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Duration of Therapeutic Hypothermia After Out-of-Hospital Cardiac Arrest
The ICECAP Randomized Clinical Trial

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IMPORTANCE Therapeutic hypothermia is widely used for neuroprotection following cardiac arrest, but clinical trials have not consistently demonstrated improved neurological outcomes, and the optimal duration of cooling remains uncertain.

OBJECTIVE To determine the duration of therapeutic hypothermia that maximizes neurological recovery in comatose survivors of out-of-hospital cardiac arrest.

DESIGN, SETTING, AND PARTICIPANTS Multicenter, randomized, adaptive-allocation clinical trial conducted at 71 hospitals in the US. Adults with out-of-hospital cardiac arrest who remained unconscious, achieved a target temperature less than 34 °C within 4 hours of cardiac arrest, and had a definitive temperature control device started were eligible. Patients were enrolled between June 2020 and June 2025.

INTERVENTIONS Therapeutic hypothermia at 33 °C with adaptive randomized allocation to cooling durations of 6, 12, 18, 24, 30, 36, 42, 48, 60, and 72 hours. The first 200 patients were randomized to 12-, 24-, and 48-hour durations in a 1:1:1 ratio. Subsequently, a response-adaptive randomization algorithm allocated preferentially to the groups most likely to be optimal and to best inform the duration-response curve separately within each rhythm type.

MAIN OUTCOMES AND MEASURES The primary outcome was neurological function at 90 days, measured using a weighted modified Rankin Scale score, analyzed using a bayesian duration-response model. The primary analysis estimated the posterior probability that each duration was optimal, wherein optimal indicates the shortest duration consistent with the best outcome observed at any duration.

RESULTS A total of 1158 patients were randomized (883 with nonshockable rhythms and 275 with shockable rhythms). Participants had a median age of 61 (IQR, 50-70) years and 39.6% were female. The trial met a prespecified stopping rule at the interim analysis. For the nonshockable rhythm cohort, the posterior probability that 6 hours was the shortest duration achieving the maximal mean weighted modified Rankin Scale score was 0.51. Results were similar in the shockable rhythm cohort. No differences were observed in secondary outcomes or mortality across cooling durations.

CONCLUSIONS AND RELEVANCE Among comatose survivors of out-of-hospital cardiac arrest treated with therapeutic hypothermia at 33 °C, increasing cooling duration did not improve neurological outcomes.

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Supplemental content

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Death and disability due to ischemic brain injury are common in patients resuscitated after cardiac arrest.[1] Effective treatments remain elusive.[2-6] Therapeutic hypothermia is robustly neuroprotective in multiple types of animal models of hypoxic ischemic brain injury and is effective in patients with other forms of cerebral ischemia.[7-9] Clinical trials of therapeutic hypothermia in adults after out-of-hospital cardiac arrest (OHCA), however, have not consistently demonstrated improved outcomes.[10-15]

Inconsistent findings from previous trials are likely multifactorial but may depend on how the therapy is implemented and how patients are selected. Effectiveness of therapeutic hypothermia may depend on how quickly patients are cooled and the cooling duration.[16,17] Preclinical data, mechanistic studies, and speculations about earlier smaller trials all suggest that hypothermia is more effective when initiated early and continued for durations longer than those typically used in adult OHCA in prior large trials and in clinical practice.[10,12,17] Patient selection may also drive outcome variability, as accumulating observational data suggest that efficacy of therapeutic hypothermia is sensitive to the severity of initial brain injury and may be limited by floor or ceiling effects in prior trials.[18,19] The optimal duration and patient selection criteria remain unknown. Patient selection based on presenting rhythm (shockable or nonshockable) can be a surrogate marker of severity.[20-22]

The Influence of Cooling Duration on Efficacy in Cardiac Arrest Patients (ICECAP) trial was designed to characterize, in comatose survivors of cardiac arrest, the duration-response curve for rapidly initiated hypothermia.[23] The objective was to determine both (1) the shortest cooling duration that provides the maximal treatment effect and (2) whether the duration-response curve implies efficacy vs no cooling. This article reports analyses related to the first of these 2 objectives. By separately including patients with both shockable and nonshockable presenting rhythms, the trial is inclusive of a wide range of injury severity and is designed to be highly representative of the population of patients presenting to emergency departments after cardiac arrest in the US.[24-26] Specific eligibility criteria and clinical standardization guidelines reduced the effects of implementation and practice variability, including in early withdrawal of life-sustaining therapy.

Key Points

Question In comatose survivors of out-of-hospital cardiac arrest treated with therapeutic hypothermia at 33 °C, what duration of cooling maximizes neurological recovery?

Findings In this multicenter, randomized, adaptive clinical trial including 1158 patients, the posterior probability that 6 hours was the shortest duration achieving maximal neurological recovery was approximately 0.5. The duration-response curve did not demonstrate improved efficacy with longer durations of therapeutic hypothermia.

Meaning Among comatose survivors of out-of-hospital cardiac arrest treated with therapeutic hypothermia at 33 °C, increasing cooling duration did not improve neurological outcomes compared with shorter durations.

Methods

Study Design and Oversight

ICECAP is an investigator-initiated multicenter, randomized, adaptive-allocation clinical trial to identify the optimal duration of induced hypothermia to 33 °C for neuroprotection in comatose survivors of cardiac arrest conducted by the Strategies to Innovate Emergency Care Clinical Trials Network (SIREN). The trial obtained a US Food and Drug Administration (FDA) Investigational Device Exemption. The protocol[23] and each site were approved by a central institutional review board. An independent data and safety monitoring board reviewed the accruing data. The trial protocol and statistical analysis plan are available in Supplement 1. This study followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline.

Setting and Participants

Patients were enrolled at 71 hospitals across the US, including academic medical centers and community hospitals. Adult patients with OHCA with either shockable or nonshockable rhythms were included (**Table 1**). Those in whom cardiac arrest was caused by sepsis were not included. Any other etiology of cardiac arrest, including overdose, was allowed. To be eligible, patients had to be unconscious and have therapeutic hypothermia initiated with a definitive closed-loop feedback temperature control device. To reduce variability, only patients with a time-to-target temperature of less than 4 hours from the time of cardiac arrest were eligible. Patients were excluded if they had preexisting conditions that precluded or confounded assessment of the primary outcome, treatment-refractory hemodynamic instability (considered nonsurvivable), or family goals of care inconsistent with 96 hours of life-sustaining therapy. The full list of eligibility criteria is available in the eAppendix in Supplement 2. Study teams screened all adult patients with OHCA who arrived at participating emergency departments and were resuscitated and admitted to the hospital. Legally authorized representatives provided written informed consent prior to enrollment and randomization to a duration.

Randomization and Adaptive Allocation

ICECAP used an adaptive duration-finding randomized trial design developed through a National Institutes of Health– and FDA-funded regulatory science initiative to facilitate innovation.[27] The response adaptive randomization algorithm could allocate patients to durations from 6 hours to 72 hours, with the allocation ratio calculated separately for shockable and nonshockable rhythms to account for possible heterogeneity of treatment effect (**Figure 1**). The first 200 patients were randomized to 12-, 24-, and 48-hour durations in a 1:1:1 ratio. Subsequently, a response-adaptive randomization algorithm allocated preferentially to the duration groups most likely to be optimal and to best inform

Table 1. Baseline Participant Characteristics

Characteristics	Rhythm type[a]	
	Nonshockable (n = 883)	Shockable (n = 275)
Age, median (IQR), y	61 (50-70)	62 (52-71)
Sex, No. (%)		
Female	365 (41.3)	93 (33.8)
Male	518 (58.7)	182 (66.2)
Race, No. (%)[b]		
American Indian or Alaska Native	4 (0.5)	0
Asian	30 (3.4)	8 (2.9)
Black or African American	360 (40.8)	88 (32)
Native Hawaiian or Other Pacific Islander	3 (0.3)	4 (1.5)
White	415 (47)	155 (56.4)
Multiple races	11 (1.2)	2 (0.7)
Unknown race	60 (6.8)	18 (6.5)
Hispanic or Latino ethnicity, No./total (%)[b]	94/853 (11)	21/265 (7.9)
Most probable cause of initial arrest, No. (%)[c]		
Cardiac	199 (22.5)	212 (77.1)
Overdose/poisoning	248 (28.1)	35 (12.7)
Respiratory	260 (29.4)	15 (5.5)
Other medical	89 (10.1)	5 (1.8)
Neurological	22 (2.5)	6 (2.2)
Other	31 (3.5)	0
Unknown	34 (3.9)	2 (0.7)
Bystander performed cardiopulmonary resuscitation, No./total (%)	433/877 (49.4)	168/274 (61.3)
Bystander applied AED, No./total (%)	107/870 (12.3)	68/274 (24.8)
First cardiac arrest rhythm monitored per EMS or at ED arrival, No. (%)[d]		
Ventricular fibrillation	2 (0.2)	178 (64.7)
Ventricular tachycardia	3 (0.3)	25 (9.1)
Asystole	454 (51.4)	12 (4.4)
Pulseless electrical activity	363 (41.1)	17 (6.2)
Unknown or other	61 (6.9)	43 (15.6)
No. of shocks prior to hospital arrival, median (IQR)	0 (0-0) [n = 872]	2 (1-4) [n = 274]
Total prehospital epinephrine, median (IQR), mg	2 (1-4) [n = 874]	2 (1-4) [n = 273]
STEMI in the ED, No./total (%)	66/882 (7.5)	52/275 (18.9)
Arterial lactate, median (IQR), mmol/L[e]	6.9 (3.1-10.9) [n = 458]	5 (2.8-8.6) [n = 137]

Abbreviations: AED, automated external defibrillator; ED, emergency department; EMS, emergency medical services; STEMI, ST segment–elevation myocardial infarction.

[a] Rhythm type indicates initial rhythm category as determined either by first responders based on response of an AED or by paramedics on initial monitoring if no AED was used.

[b] Race and ethnicity were preferentially determined by self-report of the patient or their family or representative. If self-reported race and ethnicity were unavailable, the race and ethnicity documented in the medical record were used instead.

[c] Cardiac includes acute ischemia, primary arrhythmia, and heart failure. Respiratory includes respiratory failure or arrest. Causes reported as "other medical" include pulmonary embolism; those reported as "other" included drowning, choking, spinal cord injury, anaphylaxis, hypoglycemia, trampling, withdrawal syndromes, acidosis, hyperkalemia, or multifactorial or unspecified other causes.

[d] First cardiac arrest rhythm monitored by EMS or at ED arrival reflects the ongoing cardiac arrest rhythm at the time cardiac waveform monitoring was first obtained, which occasionally differed from that determined earlier by an AED.

[e] For consistency, only the first arterial lactate measurement was collected. Potentially earlier venous lactate measurements were not collected.

the duration-response curve separately within each rhythm type. The algorithm tended to explore shorter durations if the evolving data model suggested that duration response was flat and longer durations if trending upwards. Prespecified decision rules governed opening the 6-, 60-, or 72-hour groups. Allocation ratios were updated every 50 enrollments. Clinical investigators were blinded to the allocation ratios to avoid operational bias. Enrolling study team members, treatment teams, and families were not blinded to the allocated duration. A prespecified stopping rule allowed the data and safety monitoring board to recommend discontinuing accrual for a given rhythm at an interim analysis if more than 50 patients had been allocated to the 6-hour duration and the posterior probability of 6 hours being the

Figure 1. Flow Diagram of Participants in the ICECAP Trial

ICECAP indicates Influence of Cooling Duration on Efficacy in Cardiac Arrest Patients; OHCA, out-of-hospital-cardiac arrest; and WLST, withdrawal of life-sustaining therapy. The 14 538 screened patients include all adult patients admitted alive after OHCA. For the primary analysis, the end point was imputed in the 10 patients that were lost to follow-up or who had consent withdrawn. A patient could have more than 1 reason for not being eligible. Among those found to be not eligible, the most common reasons were patients not being comatose, patients being hemodynamically unstable, nonapplication of a definitive temperature control device, and not attaining a temperature target less than 34 °C within 4 hours of cardiac arrest.

shortest duration with neurological outcomes consistent with those of the best of any other durations exceeded 50%.

Trial Intervention

Therapeutic hypothermia to 33 °C was a routine clinical practice at all sites participating in this trial. Sites used the same closed-loop definitive temperature control devices for trial patients as for those treated outside the trial. All patients in the trial had started therapeutic hypothermia as part of their standard care prior to enrollment. Time to target temperature was defined as the interval from cardiac arrest to achieving and maintaining a core temperature less than 34 °C. Time of cardiac arrest was defined as the time of the initial 911 call or the actual time of arrest in patients for whom emergency medical services witnessed the initial arrest. The allocated cooling duration was measured from the time the definitive cooling device was started. To accommodate the shortest potential allocated duration, study teams were allowed only 6 hours from the start of a definitive device to approach, screen, consent, and randomize patients. The allocated cooling duration included intervals prior to randomization and prior to patients reaching target temperature.

Shivering and sedation were managed in accordance with local practice. Controlled rewarming to 36.5 °C was initiated at the end of the allocated cooling duration. The allocated rewarming duration was defined as the rewarming duration equal to the allocated cooling duration for patients allocated to 6, 12, 18, or 24 hours of cooling and as 24 hours for those allocated to longer cooling durations. Normothermia was maintained with a definitive device until liberation from mechanical ventilation or up to 120 hours.

Clinical Standardization Including Assessment of Neurological Prognosis

A clinical standardization committee created guidelines to reduce practice variability in enrolled patients. The guidelines (eAppendix in Supplement 2) addressed blood pressure targets, oxygenation and ventilation, shivering assessment, prevention of rebound hyperthermia, management of infections, and prognostication.

Neurological prognostication leading to withdrawal of life-sustaining therapy was not to be performed within 96 hours of cardiac arrest per the study protocol, but brain death criteria could be assessed at any time after rewarming consistent with local processes.

End Points

The primary end point was the modified Rankin Scale score (mRS, a 7-point ordinal scale measuring function on which a score of 0 indicates independence and a score of 6 is death) at 90 days. The mRS was analyzed as a weighted score ranging from 0 to 10, with higher weights reflecting better outcomes. Weighting in this trial purposefully balanced the relative contributions of both the proportion of patients with a favorable outcome and their degree of residual functional impairment. Specifically, a weighted score of 10 was given for an mRS score of 0, 9 for an mRS score of 1, 8 for an mRS score of 2, 6 for an mRS score of 3, and 0 for an mRS score of 4 to 6. The mRS score was determined primarily by a blinded central assessor by telephone. A dichotomized end point reflecting poor outcome, defined as an mRS score of 4 or higher, was also specified.

Secondary end points included the dichotomized mRS score and neuropsychological testing. Neuropsychological testing was performed by blinded site neuro-outcome assessors using the National Institutes of Health Toolbox Cognition Battery, reported as fluid, crystallized, and total composite T scores fully corrected for age, education, sex, and race.[28] Fluid scores reflect core cognitive processes such as processing speed, working memory, and reasoning, whereas crystallized scores reflect accrued knowledge and long-term memory assessed in tasks like vocabulary or word pronunciation. Higher composite T scores indicate better cognitive performance and are calculated with respect to normative data in which a composite score of 50 represents the national mean with an SD of 10.

Safety and Adverse Events

The primary safety outcome was all-cause mortality at 90 days. All-cause mortality was selected because it incorporates the most severe irreversible consequences across many potential adverse events.

Secondary safety outcomes included study-defined adverse event types and all serious adverse events occurring during a patient's participation. Study-defined adverse event types were pneumonia, other infections (including urinary tract infections and bloodstream infections), malignant cardiac arrhythmias, seizures, neurological worsening, electrolyte abnormalities, venous thrombotic disease, and coagulopathies. Definitions of event types are listed in the eAppendix in Supplement 2.

Statistical Analysis

The mean weighted 90-day mRS score was analyzed with an inverted U-shaped duration-response model sufficiently flexible to also accommodate increasing, decreasing or flat response curves. Optimal duration is defined as the shortest cooling duration that provides a mean weighted mRS score consistent with the maximum mean weighted mRS score of any duration. The primary intention-to-treat analysis includes all randomized patients and reports the posterior probability that each duration is the optimal duration. The observed mean weighted mRS score and the model-based estimate of the mean weighted mRS score for each duration are also reported. Subgroup analysis of the primary outcome was conducted within each rhythm. Mortality and the dichotomized end point of an mRS score of 4 or higher are analyzed using the same model but with weighting, as specified in the statistical analysis plan (Supplement 1).

The maximal sample size of 1800 patients was determined from extensive numerical simulations of the design across a range of potential scenarios to characterize the trial's type I error and power for the primary analysis. Further details are in the Design Report appendix to the protocol (Supplement 1).

Table 2. Hospital Care of Patients

Variables	Rhythm type	
	Nonshockable (n = 883)	Shockable (n = 275)
Time from cardiac arrest to emergency department arrival, median (IQR), min	39 (30-51) [n = 865]	39 (30-50) [n = 271]
Time from cardiac arrest to device start, median (IQR), min	152.5 (113-196) [n = 874]	146 (112-188) [n = 274]
Type of definitive temperature control device, No. (%)		
Surface	477 (54)	159 (57.8)
Endovascular	406 (46)	116 (42.2)
Initial ICU to which patient was admitted, No./total (%)		
Medical ICU	547/882 (62.0)	97/274 (35.4)
Cardiology ICU	158/882 (17.9)	128/274 (46.7)
Neurological ICU	118/882 (13.4)	28/274 (10.2)
Combined or other ICU	59/882 (6.7)	21/274 (7.7)
Interventions performed during hospitalization, No. (%)		
Percutaneous coronary intervention	15 (1.7)	57 (20.7)
Coronary artery bypass graft surgery	1 (0.1)	6 (2.2)
AICD or pacemaker implanted	13 (1.5)	71 (25.8)
Continuous or intermittent hemodialysis	153 (17.3)	43 (15.6)
Withdrawal of life-sustaining therapy, No./total (%)		
Within 96 h of device start	140/881 (15.9)	31 (11.3)
During hospitalization	526 (59.6)	104 (37.8)
Rationale for withdrawal of life-sustaining therapy, No. (%)		
Poor neurological prognosis	426 (48.2)	76 (27.6)
Poor cardiac prognosis	29 (3.3)	14 (5.1)
Other poor prognosis or other reason	71 (8)	14 (5.1)

Abbreviations: AICD, automated internal cardiac defibrillator; ICU, intensive care unit.

Results

Participants and Baseline Characteristics

After randomizing 1158 patients to durations of 6 hours to 48 hours, the trial met the prespecified stopping rule at a planned interim analysis. Patients were enrolled at 71 sites between June 2020 and June 2025. Presenting rhythms were nonshockable in 883 patients and shockable in 275 patients. Demographic and baseline characteristics are reported in Table 1 and the medical care received in **Table 2**. Baseline characteristics by duration group are presented in eTable 1 in Supplement 1 and by sequential enrollment groupings in eTable 7 in Supplement 1. Baseline laboratory values and vital signs are presented in eTable 2 and eTable 9, respectively, in Supplement 1. Baseline medical history is presented in eTable 8 in Supplement 1. The sex, race, and ethnicity of the patients enrolled were representative of patients admitted but not enrolled at participating hospitals (eTable 10 in Supplement 1). Ninety-two percent of participants had a temperature below 34 °C within 4 hours of cardiac arrest, despite this being an eligibility requirement. Sites screened 14 538 patients admitted to the hospital alive after OHCA (Figure 1). The primary analysis population includes all 1158 patients.

Temperature Management

The median time from cardiac arrest to definitive temperature control device initiation was 151 minutes. A surface cooling device was used in 55% of patients and an endovascular device in 45%. Excellent separation between groups by allocated duration of therapeutic hypothermia is shown in eFigure 1 in Supplement 2.

Primary and Secondary Outcomes

Primary and secondary outcomes are described in **Table 3**. Observed mRS score distributions and the resulting mean weighted mRS scores by cohort and allocated duration are presented in eFigure 2 and eTable 3 in Supplement 2. The mean observed weighted mRS score across durations was 0.8 in the nonshockable rhythm cohort and 3.5 in the shockable rhythm cohort.

Duration response did not increase in either cohort (**Figure 2**). The posterior probability of 6 hours being the shortest duration that achieves the maximal mean weighted mRS score was 0.51 in the nonshockable rhythm cohort and 0.49 in the shockable rhythm cohort. The posterior probabilities of each duration being the optimal duration for predefined subgroups are presented in eFigure 3 in Supplement 2. No differences in neuropsychological test outcomes were identified by cooling duration.

Safety Outcomes

Overall, 90-day mortality was 74.4% (81.3% in the nonshockable rhythm cohort, 52% in the shockable rhythm cohort). The most common study-defined adverse event type was neurological worsening. Adverse event types, fatal adverse event

Table 3. Primary and Secondary Outcomes

Outcomes	Cooling duration, h							
	6	12	18	24	30	36	42	48
Nonshockable rhythm								
Primary outcome	n = 89	n = 284	n = 104	n = 134	n = 70	n = 42	n = 64	n = 89
Weighted mRS score, model-based mean (SD)[a]	0.83 (0.13)	0.87 (0.11)	0.85 (0.1)	0.84 (0.1)	0.83 (0.11)	0.82 (0.11)	0.81 (0.12)	0.78 (0.15)
Probability of being the target duration	0.507	0.305	0.073	0.035	0.023	0.016	0.017	0.013
Mortality, No. (%)[b]								
All-cause mortality at 90 d	75 (84.3)	220 (77.5)	83 (79.8)	112 (83.6)	60 (85.7)	36 (85.7)	54 (84.4)	79 (88.8)
In-hospital mortality[c]	73 (82)	214 (75.4)	77 (74)	107 (79.9)	58 (82.9)	34 (81)	52 (81.3)	75 (84.3)
Mortality after WLST at 90 d	52 (58.4)	166 (58.5)	59 (56.7)	79 (59)	42 (60)	25 (59.5)	43 (67.2)	60 (67.4)
mRS score ≥4, No. (%)[b,d]	80 (89.9)	245 (86.3)	95 (91.3)	123 (91.8)	66 (94.3)	39 (92.9)	58 (90.6)	81 (91)
NIH Toolbox Cognition Battery composite T score, mean (SD)[e]								
Fluid (n = 31)	39.7 (11.5)	39.5 (13.7)	44.5 (14.2)	28 (5.7)	35 (9.9)	37.7 (8)	58 (NA)	39 (4.2)
Crystallized (n = 32)	39.8 (8.5)	50.3 (9.5)	54.7 (12.3)	53.3 (18.9)	37.5 (4.9)	47.7 (10.6)	59 (NA)	46 (NA)
Total (n = 29)	40 (5.3)	43.2 (13.3)	49.8 (11.7)	41 (18.4)	33 (2.8)	41 (5.3)	61 (NA)	39 (NA)
Shockable rhythm								
Primary outcome	n = 44	n = 89	n = 33	n = 36	n = 17	n = 11	n = 14	n = 28
Weighted mRS score, model-based mean (SD)[a]	3.57 (0.32)	3.61 (0.3)	3.57 (0.29)	3.53 (0.3)	3.5 (0.33)	3.46 (0.36)	3.4 (0.41)	3.26 (0.51)
Probability of being the target duration	0.49	0.301	0.08	0.041	0.028	0.018	0.017	0.013
Mortality, No. (%)[b]								
All-cause mortality at 90 d	18 (40.9)	46 (51.7)	19 (57.6)	20 (55.6)	5 (29.4)	8 (72.7)	8 (57.1)	19 (67.9)
In-hospital mortality[c]	17 (38.6)	45 (50.6)	17 (51.5)	16 (44.4)	5 (29.4)	8 (72.7)	8 (57.1)	18 (64.3)
Mortality after WLST at 90 d	14 (31.8)	37 (41.6)	15 (45.5)	9 (25)	4 (23.5)	6 (54.5)	5 (35.7)	14 (50)
mRS score ≥4, No. (%)[b,d]	22 (50)	49 (55.1)	19 (57.6)	26 (72.2)	7 (41.2)	9 (81.8)	8 (57.1)	19 (67.9)
NIH Toolbox Cognition Battery composite T score, mean (SD)[e]								
Fluid (n = 58)	42.7 (13.8)	43.2 (12.4)	37.6 (11.6)	46.4 (15.9)	39.6 (8.4)	35.5 (23.3)	35 (6.1)	39.8 (16)
Crystallized (n = 61)	49.5 (5)	46.6 (7.7)	47.5 (14.1)	55 (2.2)	44.5 (8.2)	43.5 (3.5)	49.3 (2.3)	47.5 (8)
Total (n = 55)	44.7 (9.7)	44.3 (10.1)	40.6 (13.7)	51.5 (11.6)	41.3 (10.7)	38 (15.6)	40.7 (4.2)	43.3 (14.1)

Abbreviations: mRS, modified Rankin Scale; NIH, National Institutes of Health; WLST, withdrawal of life-sustaining therapy.

[a] The mRS is an ordinal scale of function; 0 indicates independence and 6, death. The weighted mRS is a score ranging from 0 to 10, with higher weights reflecting better outcomes, calculated using a score of 10 for an mRS score of 0, 9 for an mRS score of 1, 8 for an mRS score of 2, 6 for an mRS score of 3, and 0 for an mRS score of 4 to 6. The duration-response model is parameterized to allow for 3 potential phases: increasing, plateau, and decreasing. The target duration is the shortest duration with outcomes consistent with the maximal model-defined response, the leftmost elbow on the duration-response curve.

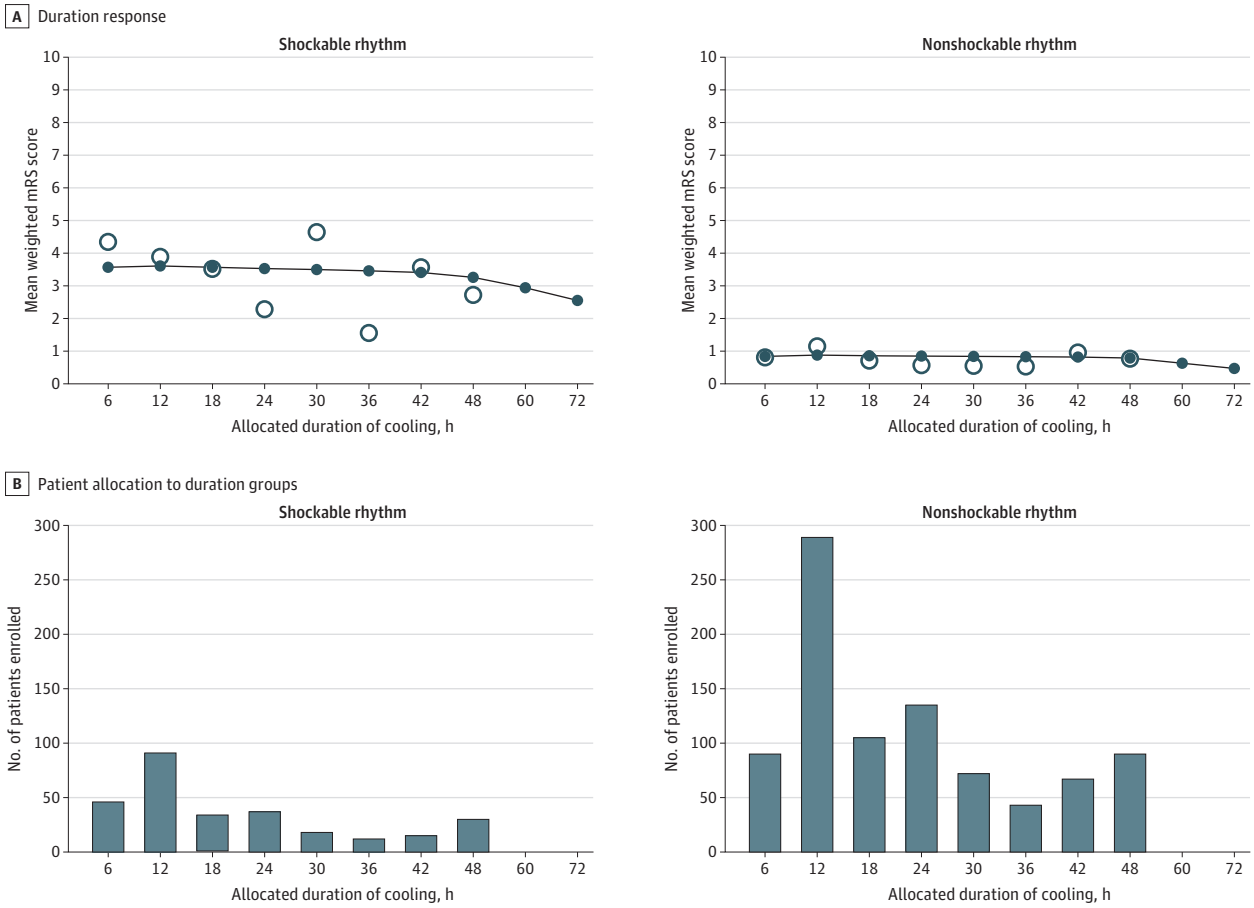
[b] These outcomes include only patients in whom primary outcome data were available.

[c] Ten cases with discharge occurring after the end of participation in the study are included in the denominator when calculating percentages.

[d] The full distribution of mRS scores (range, 0-6) is shown in eFigure 2 in Supplement 2.

[e] NIH Toolbox Cognition Battery composite scores integrate individual neuropsychiatric test results into a single metric in which higher scores indicate better cognitive performance with respect to normative data. The composite scores are fully corrected T scores in which a composite score of 50 represents the national mean with an SD of 10. Fluid scores reflect core cognitive processes such as processing speed, working memory, and reasoning, whereas crystallized scores reflect accrued knowledge and long-term memory assessed in tasks like vocabulary or word pronunciation. For single observations, standard deviations are not applicable (NA).

Figure 2. Line and Bar Graphs of Duration-Response Model by Presenting Rhythm Type



A, Duration-response curves for each rhythm type cohort. Open circles are the observed mean weighted modified Rankin Scale (mRS) scores for each allocated duration group. Closed circles and solid line represent the model-based estimates of the mean weighted mRS scores for each cooling duration. The duration-response model is parameterized to allow for 3 potential phases: increasing, plateau, and decreasing. The mean weighted mRS score ranges from 0 to 10, with higher scores reflecting better outcome. The weighted mRS score is 10 for an mRS score of 0, 9 for an mRS score of 1, 8 for an mRS score of 2, 6 for an mRS score of 3, and 0 for an mRS score of 4 to 6. B, Number of patients allocated to each duration group. The first 200 patients were randomized to 12-, 24-, and 48-hour durations in a 1:1:1 ratio. Subsequent patients were allocated preferentially by response-adaptive randomization to durations between 6 hours and 72 hours that were more likely to be optimal and best inform the duration-response curve.

types, and all serious adverse events are summarized in eTables 4-6 in Supplement 2.

Discussion

No clinical strategy has implemented therapeutic hypothermia in comatose survivors of OHCA in a manner that consistently demonstrates efficacy despite extensive preclinical research identifying the mechanisms underlying hypothermic neuroprotection in global cerebral ischemia. The results of the current study demonstrate that increasing cooling duration, as performed and evaluated in this trial in broadly representative and inclusive cohorts of patients after OHCA, does not improve outcomes.

Despite a large body of preclinical evidence demonstrating that therapeutic hypothermia improves neuronal survival following ischemia-reperfusion injury, clinical trials have yielded conflicting results. Trials from 2002 led to international guidelines recommending therapeutic hypothermia targeting 33 °C for either 12 hours or 24 hours.[10,12] A subsequent trial observed good outcomes in 69% of patients with 48 hours vs 64% with 24 hours, but was neutral as it was designed to detect a 15% absolute improvement in the primary end point.[11] Similarly, a pediatric OHCA trial showed higher 1-year survival with 48 hours of 33 °C vs normothermia, but the intervention did not show superiority on its primary neurobehavioral outcome.[29] In addition, 2 large, high-quality trials seeking to establish the superiority of either targeted temperature management at 36 °C or a reactive fever control strategy vs a target of 33 °C did not demonstrate improved outcomes.[13,15] These targeted temperature management trials focused on patients with mostly shockable initial rhythms and a presumed cardiac cause and observed similar mortality to that of the shockable rhythm cohort of this trial. An additional trial, inclusive of OHCA and in-hospital cardiac arrest and focusing on

nonshockable rhythms, found improved outcomes with 33 °C of therapeutic hypothermia within the context of high overall mortality.[14] Finally, guidelines recommend therapeutic hypothermia in the mechanistically similar disease of neonatal birth asphyxia.[30]

Clinical guidelines for therapeutic hypothermia after OHCA have evolved over the years. Following the targeted temperature management trial results, guidelines have increased the range of temperature targets recommended in adults with cardiac arrest, and practice has started to shift toward fever prevention alone, even though the individual trials used to justify these guideline changes did not demonstrate superiority of fever control strategies on patient-oriented outcomes.[31,32] Why do the current data add to the body of neutral trials that do not sufficiently inform guidelines? It may be that large trials with broad inclusion criteria cannot resolve the question of therapeutic hypothermia translation without exploring differential effects of heterogeneous injury phenotypes, clinical practice variability, or even underlying social and genetic determinants of health. We may instead need to answer the questions of in whom is it important to control temperature, and how and when is it best to deliver such care? This trial may yet help address these questions indirectly through important substudies. One is exploring the use of electroencephalography, magnetic resonance imaging, and other biomarkers to identify injury phenotypes in a subset of the ICECAP cohort.[33] Another substudy will explore the effects of practice variability and quality improvement in therapeutic hypothermia implementation at participating sites.

The relatively low rate of good recovery overall in this trial's representative cohort of patients with cardiac arrest is a sobering reminder of the high morbidity and mortality of this devastating condition and the persistent need for better treatments. However, the 20% survival rate in patients with nonshockable rhythms may be considered promising, as it is a very different outcome from the common misperception that these patients nearly all die.

Many of the strengths of this trial address concerns raised in some previous cohorts. This trial is more representative of patients seen in clinical practice in the US regarding demographics, including sex, race, and ethnicity, and in the characteristics of the cause of cardiac arrest and in resuscitation. For example, patients had a high rate of cardiac arrest due to overdose, consistent with the opioid epidemic.[34,35] Similarly, lower rates of bystander cardiopulmonary resuscitation among those enrolled in this trial are unfortunately consistent with population-based observations and dissimilar to other recent trials in which the rates were very high, a desirable but unmet goal in the US.

Limitations

This study has some limitations. First, representativeness was a strength but also a limitation of this trial. The proportion of patients with nonshockable presenting rhythms, while representative of the changing epidemiology of OHCA, was higher than initially anticipated, resulting in higher mortality and lower numbers of patients with neuropsychological outcomes.[24,36] Although consistent with the range of mortality simulated during trial design, having fewer survivors adversely affects trial operating characteristics by reducing information. Second, limiting eligibility to patients with a short time to target temperature is another strength of the trial because it reduced variability in this potentially critical clinical parameter, but it may have also been an unintended limitation. We intended to select those receiving early and effective cooling therapy but may have also inadvertently selected patients with more severe injury who arrived in hypothermia or were easier to cool because of impaired thermoregulation. Third, although we attempted to control for the effects of early withdrawal of life-sustaining therapy through eligibility and guideline-concordant neuroprognostication practices, some patients still had very early withdrawal attributed to a perceived poor neurological prognosis. The effect on clinical trials of practice variability surrounding withdrawal of life-sustaining therapy is complex, but pervasive clinical cultures of nihilism may have adversely impacted accrual and the care provided.

Conclusions

Among comatose survivors of out-of-hospital cardiac arrest treated with therapeutic hypothermia at 33 °C, increasing cooling duration did not improve neurological outcomes. Duration of therapeutic hypothermia should not be routinely extended in comatose survivors of cardiac arrest.

ARTICLE INFORMATION

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