# Monroe Livingston Region Program Agency

*Division of Prehospital Medicine, University of Rochester*
Mailing Address: 601 Elmwood Avenue, Box 655, Rochester, NY 14642
Physical Address: 120 Corporate Woods, Suite 100, Rochester, NY 14623
Phone: (585) 463-2900 Fax: (585) 463-2966 E-Mail: mlrems@urmc.rochester.edu


To: All ALS Providers and Agencies

From: Jeremy T. Cushman, MD, MS, EMT-P
Regional Medical Director

Date: December 2, 2013

Re: Advisory 13-12: Return of Spontaneous Circulation and Therapeutic Hypothermia

---

The use of therapeutic hypothermia in adult patients with return of spontaneous circulation was authorized a little more than three years ago based on preliminary evidence that there was an association with an improvement in neurologic outcome. Recently, two large, randomized, methodologically sound studies were published that suggest that the initiation of prehospital therapeutic hypothermia does not improve survival or neurologic status among patients with Return of Spontaneously Circulation (ROSC). Further, there may be some harm in that there was more frequent re-arrest in the patients that received Therapeutic Hypothermia. These two studies, published in the New England Journal of Medicine and the Journal of the American Medical Association, along with an accompanying JAMA editorial, are attached.

***As a result of this recent evidence, myself, the REMAC, and our local cardiology colleagues believe that it is no longer appropriate to initiate prehospital therapeutic hypothermia as there is no evidence of benefit, and potential harm in doing so.***

Attached to this Advisory is an updated Adult Return of Spontaneous Circulation Protocol reflecting this change. The Pediatric ROSC Protocol remains unchanged. **This protocol replaces the previous one of the same title and is effective immediately. Agencies are expected to remove any equipment used to provide therapeutic hypothermia immediately and notify all ALS providers of this change.**

The practice of medicine is evolving, and as we continue to find ways to optimize the care of our patients, we are sure to witness more changes in our expected standards of care.

# 3.2 RETURN OF SPONTANEOUS CIRCULATION

**CRITERIA**

- The following is for a patient with Return of Spontaneous Circulation (ROSC) as evidenced by a palpable pulse following CPR, electrical, or drug therapy for a patient previously pulseless.

1. Routine medical care.

2. Following ROSC, the patient should be reassessed and a complete neurologic exam, including GCS and pupillary response.

**EMT STOP**

3. Determine blood glucose and perform 12-lead EKG.

4. Maintain MAP > 65 mmHg


Dopamine 5-10 mcg/kg/min IV/IO titrated to maintain MAP >65 mmHg using a rate-limiting device. Use Y-site secondary tubing running into free-flowing normal saline primary tubing.

5. Transport to a STEMI center facility capable of performing Percutaneous Coronary Intervention regardless of the presence of STEMI Criteria on EKG. If recurrent cardiac arrest during transport, transport to closest Emergency Department.

ORIGINAL ARTICLE

# Targeted Temperature Management at 33°C versus 36°C after Cardiac Arrest

Niklas Nielsen, M.D., Ph.D., Jørn Wetterslev, M.D., Ph.D., Tobias Cronberg, M.D., Ph.D., David Erlinge, M.D., Ph.D., Yvan Gasche, M.D., Christian Hassager, M.D., D.M.Sci., Janneke Horn, M.D., Ph.D., Jan Hovdenes, M.D., Ph.D., Jesper Kjaergaard, M.D., D.M.Sci., Michael Kuiper, M.D., Ph.D., Tommaso Pellis, M.D., Pascal Stammet, M.D., Michael Wanscher, M.D., Ph.D., Matt P. Wise, M.D., D.Phil., Anders Åneman, M.D., Ph.D., Nawaf Al-Subaie, M.D., Søren Boesgaard, M.D., D.M.Sci., John Bro-Jeppesen, M.D., Iole Brunetti, M.D., Jan Frederik Bugge, M.D., Ph.D., Christopher D. Hingston, M.D., Nicole P. Juffermans, M.D., Ph.D., Matty Koopmans, R.N., M.Sc., Lars Køber, M.D., D.M.Sci., Jørund Langørgen, M.D., Gisela Lilja, O.T., Jacob Eifer Møller, M.D., D.M.Sci., Malin Rundgren, M.D., Ph.D., Christian Rylander, M.D., Ph.D., Ondrej Smid, M.D., Christophe Werer, M.D., Per Winkel, M.D., D.M.Sci., and Hans Friberg, M.D., Ph.D., for the TTM Trial Investigators*

## ABSTRACT

### BACKGROUND

Unconscious survivors of out-of-hospital cardiac arrest have a high risk of death or poor neurologic function. Therapeutic hypothermia is recommended by international guidelines, but the supporting evidence is limited, and the target temperature associated with the best outcome is unknown. Our objective was to compare two target temperatures, both intended to prevent fever.

### METHODS

In an international trial, we randomly assigned 950 unconscious adults after out-of-hospital cardiac arrest of presumed cardiac cause to targeted temperature management at either 33°C or 36°C. The primary outcome was all-cause mortality through the end of the trial. Secondary outcomes included a composite of poor neurologic function or death at 180 days, as evaluated with the Cerebral Performance Category (CPC) scale and the modified Rankin scale.

### RESULTS

In total, 939 patients were included in the primary analysis. At the end of the trial, 50% of the patients in the 33°C group (235 of 473 patients) had died, as compared with 48% of the patients in the 36°C group (225 of 466 patients) (hazard ratio with a temperature of 33°C, 1.06; 95% confidence interval [CI], 0.89 to 1.28; P=0.51). At the 180-day follow-up, 54% of the patients in the 33°C group had died or had poor neurologic function according to the CPC, as compared with 52% of patients in the 36°C group (risk ratio, 1.02; 95% CI, 0.88 to 1.16; P=0.78). In the analysis using the modified Rankin scale, the comparable rate was 52% in both groups (risk ratio, 1.01; 95% CI, 0.89 to 1.14; P=0.87). The results of analyses adjusted for known prognostic factors were similar.

### CONCLUSIONS

In unconscious survivors of out-of-hospital cardiac arrest of presumed cardiac cause, hypothermia at a targeted temperature of 33°C did not confer a benefit as compared with a targeted temperature of 36°C. (Funded by the Swedish Heart–Lung Foundation and others; TTM ClinicalTrials.gov number, NCT01020916.)

The authors' affiliations are listed in the Appendix. Address reprint requests to Dr. Nielsen at the Department of Anesthesia and Intensive Care, Intensive Care Unit, Helsingborg Hospital, S Vallgatan 5, 251 87, Helsingborg, Sweden, or at niklas.nielsen@med.lu.se.

*A complete list of investigators participating in the Target Temperature Management 33°C versus 36°C after Out-of-Hospital Cardiac Arrest (TTM) trial is provided listed in the Supplementary Appendix, available at NEJM.org.

This article was published on November 17, 2013, at NEJM.org.

N Engl J Med 2013.
DOI: 10.1056/NEJMoa1310519

Unconscious patients admitted to critical care units after out-of-hospital cardiac arrest are at high risk for death, and neurologic deficits are common among those who survive.[1] Two previous trials, involving patients who remained unconscious after resuscitation from cardiac arrest (of presumed cardiac cause, with an initial shockable rhythm), compared therapeutic hypothermia (32°C to 34°C for 12 to 24 hours) with standard treatment. These trials showed a significant improvement in neurologic function[2,3] and survival[3] with therapeutic hypothermia.

Therapeutic hypothermia (also called targeted temperature management) is now recommended in international resuscitation guidelines, and its use has been extended to cardiac arrest of other causes and with other presenting rhythms as well as to the in-hospital setting.[4] Although a Cochrane review supports these guidelines,[5] some investigators have suggested a need for additional trials to confirm or refute the current treatment strategy.[6-8] Furthermore, one trial showed that fever developed in many patients in the standard-treatment group.[3] It is therefore unclear whether the reported treatment effect was due to hypothermia or to the prevention of fever, which is associated with a poor outcome.[9-11] We conducted a trial to investigate the benefits and harms of two targeted temperature regimens, both intended to prevent fever, in a broader population of patients with cardiac arrest than previously studied.

## Methods

### Trial Design

The Target Temperature Management 33°C versus 36°C after Out-of-Hospital Cardiac Arrest (TTM) trial was a randomized clinical trial recruiting patients in 36 intensive care units (ICUs) in Europe and Australia. The rationale for and design of the trial, as well as the statistical analysis plan, have been published previously.[12,13] The protocol (available with the full text of this article at NEJM.org) was approved by the ethics committees in each participating country and institution. An independent data and safety monitoring committee reviewed the data and performed one prespecified, blinded interim analysis. The steering group (see the Supplementary Appendix, available at NEJM.org) vouches for the accuracy and completeness of the data and analysis and for the adherence of this report to the trial protocol.

### Patients

We consecutively screened patients 18 years of age or older who were unconscious (a score of <8 on the Glasgow Coma Scale [on which scores range from 3 to 15, with lower scores indicating reduced levels of consciousness]) on admission to the hospital after out-of-hospital cardiac arrest of presumed cardiac cause, irrespective of the initial rhythm. Eligible patients had more than 20 consecutive minutes of spontaneous circulation after resuscitation.[14] The main exclusion criteria were an interval from the return of spontaneous circulation to screening of more than 240 minutes, unwitnessed arrest with asystole as the initial rhythm, suspected or known acute intracranial hemorrhage or stroke, and a body temperature of less than 30°C. A full list of exclusion criteria is provided in the Supplementary Appendix. In accordance with national requirements and the principles of the Declaration of Helsinki, written informed consent was waived, delayed, or obtained from a legal surrogate, depending on the circumstances, and was obtained from each patient who regained mental capacity.[15]

### Randomization and Trial Intervention

After being screened for eligibility, patients were randomly assigned in a 1:1 ratio to targeted temperature management with a target body temperature of either 33°C or 36°C. Randomization was performed centrally with the use of a computer-generated assignment sequence. Intervention assignments were made in permuted blocks of varying size and were stratified according to site.

Health care professionals caring for the trial patients were aware of the intervention assignments because of inherent problems with blinding of body temperature. Physicians performing neurologic prognostication, assessors of neurologic follow-up and final outcome, study administrators, statisticians, and the authors were unaware of the intervention assignments. During the analysis phase, the intervention groups were identified only as 0 and 1, and the manuscript was written and approved by all the authors before the randomization code was broken.[16]

The intervention period of 36 hours commenced at the time of randomization. Sedation was mandated in both groups until the end of the intervention period. The goal was to achieve the assigned temperature as rapidly as possible with the use of ice-cold fluids, ice packs, and intravascular or surface temperature-management

devices at the discretion of the sites. Details of the trial interventions, including the management of an initial body temperature below the assigned target, are provided in the Supplementary Appendix.

After 28 hours, gradual rewarming to 37°C in hourly increments of 0.5°C was commenced in both groups. At 36 hours, mandatory sedation was discontinued or tapered. After the intervention period, the intention was to maintain the body temperature for unconscious patients below 37.5°C until 72 hours after the cardiac arrest, with the use of fever-control measures at the discretion of the sites.

### NEUROLOGIC PROGNOSTICATION AND WITHDRAWAL OF LIFE-SUSTAINING THERAPIES

A physician who was unaware of the intervention assignments performed a neurologic evaluation 72 hours after the end of the intervention for patients who remained unconscious and issued a recommendation for the continuation or withdrawal of therapy. The trial protocol established prespecified criteria for withdrawal of life-sustaining therapy[12] (see the Supplementary Appendix). All clinical decisions remained at the discretion of the treating team.

### FOLLOW-UP AND OUTCOMES

All surviving patients were followed until 180 days after the enrollment of the last patient. The primary outcome was all-cause mortality through the end of the trial. The main secondary outcome was a composite of poor neurologic function or death, defined as a Cerebral Performance Category[17,18] (CPC) of 3 to 5 and a score of 4 to 6 on the modified Rankin scale,[19,20] at or around 180 days. The CPC scale ranges from 1 to 5, with 1 representing good cerebral performance or minor disability, 2 moderate disability, 3 severe disability, 4 coma or vegetative state, and 5 brain death. Scores on the modified Rankin scale range from 0 to 6, with 0 representing no symptoms, 1 no clinically significant disability, 2 slight disability, 3 moderate disability, 4 moderately severe disability, 5 severe disability, and 6 death. Mortality at 180 days and individual neurologic scores were also analyzed separately. Other secondary outcomes were the CPC at discharge from the ICU and from the hospital and the best (numerically lowest) reported CPC during the trial period. Predefined serious adverse events[21] were recorded up to day 7 in the ICU. Data collection and verification for all trial data and for the outcome measures are described in the Supplementary Appendix.

### STATISTICAL ANALYSIS

We estimated that a sample of 900 patients would provide 90% power to detect a 20% reduction in the hazard ratio for death in the 33°C group as compared with the 36°C group, at a two-sided alpha level of 0.05. Alternatively, to detect a relative risk reduction of 20%, with the assumption of a mortality of 44% in the 33°C group versus 55% in the 36°C group, a sample of 850 patients would be needed. On the basis of these assumptions, a sample of 950 patients was chosen, to allow for a loss to follow-up of 50 patients.

The principal trial analyses were performed in the modified intention-to-treat population, defined as all randomly assigned patients except those withdrawing consent for use of all trial data and those not fulfilling inclusion criteria and never receiving the intervention.[22] Additional analyses were performed in the intention-to-treat population, which included all randomly assigned patients except those withdrawing consent, and in the per-protocol population, which excluded patients with one or more major protocol violations (listed in the Supplementary Appendix).

The Wilcoxon signed-rank test was used to compare distributions of continuous outcome measures. Kaplan–Meier survival curves were compared between the intervention groups with the use of the log-rank test. Relative risks were compared with the use of Cochran–Mantel–Haenszel statistics. Trends were assessed with the use of the Cochran–Armitage test. Logistic-regression and Cox analyses were performed as appropriate, with adjustment for site and for five baseline variables: age, sex, presence or absence of shockable rhythm, presence or absence of circulatory shock on admission, and the time from cardiac arrest (or from the emergency call for unwitnessed cardiac arrests) to the return of spontaneous circulation. Odds ratios were converted to relative risks.[23] All primary analyses were adjusted for site.[24] Temperature data were analyzed with the use of a mixed model with repeated measures. The effect of time was modeled with the use of a polynomial; the use of compound symmetry and first-order autoregressive covariance structures was compared, and the better-fitting model was used. SAS software, version 9.3, and SPSS software, version 17.1, were used for all analyses. All tests were two-sided

**Table 1. Characteristics of the Modified Intention-to-Treat Population before Randomization.***

| Characteristic | 33°C Group (N=473) | 36°C Group (N=466) |
|---|---|---|
| **Demographic characteristics** | | |
| Age — yr | 64±12 | 64±13 |
| Male sex — no. (%) | 393 (83) | 368 (79) |
| **Medical history — no. (%)** | | |
| Chronic heart failure | 32 (7) | 29 (6) |
| Previous AMI | 107 (23) | 86 (18) |
| Ischemic heart disease | 145 (31) | 115 (25) |
| Previous cardiac arrhythmia | 87 (18) | 79 (17) |
| Arterial hypertension | 193 (41) | 181 (39) |
| Previous TIA or stroke | 35 (7) | 38 (8) |
| Diabetes mellitus | 61 (13) | 80 (17) |
| Asthma or COPD | 48 (10) | 49 (11) |
| Previous percutaneous coronary intervention | 58 (12) | 50 (11) |
| Previous coronary-artery bypass grafting | 47 (10) | 42 (9) |
| **Characteristics of the cardiac arrest** | | |
| Location of cardiac arrest — no. (%)† | | |
| Place of residence | 245 (52) | 255 (55) |
| Public place | 197 (42) | 188 (40) |
| Other | 31 (7) | 22 (5) |
| Bystander witnessed cardiac arrest — no. (%) | 420 (89) | 418 (90) |
| Bystander performed CPR — no. (%) | 344 (73) | 339 (73) |
| First monitored rhythm — no. (%)† | | |
| Shockable rhythm | 375 (79) | 377 (81) |
| Ventricular fibrillation | 349 (74) | 356 (77) |
| Nonperfusing ventricular tachycardia | 12 (3) | 12 (3) |
| Unknown rhythm but responsive to shock | 5 (1) | 5 (1) |
| Perfusing rhythm after bystander-initiated defibrillation | 9 (2) | 4 (1) |
| Asystole | 59 (12) | 54 (12) |
| Pulseless electrical activity | 37 (8) | 28 (6) |
| Unknown first rhythm, not responsive to shock or not shocked | 2 (<0.5) | 6 (1) |
| Time from cardiac arrest to event — min‡ | | |
| Start of basic life support | | |
| Median | 1 | 1 |
| Interquartile range | 0–2 | 0–2 |
| Start of advanced life support | | |
| Median | 10 | 9 |
| Interquartile range | 6–13 | 5–13 |
| Return of spontaneous circulation | | |
| Median | 25 | 25 |
| Interquartile range | 18–40 | 16–40 |

**Table 1. (Continued.)**

| Characteristic | 33°C Group (N=473) | 36°C Group (N=466) |
|---|---|---|
| **Clinical characteristics on admission** | | |
| First measured body temperature — °C | 35.2±1.3 | 35.3±1.1 |
| Glasgow Coma Scale score§ | | |
| Median | 3 | 3 |
| Interquartile range | 3–4 | 3–4 |
| Corneal reflex present — no./total no. (%) | 264/407 (65) | 258/392 (66) |
| Pupillary reflex present — no./total no. (%) | 344/460 (75) | 363/458 (79) |
| Serum pH | 7.2±0.2 | 7.2±0.2 |
| Serum lactate — mmol/liter | 6.7±4.5 | 6.7±4.5 |
| Circulatory shock — no. (%)¶ | 70 (15) | 67 (14) |
| ST-segment elevation myocardial infarction — no. (%) | 190 (40) | 194 (42) |

* Plus–minus values are means ±SD. P>0.05 for all comparisons. AMI denotes acute myocardial infarction, COPD chronic obstructive pulmonary disease, CPR cardiopulmonary resuscitation, and TIA transient ischemic attack.
† In the 36°C group, data for location of cardiac arrest and first monitored rhythm were missing for one patient.
‡ For unwitnessed arrests, intervals were calculated from the time of the emergency call.
§ Scores on the Glasgow Coma Scale range from 3 to 15, with lower scores indicating reduced levels of consciousness. The distribution of Glasgow Coma Scale motor scores is provided in Table S1 in the Supplementary Appendix.
¶ Circulatory shock was defined as a systolic blood pressure of less than 90 mm Hg for more than 30 minutes or end-organ hypoperfusion (cool extremities, a urine output of <30 ml per hour, and a heart rate of <60 beats per minute).

and adjusted for multiple comparisons. A P value of 0.05 or less was considered to indicate statistical significance.

## RESULTS

### PATIENTS

A total of 950 patients were enrolled between November 2010 and January 2013; of these patients, 476 were randomly assigned to the 33°C group and 474 to the 36°C group. The modified intention-to-treat population (the primary-analysis population) consisted of 473 patients assigned to 33°C and 466 assigned to 36°C (Fig. S1 in the Supplementary Appendix). The two groups had similar prerandomization characteristics (Table 1). Glasgow Coma Scale scores on admission, cardiovascular Sequential Organ Failure Assessment scores, and details of diagnostic procedures, interventions, and the use of health services are provided in Tables S1, S2, and S3, respectively, in the Supplementary Appendix.

### TEMPERATURE INTERVENTION

The mean values of the initial recorded body temperature (tympanic) were 35.2°C and 35.3°C in the 33°C and 36°C groups, respectively. Temperature was managed with an intravascular cooling catheter in 24% of patients and with a surface cooling system in 76% of patients in both groups. The temperature curves are depicted in Figure 1 (P<0.001 for separation of the curves). Three patients in the 33°C group and four in the 36°C group did not receive the assigned intervention (Table S4 in the Supplementary Appendix). Sixteen patients assigned to the 33°C group were rewarmed before reaching the intended time point of 28 hours after randomization, at the discretion of the treating physician and as allowed by the protocol (Table S5 in the Supplementary Appendix). Additional information regarding shivering and fever is available in the Supplementary Appendix.

### WITHDRAWAL OF LIFE-SUSTAINING THERAPY

During the first 7 days of hospitalization, life-sustaining therapy was withdrawn in 247 patients (132 in the 33°C group and 115 in the 36°C group). Reasons for withdrawal of life-sustaining therapy included brain death, multiorgan failure, and ethical concerns (Table S7 in the Supplementary Appendix). A protocol-defined approach to neu-

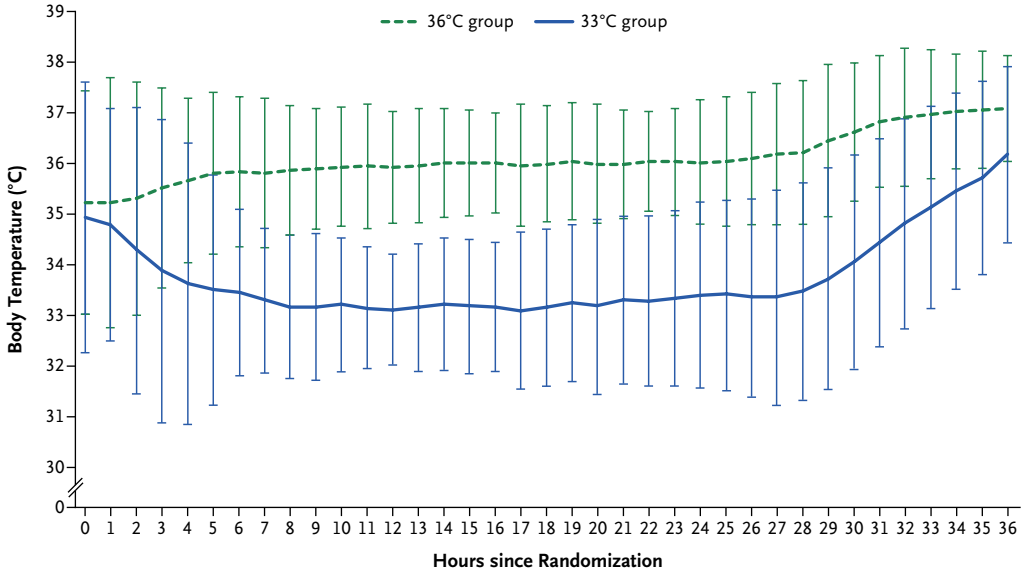



**Figure 1. Body Temperature during the Intervention Period.**

Shown are body-temperature curves in the 33°C and 36°C groups for the 860 patients in whom a bladder temperature was recorded. In the remaining 79 patients, the temperature was recorded with an intravascular or esophageal probe, with a similar temperature profile (data not shown). Rewarming was commenced at 28 hours after randomization. The temperature curves display the means, and the I bars indicate ±2 SD (95% of the observations are within the error bars).

**Table 2. Outcomes.**

| Outcome | 33°C Group | 36°C Group | Hazard Ratio or Risk Ratio (95% CI)* | P Value |
|---|---|---|---|---|
| | *no./total no. (%)* | | | |
| Primary outcome: deaths at end of trial | 235/473 (50) | 225/466 (48) | 1.06 (0.89–1.28) | 0.51 |
| Secondary outcomes | | | | |
| Neurologic function at follow-up† | | | | |
| CPC of 3–5 | 251/469 (54) | 242/464 (52) | 1.02 (0.88–1.16) | 0.78 |
| Modified Rankin scale score of 4–6 | 245/469 (52) | 239/464 (52) | 1.01 (0.89–1.14) | 0.87 |
| Deaths at 180 days | 226/473 (48) | 220/466 (47) | 1.01 (0.87–1.15) | 0.92 |

* The hazard ratio is shown for the primary outcome, and risk ratios are shown for the secondary outcomes. CI denotes confidence interval.

† The neurologic follow-up was specified in the protocol to be performed at 180 days ±2 weeks, but the time to follow-up was in some cases several weeks longer for logistic reasons. The Cerebral Performance Category (CPC) scale ranges from 1 to 5, with 1 representing good cerebral performance or minor disability, 2 moderate cerebral disability (function is sufficient for independent activities of daily life), 3 severe cerebral disability, 4 coma or vegetative state, and 5 brain death. Scores on the modified Rankin scale range from 0 to 6, with 0 representing no symptoms, 1 no clinically significant disability despite some symptoms, 2 slight disability (patient is able to look after own affairs without assistance), 3 moderate disability (patient requires some help but is able to walk unassisted), 4 moderately severe disability (patient is unable to attend to own bodily needs), 5 severe disability (patient is bedridden), and 6 death.

rologic prognostication was used to make recommendations regarding the continuation or withdrawal of life-sustaining therapy (Table S8 in the Supplementary Appendix).

### FOLLOW-UP AND OUTCOMES

Follow-up was obtained by means of a face-to-face interview with the patient (for 86% of patients), a structured telephone interview with the patient (6%), a telephone call to the patient or a relative (5%), or a telephone call to a proxy provider of information (i.e., a staff member of a nursing home or a general practitioner) (3%). The last follow-up assessment was performed on July 9, 2013. The mean period of follow-up for all patients was 256 days.

At the end of the trial, 235 of 473 patients in the 33°C group (50%) and 225 of 466 patients in the 36°C group (48%) had died (hazard ratio in the 33°C group, 1.06; 95% confidence interval [CI], 0.89 to 1.28; P=0.51) (Table 2 and Fig. 2). The groups did not differ significantly with respect to the composite outcome of death or poor neurologic function at 180 days with the use of either the CPC or the modified Rankin scale score (risk ratio for a CPC of 3 to 5 in the 33°C group, 1.02; 95% CI, 0.88 to 1.16; P=0.78; and risk ratio for a score of 4 to 6 on the modified Rankin scale in the 33°C group, 1.01; 95% CI, 0.89 to 1.14; P=0.87) (Table 2). The neurologic scores on both scales are shown in Table 3 and in Table S9 in the Supplementary Appendix. There were no significant differences in the distribution of CPCs or modified Rankin scale scores between the two groups (P=0.85 and P=0.67 for trend, respectively). With the use of the best reported CPC during the trial (Table 3), the relative risk of death or poor neurologic function in the 33°C group was 1.04 (95% CI, 0.89 to 1.17; P=0.67).

Similar results were obtained in adjusted analyses and in the intention-to-treat and per-protocol populations (see the Supplementary Appendix, including Tables S10 and S11). The effect of the intervention was consistent across predefined subgroups (Fig. S2 in the Supplementary Appendix).

One or more serious adverse events occurred in 439 of 472 patients in the 33°C group (93%) as compared with 417 of 464 patients in the 36°C group (90%) (risk ratio, 1.03; 95% CI, 1.00 to 1.08; P=0.09). Hypokalemia was more frequent in the 33°C group (19%, vs. 13% in the 36°C group, P=0.02). For the full list of serious adverse events, see Table S12 in the Supplementary Appendix. The presumed causes of death as assessed by the trial investigators were similar in the two groups (Table S13 in the Supplementary Appendix).

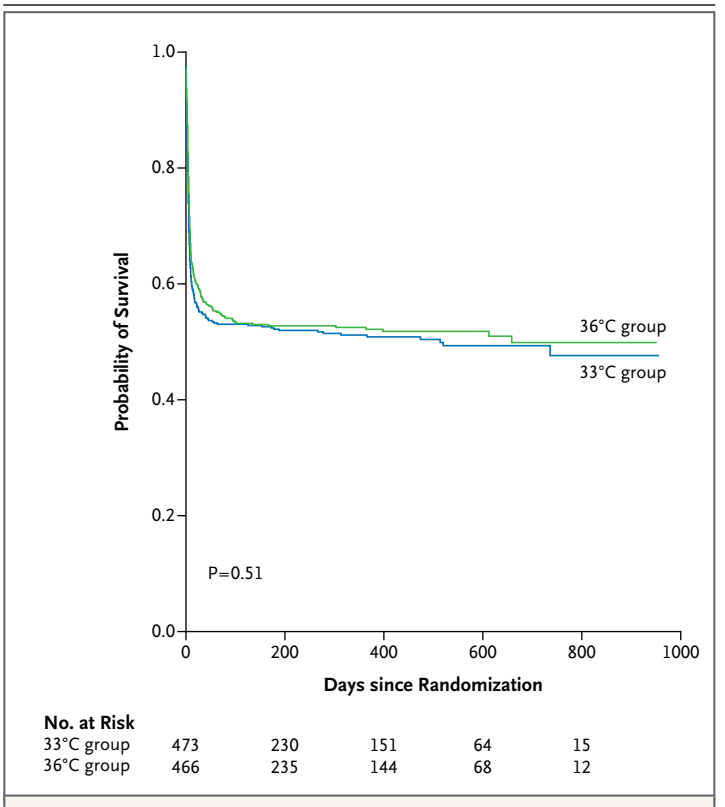



**Figure 2. Probability of Survival through the End of the Trial.**

Shown are Kaplan–Meier estimates of the probability of survival for patients assigned to a target temperature of either 33°C or 36°C and the number of patients at risk at each time point. The P value was calculated by means of Cox regression, with the effect of the intervention adjusted for the stratification variable of study site.

## DISCUSSION

In this international, multicenter, randomized trial, we compared a target body temperature of 33°C with one of 36°C in patients who had been resuscitated after out-of-hospital cardiac arrest of presumed cardiac cause. There were no significant differences between the two groups in overall mortality at the end of the trial or in the composite of poor neurologic function or death at 180 days. The results were consistent in six predefined subgroups. We did not find any harm with a targeted temperature of 33°C as compared

**Table 3. Neurologic Scores.***

| Variable | 33°C Group | 36°C Group |
|---|---|---|
| **CPC at follow-up†** | | |
| Total no. of patients | 469 | 464 |
| Category — no. (%) | | |
| 1 | 195 (42) | 183 (39) |
| 2 | 23 (5) | 39 (8) |
| 3 | 17 (4) | 20 (4) |
| 4 | 6 (1) | 2 (0.5) |
| 5 | 228 (49) | 220 (47) |
| P value for trend | 0.85 | |
| **Best, or lowest numerical, CPC during trial** | | |
| Total no. of patients | 472 | 466 |
| Category — no. (%) | | |
| 1 | 209 (44) | 205 (44) |
| 2 | 25 (5) | 41 (9) |
| 3 | 37 (8) | 37 (8) |
| 4 | 201 (43) | 183 (39) |
| 5 | NA | NA |
| P value for trend | 0.89 | |
| **Modified Rankin scale score at follow-up†** | | |
| Total no. of patients | 469 | 464 |
| Score — no. (%) | | |
| 0 | 88 (19) | 89 (19) |
| 1 | 69 (15) | 83 (18) |
| 2 | 50 (11) | 34 (7) |
| 3 | 17 (4) | 19 (4) |
| 4 | 8 (2) | 11 (2) |
| 5 | 9 (2) | 8 (2) |
| 6 | 228 (49) | 220 (47) |
| P value for trend | 0.67 | |

* P values for trend were calculated with the use of the Cochran–Armitage test. NA denotes not applicable.
† The neurologic follow-up was specified in the protocol to be at 180±14 days, but the time to follow-up was in some cases several weeks longer for logistic reasons.

with 36°C. However, it is worth recognizing that for all outcomes, none of the point estimates were in the direction of a benefit for the 33°C group. On the basis of these results, decisions about which temperature to target after out-of-hospital cardiac arrest require careful consideration.

After publication of the seminal trials of therapeutic hypothermia after cardiac arrest,[2,3] this approach was recommended in international guidelines,[4] despite arguments by some investigators that the evidence was weak, owing to the risk of bias and small samples.[6,25] The subsequent debate has focused on two issues. The first issue is whether therapeutic hypothermia should be extended to patients outside the originally described populations.[26-28] It may be reasoned that the potential benefits of temperature management on brain injury due to circulatory arrest would be the same irrespective of the cause of arrest. However, whole-body hypothermia influences all organ systems, and any potential benefit should be balanced against possible side effects.[29] The population of patients with cardiac arrest is heterogeneous, and the potential risks and benefits of temperature intervention may not be the same across subgroups. The second issue is the most beneficial target temperature for therapeutic hypothermia.[30] The recommended temperature of 32° to 34°C has been extrapolated from experiments in animals[31,32]; however, similar results have been observed with milder cooling.[33]

A difference between our trial and earlier trials[2,3] is that we did not allow the natural trajectory of temperature evolution in either group; we actively controlled the temperature during the intervention period and aimed to prevent fever during the first 3 days after cardiac arrest. We enrolled patients with out-of-hospital arrests of presumed cardiac cause, in line with enrollment in earlier trials, but our sample was larger and we had fewer exclusion criteria, with approximately 20% of participants having nonshockable rhythms. Other published studies involving patients with cardiac arrest who were admitted to the ICU have shown baseline characteristics and mortality that are in keeping with our findings, supporting the generalizability of our results.[34-38]

Our trial had several limitations. First, ICU staff members were aware of the assigned target temperature during the stay in the ICU. We aimed to minimize this problem by using robust outcomes and blinded outcome assessment. We also applied rigorous guidelines for neurologic prognostication and end-of-life decisions. Second, in one country, ethical approval required written consent from a legal surrogate before randomization, resulting in exclusion of a substantial proportion of eligible patients. Third, we do not have detailed data on the dose and type of sedation or the use of neuromuscular blocking agents. However, the sites were instructed to

treat the groups similarly, and surrogate markers (e.g., the presence of shivering and the number of days that sedation affected neurologic evaluation) did not differ between groups.

The mortality in both groups in our trial may be lower than that in the control group of the Hypothermia after Cardiac Arrest trial.[3] These two trials are not easily comparable with respect to study populations. Furthermore, prehospital and critical care management have changed during the past decade.[36,39] Nevertheless, it is important to acknowledge that there may be a clinically relevant benefit of controlling the body temperature at 36°C, instead of allowing fever to develop in patients who have been resuscitated after cardiac arrest.[9]

In conclusion, our trial does not provide evidence that targeting a body temperature of 33°C confers any benefit for unconscious patients admitted to the hospital after out-of-hospital cardiac arrest, as compared with targeting a body temperature of 36°C.

Supported by independent research grants from the Swedish Heart–Lung Foundation, Arbetsmarknadens Försäkringsaktiebolag Insurance Foundation, Swedish Research Council, Region Skåne (Sweden), National Health Service (Sweden), Thelma Zoega Foundation, Krapperup Foundation, Thure Carlsson Foundation, Hans-Gabriel and Alice Trolle-Wachtmeister Foundation for Medical Research, Skåne University Hospital, TrygFonden (Denmark), and European Clinical Research Infrastructures Network.

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

## APPENDIX

The authors' affiliations are as follows: the Department of Anesthesiology and Intensive Care, Helsingborg Hospital, Helsingborg (N.N.), the Departments of Clinical Sciences (N.N., T.C., D.E., G.L., M.R., H.F.) and Cardiology (D.E.), Lund University, Lund, the Departments of Neurology (T.C), Anesthesiology and Intensive Care (M.R., H.F.), and Rehabilitation Medicine (G.L.), Skåne University Hospital, Lund, and the Department of Anesthesiology and Intensive Care, Sahlgrenska University Hospital, Gothenburg (C.R.) — all in Sweden; Copenhagen Trial Unit, Center of Clinical Intervention Research (J.W., P.W.), and the Departments of Cardiology (C.H., J.K., S.B., J.B.-J., L.K., J.E.M.) and Cardiothoracic Anesthesiology (M.W.), the Heart Center, Copenhagen University Hospital Rigshospitalet — both in Copenhagen; the Department of Anesthesiology, Pharmacology, and Intensive Care, Geneva University Hospital, Geneva (Y.G.); the Department of Intensive Care, Academic Medical Center, Amsterdam (J. Horn, N.P.J., M. Kuiper); the Department of Anesthesiology, Oslo University Hospital, Rikshospitalet, Oslo (J. Hovdenes, J.F.B.); the Department of Intensive Care, Medical Center Leeuwarden, Leeuwarden, the Netherlands (M. Kuiper, M. Koopmans); Intensive Care Unit, Santa Maria degli Angeli, Pordenone (T.P.), and the Department of Intensive Care, Istituto di Ricovero e Cura a Carattere Scientifico San Martino, Istituto Scientifico Tumori, University of Genoa, Genoa (I.B.) — both in Italy; the Department of Anesthesiology and Intensive Care, Centre Hospitalier de Luxembourg, Luxembourg (P.S., C.W.); Adult Critical Care, University Hospital of Wales, Cardiff, United Kingdom (M.P.W., C.D.H.); the Department of Intensive Care, Liverpool Hospital, Sydney (A.Å.); the Department of Intensive Care, St. George's Hospital, London (N.A.-S.); the Department of Heart Diseases, Haukeland University Hospital, Bergen, Norway (J.L.); and 2nd Department of Internal Medicine, Cardiology and Angiology, General University Hospital in Prague, Prague, Czech Republic (O.S.).

## REFERENCES

1. Moulaert VR, Verbunt JA, van Heugten CM, Wade DT. Cognitive impairments in survivors of out-of-hospital cardiac arrest: a systematic review. Resuscitation 2009;80:297-305.
2. Bernard SA, Gray TW, Buist MD, et al. Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. N Engl J Med 2002;346:557-63.
3. The Hypothermia after Cardiac Arrest Study Group. Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. N Engl J Med 2002; 346:549-56. [Erratum, N Engl J Med 2002; 346:1756.]
4. Peberdy MA, Callaway CW, Neumar RW, et al. Post-cardiac arrest care: 2010 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. Circulation 2010; 122:Suppl 3:S768-S786. [Errata, Circulation 2011;123(6):e237, 124(15):e403.]
5. Arrich J, Holzer M, Havel C, Müllner M, Herkner H. Hypothermia for neuroprotection in adults after cardiopulmonary resuscitation. Cochrane Database Syst Rev 2012;9:CD004128.
6. Nielsen N, Friberg H, Gluud C, Herlitz J, Wetterslev J. Hypothermia after cardiac arrest should be further evaluated — a systematic review of randomised trials with meta-analysis and trial sequential analysis. Int J Cardiol 2010.
7. Fisher GC. Hypothermia after cardiac arrest: feasible but is it therapeutic? Anaesthesia 2008;63:885-6.
8. Moran JL, Solomon PJ. Therapeutic hypothermia after cardiac arrest — once again. Crit Care Resusc 2006;8:151-4.
9. Zeiner A, Holzer M, Sterz F, et al. Hyperthermia after cardiac arrest is associated with an unfavorable neurologic outcome. Arch Intern Med 2001;161:2007-12.
10. Bro-Jeppesen J, Hassager C, Wanscher M, et al. Post-hypothermia fever is associated with increased mortality after out-of-hospital cardiac arrest. Resuscitation 2013 August 2 (Epub ahead of print).
11. Leary M, Grossestreuer AV, Iannacone S, et al. Pyrexia and neurologic outcomes after therapeutic hypothermia for cardiac arrest. Resuscitation 2013;84:1056-61.
12. Nielsen N, Wetterslev J, al-Subaie N, et al. Target temperature management after out-of-hospital cardiac arrest — a randomized, parallel-group, assessor-blinded clinical trial — rationale and design. Am Heart J 2012;163:541-8.
13. Nielsen N, Winkel P, Cronberg T, et al. Detailed statistical analysis plan for the target temperature management after out-of-hospital cardiac arrest trial. Trials 2013;14:300.
14. Jacobs I, Nadkarni V, Bahr J, et al. Cardiac arrest and cardiopulmonary resuscitation outcome reports: update and simplification of the Utstein templates for resuscitation registries: a statement for healthcare professionals from a task force of the International Liaison Committee on Resuscitation (American Heart Association, European Resuscitation Council, Australian Resuscitation Council, New Zealand Resuscitation Council, Heart and Stroke Foundation of Canada, InterAmerican Heart Foundation, Resuscitation Councils of Southern Africa). Circulation 2004; 110:3385-97.
15. World Medical Association. WMA Declaration of Helsinki — ethical principles for medical research involving hu-

man subjects. 59th WMA General Assembly. October 2008 (http://www.wma.net/en/30publications/10policies/b3/).
**16.** Gøtzsche PC. Blinding during data analysis and writing of manuscripts. Control Clin Trials 1996;17:285-93.
**17.** Jennett B, Bond M. Assessment of outcome after severe brain damage. Lancet 1975;1:480-4.
**18.** Brain Resuscitation Clinical Trial I Study Group. Randomized clinical study of thiopental loading in comatose survivors of cardiac arrest. N Engl J Med 1986;314:397-403.
**19.** Rankin J. Cerebral vascular accidents in patients over the age of 60. II. Prognosis. Scott Med J 1957;2:200-15.
**20.** van Swieten JC, Koudstaal PJ, Visser MC, Schouten HJ, van Gijn J. Interobserver agreement for the assessment of handicap in stroke patients. Stroke 1988;19:604-7.
**21.** ICH harmonised tripartite guideline: statistical principles for clinical trials. Stat Med 1999;18:1905-42.
**22.** Fergusson D, Aaron SD, Guyatt G, Hébert P. Post-randomisation exclusions: the intention to treat principle and excluding patients from analysis. BMJ 2002;325:652-4.
**23.** Zhang J, Yu KF. What's the relative risk? A method of correcting the odds ratio in cohort studies of common outcomes. JAMA 1998;280:1690-1.
**24.** Kahan BC, Morris TP. Improper analysis of trials randomised using stratified blocks or minimisation. Stat Med 2012;31:328-40.
**25.** Gibson A, Andrews PJ. Therapeutic hypothermia, still "too cool to be true?" F1000Prime Rep 2013;5:26-9.
**26.** Dumas F, Rea TD. Long-term prognosis following resuscitation from out-of-hospital cardiac arrest: role of aetiology and presenting arrest rhythm. Resuscitation 2012;83:1001-5.
**27.** Nichol G, Huszti E, Kim F, et al. Does induction of hypothermia improve outcomes after in-hospital cardiac arrest? Resuscitation 2013;84:620-5.
**28.** Dumas F, Grimaldi D, Zuber B, et al. Is hypothermia after cardiac arrest effective in both shockable and nonshockable patients? Insights from a large registry. Circulation 2011;123:877-86.
**29.** Nielsen N, Sunde K, Hovdenes J, et al. Adverse events and their relation to mortality in out-of-hospital cardiac arrest patients treated with therapeutic hypothermia. Crit Care Med 2011;39:57-64.
**30.** Holzer M. Targeted temperature management for comatose survivors of cardiac arrest. N Engl J Med 2010;363:1256-64.
**31.** Colbourne F, Corbett D. Delayed and prolonged post-ischemic hypothermia is neuroprotective in the gerbil. Brain Res 1994;654:265-72.
**32.** Sterz F, Safar P, Tisherman S, Radovsky A, Kuboyama K, Oku K. Mild hypothermic cardiopulmonary resuscitation improves outcome after prolonged cardiac arrest in dogs. Crit Care Med 1991;19:379-89.
**33.** Logue ES, McMichael MJ, Callaway CW. Comparison of the effects of hypothermia at 33 degrees C or 35 degrees C after cardiac arrest in rats. Acad Emerg Med 2007;14:293-300.
**34.** Gräsner JT, Meybohm P, Caliebe A, et al. Postresuscitation care with mild therapeutic hypothermia and coronary intervention after out-of-hospital cardiopulmonary resuscitation: a prospective registry analysis. Crit Care 2011;15:R61.
**35.** Mooney MR, Unger BT, Boland LL, et al. Therapeutic hypothermia after out-of-hospital cardiac arrest: evaluation of a regional system to increase access to cooling. Circulation 2011;124:206-14.
**36.** Tømte O, Andersen GO, Jacobsen D, Drægni T, Auestad B, Sunde K. Strong and weak aspects of an established post-resuscitation treatment protocol — a five-year observational study. Resuscitation 2011;82:1186-93.
**37.** Nielsen N, Hovdenes J, Nilsson F, et al. Outcome, timing and adverse events in therapeutic hypothermia after out-of-hospital cardiac arrest. Acta Anaesthesiol Scand 2009;53:926-34.
**38.** Lindner TW, Langorgen J, Sunde K, et al. Factors predicting the use of therapeutic hypothermia and survival in unconscious out-of-hospital cardiac arrest patients admitted to the ICU. Crit Care 2013;17:R147.
**39.** Adielsson A, Hollenberg J, Karlsson T, et al. Increase in survival and bystander CPR in out-of-hospital shockable arrhythmia: bystander CPR and female gender are predictors of improved outcome: experiences from Sweden in an 18-year perspective. Heart 2011;97:1391-6.

Original Investigation

# Effect of Prehospital Induction of Mild Hypothermia on Survival and Neurological Status Among Adults With Cardiac Arrest
## A Randomized Clinical Trial

Francis Kim, MD; Graham Nichol, MD, MPH; Charles Maynard, PhD; Al Hallstrom, PhD; Peter J. Kudenchuk, MD; Thomas Rea, MD, MPH; Michael K. Copass, MD; David Carlbom, MD; Steven Deem, MD; W. T. Longstreth Jr, MD; Michele Olsufka, RN; Leonard A. Cobb, MD

**IMPORTANCE** Hospital cooling improves outcome after cardiac arrest, but prehospital cooling immediately after return of spontaneous circulation may result in better outcomes.

**OBJECTIVE** To determine whether prehospital cooling improves outcomes after resuscitation from cardiac arrest in patients with ventricular fibrillation (VF) and without VF.

**DESIGN, SETTING, AND PARTICIPANTS** A randomized clinical trial that assigned adults with prehospital cardiac arrest to standard care with or without prehospital cooling, accomplished by infusing up to 2 L of 4°C normal saline as soon as possible following return of spontaneous circulation. Adults in King County, Washington, with prehospital cardiac arrest and resuscitated by paramedics were eligible and 1359 patients (583 with VF and 776 without VF) were randomized between December 15, 2007, and December 7, 2012. Patient follow-up was completed by May 1, 2013. Nearly all of the patients resuscitated from VF and admitted to the hospital received hospital cooling regardless of their randomization.

**MAIN OUTCOMES AND MEASURES** The primary outcomes were survival to hospital discharge and neurological status at discharge.

**RESULTS** The intervention decreased mean core temperature by 1.20°C (95% CI, −1.33°C to −1.07°C) in patients with VF and by 1.30°C (95% CI, −1.40°C to −1.20°C) in patients without VF by hospital arrival and reduced the time to achieve a temperature of less than 34°C by about 1 hour compared with the control group. However, survival to hospital discharge was similar among the intervention and control groups among patients with VF (62.7% [95% CI, 57.0%-68.0%] vs 64.3% [95% CI, 58.6%-69.5%], respectively; *P* = .69) and among patients without VF (19.2% [95% CI, 15.6%-23.4%] vs 16.3% [95% CI, 12.9%-20.4%], respectively; *P* = .30). The intervention was also not associated with improved neurological status of full recovery or mild impairment at discharge for either patients with VF (57.5% [95% CI, 51.8%-63.1%] of cases had full recovery or mild impairment vs 61.9% [95% CI, 56.2%-67.2%] of controls; *P* = .69) or those without VF (14.4% [95% CI, 11.3%-18.2%] of cases vs 13.4% [95% CI,10.4%-17.2%] of controls; *P* = .30). Overall, the intervention group experienced rearrest in the field more than the control group (26% [95% CI, 22%-29%] vs 21% [95% CI, 18%-24%], respectively; *P* = .008), as well as increased diuretic use and pulmonary edema on first chest x-ray, which resolved within 24 hours after admission.

**CONCLUSION AND RELEVANCE** Although use of prehospital cooling reduced core temperature by hospital arrival and reduced the time to reach a temperature of 34°C, it did not improve survival or neurological status among patients resuscitated from prehospital VF or those without VF.

**TRIAL REGISTRATION** clinicaltrials.gov Identifier: NCT00391469

*JAMA*. doi:10.1001/jama.2013.282173
Published online November 17, 2013.

Editorial

Supplemental content at jama.com

**Author Affiliations:** Department of Medicine, School of Medicine, University of Washington, Seattle (Kim, Nichol, Kudenchuk, Rea, Carlbom, Olsufka, Cobb); Department of Health Services, School of Public Health, University of Washington, Seattle (Maynard); Department of Biostatistics, School of Public Health, University of Washington, Seattle (Hallstrom); Department of Neurology, School of Medicine, University of Washington, Seattle (Copass, Longstreth); Department of Anesthesiology, School of Medicine, University of Washington, Seattle (Deem); Department of Epidemiology, School of Public Health, University of Washington, Seattle (Longstreth).

**Corresponding Author:** Francis Kim, MD, Harborview Medical Center, 325 Ninth Ave, Seattle, WA 98104 (fkim@u.washington.edu).

Brain injury causes morbidity and mortality after resuscitation from cardiac arrest, and many patients never awaken.[1-4] Hypothermia is a promising treatment that can help brain recovery. In randomized trials of humans resuscitated from prehospital ventricular fibrillation (VF), mild hypothermia (32-34°C) for 12 to 24 hours improved neurological recovery and survival despite delays of 4 to 8 hours in achieving goal temperatures.[5,6] Hospital-based induction of hypothermia is now recommended for patients who remain comatose after resuscitation from VF.[7,8]

The optimal timing for induction of hypothermia is uncertain. In animal models of cardiac arrest, the benefit of hypothermia declines when it is started more than 15 minutes after reperfusion.[9] Bernard et al[10,11] hypothesized that early initiation of cooling in the field after return of spontaneous circulation (ROSC) would improve both survival and neurological outcome. Rapid cooling after resuscitation from cardiac arrest with an intravenous infusion of cold saline appears feasible and safe.[12] However, no benefit was observed among 234 patients resuscitated from prehospital VF and then randomized to early field cooling.[13]

The only randomized trial of prehospital hypothermia in patients resuscitated from cardiac arrest without VF (ie, first rhythm of asystole or pulseless electrical activity) lacked power to detect a difference in outcomes.[14] Therefore, we evaluated whether early prehospital cooling improved survival to hospital discharge and neurological outcome in patients with a presenting arrest rhythm of VF or without VF. We also examined whether prehospital cooling was associated with adverse effects in the prehospital and hospital phases of care.

## Methods

### Participants

The trial was conducted under waiver from informed consent during emergency research conditions in accordance with all applicable federal regulations, including investigational new drug provisions by the US Food and Drug Administration, approval by the institutional review board at the University of Washington and all the acute care hospitals in Seattle and King County, Washington, and oversight by an independent data and safety monitoring board. Study personnel contacted the patient's family as soon as feasible after enrollment to explain the study and seek written informed consent to review the medical records of each patient. Families of deceased patients were notified of their participation by mail.

### Study Setting and Population

This randomized trial assigned adults with prehospital cardiac arrest to standard care with or without prehospital cooling with an infusion of up to 2 L of 4°C normal saline as soon as possible following ROSC.

Seattle and King County, Washington, emergency medical services (EMS) serve a population of nearly 2 million residents and respond to more than 1100 nontraumatic cardiac arrests annually using a 2-tiered response. First-tier responders are trained in high-performance cardiopulmonary resuscitation and are equipped with automated external defibrillators. Second-tier responders are paramedics who provide advanced cardiac life support including defibrillation, intubation, and administration of resuscitation drugs.

Cardiac arrest was defined as being unconscious due to a sudden pulseless collapse and ROSC was defined as a return of a palpable pulse after cardiac arrest. The inclusion criteria included ROSC, tracheal intubation, intravenous access, successful placement of esophageal temperature probe, and unconsciousness. Exclusion criteria included traumatic cardiac arrest, age younger than 18 years, being awake, following commands, and having a temperature of less than 34°C. All causes of cardiac arrest were considered, including those presenting with VF and those without VF. Eligible patients were randomized to receive standard care alone (control) or standard care plus induction of mild hypothermia (intervention). Paramedics called an emergency department (ED) physician at Harborview Medical Center to verify eligibility and to learn treatment assignment. Randomization was stratified by first recorded rhythm (VF or without VF) and destination hospital and by using randomly permuted blocks of concealed size to ensure temporal equality of assignment in each stratum.

### Sample Size

We based the sample size calculations on the results of our pilot study[12] and planned separate analyses for patients with VF and those without VF. For patients with initial VF, we assumed a survival rate of 65% with the intervention and 50% with the control (standard care alone). With a 2-sided significance level of .05, a power of 90%, and 6 interim analyses with a conservative O'Brien-Fleming boundary, 483 patients with VF were needed to detect a 30% relative improvement in survival with cooling in the field. The sample size for patients without VF was determined by the expected recruitment of patients with VF and was estimated to be approximately 756. This provided a power of 90% to detect a worsening of survival from 20% to 10% with a $P$ value of .05 (1-sided test).

### Study Intervention

For patients randomized to the intervention group, paramedics gave up to 2 L of 4°C normal saline, 7 to 10 mg of pancuronium, and 1 to 2 mg of diazepam.[12] The saline was infused through a peripheral intravenous line, 18-gauge or larger, using a pressure bag inflated to 300 mm Hg, with a goal temperature of less than 34°C. If the patient had recurrent arrest during transport, standard resuscitation protocols were started, and the saline infusion was stopped until circulation again returned. The intervention and control groups were otherwise treated the same according to standard prehospital resuscitation protocols.

Paramedics transported patients to all acute care hospitals in King County, Washington, and provided information sheets describing the study to ED physicians and nurses. All participating hospitals in King County receiving patients resuscitated from VF and 1 hospital receiving patients without VF used cooling protocols involving surface and intravascular cooling devices for up to 24 hours. Serial temperatures (measured by esophageal or tympanic thermometers) and whether the patient received hospital cooling were abstracted from the hospital charts.

### Outcome Measures

The primary outcomes were survival and neurological status at hospital discharge. Paramedics, ED staff, inpatient physicians, and nursing staff at receiving hospitals were not blinded to treatment assignment; however, study personnel who abstracted the medical records for the primary outcome were unaware of study allocation.

Safety data were collected as follows. We collected initial blood pressure, heart rate, use of pressors, rearrest or recurrent VF from standard run reports that provide paramedic documentation of the resuscitation. From hospital records, we collected data on demographics; whether cooling was initiated or continued in the hospital; blood pressure, heart rate, and pulse oximetry data during the first 12 hours; first arterial blood gas; first chest film interpretations (we abstracted data when the interpreting radiologist mentioned pulmonary edema, pulmonary congestion, hilar abnormalities, cardiomegaly, pleural effusion); use of intravenous diuretics; and use of pressors (eg, dobutamine, dopamine, norepinephrine, epinephrine, phenylephrine). We also collected data on the number of days ventilated and performance of reintubation as indirect measures of adverse pulmonary effects from fluid administration. Any use of antibiotics during hospital stay was used as a surrogate for infection.

We determined the number of days to death without awakening and to awakening, which was defined as the patient following commands, having comprehensible speech, or both. Neurological status at time of discharge was assessed by reviewing daily progress records and nursing notes and was assigned as full recovery, mildly to moderately impaired, severely impaired, comatose, or dead.[15,16]

### Statistical Methods

Safety analyses were performed on the combined groups with VF and without VF. Efficacy analyses were performed separately for the groups with VF and without VF and were based on the intention-to-treat principle. We used SPSS version 19.0 (SPSS Inc) to perform the statistical analyses. Differences between the groups were analyzed with the *t* test for normal variables, the Wilcoxon rank sum test for nonnormal variables, and the $\chi^2$ statistic for categorical variables. Two-tailed tests were performed with an $\alpha$ level of .05. Continuous values were presented as mean ± 1 SD.

## Results

### Enrollment and Randomization

The study began on December 15, 2007, and the 1364th patient was enrolled on December 7, 2012. Patient follow-up was completed on May 1, 2013. During the enrollment period, participating paramedics attended to 5696 patients with cardiac arrest (**Figure 1**). Most patients (n = 3319; 58%) were ineligible because cardiopulmonary resuscitation was not successful. A total of 1013 eligible patients were not enrolled because 497 were simply missed (49%), 211 were deemed by the paramedics as being too unstable (21%), and 305 were due to other reasons (30%) (eg, equipment failure, hospital arrival prior to randomization, and inability to obtain randomization information). Of 2377 eligible patients, 1364 were enrolled (57%).

Five patients were withdrawn from the study and their data records were not used because they were incarcerated at the time of enrollment. Their unintentional enrollments were recorded and reported as protocol violations to the institutional review board. Thus, 1359 patients were included in the primary analysis. Eleven patients or their representatives did not consent for review of hospital medical records, and only their prehospital, ED, and discharge data were used in the primary analysis. Two patients were enrolled who did not meet all eligibility requirements; however, both were included in the primary analysis.

Baseline characteristics of the enrolled patients appear in **Table 1** and were not significantly different by VF status between the 2 treatment groups.

### Interventions

None of the patients randomized to standard care alone (291 with VF and 380 without VF) received prehospital cooling. Most but not all of the patients randomized to cooling (292 with VF and 396 without VF) received 4°C normal saline intravenously before hospital arrival. The intervention decreased mean core temperature by 1.20°C (95% CI, −1.33°C to −1.07°C) in patients with VF and by 1.30°C (95% CI, −1.40°C to −1.20°C) in patients without VF by hospital arrival and reduced the time to achieve a temperature of less than 34°C by about 1 hour compared with the control group. Twelve patients with VF (4%) and 27 patients without VF (7%) did not receive any fluid. Almost 50% of all patients (with VF or without VF) received 2 L of fluid (eTable 1 in Supplement). The reasons why the full 2 L were not administered included recurrent arrest, death in the field, and lack of time before hospital arrival to complete the infusion.

Temperatures at randomization did not differ between treatment groups for patients either with VF or without VF, but those at admission to the ED did differ significantly, as did the temperature differences between the time of randomization and hospital arrival (eTable 1 in Supplement). Among patients with VF, 26% (95% CI, 21%-31%) of the intervention group had a temperature of less than 34°C at the time of hospital arrival. Among patients without VF, 29% (95% CI, 25%-34%) of the intervention group had a temperature of less than 34°C.

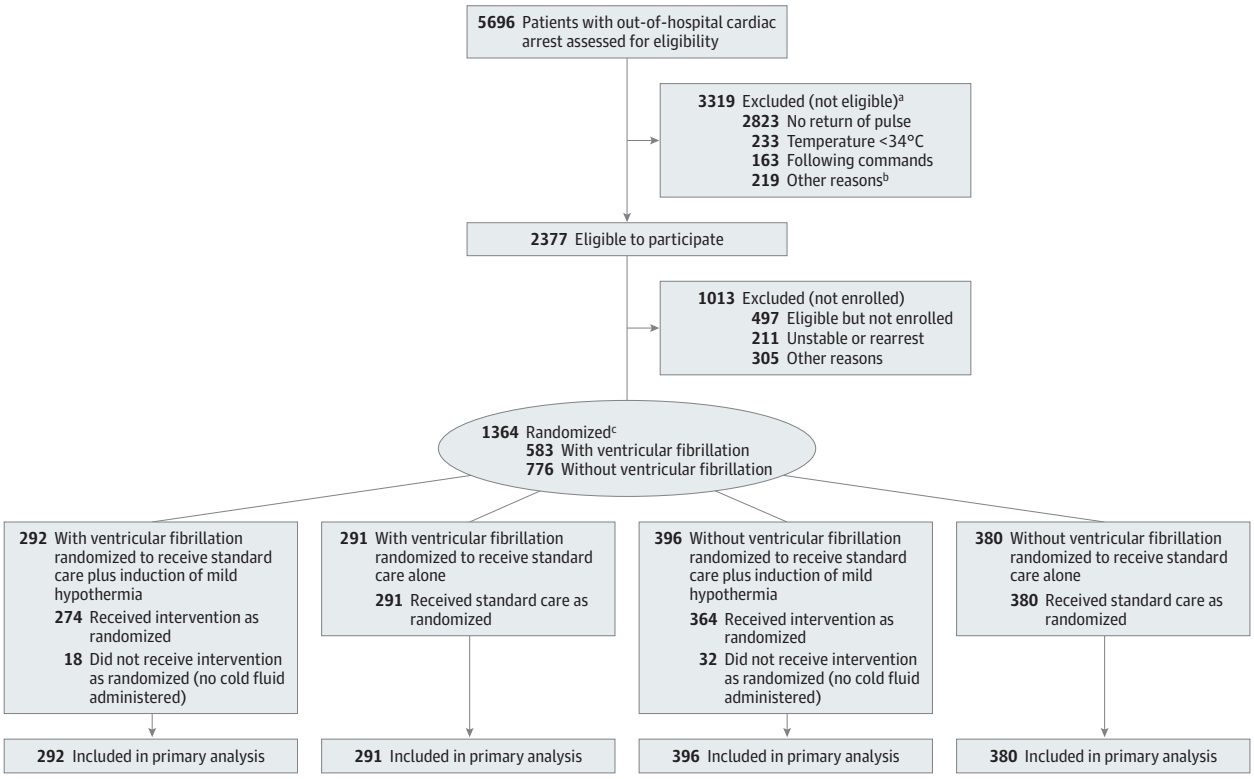
Of enrolled patients with VF who survived to hospital admission, 448 (77%) received hospital cooling with an equal number having field cooling (n = 224) or not (n = 224). The average time to reach a goal temperature was calculated for patients who reached a temperature of less than 34°C. Patients randomized to prehospital cooling and who also received hospital cooling achieved a goal temperature by a mean (SD) of 4.2 (3.0) hours (95% CI, 3.8-4.6 hours) compared with 5.5 (3.7) hours (95% CI, 5.0-6.0 hours) in patients who only received hospital cooling ($P < .001$; eTable 2 in Supplement), suggesting that out-of-hospital cooling reduced time to goal temperature by more than 1 hour. A similar effect was observed in patients without VF.

### Outcomes

Among patients with VF, 62.7% (95% CI, 57.0%-68.0%) of the intervention group and 64.3% (95% CI, 58.6%-69.5%) of the control group survived to discharge ($P = .69$). Among patients without VF, 19.2% (95% CI, 15.6%-23.4%) of the intervention group and 16.3% (95% CI, 12.9%-20.4%) of the control

group survived to discharge ($P$ = .30). Among both patients with VF and those without VF, significant differences in neurological status at time of discharge between the intervention and control groups were not evident (**Table 2**). The intervention was also not associated with improved neurological status of full recovery or mild impairment at discharge for either the group with VF (57.5% [95% CI, 51.8%-63.1%] of cases had full recovery or mild impairment vs 61.9% [95% CI, 56.2%-67.2%] of con-

Figure 1. Study Flow Diagram




No patients were lost to follow-up.

[a] Some patients were excluded for more than 1 reason.

[b] Included traumatic cardiac arrest, age younger than 18 years, no esophageal temperature, or no intravenous catheter.

[c] Of the 1364 patients enrolled, prehospital emergency medical services records and discharge data from only 1359 patients were used for the analyses of primary outcomes because 5 patients were later found to be incarcerated at the time of enrollment, thus data from these patients were not included in any of the analyses.

Table 1. Baseline Characteristics of Randomized Eligible Patients (n=1359)[a]

| | With Ventricular Fibrillation | | Without Ventricular Fibrillation | |
|---|---|---|---|---|
| | Intervention (n = 292) | Control (n = 291) | Intervention (n = 396) | Control (n = 380) |
| Age, y | 62.1 (14.2) | 62.1 (15.6) | 68.3 (16.3) | 67.5 (16.5) |
| Men, No. (%) | 227 (78) | 217 (75) | 216 (55) | 205 (54) |
| Witnessed cardiac arrest, No. (%) | 208 (71) | 215 (74) | 212 (54) | 196 (52) |
| CPR before EMS arrival, No. (%) | 199 (68) | 186 (64) | 196 (50) | 200 (53) |
| Time from call to randomization, min | (n = 288) 32.9 (10.6) | (n = 286) 32.5 (9.5) | (n = 389) 34.4 (10.6) | (n = 373) 35.2 (12.6) |
| Time from call to first responder arrival, min | (n = 290) 5.3 (2.0) | (n = 291) 5.2 (2.1) | (n = 395) 5.4 (2.1) | (n = 379) 5.2 (2.1) |
| Sustained ROSC, No. (%) | 273 (94) | 274 (94) | 354 (89) | 343 (90) |
| Time from call to sustained ROSC, min | (n = 142) 25 (14) | (n = 146) 24 (13) | (n = 178) 28 (14) | (n = 159) 27 (14) |
| Time to first shock, min[b] | (n = 175) 9.4 (3.3) | (n = 179) 9.2 (2.5) | NA | NA |
| Heart rate at randomization, beats/min | (n = 284) 109 (28) | (n = 285) 113 (28) | (n = 389) 110 (30) | (n = 370) 106 (31) |
| Systolic blood pressure at randomization, mm Hg | (n = 271) 140 (37) | (n = 275) 144 (39) | (n = 374) 130 (43) | (n = 354) 131 (41) |

Abbreviations: CPR, cardiopulmonary resuscitation; EMS, emergency medical services; NA, not applicable; ROSC, return of spontaneous circulation.

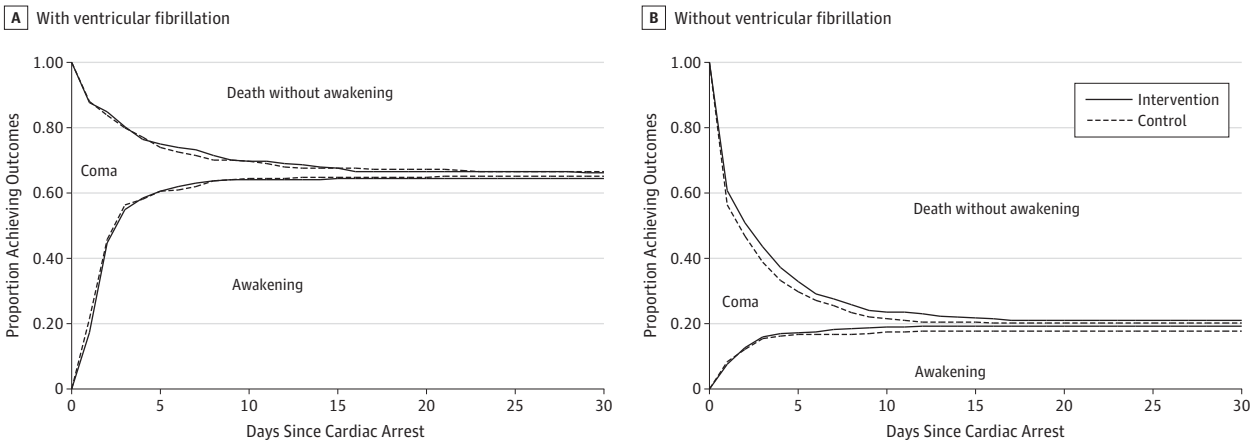
[a] Values are expressed as mean (SD) unless otherwise indicated.

[b] For cardiac arrest occurring before EMS arrival.

Table 2. Status at Time of Discharge

| | With Ventricular Fibrillation (n = 583) | | | Without Ventricular Fibrillation (n = 776) | | |
|---|---|---|---|---|---|---|
| | No. (%) [95% CI] | | | No. (%) [95% CI] | | |
| | Intervention (n = 292) | Control (n = 291) | *P* Value | Intervention (n = 396) | Control (n = 380) | *P* Value |
| Vital status | | | | | | |
| Dead | 109 (37.3) [32.0-43.0] | 104 (35.7) [30.5-41.4] | .69 | 320 (80.8) [76.6-84.4] | 318 (83.7) [79.6-87.1] | .30 |
| Alive | 183 (62.7) [57.0-68.0] | 187 (64.3) [58.6-69.5] | | 76 (19.2) [15.6-23.4] | 62 (16.3) [12.9-20.4] | |
| Neurological status at discharge | | | | | | |
| Full recovery | 125 (42.8) [37.3-48.5] | 145 (49.8) [40.7-52.1] | .59 | 36 (9.1) [6.6-12.3] | 34 (8.9) [6.5-12.2] | .74 |
| Mildly impaired | 43 (14.7) [11.1-19.2] | 35 (12.0) [8.8-16.3] | | 21 (5.3) [3.5-8.0] | 17 (4.5) [2.8-7.0] | |
| Severely impaired | 6 (2.1) [0.9-4.4] | 8 (2.7) [1.4-5.3] | | 5 (1.3) [0.5-2.9] | 2 (0.5) [0.1-1.9] | |
| Disabled (severity unknown) | 2 (0.7) [0.2-2.5] | 0 | | 0 | 0 | |
| Comatose | 4 (1.4) [0.5-3.5] | 7 (2.4) [1.2-4.9] | | 12 (3.0) [1.7-5.2] | 7 (1.8) [0.9-3.8] | |
| Alive (status unknown) | 3 (1.0) [0.4-3.0] | 2 (0.7) [0.2-2.5] | | 2 (0.5) [0.1-1.8] | 2 (0.5) [0.1-1.9] | |

Figure 2. The Proportion of Comatose Patients Achieving Either Death Without Awakening or Awakening as a Function of Days After Cardiac Arrest for Enrolled Patients




The area between the 2 curves represents the proportion of patients who remain comatose. All patients at time = 0 are comatose and over time either awaken or die without awakening. A, There were 568 patients with ventricular fibrillation (VF) and known event times (284 in intervention group and 284 in control group). For patients with initial rhythm of VF at 7 days, 157 patients died without awakening (28%), 355 had awakened (62%), and 56 were still comatose (10%). At 30 days, 34 more patients died without awakening, 14 more had awakened, and 8 patients remained comatose. B, There were 771 patients without VF but with known event times (395 in the intervention group and 376 in the control group). At 7 days, 566 patients died without awakening (73%), 138 had awakened (18%), and 67 were still comatose (9%). At 30 days, 46 more patients died without awakening, 8 more had awakened, and 13 patients remained comatose.

trols; $P = .69$) or without VF (14.4% [95% CI, 11.3%-18.2%] of cases vs 13.4% [95% CI,10.4%-17.2%] of controls).

Next we examined the effect of intervention groups on the proportion of patients who either awakened from a coma or died without awakening (**Figure 2**). For randomized patients with VF, the proportion of patients who awakened was higher than the proportion who died without awakening; however, significant differences between the intervention and control groups were absent (Figure 2A). Most randomized patients without VF died without awakening, but again significant differences between the intervention and control groups were lacking (Figure 2B). Median length of stay was similar for the intervention and control groups among those with VF (9.1 days [25th-75th percentiles, 6.4-15.2 days] and 9.4 days [25th-75th percentiles, 6.2-15.3 days], respectively, $P = .75$ by Wilcoxon rank sum test) and among those without VF (11.8 days [25th-75th percentiles, 8.4-16.6 days] and 10.5 days [25th-75th percentiles, 6.3-16.8 days], respectively, $P = .45$ by Wilcoxon rank sum test).

Post hoc analyses examined use of coronary angiography within 6 hours of hospital admission and any withdrawal or

Table 3. Prehospital, Emergency Department, and In-Hospital Safety Data

| | Intervention | Control | *P* Value |
|---|---|---|---|
| Rearrest postrandomization[a] | (n = 686)<br>176 (26) [22 to 29] | (n = 671)<br>138 (21) [18 to 24] | .008 |
| Use of pressors postrandomization[a] | (n = 686)<br>62 (9) [7 to 11] | (n = 671)<br>59 (9) [7 to 11] | .82 |
| Prehospital deaths[a] | (n = 688)<br>9 (1.3) [0.7 to 2.5] | (n = 671)<br>11 (1.6) [0.9 to 2.5] | .61 |
| Time from first dispatch to hospital arrival, min[b] | (n = 654)<br>51 (50 to 52) [13] | (n = 629)<br>49 (48 to 50) [14] | .006 |
| First heart rate on ED arrival, beats/min[b] | (n = 665)<br>89 (86 to 92) [39] | (n = 632)<br>93 (90 to 96) [40] | .07 |
| First systolic blood pressure on ED arrival, mm Hg[b] | (n = 666)<br>116 (112 to 120) [54] | (n = 637)<br>116 (112 to 120) [51] | .84 |
| Difference from randomization to ED arrival | | | |
| Heart rate, beats/min[b] | (n = 651)<br>−21 (−24 to −18) [40] | (n = 616)<br>−17 (−20 to −14) [40] | .09 |
| Systolic blood pressure, mm Hg[b] | (n = 624)<br>−18 (−22 to −14) [56] | (n = 647)<br>−20 (−24 to −16) [56] | .47 |
| Deaths in emergency department[a] | (n = 688)<br>88 (12.8) [10.5 to 15.5] | (n = 671)<br>85 (12.7) [10.4 to 15.4] | .95 |
| Use within first 12 h of arrival | | | |
| Pressors[a] | (n = 674)<br>374 (56) [52 to 59] | (n = 647)<br>365 (56) [53 to 60] | .93 |
| Diuretics[a] | (n = 674)<br>119 (18) [15 to 21] | (n = 648)<br>81 (13) [10 to 15] | .009 |
| Use of diuretics within 12-48 h of arrival[a] | (n = 667)<br>151 (23) [20 to 26] | (n = 640)<br>109 (17) [14 to 20] | .01 |
| First arterial blood gas | | | |
| pH[b] | (n = 612)<br>7.16 (7.14 to 7.18) [0.23] | (n = 590)<br>7.20 (7.18 to 7.22) [0.29] | .005 |
| $Pao_2$, mm Hg[b] | (n = 609)<br>189 (178 to 200) [135] | (n = 585)<br>218 (206 to 230) [144] | <.001 |
| $Paco_2$, mm Hg[b] | (n = 670)<br>59 (57 to 61) [28] | (n = 641)<br>58 (55 to 61) [34] | .36 |
| First $Sao_2$ on ED arrival, %[b] | (n = 601)<br>94 (93 to 95) [10] | (n = 573)<br>96 (95 to 97) [8] | .02 |
| Pulmonary edema | | | |
| First chest film[a] | (n = 631)<br>256 (41) [37 to 44] | (n = 609)<br>184 (30) [27 to 34] | <.001 |
| Second chest film[a] | (n = 498)<br>133 (27) [23 to 31] | (n = 464)<br>123 (27) [23 to 31] | .95 |
| Third chest film[a] | (n = 420)<br>104 (25) [21 to 29] | (n = 392)<br>81 (21) [17 to 25] | .23 |
| Antibiotic use[a] | (n = 673)<br>434 (64) [61 to 68] | (n = 649)<br>418 (64) [61 to 68] | .98 |
| Glucose >300 mg/dL[a] | (n = 674)<br>168 (25) [22 to 28] | (n = 648)<br>208 (32) [29 to 36] | .004 |

Abbreviations: ED, emergency department; $Sao_2$, oxygen saturation.

[a] Indicates values are expressed as No. (%) [95% CI].

[b] Indicates values are expressed as mean (95% CI) [SD].

change in the level of life support during hospitalization to assess whether randomization to prehospital cooling was associated with treatment decisions for admitted patients. Among patients admitted to the hospital, no significant differences between treatment groups were evident for early coronary angiography within 6 hours from hospital arrival (25% for the intervention groups vs 27% for the control groups) or reduction in level or withdrawal of life support (44% for both intervention and control groups).

## Safety

Prehospital deaths and deaths in the ED between the intervention and control groups did not differ significantly for patients with VF or those without VF (**Table 3**). The use of pressors by paramedics was similar (9% for both treatment groups); however, the proportion of patients who had a rearrest during transport (defined as loss of pulse) was 26% in the intervention group compared with 21% in the control group (*P* = .008). The intervention group had significantly lower oxygenation, increased pulmonary edema on first chest x-ray, and greater use of diuretics during the first 12 hours of hospitalization compared with the control group (Table 3). The incidence of pulmonary edema noted on subsequent chest x-rays during hospitalization, the number of days receiving ventilation, the incidence of reintubation, and the use of antibiotics (a surrogate marker for infection) were not significantly different between the treatment groups.

# Discussion

This large randomized trial found that prehospital, rapid infusion of up to 2 L of 4°C normal saline did induce mild hypo-

thermia faster than standard care but did not improve survival or neurological status at discharge after resuscitation from prehospital shockable (VF) or nonshockable (without VF) cardiac arrest. The resuscitation and intervention were performed by paramedics from EMS agencies with a high overall rate of resuscitation. The intervention reduced core body temperature by hospital arrival, and patients reached the goal temperature about 1 hour sooner than in the control group. The intervention was associated with significantly increased incidence of rearrest during transport, time in the prehospital setting, pulmonary edema, and early diuretic use in the ED. Mortality in the out-of-hospital setting or ED and hospital length of stay did not differ significantly between the treatment groups.

Current guidelines for postresuscitation care recommend application of induced hypothermia in the hospital to patients resuscitated from prehospital VF.[8] The optimal timing, duration, and method of cooling remain unclear but animal studies have provided a strong rationale for early induction of therapeutic hypothermia soon after ROSC.[9] Infusion of cold intravenous fluid is an attractive strategy to achieve early cooling because of its portability, ease in administration, and potential widespread availability in the prehospital setting.

During the enrollment period of the current trial, Bernard et al[13] published their results from a prehospital cooling study in patients resuscitated from VF. There were 234 patients with VF randomized to rapid cooling with 2 L of ice-cold lactated Ringer solution or to cooling after hospital admission and 47.5% of the paramedic-cooled group had a favorable outcome at hospital discharge vs 52.6% of the hospital-cooled group. Even though the paramedic-cooled group was colder at hospital arrival, differences in temperature between the intervention and control groups disappeared within 1 hour.

The results of the current randomized study, in conjunction with the prior randomized human investigation,[13] do not support the routine use of cold saline following ROSC among patients resuscitated from prehospital cardiac arrest. Why did prehospital hypothermia not improve outcomes in this study given prior promising results? Potential bias from incomplete blinding seems an unlikely explanation. Perhaps early cooling needs to be applied during resuscitation and not after ROSC to achieve the desired benefit.

Early cooling during resuscitation might attenuate the cascade of reperfusion injury that begins with ROSC.[17] This use of intra-arrest cooling is supported by animal studies, although a recent trial that used evaporative intranasal cooling during attempted resuscitation suggests that intra-arrest hypothermia was not associated with a large clinical effect.[18] Whether earlier cooling will improve survival and outcomes in humans awaits further study.

The dose or method of hypothermia may have been suboptimal. The study used a goal threshold temperature of 34°C rather than 33°C. A lower temperature goal may have afforded better clinical outcomes. Importantly, the method of prehospital hypothermia may have been associated with early harm that could have masked subsequent improvement.

There are some potential limitations of the current trial. First, patients randomized to the intervention were more likely to experience rearrest and pulmonary edema, although early deaths did not differ by treatment status. Rearrest possibly worsened brain ischemia that did not affect early mortality but manifested as increased risk of death later during the hospitalization.

Second, in an animal model of cardiac arrest, induction of hypothermia using intravenous volume loading was associated with significantly decreased coronary artery perfusion pressure compared with postresuscitation surface cooling methods.[19] In animal and human studies, decreased coronary artery perfusion pressure is associated with a decrease in survival. In addition, cold prehospital fluid administration was associated with significant reduction in first arterial blood gas pH and $Pao_2$ levels (Table 3), which are both predictors of poor outcomes. Thus, a potential benefit from prehospital cooling may have been mitigated by these associated adverse effects.

Third, we measured end points at the time of hospital discharge to help ensure comprehensive outcome ascertainment. Functional status can improve for at least 6 months after resuscitation from cardiac arrest,[20] but the current study could not detect such a late intervention effect. However, functional status at hospital discharge is a strong predictor of long-term survival.[21]

These potential limitations should be considered in the context of the trial's strengths. The investigation evaluated a generalizable, low-cost intervention for a condition that accounts for substantial public health mortality. The study was conducted in an EMS system with an established record of research and prehospital resuscitation, which are characteristics essential for successfully completion of such a trial. The investigation achieved robust randomization and had adequate power to detect clinically significant differences in survival or neurological status at discharge in patients resuscitated from VF. The effect of prehospital hypothermia in this trial was not likely to be modified or confounded by the quality of prehospital emergency care because the baseline outcomes achieved by EMS agencies that participated in this study were high.

In addition, the effect of out-of-hospital hypothermia was unlikely to be modified by the quality of hospital-based care because post hoc secondary analyses did not demonstrate a relationship between outcomes and early angiography or withdrawal of life support. Lastly, a high percentage of admitted patients received hospital cooling and achieved temperatures of less than 34°C, thereby minimizing the effects of hospital cooling on outcomes. Thus, we believe that our results have both internal and external validity.

## Conclusions

Early out-of-hospital cooling by rapid infusion with 4°C of normal saline reduced core temperature by more than 1°C and reduced the time to achieve the therapeutic temperature goal of 34°C by more than 1 hour. Nonetheless, early, rapid cooling did not improve survival or neurological status at discharge in patients with VF or without VF. Rapid fluid administration was associated with higher rates of rearrest during transport

and increased transient pulmonary edema, which resolved within the first 24 hours. Although hypothermia is a promising strategy to improve resuscitation and brain recovery following cardiac arrest, the results of the current study do not support routine use of cold intravenous fluid in the prehospital setting to improve clinical outcomes.

## ARTICLE INFORMATION

**Published Online:** November 17, 2013. doi:10.1001/jama.2013.282173.

**Author Contributions:** Drs Kim and Maynard had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
*Study concept and design:* Kim, Nichol, Hallstrom, Kudenchuk, Carlbom, Deem, Longstreth, Olsufka, Cobb.
*Acquisition of data:* Kim, Maynard, Hallstrom, Rea, Copass, Carlbom, Olsufka, Cobb.
*Analysis and interpretation of data:* Kim, Nichol, Maynard, Hallstrom, Kudenchuk, Rea, Olsufka, Cobb.
*Drafting of the manuscript:* Kim, Nichol.
*Critical revision of the manuscript for important intellectual content:* Kim, Nichol, Maynard, Hallstrom, Kudenchuk, Rea, Copass, Carlbom, Deem, Longstreth, Cobb.
*Statistical analysis:* Maynard, Hallstrom.
*Obtained funding:* Kim, Cobb.
*Administrative, technical, or material support:* Kim, Kudenchuk, Rea, Copass, Carlbom, Deem.
*Study supervision:* Kim, Copass, Cobb.

**Conflict of Interest Disclosures:** The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Nichol reported receiving institutional grant funding from the Asmund S. Laerdal Foundation for Acute Medicine, the National Heart, Lung, and Blood Institute, the National Institutes of Health, Medtronic Foundation, Velomedix Inc, Philips Healthcare Inc, Physio-Control Inc, HealthSine Technologies Inc, and Zoll Inc; serving on the board of Medic One Foundation; being part of a patent assigned to the University of Washington; and receiving travel reimbursement from the American Heart Association. Dr Hallstrom reported receiving grants, support for travel to meetings, fees for participating in review activities, payment for writing or reviewing a manuscript, and provision for writing assistance, medicines, equipment, or administrative support from the National Heart, Lung, and Blood Institute; and serving as a consultant to Amarin and St Jude Medical for data and safety monitoring board activity on several trials. Dr Rea reported receiving grant support for community-based resuscitation from Medtronic Foundation. Dr Deem reported receiving institutional grant funding from the National Institutes of Health and Medic One Foundation. No other author reported disclosures.

**Funding/Support:** This study was funded by grants RO1 HL089554 and 5U01HL07786 from the National Heart, Lung, and Blood Institute and with additional support from the Medic One Foundation (Seattle, Washington).

**Role of Sponsor:** The National Heart, Lung, and Blood Institute and the Medic One Foundation had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

**Data and Safety Monitoring Committee:** Kyra Becker, MD (chair); Margaret Neff, MD; Tina Chang, MD; Karl B. Kern, MD; Nancy Temkin, PhD; Ralph D'Agostino, PhD; Chief Earl Sodeman, Seattle Fire Department; Thomas Hearne; and Michele Plorde, King County Public Health, Emergency Medical Services Division.

**Medical Directors:** *Seattle Medic One:* Michael Copass, MD, Jonathan Larsen (medical services captain). *King County Medic One:* Mickey Eisenberg, MD. *Evergreen Medic One:* Adrian Whorton, MD. *Shoreline Medic One*: Gary Sommers, MD. *Bellevue Medic One*: James Boehl, MD. *Vashon Island Medic One:* Sam Warren, MD.

**Participant Applications:** Tony J. Gerbino, MD (Virginia Mason Medical Center); Mark Reisman, MD (Swedish Medical Center); Steve Marshall, MD (Overlake Medical Center); and Daniel Markowitz, MD (Steven's Hospital).

**Study Nurses:** Dianne K. Staloch, Karen Dong, Sue Scruggs, Alana C. Clark, Jane Edelson, Debi Solberg, Sally Ragsdale, Kathleen Fair, and Barbara Ricker.

**Review of Prehospital Records:** Roy Waugh, Dianne K. Staloch, and Karen Dong.

**Database Entry and Management:** Regina LaVassaur and Lihua Yin.

**Additional Contributions:** We thank the paramedics from Seattle Medic One, King County Medic One, Bellevue Medic One, Evergreen Medic One, Shoreline Medic One, and Vashon Island Medic One. We also thank the emergency department physicians and medical resident physicians rotating through the emergency department at Harborview Medical Center for providing randomization assignment to the paramedics.

## REFERENCES

1. Raichle ME. The pathophysiology of brain ischemia. *Ann Neurol*. 1983;13(1):2-10.

2. Rea TD, Eisenberg MS, Becker LJ, et al. Emergency medical services and mortality from heart disease: a community study. *Ann Emerg Med*. 2003;41(4):494-499.

3. Longstreth WT Jr. Brain resuscitation after cardiopulmonary arrest. *Acta Anaesthesiol Belg*. 1988;39(3)(suppl 2):115-119.

4. Longstreth WT Jr, Fahrenbruch CE, Olsufka M, et al. Randomized clinical trial of magnesium, diazepam, or both after out-of-hospital cardiac arrest. *Neurology*. 2002;59(4):506-514.

5. Hypothermia after Cardiac Arrest Study Group. Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. *N Engl J Med*. 2002;346(8):549-556.

6. Bernard SA, Gray TW, Buist MD, et al. Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. *N Engl J Med*. 2002;346(8):557-563.

7. Nolan JP, Morley PT, Vanden Hoek TL, et al; International Liaison Committee on Resuscitation. Therapeutic hypothermia after cardiac arrest. *Circulation*. 2003;108(1):118-121.

8. Peberdy MA, Callaway CW, Neumar RW, et al; American Heart Association. Part 9: post-cardiac arrest care: 2010 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation*. 2010;122(18)(suppl 3):S768-S786.

9. Kuboyama K, Safar P, Radovsky A, et al. Delay in cooling negates the beneficial effect of mild resuscitative cerebral hypothermia after cardiac arrest in dogs. *Crit Care Med*. 1993;21(9):1348-1358.

10. Bernard S. Hypothermia after cardiac arrest. *Crit Care Med*. 2004;32(3):897-899.

11. Bernard S, Buist M, Monteiro O, Smith K. Induced hypothermia using large volume, ice-cold intravenous fluid in comatose survivors of out-of-hospital cardiac arrest: a preliminary report. *Resuscitation*. 2003;56(1):9-13.

12. Kim F, Olsufka M, Longstreth WT Jr, et al. Pilot randomized clinical trial of prehospital induction of mild hypothermia in out-of-hospital cardiac arrest patients with a rapid infusion of 4 degrees C normal saline. *Circulation*. 2007;115(24):3064-3070.

13. Bernard SA, Smith K, Cameron P, et al; Rapid Infusion of Cold Hartmanns (RICH) Investigators. Induction of therapeutic hypothermia by paramedics after resuscitation from out-of-hospital ventricular fibrillation cardiac arrest: a randomized controlled trial. *Circulation*. 2010;122(7):737-742.

14. Bernard SA, Smith K, Cameron P, et al; Rapid Infusion of Cold Hartmanns Investigators. Induction of prehospital therapeutic hypothermia after resuscitation from nonventricular fibrillation cardiac arrest. *Crit Care Med*. 2012;40(3):747-753.

15. Brain Resuscitation Clinical Trial II Study Group. A randomized clinical trial of calcium entry blocker administration to comatose survivors of cardiac arrest: design, methods, and patient characteristics. *Control Clin Trials*. 1991;12(4):525-545.

16. Jennett B, Bond M. Assessment of outcome after severe brain damage. *Lancet*. 1975;1(7905):480-484.

17. Neumar RW, Nolan JP, Adrie C, et al. Post-cardiac arrest syndrome: epidemiology, pathophysiology, treatment, and prognostication. *Circulation*. 2008;118(23):2452-2483.

18. Castrén M, Nordberg P, Svensson L, et al. Intra-arrest transnasal evaporative cooling. *Circulation*. 2010;122(7):729-736.

19. Yannopoulos D, Zviman M, Castro V, et al. Intra-cardiopulmonary resuscitation hypothermia with and without volume loading in an ischemic model of cardiac arrest. *Circulation*. 2009;120(14):1426-1435.

20. Roine RO, Kajaste S, Kaste M. Neuropsychological sequelae of cardiac arrest. *JAMA*. 1993;269(2):237-242.

21. Phelps R, Dumas F, Maynard C, Silver J, Rea T. Cerebral performance category and long-term prognosis following out-of-hospital cardiac arrest. *Crit Care Med*. 2013;41(5):1252-1257.

EDITORIAL



# Randomized Clinical Trial Progress to Inform Care for Out-of-Hospital Cardiac Arrest

Christopher B. Granger, MD; Lance B. Becker, MD

**Approximately 300 000 patients** experience out-of-hospital cardiac arrest per year in the United States, and less than 10% survive to hospital discharge.[1] Regional heterogeneity in outcomes, with a 5-fold greater likelihood of survival following ventricular fibrillation arrest in Seattle, Washington, than in counties in Alabama, has underscored the opportunity to improve care.[1] National programs that define best practice around community, emergency medical services (EMS), and hospital strategies to improve care are being implemented[2,3] and promise to substantially improve survival. An important element of evidence-based care is therapeutic hypothermia.[4,5] In this issue of *JAMA*, Kim and colleagues[6] report findings from an ambitious and successful large randomized clinical trial that provides the first good new evidence in more than 10 years, and the first generated in the United States, regarding hypothermia following cardiac arrest.

Related article

The clinical evidence for the benefit of hypothermia has been primarily derived from 2 randomized trials published a decade ago with a total of 352 patients with out-of-hospital cardiac arrest who had ventricular fibrillation (VF) or pulseless ventricular tachycardia. In an Australian trial, 77 patients were randomized (according to day of the week) within 2 hours of return of spontaneous circulation (ROSC) to a group that received surface cooling or to a control group that included passive rewarming.[7] In the cooling group, a temperature of 33.5°C was achieved after 120 minutes of cooling, and cooling was continued for 12 hours. The second trial, from Austria, randomized 275 patients with VF to surface cooling to a target of 32°C to 34°C for core temperature vs normothermia.[8] Cooling began at a median time of 105 minutes and target temperature was achieved a median of 8 hours after ROSC and continued for 24 hours. In each trial, there was a 16% to 24% absolute improvement in favorable neurological outcome.

However, there are many unanswered questions regarding therapeutic hypothermia. Would more trials be helpful to be certain about the degree of benefit of hypothermia in VF arrest? Does cooling work for patients with arrest and asystole or pulseless electrical activity? Is there an optimal duration of treatment? What is the optimal target temperature? Is intravascular cooling as or more effective than surface cooling? Is there greater benefit in earlier initiation of cooling, earlier achievement of target temperature, or both? These questions have not been addressed in adequate randomized clinical trials, although extension or amplification of the benefits seen in the early trials might have major health consequences. In addition, randomized clinical trials of cardiac arrest, particularly in the out-of-hospital setting, are enormously challenging, because of the need both to follow procedures involving authorization for waiver of informed consent and to conduct trials in the underresourced and fragmented environment of EMS.

It is in this context that the trial by Kim and colleagues[6] is an important contribution. A total of 1359 patients, which is more than 3 times as many as in the prior trials[7,8] combined, with out-of-hospital cardiac arrest (583 with VF and 776 without VF) were randomly assigned to prehospital cooling with up to 2 L of 4°C saline or control. Mean core temperature decreased by more than 1°C by the time of hospital arrival with prehospital cooling. The interval required to reach target temperature decreased from 5.5 hours (hospital only cooling) to 4.2 hours (prehospital and hospital cooling) in the VF group and from 4.0 hours to 3.0 hours in the group without VF. Despite these differences in achieving earlier cooling, the primary outcome, survival to hospital discharge, was not improved with hypothermia initiated in the out-of-hospital setting. Among the 583 patients with VF, 62.7% of the intervention group and 64.3% of the control group survived to discharge, whereas among the 776 patients without VF, 19.2% of the intervention group and 16.3% of the control group survived to discharge. There were no significant differences in neurological status at time of discharge between the intervention and control groups.

Why was survival not improved? Either the modestly faster achievement of hypothermia was not sufficiently beneficial to show better survival, or there was harm that balanced the benefit of the faster hypothermia. The hypothesis was a good one. If hypothermia is beneficial after cardiac arrest, it stands to reason that earlier application of hypothermia should be better than delayed cooling. Earlier application of hypothermia has been shown to be beneficial in animal models,[9,10] and more rapid induction of hypothermia could be protective against a cascade of reperfusion injury events, inflammatory insults, and cellular deterioration that develop during the postresuscitation period. However, these animal studies demonstrated no difference in outcome when cooling was performed at 1 hour following ROSC compared with 4 hours following ROSC, which is consistent with the findings in the study by Kim et al. The benefit of earlier cooling in animal studies is associated with cooling immediately upon ROSC[9] or with cooling during the cardiac arrest (termed *intra-arrest cooling*) prior to ROSC.[10] Consistent with the animal data, the current study suggests that improving the time from achieving target temperature from 5 hours to 4 hours does not substantially improve clinical outcome.

Additionally, there is some evidence of harm associated with the cooling method used in the study by Kim et al.[6] There was an 11% higher absolute rate of pulmonary edema on the initial chest radiograph and lower oxygen saturation on emergency department arrival with the intervention group. The volume of saline (2 L given rapidly) appears to have produced negative hemodynamic effects in the period after ROSC for some patients. This is consistent with animal data that demonstrate a reduction in coronary perfusion pressure when saline volume loading is done to achieve cooling.[11] This adverse effect on hemodynamics was not observed when cooling was achieved without delivering a large volume of saline. Thus this may be an adverse effect from the method of cooling selected for the study, not an effect of hypothermia. Alternate methods of cooling such as external skin cooling devices, intravenous cooling catheters, and intranasal cooling devices that do not rely on large volume saline infusions are available. The use of intravenous saline for cooling after cardiac arrest is common in the United States, and this study should provide a note of caution for the use of rapid infusions for hypothermia by all clinicians who use this method. In addition, even though this trial is large, it was powered to show a 30% improvement in outcome and a modest treatment effect may have been missed. Ongoing trials[12] could reinforce or challenge the results of this trial.

How should this trial influence practice? One question is whether the results are broadly generalizable because quality of cardiac arrest care is very high in Seattle, as reflected by 64% hospital survival and 58% survival with good neurological recovery for patients with VF in this trial. Yet the trial provides clear evidence that in the setting of high-quality care, out-of-hospital hypothermia by infusion of cold saline does not substantially improve survival. Emergency medical services agencies should concentrate on other means to improve survival from cardiac arrest. These include optimizing dispatch processes, ensuring quality cardiopulmonary resuscitation, transporting of patients to hospitals capable of providing quality cardiac arrest care, and measuring and continuously improving quality measures of cardiac arrest care.[2] Moreover, the study conclusions apply to out-of-hospital initiation of cooling with rapid infusion of cold saline, and they should not be extended to use of other methods of hypothermia initiated in the emergency department or continued during the initial phase of postresuscitation care in the intensive care unit.

The clinical trial by Kim et al[6] also highlights the importance of conducting rigorous randomized trials of interventions, such as hypothermia, for out-of-hospital cardiac arrest in the United States. Even though thousands of cardiac arrest patients in the United States are treated with hypothermia, it is unfortunate that it has taken 10 years since the publication of the initial randomized hypothermia trials for the first such US study to be published. More trials are needed to answer vital questions regarding the use of hypothermia. This randomized trial, and others being conducted, will lead to better care, more efficient use of resources, and improved outcomes for patients with out-of-hospital cardiac arrest.

## ARTICLE INFORMATION

**Author Affiliations:** Duke Clinical Research Institute, Durham, North Carolina (Granger); Center for Resuscitation Science, University of Pennsylvania Health System, Philadelphia (Becker).

**Corresponding Author:** Christopher B. Granger, MD, Duke Clinical Research Institute, 2400 Pratt St, Durham, NC 27705 (christopher.granger@duke.edu).

**Published Online:** November 17, 2013. doi:10.1001/jama.2013.282174.

**Conflict of Interest Disclosures:** The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Granger reported receiving institutional grant funding from Medtronic Foundation. Dr Becker is the director of the Center for Resuscitation Science at the University of Pennsylvania, which includes being responsible for the scientific direction of the center and ensuring adequate financial support for the center by actively pursuing federal, industrial, foundation, and philanthropic funding for the projects of the center.

## REFERENCES

1. Nichol G, Thomas E, Callaway CW, et al; Resuscitation Outcomes Consortium Investigators. Regional variation in out-of-hospital cardiac arrest incidence and outcome. *JAMA*. 2008;300(12):1423-1431.

2. van Diepen S, Abella BS, Bobrow BJ, et al. Multistate implementation of guideline-based cardiac resuscitation systems of care: description of the HeartRescue Project. *Am Heart J*. 2013;166(4):647-653; e2.

3. American Heart Association. STEMI and cardiac resuscitation systems of care. http://www.heart.org/HEARTORG/HealthcareResearch/MissionLifelineHomePage/LearnAboutMissionLifeline/STEMI-and-Cardiac-Resuscitation-Systems-of-Care_UCM_439066_SubHomePage.jsp. Accessed October 31, 2013.

4. Nolan JP, Hazinski MF, Billi JE, et al. Part 1: executive summary: 2010 international consensus on cardiopulmonary resuscitation and emergency cardiovascular care science with treatment recommendations. *Resuscitation*. 2010;81(suppl 1):e1-e25.

5. Peberdy MA, Callaway CW, Neumar RW, et al; American Heart Association. Part 9: post-cardiac arrest care: 2010 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation*. 2010;122(18)(suppl 3):S768-S786.

6. Kim F, Nichol G, Maynard C, et al. Effect of prehospital induction of mild hypothermia on survival and neurological status among adults with cardiac arrest: a randomized clinical trial. *JAMA*. doi:10.1001/jama.2013.282173.

7. Bernard SA, Gray TW, Buist MD, et al. Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. *N Engl J Med*. 2002;346(8):557-563.

8. Hypothermia after Cardiac Arrest Study Group. Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. *N Engl J Med*. 2002;346(8):549-556.

9. Che D, Li L, Kopil CM, Liu Z, Guo W, Neumar RW. Impact of therapeutic hypothermia onset and duration on survival, neurologic function, and neurodegeneration after cardiac arrest. *Crit Care Med*. 2011;39(6):1423-1430.

10. Abella BS, Zhao D, Alvarado J, Hamann K, Vanden Hoek TL, Becker LB. Intra-arrest cooling improves outcomes in a murine cardiac arrest model. *Circulation*. 2004;109(22):2786-2791.

11. Yannopoulos D, Zviman M, Castro V, et al. Intra-cardiopulmonary resuscitation hypothermia with and without volume loading in an ischemic model of cardiac arrest. *Circulation*. 2009;120(14):1426-1435.

12. Deasy C, Bernard S, Cameron P, et al; RINSE investigators. Design of the RINSE trial: the rapid infusion of cold normal saline by paramedics during CPR. *BMC Emerg Med*. 2011;11:17.