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

Editorial page 31

Supplemental content at jama.com

**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*. 2014;311(1):45-52. doi:10.1001/jama.2013.282173
Published online November 17, 2013.

**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).



Copyright 2014 American Medical Association. All rights reserved.

Downloaded From: http://jama.jamanetwork.com/ on 05/30/2015

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.



Copyright 2014 American Medical Association. All rights reserved.

Downloaded From: http://jama.jamanetwork.com/ on 05/30/2015

### 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

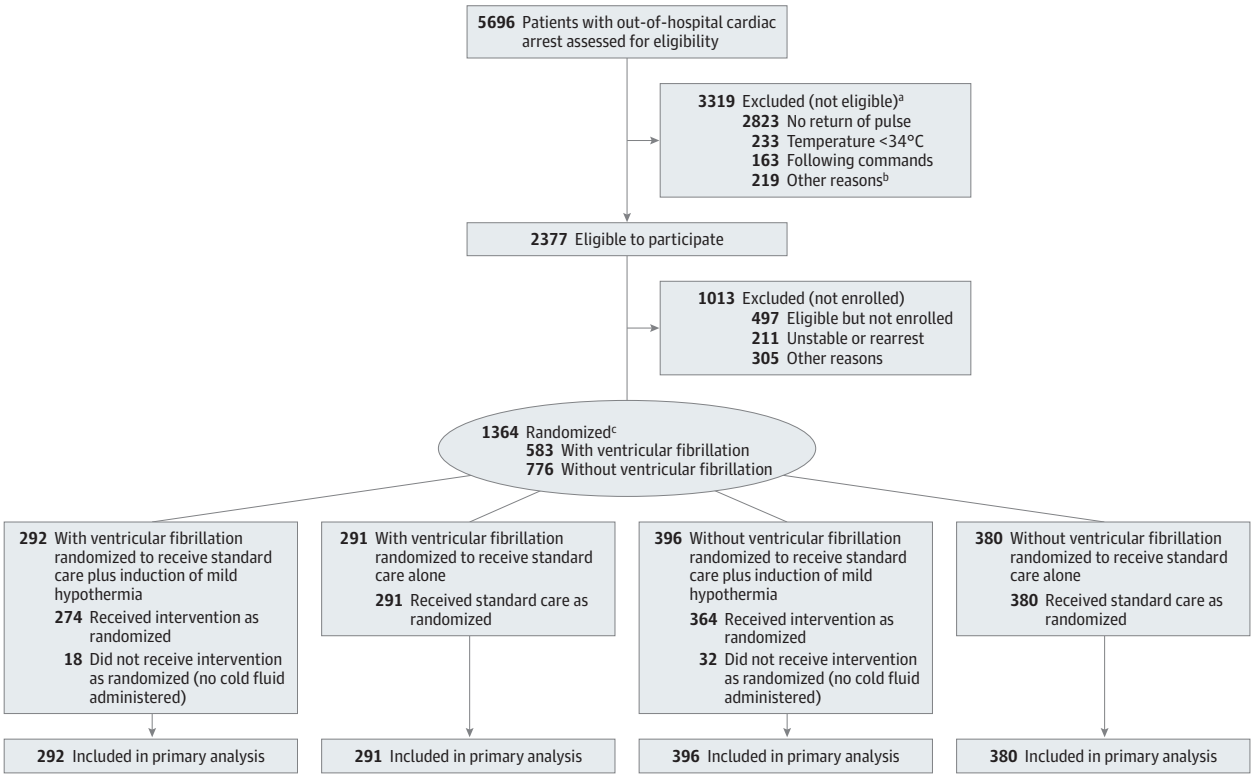


Copyright 2014 American Medical Association. All rights reserved.

Downloaded From: http://jama.jamanetwork.com/ on 05/30/2015

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.



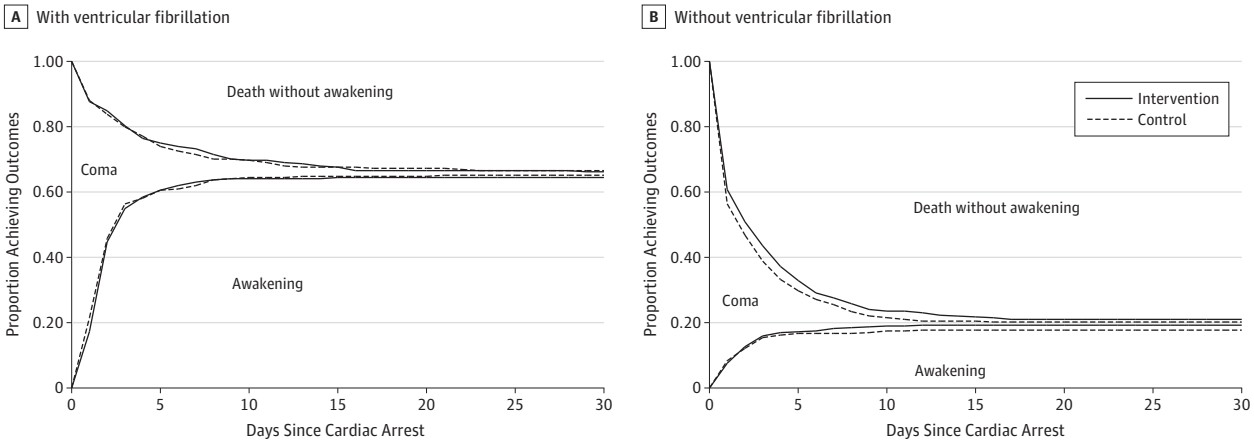
Copyright 2014 American Medical Association. All rights reserved.

Downloaded From: http://jama.jamanetwork.com/ on 05/30/2015

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



Copyright 2014 American Medical Association. All rights reserved.

Downloaded From: http://jama.jamanetwork.com/ on 05/30/2015

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 |
| $Pa_{O_2}$, mm Hg[b] | (n = 609)<br>189 (178 to 200) [135] | (n = 585)<br>218 (206 to 230) [144] | <.001 |
| $Pa_{CO_2}$, mm Hg[b] | (n = 670)<br>59 (57 to 61) [28] | (n = 641)<br>58 (55 to 61) [34] | .36 |
| First $Sa_{O_2}$ 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; $Sa_{O_2}$, 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-



Copyright 2014 American Medical Association. All rights reserved.

Downloaded From: http://jama.jamanetwork.com/ on 05/30/2015

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 $Pa_{O_2}$ 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



Copyright 2014 American Medical Association. All rights reserved.

Downloaded From: http://jama.jamanetwork.com/ on 05/30/2015

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.



Copyright 2014 American Medical Association. All rights reserved.

Downloaded From: http://jama.jamanetwork.com/ on 05/30/2015