-of-hospital cardiac arrest showed that therapeutic hypothermia was not associated with improved outcomes.[12,13]

Cardiac arrests in children and adolescents in the in-hospital setting can be distinguished from those in the out-of-hospital setting on the basis of multiple factors, including preexisting conditions, the initial cardiac rhythm in the patients, the cause of the cardiac arrest, response times and resuscitation skills of the initial responders, and causes of death in nonsurvivors.[8] Thus, patients who have in-hospital cardiac arrests represent a pathophysiologically distinct population from those who have out-of-hospital cardiac arrests, and the potential efficacy of an intervention such as therapeutic hypothermia may differ in the two populations. Therefore, we conducted independent, parallel Therapeutic Hypothermia after Pediatric Cardiac Arrest (THAPCA) trials, one in the out-of-hospital setting (THAPCA-OH) and one in the in-hospital setting (THAPCA-IH).[14,15] The results of the THAPCA-OH trial were recently reported in the *Journal*.[5] We now report the results of the THAPCA-IH trial, in which we compared the efficacy of therapeutic hypothermia (target temperature, 33.0°C) with that of therapeutic normothermia (target temperature, 36.8°C) in comatose children and adolescents who were resuscitated after in-hospital cardiac arrest.

METHODS

TRIAL DESIGN AND OVERSIGHT

This randomized trial was conducted in pediatric intensive care units at 37 children's hospitals in the United States, Canada, and the United Kingdom. The rationale, trial design, outcome selection process, protocol summary, and 12-month pilot vanguard phase have been described previously.[5,14-16]

The National Heart, Lung, and Blood Institute (NHLBI) funded the trial. 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.[17] 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 fidelity of the study to the trial protocol (available at NEJM.org).

PATIENT POPULATION

Children older than 48 hours and younger than 18 years of age were eligible for inclusion if they had a cardiac arrest that began within the walls of a hospital, received chest compressions for at least 2 minutes, and remained dependent on mechanical ventilation after the return of circulation. Major exclusion criteria were 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 worse function), the inability to undergo randomization within 6 hours after the return of circulation, active and refractory severe bleeding, a preexisting illness associated with a life expectancy of less than 12 months, and a decision by the clinical team to withhold aggressive treatment. A full list of 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 therapeutic hypothermia or therapeutic normothermia. Randomization was performed with the use of permuted blocks stratified according to clinical center and age category (<2 years, 2 to <12 years, or ≥12 years).

Targeted temperature management was actively maintained for 120 hours in each group. Patients 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 patients 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. Patients who were assigned to therapeutic normothermia received identical care except that the core temperature was actively maintained with the temperature-management 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. In the patients who received extracorporeal membrane oxygenation (ECMO) at the time of randomization or later, ECMO with a single monitor of central temperature was used for temperature control. All other aspects of care were determined by the clinical teams.

OUTCOMES

The primary outcome was survival with a favorable neurobehavioral outcome at 12 months of follow-up. A favorable 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).[18] 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 protocol, enrolled children with a VABS-II score of less than 70 before cardiac arrest (on the basis of data from a caregiver questionnaire completed at each site within 24 hours after randomization) were excluded from the primary efficacy analysis. Patients with no baseline VABS-II score were considered to be eligible for inclusion in the primary analysis if their baseline Pediatric Overall Performance Category (POPC) and Pediatric Cerebral Performance Category (PCPC) scores were in the normal or mild disability category.[19,20] On both these scales, scores range from 1 to 6, with lower scores indicating less disability; patients with a score of 1 or 2 on both scales were eligible for inclusion in the primary analysis.

Secondary outcomes were survival at 12 months after cardiac arrest and change in neurobehavioral function, which was measured as the difference between the baseline measurement (before cardiac arrest) and the 12-month measurement on the VABS-II. Patients who had died and patients with the lowest possible VABS-II score were assigned the worst possible outcomes, regardless of baseline function. A tertiary outcome was a global cognitive score that was based on the results of neuropsychological testing (see the Supplementary Appendix). Safety outcomes included the incidences of blood-product use, infection, and serious arrhythmias within 7 days after randomization, as well as 28-day mortality. Details of the methods used for outcome assessment are provided in the Supplementary Appendix.

STATISTICAL ANALYSIS

We calculated the target sample size assuming an estimated favorable primary outcome rate of 35 to 55% in the normothermia group. Assuming that 5% of the patients would be excluded owing to baseline neurologic deficit and that 5% of the patients would be lost to follow-up, we estimated that 558 patients would need to be enrolled to provide the trial with 90% power to detect a 15-percentage-point absolute treatment effect.

We performed the analysis for the primary efficacy outcome using a prespecified modified intention-to-treat approach, excluding children who had poor neurobehavioral function before cardiac arrest. Secondary efficacy outcomes were analyzed among all children who could be evaluated. Safety analyses were performed in treated patients only, according to the treatment received. The primary outcome and 12-month survival 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,[21] with stratification according to age category, treatment of death as the worst outcome, and treatment of the lowest possible VABS-II score at 12 months 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 from 0 to 365 days was evaluated by comparison of survival curves between treatment groups with the use of a log-rank test stratified according to age category. Analyses were performed with the use of SAS software, version 9.4 (SAS Institute).

When reviewing interim efficacy analyses, the data and safety monitoring board used an informal threshold for conditional power (i.e., the chance of detecting a significant treatment effect if the trial were to be continued) of 20%. Conditional power below this threshold would lead the board to consider stopping further enrollment because of futility.

RESULTS

PATIENTS

The trial was stopped on February 27, 2015, because of futility after a review of interim efficacy analyses by the data and safety monitoring board. Between September 1, 2009, and February 27, 2015, a total of 2791 patients were screened for eligibility and met the trial inclusion criteria (Fig. 1). Of these patients, 746 were eligible for enrollment. The families of 334 of these patients provided consent, and 329 patients underwent randomization at 37 sites in the United States, Canada, and the United Kingdom (9 sites did not enroll any patients); 166 were assigned to therapeutic hypothermia, and 163 to therapeutic normothermia. A total of 5 patients who were assigned to hypothermia and 3 who were assigned to normothermia did not receive an intervention.

Of the 329 patients who underwent randomization, 31 in the hypothermia group and 29 in the normothermia group were ineligible for inclusion in the primary analysis because they had a baseline VABS-II score of less than 70 or a POPC or PCPC score of 3 or higher. At 12 months, vital status was unknown in 2 patients in the normothermia group, and VABS-II scores were not obtained for 2 surviving children in the hypothermia group and 8 in the normothermia group (Fig. 1). Thus, 257 patients could be evaluated for the primary outcome, 317 could be evaluated for the secondary outcome of change in neurobehavioral function, and 327 could be evaluated for the secondary outcome of 1-year survival.

BASELINE CHARACTERISTICS AND TEMPERATURE INTERVENTION

The baseline characteristics of the patients were similar in the two treatment groups (Table 1, and Tables S1 and S2 in the Supplementary Appendix). There were statistically significant differences between the two groups at baseline in alanine aminotransferase, aspartate aminotransferase, and hemoglobin levels, but these differences were not clinically significant (Table S3 in the Supplementary Appendix). The median age of the patients was 1 year, 196 patients (60%) were male, and 299 patients (91%) had a preexisting medical condition. The initial rhythm was bradycardia in 189 patients (57%) and ventricular fibrillation or ventricular tachycardia in 34 (10%). The median time from cardiac arrest to cardiopulmonary resuscitation (CPR) was 0 minutes, and the median duration of CPR was 22.0 minutes (interquartile range, 7.0 to 47.0). Cardiac arrest occurred at a trial hospital in 307 patients (93%). Baseline functional status based on the VABS-II, PCPC, and POPC scores is shown in Table S4 in the Supplementary Appendix.

The median time from the return of circulation to the initiation of treatment was 4.9 hours (interquartile range, 3.9 to 5.8) in the hypothermia group and 4.7 hours (interquartile range, 4.0 to 5.7) in the normothermia group. Figure S1 in the Supplementary Appendix shows the primary central (core) temperatures recorded for the two groups. Additional information regarding temperature control is provided in the Supplementary Appendix.

OUTCOMES

The percentage of children with a VABS-II score of 70 or higher at 12 months did not differ sig-

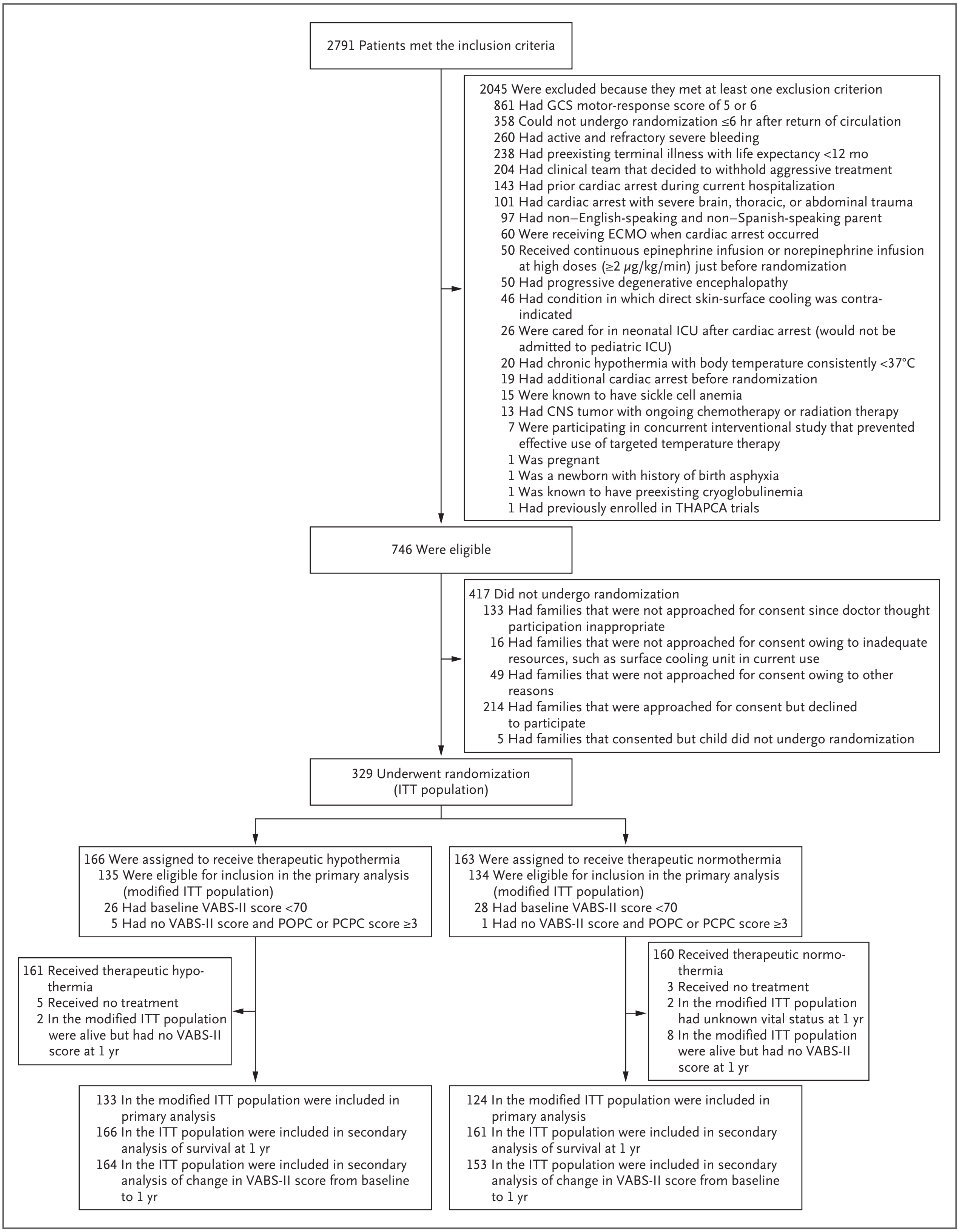

2791 Patients met the inclusion criteria
2045 Were excluded because they met at least one exclusion criterion
861 Had GCS motor-response score of 5 or 6
358 Could not undergo randomization ≤6 hr after return of circulation
260 Had active and refractory severe bleeding
238 Had preexisting terminal illness with life expectancy <12 mo
204 Had clinical team that decided to withhold aggressive treatment
143 Had prior cardiac arrest during current hospitalization
101 Had cardiac arrest with severe brain, thoracic, or abdominal trauma
97 Had non–English-speaking and non–Spanish-speaking parent
60 Were receiving ECMO when cardiac arrest occurred
50 Received continuous epinephrine infusion or norepinephrine infusion at high doses (≥2 μg/kg/min) just before randomization
50 Had progressive degenerative encephalopathy
46 Had condition in which direct skin-surface cooling was contraindicated
26 Were cared for in neonatal ICU after cardiac arrest (would not be admitted to pediatric ICU)
20 Had chronic hypothermia with body temperature consistently <37°C
19 Had additional cardiac arrest before randomization
15 Were known to have sickle cell anemia
13 Had CNS tumor with ongoing chemotherapy or radiation therapy
7 Were participating in concurrent interventional study that prevented effective use of targeted temperature therapy
1 Was pregnant
1 Was a newborn with history of birth asphyxia
1 Was known to have preexisting cryoglobulinemia
1 Had previously enrolled in THAPCA trials
746 Were eligible
417 Did not undergo randomization
133 Had families that were not approached for consent since doctor thought participation inappropriate
16 Had families that were not approached for consent owing to inadequate resources, such as surface cooling unit in current use
49 Had families that were not approached for consent owing to other reasons
214 Had families that were approached for consent but declined to participate
5 Had families that consented but child did not undergo randomization
329 Underwent randomization (ITT population)
166 Were assigned to receive therapeutic hypothermia
135 Were eligible for inclusion in the primary analysis (modified ITT population)
26 Had baseline VABS-II score <70
5 Had no VABS-II score and POPC or PCPC score ≥3
163 Were assigned to receive therapeutic normothermia
134 Were eligible for inclusion in the primary analysis (modified ITT population)
28 Had baseline VABS-II score <70
1 Had no VABS-II score and POPC or PCPC score ≥3
161 Received therapeutic hypothermia
5 Received no treatment
2 In the modified ITT population were alive but had no VABS-II score at 1 yr
160 Received therapeutic normothermia
3 Received no treatment
2 In the modified ITT population had unknown vital status at 1 yr
8 In the modified ITT population were alive but had no VABS-II score at 1 yr
133 In the modified ITT population were included in primary analysis
166 In the ITT population were included in secondary analysis of survival at 1 yr
164 In the ITT population were included in secondary analysis of change in VABS-II score from baseline to 1 yr
124 In the modified ITT population were included in primary analysis
161 In the ITT population were included in secondary analysis of survival at 1 yr
153 In the ITT population were included in secondary analysis of change in VABS-II score from baseline to 1 yr

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

Characteristic	Hypothermia Group (N = 166)	Normothermia Group (N = 163)
Demographic characteristics		
Age — yr		
Median	1.4	0.6
Interquartile range	0.3–5.7	0.2–6.3
Age category — no. (%)		
<2 yr	97 (58)	104 (64)
2 to <12 yr	48 (29)	35 (21)
≥12 yr	21 (13)	24 (15)
Male sex — no. (%)	97 (58)	99 (61)
Characteristics of the cardiac arrest		
Initial cardiac rhythm — no. (%)		
Asystole	14 (8)	10 (6)
Bradycardia	95 (57)	94 (58)
Pulseless electrical activity	33 (20)	36 (22)
Ventricular fibrillation or tachycardia	17 (10)	17 (10)
Unknown	7 (4)	6 (4)
Cardiac arrest occurred at a trial hospital — no. (%)	155 (93)	152 (93)
Time from cardiac arrest to CPR in 314 patients — min		
Median	0	0
Interquartile range	0–0	0–0
Duration of CPR in 321 patients — min		
Median	23.0	22.0
Interquartile range	7.0–42.0	7.0–51.0
No. of doses of epinephrine administered in 328 patients		
Median	4.0	5.0
Interquartile range	2.0–9.0	2.0–8.0
ECMO used after cardiac arrest and before randomization — no. (%)	87 (52)	95 (58)
ECMO used at the time of treatment initiation — no. (%)	85 (51)	95 (58)

* There were no significant differences between the two groups at baseline. Percentages may not total 100 because of rounding. CPR denotes cardiopulmonary resuscitation, and ECMO extracorporeal membrane oxygenation.

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 worse 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; the VABS-II has an age-corrected mean score of 100. CNS denotes central nervous system, ECMO extracorporeal membrane oxygenation, ICU intensive care unit, ITT intention to treat, and THAPCA Therapeutic Hypothermia after Pediatric Cardiac Arrest.

Table 2. Primary and Secondary Outcomes.*

Outcome	Hypothermia Group	Normothermia Group	Risk Difference	Relative Risk (95% CI)	P Value
	no./total no. (%)		*percentage points (95% CI)*		
Primary outcome					
Alive with VABS-II score ≥70 at 1 yr	48/133 (36)	48/124 (39)	−2.6 (−14.5 to 9.2)	0.92 (0.67 to 1.27)	0.63†
Detailed supportive analysis‡					0.85§
Death	65/133 (49)	67/124 (54)			
VABS-II score					
<45 or lowest possible	2/133 (2)	0/124			
45–69	18/133 (14)	9/124 (7)			
≥70	48/133 (36)	48/124 (39)			
Secondary outcomes					
Alive at 1 yr	81/166 (49)	74/161 (46)	2.8 (−8.0 to 13.7)	1.07 (0.85 to 1.34)	0.56†
Change in VABS-II score from baseline to 1 yr¶					0.70‖
Death	85/164 (52)	87/153 (57)			
Lowest possible VABS-II score	1/164 (1)	0/153			
Decrease in VABS-II score from baseline					
>30 points	12/164 (7)	8/153 (5)			
16–30 points	17/164 (10)	14/153 (9)			
≤15 points or improved	49/164 (30)	44/153 (29)			

* The primary outcome was evaluated in patients with a baseline score of 70 or higher on the Vineland Adaptive Behavior Scales, second edition (VABS-II, on which scores 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.

‡ Patients who had died and patients with the lowest possible VABS-II score were assigned ranks of −2000 and −1000, respectively (i.e., the worst possible scores). A VABS-II score of less than 45 or the lowest possible score indicated profound disability, a score of 45 to 69 moderate-to-severe disability, and a score of 70 or higher good functional status.

§ The P value was calculated by means of the Mann–Whitney test on the basis of the 1-yr continuous VABS-II score, with stratification according to age category.

¶ Patients who had died and patients with the lowest possible VABS-II score were assigned ranks of −2000 and −1000, respectively (i.e., the worst possible scores).

‖ The P value was calculated by means of the Mann–Whitney test on the basis of the continuous change in VABS-II score, with stratification according to age category.

nificantly between the hypothermia group and the normothermia group (36% [48 of 133 patients] and 39% [48 of 124 patients], respectively; relative risk, 0.92; 95% confidence interval [CI], 0.67 to 1.27; P=0.63) (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). Results of analyses in subgroups defined according to demographic characteristics and characteristics related to the cardiac arrest did not differ significantly between the two treatment groups (Tables S9 and S10 in 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 treatment groups (P=0.70). The overall percentage of patients with 12-month VABS-II scores that did not decrease by more than 15 points (1 SD) from their baseline measurements did not differ significantly between the hypothermia group and the normothermia group (30% [49 of 164 patients] and 29% [44 of 153 patients], respectively) (Table 2).

The rate of survival at 12 months among all patients who underwent randomization and had a known vital status (99% [327 of 329 patients]) did not differ significantly between the hypothermia group and the normothermia group (49% [81 of 166 patients] and 46% [74 of 161 patients], respectively; relative risk, 1.07; 95% CI, 0.85 to 1.34; P=0.56) (Table 2). Estimates of survival from 0 to 365 days also did not differ significantly between the groups (P=0.45) (Fig. 2). The primary cause of death was brain death or withdrawal of life support owing to a poor neurologic prognosis (in 39% [33 of 85 patients] in the hypothermia group and 33% [29 of 88 patients] in the normothermia group) or cardiovascular failure (in 31% [26 of 85 patients] in the hypothermia group and 38% [33 of 88 patients] in the normothermia group), with no significant differences between the groups (Table S5 in the Supplementary Appendix).

Data on global cognitive functioning in survivors are shown in Table S6 in the Supplementary Appendix. The Early Learning Composite scores on the Mullen Scales of Early Learning[22] did not differ significantly between the groups; there were also no significant differences between the groups in the IQ score distributions on the Wechsler Abbreviated Scale of Intelligence[23] or in the combined categories from both the Mullen and Wechsler tests.

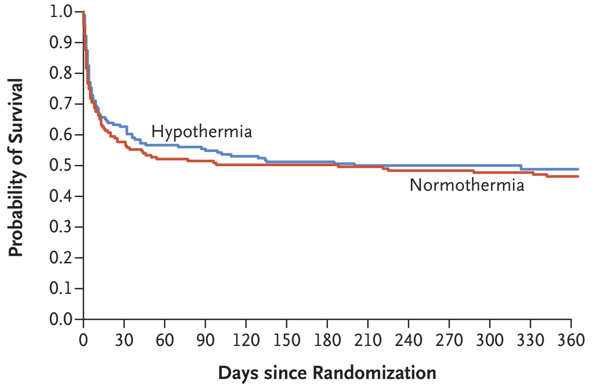
SAFETY

The incidences of infection, blood-product use, and serious arrhythmias within 7 days after randomization were similar in the 161 patients who received therapeutic hypothermia and the 160 who received therapeutic normothermia (Table 3). Mortality at 28 days did not differ significantly between the hypothermia group and the normothermia group (37% [59 of 161 patients] and 41% [66 of 160 patients], respectively; P=0.40). Data regarding other adverse events are provided in Tables S7 and S8 in the Supplementary Appendix; there were no significant differences between the groups in any of the other adverse events.

DISCUSSION

The THAPCA-IH trial evaluated the efficacy of therapeutic hypothermia (target temperature, 33.0°C) and therapeutic normothermia (target temperature, 36.8°C) in improving outcomes after in-hospital cardiac arrest in children. There was no significant difference between the groups in the primary outcome of survival with a favorable neurobehavioral outcome (VABS-II score of ≥70) at 12 months. The secondary outcome of change in the VABS-II score from baseline to 1 year did not differ significantly between the groups; the proportion of patients with 12-month VABS-II scores that did not decrease by more than 15 points (1 SD) from their baseline scores was similar in the two groups. Survival at 1 year and Kaplan–Meier estimates of survival from 0 to 365 days did not differ significantly between the groups.

An important limitation in the interpretation of our findings is that the trial was stopped at the recommendation of the data and safety monitoring board because of an assessment of futility before attainment of the target trial enrollment. Although slower-than-expected patient recruitment was a factor, termination of enrollment was based primarily on the low conditional power of the trial to show a significant treatment effect if continued, since no trend was observed with respect to the primary or secondary outcomes. Given the number of patients who could be evaluated, the confidence intervals for treatment effect are wide; however, the 15-percentage-point absolute benefit of hypothermia that was postulated during the trial design can be ruled out. Another possible limitation was the relatively long time from the return of circu-



No. at Risk													
Hypothermia	166	104	94	92	88	85	85	83	83	83	83	81	81
Normothermia	163	94	84	82	80	80	80	79	77	77	76	76	74

Figure 2. Kaplan–Meier Estimates of Survival from 0 to 365 Days after Cardiac Arrest.

Shown are Kaplan–Meier estimates of survival from 0 to 365 days after cardiac arrest in the therapeutic hypothermia group and the therapeutic normothermia group (P=0.45 by log-rank test stratified according to age category).

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

Outcome	Hypothermia Group (N=161)	Normothermia Group (N=160)	P Value*
Blood-product use — no. (%)			
Any	139 (86)	140 (88)	0.76
Cryoprecipitate	53 (33)	67 (42)	0.10
Fresh-frozen plasma	96 (60)	92 (58)	0.70
Packed red cells or whole blood	129 (80)	133 (83)	0.49
Platelets	106 (66)	104 (65)	0.88
Arrhythmias — no. (%)			
Serious	25 (16)	23 (14)	0.78
Asystole	3 (2)	5 (3)	0.50
Atrial†	7 (4)	4 (2)	0.39
Pulseless electrical activity	3 (2)	5 (3)	0.50
Ventricular‡	8 (5)	7 (4)	0.81
Other	11 (7)	9 (6)	0.66
Culture-proven infections			
Any — no. (%)	44 (27)	46 (29)	0.78
No. of infections	55	52	
No. of days at risk	1107	1059	
No. of infections per 100 days (95% CI)§	5.0 (3.7–6.5)	4.9 (3.7–6.4)	1.00
All-cause mortality at 28 days — no. (%)	59 (37)	66 (41)	0.40

* The P values are two-sided mid–P values calculated by means of an exact likelihood-ratio test.

† Atrial arrhythmias include supraventricular tachycardia, atrial flutter, and junctional ectopic tachycardia.

‡ Ventricular arrhythmias include sustained ventricular tachycardia (>30 sec), ventricular fibrillation, and torsades de pointes.

§ The confidence intervals are exact two-sided 95% confidence intervals, and the P value was calculated by means of an exact test of homogeneity of event rates between the hypothermia group and the normothermia group, under the assumption that the event data followed Poisson distributions.

lation to the achievement of a temperature within the target temperature range (median time, approximately 6 hours). We did not conduct a pretrial site phase-in or use only high-enrolling sites; such strategies have been suggested in other hypothermia trials.[24-28] Other limitations are similar to those previously described in the THAPCA-OH trial report.[5]

Our overall findings in the THAPCA-IH trial are consistent with those of recent trials investigating the efficacy of hypothermia versus normothermia after out-of-hospital cardiac arrest.[4,5] In contrast to earlier trials in the out-of-hospital setting involving only adults,[2,3] in more recent trials involving adults and children,[4,5] fever was prevented in the normothermia group through an active intervention similar to that used in our normothermia group. The duration of temperature control was identical in the THAPCA-OH trial and the THAPCA-IH trial (120 hours) but was longer than the duration used in both the earlier and the more recent trials involving only adults. The characteristics of the in-hospital population included in the THAPCA-IH trial differed markedly from those of the out-of-hospital population included in the THAPCA-OH trial, as expected on the basis of the results of our pretrial cohort study.[8] The leading cause of cardiac arrest in the THAPCA-IH trial was a cardiac cause or a cause related to congenital heart disease (in 50% and 16% of patients, respectively, or in 65% of patients combined); in contrast, in the THAPCA-OH trial, 72% of patients had a respiratory cause of cardiac arrest. A lower percentage of patients in the THAPCA-IH trial than in the THAPCA-OH trial had asystole (7% vs. 58%), and a much higher percentage had bradycardia (57% vs. 6%). Shockable rhythms were infrequent in both trials (occurring in 8 to 10% of patients). Brain death or withdrawal of life support owing to a poor neurologic prognosis was the cause of death in approximately 79% of patients in the THAPCA-OH trial but in only 36% of patients in the THAPCA-IH trial, whereas a cardiac cause of death was more common in the THAPCA-IH trial than in the THAPCA-OH trial (in 34% vs. 13% of patients). A favorable primary outcome occurred in a substantially higher percentage of patients in the THAPCA-IH trial than in the THAPCA-OH trial (37% [96 of 257 patients] vs. 16% [42 of 260 patients]).

Trials comparing therapeutic hypothermia with therapeutic normothermia have shown no significant differences between the two interventions in outcomes.[4,5] A possible mechanism underlying the initial reports[2,3] of a benefit of hypothermia over conventional treatment (i.e., care that does not include targeted temperature management to prevent fever) is that therapeutic normothermia is also beneficial. Fever commonly occurs after hypoxic–ischemic brain injury.[29-32] In initial trials of hypothermia for neonatal asphyxial encephalopathy and adult out-of-hospital cardiac arrest, the control groups did not receive therapeutic normothermia.[2,33-35] A small trial of cooling versus normal temperature control in neonates who were receiving ECMO and were at high risk for neurologic injury showed no difference in outcome between the two interventions.[36] Studies of hypothermia in children with traumatic brain injury showed that hypothermia had no efficacy and may have resulted in higher mortality.[24,37] A recent registry report of outcomes in adults who had in-hospital cardiac arrest showed higher mortality and lower survival with a favorable neurologic outcome among patients who received therapeutic hypothermia than among those who received usual care.[38] In contrast, we found no trends toward higher mortality or higher incidences of infection, arrhythmias, blood-product use, or other serious adverse events in the therapeutic hypothermia group than in the therapeutic normothermia group in the THAPCA-IH trial.

Unanswered questions remain regarding the role of targeted temperature management in children after in-hospital cardiac arrest. A different therapeutic window for attaining the target temperature (shorter), a different duration of temperature control (longer or shorter), and different depths of temperature control (higher or lower) are modifications that have been suggested previously and might be considered for future trials.[5] In neonates with hypoxic–ischemic encephalopathy, use of a lower target temperature (32.0°C vs. 33.5°C) and a longer duration of temperature control (120 hours vs. 72 hours) did not decrease mortality.[39] Modification of inclusion and exclusion criteria and the combination of targeted temperature management with neuroprotective agents might also be considered in future trials of therapies after cardiac arrest in children.[40]

In conclusion, in comatose children who survived in-hospital cardiac arrest, therapeutic hypothermia (target temperature, 33.0°C), as compared with therapeutic normothermia (target temperature, 36.8°C), did not confer a significant benefit with respect to survival with a good functional outcome at 1 year.

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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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