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Effect of Moderate vs Mild Therapeutic Hypothermia on Mortality and Neurologic Outcomes in Comatose Survivors of Out-of-Hospital Cardiac Arrest

The CAPITAL CHILL Randomized Clinical Trial

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IMPORTANCE Comatose survivors of out-of-hospital cardiac arrest experience high rates of death and severe neurologic injury. Current guidelines recommend targeted temperature management at 32 °C to 36 °C for 24 hours. However, small studies suggest a potential benefit of targeting lower body temperatures.

OBJECTIVE To determine whether moderate hypothermia (31 °C), compared with mild hypothermia (34 °C), improves clinical outcomes in comatose survivors of out-of-hospital cardiac arrest.

DESIGN, SETTING, AND PARTICIPANTS Single-center, double-blind, randomized, clinical superiority trial carried out in a tertiary cardiac care center in eastern Ontario, Canada. A total of 389 patients with out-of-hospital cardiac arrest were enrolled between August 4, 2013, and March 20, 2020, with final follow-up on October 15, 2020.

INTERVENTIONS Patients were randomly assigned to temperature management with a target body temperature of 31 °C (n = 193) or 34 °C (n = 196) for a period of 24 hours.

MAIN OUTCOMES AND MEASURES The primary outcome was all-cause mortality or poor neurologic outcome at 180 days. Neurologic outcome was assessed using the Disability Rating Scale, with poor neurologic outcome defined as a score greater than 5 (range, 0-29, with 29 being the worst outcome [vegetative state]). There were 19 secondary outcomes, including mortality at 180 days and length of stay in the intensive care unit.

RESULTS Among 367 patients included in the primary analysis (mean age, 61 years; 69 women [19%]), 366 (99.7%) completed the trial. The primary outcome occurred in 89 of 184 patients (48.4%) in the 31 °C group and in 83 of 183 patients (45.4%) in the 34 °C group (risk difference, 3.0% [95% CI, 7.2%-13.2%]; relative risk, 1.07 [95% CI, 0.86-1.33]; *P* = .56). Of the 19 secondary outcomes, 18 were not statistically significant. Mortality at 180 days was 43.5% and 41.0% in patients treated with a target temperature of 31 °C and 34 °C, respectively (*P* = .63). The median length of stay in the intensive care unit was longer in the 31 °C group (10 vs 7 days; *P* = .004). Among adverse events in the 31 °C group vs the 34 °C group, deep vein thrombosis occurred in 11.4% vs 10.9% and thrombus in the inferior vena cava occurred in 3.8% and 7.7%, respectively.

CONCLUSIONS AND RELEVANCE In comatose survivors of out-of-hospital cardiac arrest, a target temperature of 31 °C did not significantly reduce the rate of death or poor neurologic outcome at 180 days compared with a target temperature of 34 °C. However, the study may have been underpowered to detect a clinically important difference.

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Visual Abstract

Supplemental content

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Despite significant advances in resuscitation medicine in recent decades, the prognosis of comatose survivors of out-of-hospital cardiac arrest remains poor. Among patients who survive to hospital admission, mortality remains high and survivors are subject to substantial neurologic dysfunction.[1]

Two early pivotal trials demonstrated improved clinical outcomes in comatose survivors of out-of-hospital cardiac arrest managed with therapeutic hypothermia.[2,3] The trial conducted by Bernard et al[3] compared a target core temperature of 33 °C with normothermia, while the Hypothermia After Cardiac Arrest (HACA) trial[2] compared a target core temperature between 32 °C and 34 °C with normothermia. Both trials limited enrollment to comatose survivors of out-of-hospital cardiac arrest secondary to a shockable rhythm. More recently, the Therapeutic Hypothermia After Cardiac Arrest in Nonshockable Rhythm (HYPERION) trial[4] showed favorable neurologic outcomes with a target temperature of 33 °C, compared with normothermia, in comatose survivors of cardiac arrest with a nonshockable rhythm.

In contrast, in the Target Temperature Management at 33 °C vs 36 °C After Out-of-Hospital Cardiac Arrest (TTM) trial,[5] a temperature target of 33 °C compared with 36 °C did not confer a reduction in the rate of death or poor neurologic function. As a result, post–cardiac arrest care guidelines were modified to recommend target temperatures of 32 °C to 36 °C.[6-8]

Animal studies, observational studies in humans, and a small pilot trial have suggested that moderate therapeutic hypothermia with a target temperature between 28 °C and 32 °C confers neuroprotection and could improve clinical outcomes in comatose survivors of cardiac arrest.[9-11] However, to date, no randomized clinical trial has evaluated a target temperature less than 32 °C. The Moderate vs Mild Therapeutic Hypothermia in Comatose Survivors of Out-of-Hospital Cardiac Arrest (CAPITAL CHILL) trial was designed to assess whether moderate hypothermia (target temperature of 31 °C), compared with mild hypothermia (target temperature of 34 °C), improves clinical outcomes in comatose survivors of out-of-hospital cardiac arrest.

Key Points

Question Does moderate hypothermia (target temperature of 31 °C) compared with mild hypothermia (target temperature of 34 °C) reduce the rate of death or poor neurologic outcome in comatose survivors of out-of-hospital cardiac arrest?

Findings In this randomized clinical trial that included 367 adults with out-of-hospital cardiac arrest, 180-day all-cause mortality or poor neurologic outcome among those randomized to receive hypothermia treatment at 31 °C vs 34 °C was 48.4% vs 45.4%, respectively. This difference was not statistically significant.

Meaning In comatose survivors of out-of-hospital cardiac arrest, a target temperature of 31 °C did not significantly reduce the rate of death or poor neurologic outcome at 180 days compared with a target temperature of 34 °C.

Methods

Trial Design

This study was a single-center, double-blind, randomized clinical trial. Patients with out-of-hospital cardiac arrest surviving to hospital admission and referred for post–cardiac arrest care were recruited at the University of Ottawa Heart Institute, a tertiary cardiac care center servicing a population of more than 1.2 million people in eastern Ontario, Canada. In this regional system of care, patients presenting with out-of-hospital cardiac arrest were assessed in the emergency department of referring hospitals and transferred immediately to the cardiac center if the cause of the arrest was deemed likely to be cardiac.

The study protocol and statistical analysis plan are provided in Supplement 1. The Cardiovascular Research Methods Centre at the University of Ottawa Heart Institute conducted and coordinated the trial and was responsible for collecting all trial data. Members of an independent adjudication committee, blinded to the study group assignments, reviewed the events; members of an independent data and safety monitoring committee oversaw the safety of the trial. The study was approved by the Ottawa Health Science Network Research Ethics Board. Written informed consent was obtained from substitute decision makers, as soon as circumstances permitted, and from patients with sufficient neurologic recovery.

Patients

We included patients 18 years of age or older following out-of-hospital cardiac arrest who at the time of admission remained comatose, as defined by a Glasgow Coma Scale score of 8 or lower. Patients were recruited irrespective of initial rhythm found at the time of the cardiac arrest. The main exclusion criteria were known inability to perform activities of daily living, cardiac arrest secondary to intracranial bleed, severe coagulopathy with clinical evidence of major bleeding, coma not attributable to the cardiac arrest, and life expectancy of less than 1 year due to reasons unrelated to the cardiac arrest.

Randomization

Eligible patients were randomly assigned to temperature management with a target body temperature of either 31 °C (moderate hypothermia) or 34 °C (mild hypothermia) in a 1:1 ratio immediately after insertion of an endovascular cooling catheter. Randomization was performed with the use of permuted blocks of size 4 and 6 and stratified by first documented rhythm at the time of the cardiac arrest. Initial rhythms were classified as shockable (ventricular fibrillation or pulseless ventricular tachycardia) or nonshockable (asystole or pulseless electrical activity). Sets of patient numbers and associated treatments were provided in sealed, opaque, serially numbered envelopes to ensure allocation concealment and avoid selection bias.

Blinding

The treating physician, patients, and family members were blinded to group allocation. Bedside nurses were the only

members of the health care team aware of temperature assignment and were responsible for managing the endovascular cooling catheter as per trial protocol. Covers were used to conceal all temperature monitors, and temperature charts were kept separate from patients' records. Physicians performing follow-up assessments were blinded to group allocation, as were all members of the event adjudication committee.

Targeted Temperature Management and Interventions

Paramedics and transferring facilities were encouraged to initiate temperature management using ice packs as soon as possible after return of spontaneous circulation. On arrival at the cardiac center, active cooling was performed using an endovascular cooling catheter (Zoll Quattro catheter) inserted via the femoral vein into the inferior vena cava and connected to a temperature management system (Thermogard XP Temperature Management System, Zoll Medical Corporation). This system consists of a pump that circulates sterile saline from the external device through balloons mounted on a catheter, enabling direct cooling or warming of blood. In this study, the device controlled the temperature of the saline by remotely sensing a patient's temperature via a nasopharyngeal probe when feasible or by a temperature-sensing urinary bladder catheter. All patients received anticoagulation therapy with intravenous unfractionated heparin to prevent thrombus formation on the endovascular cooling catheter.[12] As immediate coronary angiography was recommended for all patients on arrival at the cardiac center, the cooling catheter was inserted in the catheterization laboratory; if the decision was to proceed without immediate cardiac catheterization, then the cooling catheter was inserted in the intensive care unit. The sedation, analgesia, and neuromuscular blockade protocols used during therapeutic hypothermia are provided in Supplement 1.

Patients were maintained at their assigned target temperature for 24 hours. After this period, patients were actively rewarmed at a rate of 0.25 °C/h until a temperature of 37 °C was reached. This temperature was maintained such that the duration of rewarming plus normothermia totaled 48 hours.

If therapeutic hypothermia was considered to be contributing to a serious adverse event, a temperature increment of 3 °C was permitted at the discretion of the treating physician. In cases in which, despite this temperature increment, therapeutic hypothermia was still considered to be contributing to a serious adverse event, a second increment of 3 °C to reach a temperature of 37 °C was permitted if applicable (ie, if temperature was already 37 °C, then no change was made). This process was completed without revealing treatment assignment.

Decisions to withdraw life-sustaining therapy were based on a multimodal neuroprognostication strategy that included serial neurologic examinations, electroencephalography, computed tomography, and magnetic resonance imaging of the brain. Decisions were made by a multidisciplinary team that included a critical care physician, a neurologist, and a palliative care specialist, working in conjunction with patients' families.

Study Outcomes

The primary outcome was a composite of all-cause mortality or poor neurologic outcome at 180 days after randomization. Neurologic outcome was assessed using the Disability Rating Scale (DRS), an 8-item ordinal scale that evaluates functional dependence.[13] This functional scale was used as a proxy for assessing neurologic recovery: the maximum score a patient can obtain on the DRS is 29 (extreme vegetative state): a person with no disability would score 0. In this study, poor neurologic outcome was defined as a DRS score greater than 5. The DRS was chosen because of its reliability and validity in the assessment of neurologic function following acquired brain injury.[14] As an additional assessment, the Modified Rankin Scale, which ranges from 0 to 6, with 0 representing no symptoms and 6 representing death, was used.[15,16] A Modified Rankin Scale score between 4 and 6 was used to define a poor neurologic outcome. Neurologic outcomes were assessed by a specialist in rehabilitation medicine.

Secondary outcomes included death during the initial hospitalization, at 30 days, and at 180 days; stroke during the initial hospitalization and at 180 days; stent thrombosis; seizures; kidney replacement therapy; pneumonia; cardiogenic shock; need for antiarrhythmic therapy (other than β-blockers); recurrent cardiac arrest after randomization requiring cardiopulmonary resuscitation; major bleeding; proportion of survivors discharged home from the hospital; peak creatinine kinase level; left ventricular ejection fraction measured by transthoracic echocardiography at 3 days and at 3 months; length of stay in the unit; and length of stay in the hospital. A central committee, blinded to treated assignment, adjudicated the primary outcome, stroke, and stent thrombosis. A neurologist, blinded to treated assignment, adjudicated seizures.

Neurologic outcomes were reported as nonprespecified neurologic outcomes. Thrombus found in the inferior vena cava detected by abdominal ultrasound and deep vein thrombosis by Doppler ultrasound of the lower extremities were reported as serious adverse events; it was established practice to obtain these tests on days 3 and 5, respectively, for all patients during the study period.

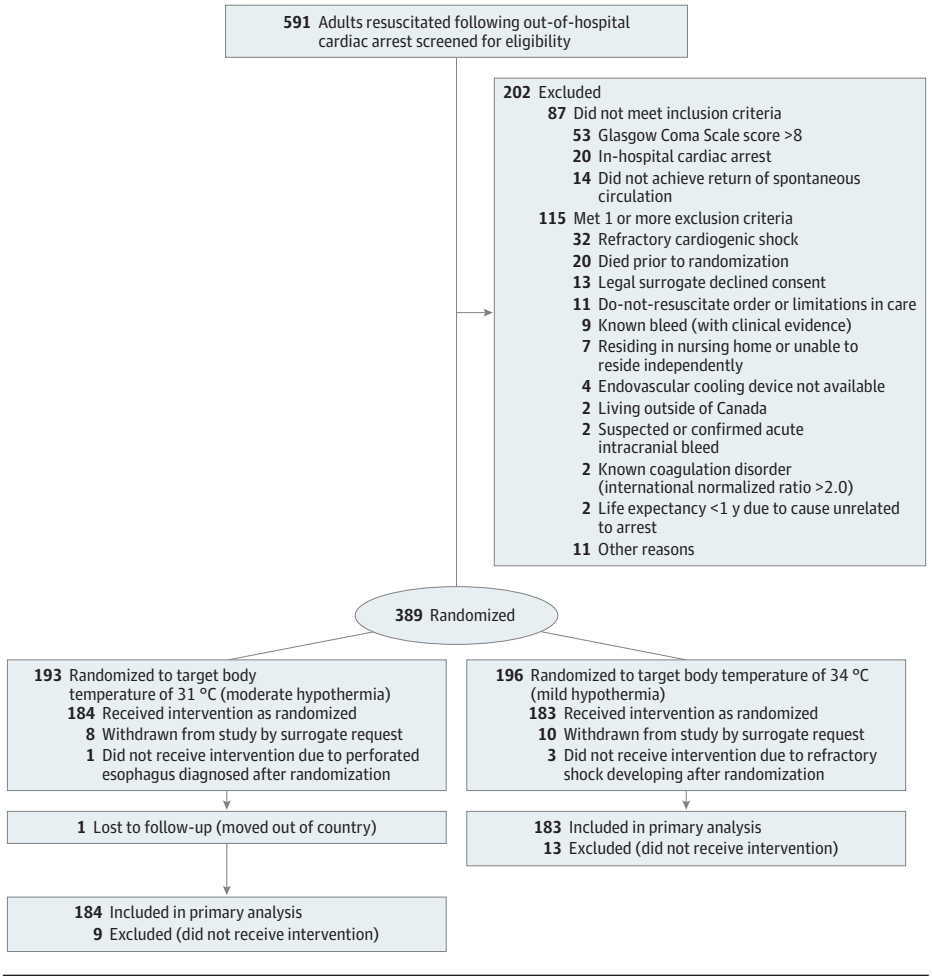
Subgroups

Subgroup analyses were performed to assess the robustness of the results in relation to specific variables of interest. The following subgroups were prespecified: age, initial rhythm, ST-segment elevation myocardial infarction, and timing of cardiac catheterization and percutaneous coronary intervention. Sex was added as a subgroup post hoc.

Sample Size Calculation

The sample size was calculated with an expected rate of the primary outcome of 50% in the 34 °C group based on available studies.[2,3,17] A sample size of 340 patients was required to detect a 30% relative risk reduction, a reduction that was used in other studies,[2,3] with 80% power and a type I error of .05. Minimal loss to follow-up was expected. However, the sample size was increased to 360 patients

Figure 1. Participant Flow



Randomization was stratified by first documented rhythm at the time of the cardiac arrest. Initial rhythms were classified as shockable (ventricular fibrillation or pulseless ventricular tachycardia) or nonshockable (asystole or pulseless electrical activity). All cases of withdrawal of consent were by a legal surrogate.

(180 per group) to account for a potential crossover rate of 3%. No interim analysis was planned.

Statistical Analysis

The primary analysis was performed including all patients who were randomized to a study therapy group and received the therapy. A secondary analysis was performed including all patients who were randomized to a study therapy group, regardless of whether or not they received the therapy. In addition, a per-protocol analysis was performed that included all patients who received the intended study therapy without a major protocol violation or loss to follow-up. Multiple imputations were used for any missing outcomes using the Markov chain Monte Carlo method with Jeffreys noninformative prior distribution.

Descriptive statistics were used to compare patients randomized to 31 °C or 34 °C target temperatures with respect to baseline variables. For the primary outcome analysis, the χ^2 test was used to compare the 31 °C and 34 °C target temperature groups, and relative risks (RRs) and 95% CIs were calculated as well as risk differences and their 95% CIs. A $P < .05$ was considered statistically significant.

A logistic regression analysis was conducted to assess the consistency of the target temperature on the primary outcome, taking the randomization stratification factor (ventricular fibrillation or pulseless ventricular tachycardia initial rhythm) into consideration; as well, a logistic regression analysis was conducted as a sensitivity analysis to assess the effect of the target temperature on the primary outcome while accounting for a priori clinically important baseline characteristics (ie, age, sex, prior stroke, diabetes, kidney function, and presence of ST-segment elevation myocardial infarction).

For discrete secondary outcomes, RRs, risk differences and their 95% CIs were calculated. In addition, the cumulative incidence of mortality at 180 days was estimated using the Kaplan-Meier method and hazard ratios (HRs) and 95% CIs were calculated. The proportional hazards assumption was assessed using graphical tests (ie, log-negative-log plot) and numerical tests (ie, test of the interaction term group × time).

For continuous secondary outcomes, mean differences and 95% CIs were calculated. For the subgroup analyses, RRs and 95% CIs for the primary outcome were calculated for each subgroup, and subgroup differences were assessed based on the test for the interaction of the treatment group by subgroup

Table 1. Baseline Participant Characteristics[a]

Characteristics	Moderate hypothermia (31 °C) (n = 184)	Mild hypothermia (34 °C) (n = 183)
Age, mean (SD), y	61.0 (14.2)	61.7 (13.3)
≥75, No. (%)	37 (20.1)	32 (17.5)
Sex, No. (%)		
Female	32 (17.4)	37 (20.2)
Male	152 (82.6)	146 (79.8)
Medical history, No. (%)		
Hypertension	109 (59.2)	102 (55.7)
Dyslipidemia	98 (53.3)	89 (48.6)
Current smoker	69 (37.5)	74 (40.4)
Diabetes	47 (25.5)	41 (22.4)
Previous myocardial infarction	47 (25.5)	31 (16.9)
Previous percutaneous coronary intervention	27 (14.7)	16 (8.7)
Previous coronary artery bypass graft surgery	24 (13.0)	13 (7.1)
Previous stroke or transient ischemic attack	15 (8.2)	6 (3.3)
Body mass index, mean (SD)[b]	29.0 (9.9)	28.3 (5.7)
Systolic blood pressure, mean (SD), mm Hg[c]	128.3 (31.5)	128.7 (29.4)
Heart rate, mean (SD) /min[c]	100.3 (26.7)	97.8 (27.5)
Bystander witnessed cardiac arrest, No. (%)	157 (85.3)	152 (83.1)
Bystander performed cardiopulmonary resuscitation, No. (%)	127 (69.0)	124 (67.8)
First monitored rhythm, No. (%)		
Shockable (ventricular fibrillation or pulseless ventricular tachycardia)	158 (85.9)	158 (86.3)
Nonshockable (asystole or pulseless electrical activity)	26 (14.1)	25 (13.6)
Glasgow Coma Scale score, median (IQR)[d]	3 (3-3)	3 (3-3)
Baseline laboratory values		
Serum pH, mean (SD)	7.3 (0.1)	7.3 (0.1)
Serum lactate, mean (SD), mmol/L[e]	4.6 (3.4)	4.4 (3.8)
Creatinine clearance, mean (SD), mL/min	82.2 (33.0)	81.7 (35.1)
Inotropic or pressor support, No. (%)	79 (42.9)	77 (42.3)
ST-segment elevation myocardial infarction, No. (%)[f]	64 (34.8)	73 (39.9)
Fibrinolytic agent following resuscitation, No. (%)[g]	8 (4.4)	11 (6.0)
Critical time intervals, median (IQR), min		
From 911 call to basic life support[h]	0 (0-2)	0 (0-2)
From 911 call to advanced life support[i]	9 (6-12)	9 (6-12)
From 911 call to return of spontaneous circulation[j]	23 (15-35)	20 (14-31)
From basic life support to return of spontaneous circulation[j]	20 (14-35)	18 (12-25)
From 911 call to randomization	228 (167-313)	204 (146-297)

[a] Data were collected on a daily basis by the research coordinator who had access to medical charts and ambulance call reports.

[b] Calculated as weight in kilograms divided by the square of height in meters.

[c] Baseline blood pressure and heart rate information was obtained from emergency department records.

[d] The Glasgow Coma Scale assesses neurologic state based on eye, motor, and verbal responsiveness. Scores range from 3 to 15; a score of 3 indicates complete unresponsiveness; 15 is normal. Score information was obtained from emergency department records; 17% had a score greater than 3.

[e] Normal range for serum lactate is 0.5-2.5 mmol/L.

[f] Diagnosis was established on the first electrocardiogram performed in the ambulance or in the emergency department demonstrating ST-segment elevation myocardial infarction.

[g] Fibrinolytic therapy was given for ST-segment elevation myocardial infarction after return of spontaneous circulation.

[h] Basic life support was defined as bystander-initiated cardiopulmonary resuscitation.

[i] Advanced life support was defined by the arrival of the paramedics at a patient's side.

[j] Times were estimated from ambulance call reports if return of spontaneous circulation occurred before ambulance arrival.

within the generalized linear model using the binomial distribution and a log link.

Because of the potential for type I error due to multiple comparisons, findings for analyses of secondary end points should be interpreted as exploratory. Analyses were conducted using SAS version 9.4 (SAS Institute Inc).

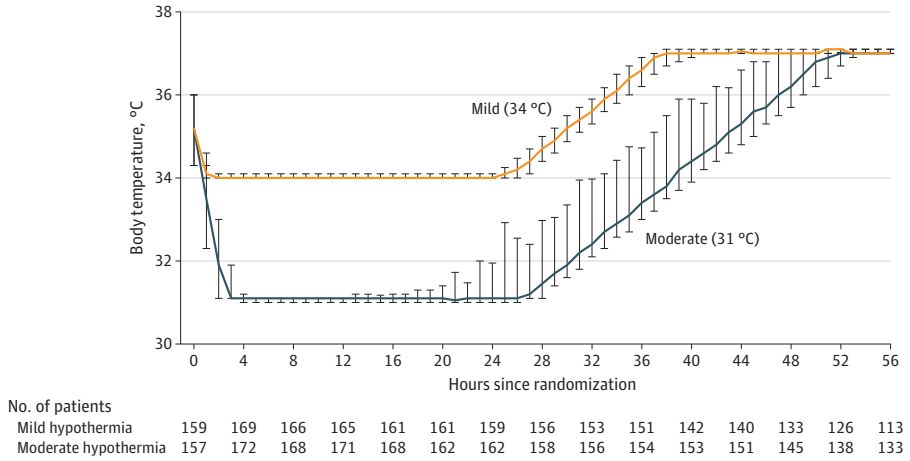
Results

Patient Characteristics

Between August 2013 and March 2020, 591 patients with out-of-hospital cardiac arrest were screened; 504 met the inclusion criteria (**Figure 1**). Of these, 115 had at least 1 exclusion criteria. Among the 389 patients randomized in the study, consent was subsequently withdrawn by a legal surrogate for 8 patients in the 31 °C group and for 10 patients in the 34 °C group. One patient in the 31 °C group and 3 patients in the 34 °C group did not receive the intervention for clinical reasons, leaving 184 and 183 patients, respectively, for inclusion in the primary analysis. One patient in the 31 °C group was lost to follow-up after hospital discharge.

The baseline characteristics of patients were similar between the 2 groups (**Table 1**). The mean age of patients was 61.0 years in the 31 °C group and 61.7 years in the 34 °C group; 82.6% and 79.8% were men, respectively. The cause

Figure 2. Median Body Temperature During the Intervention in Patients Randomized to Moderate Hypothermia (31 °C) or Mild Hypothermia (34 °C)



No. of patients

Mild hypothermia	159	169	166	165	161	161	159	156	153	151	142	140	133	126	113
Moderate hypothermia	157	172	168	171	168	162	162	158	156	154	153	151	145	138	133

The early postresuscitative state of patients and the use of ice packs prior to arrival at the cardiac center may have contributed to baseline temperatures being below normal. Randomization was done immediately once the endovascular device was inserted and shown to be functional. Rewarming was commenced 24 hours after reaching the target temperature at a rate of 0.25 °C/h until 37 °C was reached. This temperature was maintained such that the total period from the onset of rewarming was 48 hours. The curves show the medians; error bars indicate IQRs. The median time from randomization to target temperature was 208 (IQR, 163-282) minutes in the 31 °C group and 120 (IQR, 80-174) minutes in the 34 °C group. Nonadherence to the study protocol was noted for 7 patients in each group. In addition, per protocol, temperature was adjusted upward by 3 °C for hemodynamic reasons in 31 patients (16.8%) in the 31 °C group and in 10 patients (5.5%) in the 34 °C group (P = .001).

of arrest was cardiac in 96.7% of patients in the 31 °C group and in 94.6% in the 34 °C group (eTable 1 in Supplement 2). Immediate coronary angiography was performed in 97.3% of patients in the 31 °C group and in 96.7% in the 34 °C group (eTable 2 in Supplement 2). Percutaneous coronary intervention was performed in 56.3% and 58.7% of patients, respectively. Mechanical support with an intra-aortic balloon was required for 6.1% and 10.7% of patients, respectively. Concomitant medications and procedures in the intensive care unit are listed in eTable 3 in Supplement 2.

Target Temperature Management

The median temperature at the time of randomization was 35.2 °C in both groups. **Figure 2** depicts the temperature curves for the 2 groups expressed as medians and IQRs. The median time from randomization to target temperature achievement was 208 minutes in the 31 °C group and 120 minutes in the 34 °C group.

Outcomes

Primary Outcome

Follow-up information at 180 days was available for 366 of 367 patients. The primary outcome occurred among 89 of 184 patients (48.4%) randomized to the 31 °C group and among 83 of 183 patients (45.4%) randomized to the 34 °C group (risk difference, 3.0% [95% CI, −7.2% to 13.2%]; RR, 1.07 [95% CI, 0.86-1.33]; P = .56) (**Table 2**). The lack of a significant difference in the primary outcome was consistent after adjusting for baseline covariates (eTable 4 in Supplement 2) as well as across all subgroups, as illustrated in the eFigure in Supplement 2.

Secondary Outcomes

Secondary outcomes are listed in Table 2. All-cause mortality at 180 days was 43.5% in the 31 °C group and 41.0% in the 34 °C group (risk difference, 2.5% [95% CI, −7.6% to 12.6%]; RR, 1.06 [95% CI, 0.83-1.35]; P = .63). The Kaplan-Meier curves for probability of survival at 180 days for all patients randomized to a target temperature of 31 °C or a target temperature of 34 °C are shown in **Figure 3** (HR, 1.09 [95% CI, 0.80-1.50]; P = .58); Figure 3 also shows the curves for patients presenting with a shockable rhythm (HR, 1.20 [95% CI, 0.82-1.73]; P = .34) and for those presenting with a nonshockable rhythm (HR, 0.78 [95% CI, 0.43-1.43]; P = .40). There was evidence supporting the proportional hazards assumption (P = .49).

The median length of stay in the intensive care unit was longer in the 31 °C group compared with the 34 °C group (10 days vs 7 days, respectively; P = .004). Otherwise, there were no significant differences in secondary outcomes between the 2 groups (Table 2).

Nonprespecified Outcomes

Among patients surviving to 180 days, poor neurologic outcome, as measured by a DRS score greater than 5, was recorded for 8.7% in the 31 °C group and 7.4% in the 34 °C group (risk difference, 1.3% [95% CI, −6.1% to 8.6%]; RR, 1.17 [95% CI, 0.47-2.91]; P = .74). The breakdown of neurologic scores is shown in eTable 5 in Supplement 2. Likewise, no difference was found between the 2 groups when poor neurologic outcome was defined as a score of 4 to 6 at 180 days on the Modified Rankin Scale (45.9% vs. 43.7%, respectively; risk difference, 2.2% [95% CI, −8.0% to 12.4%]; RR, 1.05 [95% CI, 0.84-1.32]; P = .76).

Table 2. Primary and Secondary Outcomes[a]

Outcomes	Moderate hypothermia (31 °C) (n = 184)	Mild hypothermia (34 °C) (n = 183)	Difference, % (95% CI)	Relative risk (95% CI)	*P* value
Primary outcome					
Death or poor neurologic outcome (DRS score >5) at 180 d[b]	89 (48.4)	83 (45.4)	3.0 (−7.2 to 13.2)	1.07 (0.86-1.33)	.56
Secondary outcomes					
Death during initial hospitalization	80 (43.5)	74 (40.4)	3.0 (−7.1 to 13.1)	1.08 (0.85-1.37)	.56
Death at 30 d	79 (42.9)	73 (39.9)	3.0 (−7.0 to 13.1)	1.08 (0.84-1.37)	.55
Death at 180 d	80 (43.5)	75 (41.0)	2.5 (−7.6 to 12.6)	1.06 (0.83-1.35)	.63
Stroke during initial hospitalization	8 (4.4)	3 (1.6)	2.7 (−0.8 to 6.2)	2.65 (0.71-9.84)	.22
Stroke at 180 d	8 (4.4)	3 (1.6)	2.7 (−0.8 to 6.2)	2.65 (0.71-9.84)	.22
Stent thrombosis	2 (1.1)	4 (2.2)	−1.1 (−3.7 to 1.5)	0.50 (0.09-2.68)	.45
Seizures	23 (12.5)	13 (7.1)	5.4 (−0.7 to 11.5)	1.76 (0.92-3.37)	.08
Kidney replacement therapy	17 (9.2)	17 (9.3)	0.1 (−6.0 to 5.9)	0.99 (0.52-1.89)	.99
Pneumonia	124 (67.4)	116 (63.4)	4.0 (−5.7 to 13.7)	1.06 (0.92-1.23)	.42
Cardiogenic shock	71 (38.6)	61 (33.3)	5.3 (−4.6 to 15.1)	1.16 (0.88-1.52)	.29
Need for anti-arrhythmic therapy[c]	56 (30.4)	66 (36.1)	−5.6 (−15.3 to 4.0)	0.84 (0.63-1.13)	.25
Recurrent cardiac arrest requiring CPR	20 (10.9)	17 (9.3)	1.6 (−4.6 to 7.7)	1.17 (0.63-2.16)	.62
TIMI non-CABG major bleeding within 7 d[d]	43 (23.4)	36 (19.7)	3.7 (−4.7 to 12.1)	1.19 (0.80-1.76)	.39
Blood transfusion	36 (19.6)	41 (22.4)	−2.8 (−11.2 to 5.5)	0.87 (0.59-1.30)	.50
Survivors discharged to home from hospital[e]	93/103 (90.3)	99/107 (92.5)	2.2 (−9.8 to 5.4)	0.98 (0.90-1.06)	.56
Peak creatine kinase, mean (SD), IU/L[f]	3400 (4039)	2882 (3679)	518 (−277 to 1312)		.20
LVEF at 3 d, mean (SD), %	41.6 (13.8)	41.8 (15.1)	−0.2 (−3.3 to 2.9)		.89
LVEF at 3 mo, mean (SD), %[g]	46.2 (12.1)	50.7 (13.3)	−4.5 (−11.0 to 2.0)		.17
Length of stay in unit, median, (IQR), d	10 (7-15)	7 (6-12)	1.4 (−1.2 to 4.1)[h]		.004
Length of hospital stay, median (IQR), d[i]	22 (16-30)	20 (13-36)	−0.4 (−5.1 to 4.3)[h]		.27
Adverse events					
Deep vein thrombosis	21 (11.4)	20 (10.9)	0.5 (−6.0 to 6.9)	1.04 (0.59-1.86)	.88
Inferior vena cava thrombus	7 (3.8)	14 (7.7)	−3.9 (−8.6 to 0.9)	0.50 (0.21-1.20)	.11

Abbreviations: CABG, coronary artery bypass graft surgery; CPR, cardiopulmonary resuscitation; LVEF, left ventricular ejection fraction; TIMI, thrombolysis in myocardial infarction.

[a] Data are expressed as No. (%) of patients unless otherwise specified. Secondary outcomes were recorded during the initial hospitalization unless otherwise specified.

[b] The Disability Rating Scale (DRS) score ranges from 0 to 29, with 29 being the worst outcome (vegetative state).

[c] Excluding β-blockers.

[d] TIMI non-CABG major bleeding was defined as any intracranial bleeding or clinically overt signs of hemorrhage associated with a decrease in hemoglobin of ≥5 g/dL (or, when hemoglobin was not available, an absolute decrease in hematocrit of ≥15%). Non-CABG bleeding indicates that bleeding did not take place in the context of CABG.

[e] Data missing for 3 patients; unknown if discharged directly to home from hospital.

[f] The normal range for creatinine kinase is 30-250 IU/L.

[g] Data missing for 157 patients.

[h] Expressed as difference in means (95% CI).

[i] Excludes rehabilitation and palliative centers.

Post Hoc Outcomes

Withdrawal of life-sustaining therapy occurred for 61 patients (33.2%) in the 31 °C group and for 65 patients (35.5%) in the 34 °C group (eTable 6 in Supplement 2). The main reason for withdrawal of life-sustaining therapy was neurologic futility. The median time to withdrawal of life-sustaining therapy was 5 days in the 2 groups (*P* = .78).

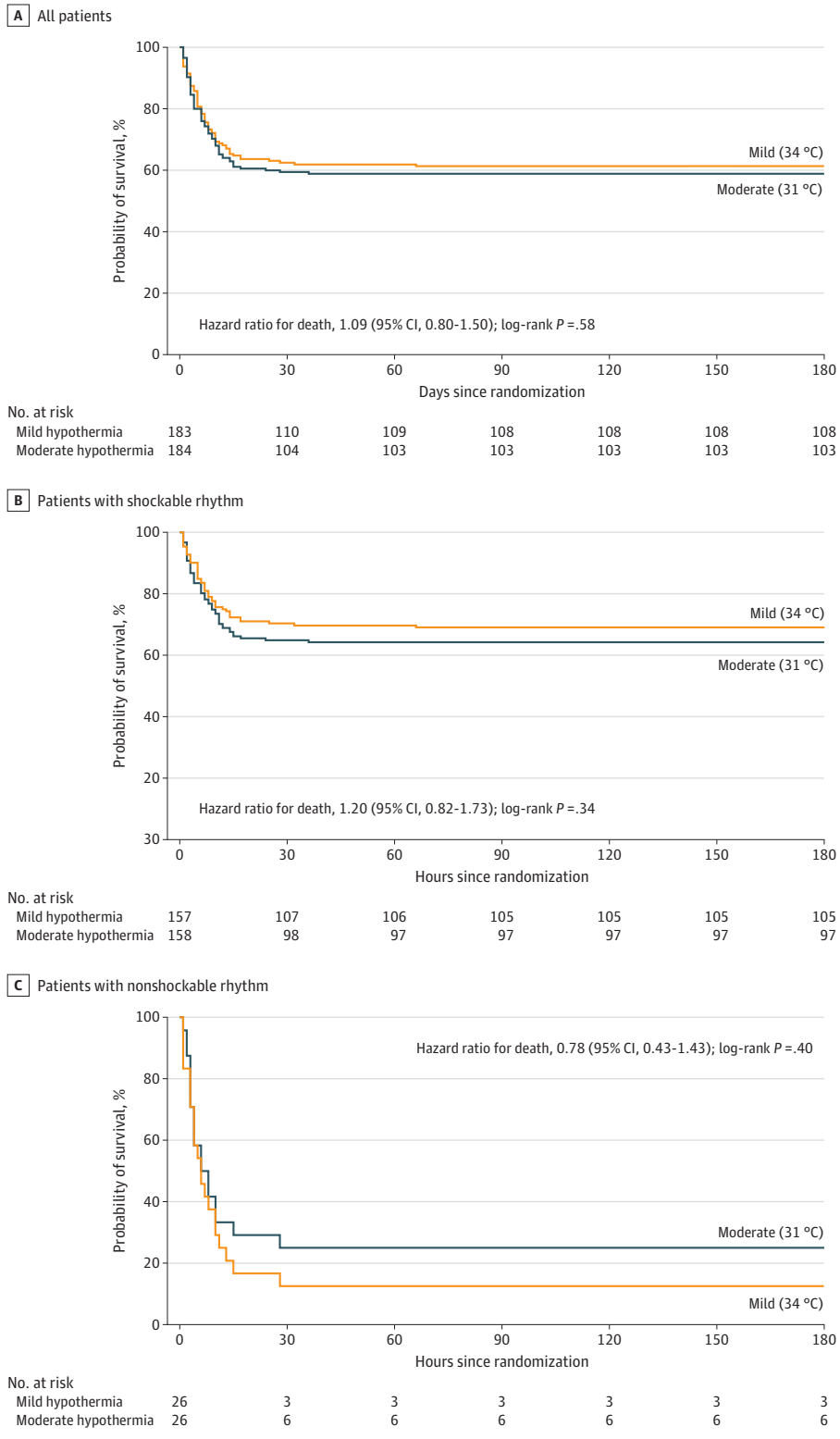
Adverse Events

Deep vein thrombosis occurred in 21 of 184 patients (11.4%) randomized to the 31 °C group and in 20 of 183 patients (10.9%) randomized to the 34 °C group (risk difference, 0.5% [95% CI, −6.0% to 6.9%]; RR, 1.04 [95% CI, 0.59-1.86]; *P* = .88). Thrombus in the inferior vena cava was documented by abdominal ultrasound in 7 of 184 patients (3.8%) randomized to the 31 °C group and in 14 of 183 patients (7.7%) randomized to the 34 °C group (risk difference, −3.9% [95% CI, −8.6% to 0.9%]; RR, 0.50 [95% CI, 0.21-1.20]; *P* = .11).

Secondary Analysis

As shown in eTable 7 and eTable 8 in Supplement 2, there were no differences in the results when the primary outcome was analyzed for the population that included all patients who were randomized to a study therapy group, regardless of whether or not they received the therapy (risk difference, 2.4% [95% CI, −7.8% to 12.6%]; RR, 1.05 [95% CI, 0.85-1.30]; *P* = .64), and for the population that included all patients who received the intended study therapy without a major protocol violation or loss to follow-up (risk difference, 4.4% [95% CI, −6.2% to 14.7%]; RR, 1.10 [95% CI, 0.88-1.37]; *P* = .42).

Figure 3. Probability of Survival at 180 Days for All Patients, Patients Presenting With a Shockable Rhythm, and Patients Presenting Without a Shockable Rhythm



Kaplan-Meier curves estimating the probability of survival at 180 days for patients randomized to moderate hypothermia (target temperature of 31 °C) or mild hypothermia (target temperature of 34 °C). The follow-up time for all patients was 180 days. Initial rhythms were classified as shockable (ventricular fibrillation or pulseless ventricular tachycardia) or nonshockable (asystole or pulseless electrical activity) on the basis of the first documented rhythm at the time of the cardiac arrest.

Discussion

In this randomized clinical trial conducted in comatose survivors of out-of-hospital cardiac arrest admitted to a tertiary cardiac center, moderate therapeutic hypothermia targeting a body temperature of 31 °C, compared with mild therapeutic hypothermia targeting a body temperature of 34 °C, did not show a significant difference in the rate of all-cause mortality or poor neurologic outcome at 180 days. This result was consistent across subgroups. The rates of secondary outcomes were similar between the 2 groups, except that there was a longer length of stay in the intensive care unit in the 31 °C group compared with the 34 °C group.

There are limited data to assess the effect of moderate therapeutic hypothermia in comatose survivors of out-of-hospital cardiac arrest. In a study by Lopez-de-Sa et al,[11] 36 patients with a witnessed out-of-hospital cardiac arrest were randomly assigned to target temperature management with either 32 °C or 34 °C. Among those with an initial shockable rhythm, significantly more patients were alive and free of severe dependence at 6 months in the group randomized to 32 °C compared with those randomized to 34 °C (61.5% vs 15.4%). Subsequently, the Finding the Optimal Cooling Temperature After Out-of-Hospital Cardiac Arrest I (FROST-I) trial[18] randomly assigned 150 comatose survivors of a witnessed cardiac arrest with initial shockable rhythm in a 1:1:1 ratio to target temperature management with either 32 °C, 33 °C, or 34 °C. This relatively small trial, which may have been underpowered, did not find a difference in neurologic outcomes at 90 days between the different temperature targets.

The results of the current trial do not support the use of moderate therapeutic hypothermia to improve neurologic outcomes in comatose survivors of out-of-hospital cardiac arrest. Furthermore, the longer length of stay in the cardiac intensive care unit in the 31 °C group compared with the 34 °C group would likely add to overall costs.

To our knowledge, this study is the first randomized clinical trial to evaluate the benefits of therapeutic hypothermia with a target temperature below 32 °C. An endovascular cooling device was used in all patients, which allowed rapid cooling, rigorous maintenance of target temperatures, and controlled active rewarming. This trial evaluated the treatment effect of moderate therapeutic hypothermia in comatose survivors of out-of-hospital cardiac arrest and should be interpreted alongside the TTM trial[5] (33 °C vs 36 °C), the FROST-I trial[18] (32 °C vs 33 °C vs 34 °C), and the Time-Differentiated Therapeutic Hypothermia (TTH48) trial[19] (24 hours vs 48 hours of target temperature at 33 °C), all of which have reported neutral results.

One important consideration is that there may not be a single, optimal target temperature for all patients with cardiac arrest, as the treatment effect of therapeutic hypothermia could be modulated by several clinical variables.[20-22] Many experts advocate a move toward a personalized approach to targeted temperature management following cardiac arrest guided by patient and index event characteristics, risk factor profile, biological markers, and response to early therapies.[23] Although this trial was not designed to address this question, significant differences in subgroups analyses were not found.

There has been much controversy as to the value of hypothermia. The Targeted Hypothermia vs Targeted Normothermia After Out-of-Hospital Cardiac Arrest (TTM2) trial[24] has recently reported that targeted hypothermia at 33 °C did not improve survival at 180 days compared with targeted normothermia at 37.5 °C or less. The current study adds to the spectrum of target temperature management, as it did not find any benefit of even further lowering temperatures to 31 °C.

Targeted hypothermia was the first neuroprotective intervention thought to improve outcomes in comatose survivors of out-of-hospital cardiac arrest. The uncertainty that has surrounded the optimal target temperature has stimulated 2 decades of research and has led to improvement in multiple facets of post-cardiac arrest care. It remains unknown whether avoidance of fever is protective.

Limitations

This study has several limitations. First, the majority of patients in this study had cardiac arrest secondary to a primary cardiac etiology. As a result, the findings may not be applicable to cardiac arrest of all etiologies. Second, the trial was conducted in a single center. However, the trial protocol was highly standardized and the trial was conducted in a highly specialized cardiac arrest center. Third, the sample size was based on a 15% absolute risk reduction, and there may be a concern that the study was underpowered. Fourth, the number of patients presenting with a nonshockable rhythm was relatively small, and further research may be needed for this subgroup.

Conclusions

In comatose survivors of out-of-hospital cardiac arrest, a target temperature of 31 °C did not significantly reduce the rate of death or poor neurologic outcome at 180 days compared with a target temperature of 34 °C. However, the study may have been underpowered to detect a clinically important difference.

ARTICLE INFORMATION

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Author Contributions: The principal investigator, Dr Le May, had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Le May, Glover, Hibbert, Labinaz, Marshall, Maze, Wells.
Acquisition, analysis, or interpretation of data: Le May, Osborne, Russo, So, Chong, Dick, Froeschl, Glover, Hibbert, Marquis, De Roock, Labinaz, Bernick, Marshall.
Drafting of the manuscript: Le May, Russo, So, Maze.
Critical revision of the manuscript for important intellectual content: Le May, Osborne, Russo, So, Chong, Dick, Froeschl, Glover, Hibbert, Marquis, De Roock, Labinaz, Bernick, Marshall, Wells.
Statistical analysis: Russo, Hibbert, Bernick, Wells.
Obtained funding: Le May.
Administrative, technical, or material support: Le May, Osborne, Dick, Glover, Hibbert, Labinaz, Marshall.
Supervision: Le May, Chong, Froeschl, Marquis, Labinaz.

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Data Sharing Statement: See Supplement 3.

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