Duration of Coma in Out-of-Hospital Cardiac Arrest Survivors Treated With Targeted Temperature Management

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Study objective: We evaluate the time to awakening after out-of-hospital cardiac arrest in patients treated with targeted temperature management and determine whether there was an association with any patient or event characteristics.

Methods: This was a prospective, observational cohort study of consecutive adult survivors of out-of-hospital cardiac arrest of presumed cardiac cause who were treated with targeted temperature management between January 1, 2008, and March 31, 2014. Data were obtained from hospitals and emergency medical services agencies responding to approximately 90% of Arizona's population as part of a state-sponsored out-of-hospital cardiac arrest quality improvement initiative.

Results: Among 573 out-of-hospital cardiac arrest patients who completed targeted temperature management, 316 became responsive, 60 (19.0%) of whom woke up at least 48 hours after rewarming. Eight patients (2.5%) became responsive more than 7 days after rewarming, 6 of whom were discharged with a good Cerebral Performance Category score (1 or 2). There were no differences in standard Utstein variables between the early and late awakeners. The early awakeners were more likely to be discharged with a good Cerebral Performance Category score (odds ratio 2.93; 95% confidence interval 1.09 to 7.93).

Conclusion: We found that a substantial proportion of adult out-of-hospital cardiac arrest survivors treated with targeted temperature management became responsive greater than 48 hours after rewarming, with a resultant good neurologic outcome. [Ann Emerg Med. 2016;■:1-8.]

Please see page XX for the Editor's Capsule Summary of this article.

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INTRODUCTION

Background

Approximately 424,000 out-of-hospital cardiac arrests are assessed by emergency medical services (EMS) annually in the United States.[1] Although approximately 50% of patients achieve return of spontaneous circulation and undergo further resuscitation efforts inside the hospital, less than 10% survive to hospital discharge.[1] The American Heart Association and the International Liaison Committee on Resuscitation recommend targeted temperature management as one intervention that improves outcomes for comatose adult victims of out-of-hospital cardiac arrest.[2,3]

Time to regaining consciousness after out-of-hospital cardiac arrest varies widely, and no physical examination findings or diagnostic tests have been shown to accurately prognosticate awakening after cardiac arrest. In 2006, the American Academy of Neurology published an article describing neurologic prognostication after cardiac arrest by using the physical examination, somatosensory evoked potentials, and neuron-specific enolase in the first 72 hours after return of spontaneous circulation.[4] Unfortunately, this approach has been found to be unreliable in the era of targeted temperature management.[5] The lack of a clear method of prognostication presents a dilemma for hospital-based practitioners and emergency physicians who are expected to provide reliable prognostic answers for loved ones while limiting the use of resources on futile efforts.

Goals of This Investigation

The purpose of this study was to investigate the time to awakening after out-of-hospital cardiac arrest in adults treated with targeted temperature management and to determine whether there was an association with any patient-specific or event characteristics to help predict outcomes in the emergency department (ED).

MATERIALS AND METHODS

Setting

In 2014, Arizona had 6.7 million residents living in 15 counties.[6] The Arizona Department of Health Services establishes EMS protocols, scope of practice, and EMS provider certification. EMS crew configuration, vehicle

Editor's Capsule Summary

What is already known on this topic

Targeted temperature management is a recommended strategy for comatose adult out-of-hospital cardiac arrest survivors. There is no validated system for predicting when patients receiving targeted temperature management will awake from their coma.

What question this study addressed

When do patients awake, and can the timing of awakening be predicted?

What this study adds to our knowledge

In this multicenter study, 19% of patients who awoke did so more than 48 hours after rewarming; 15%, more than 72 hours. A few awoke after a week. No patient or event characteristics reliably identified early versus late awakeners.

How this is relevant to clinical practice

Avoiding inaccurate early prediction may lead to better outcomes, and accurate clinical guidelines are needed.

deployment, dispatch, and response intervals vary widely across the state. One hundred fifty EMS agencies and 35 cardiac receiving centers responding to approximately 90% of Arizona's population participate in the state-sponsored Save Hearts in Arizona Registry and Education (SHARE) program (http://www.azshare.gov), which provided the infrastructure for this study and has been described previously.[7-11] To be recognized as a cardiac receiving center, a hospital must have a dedicated targeted temperature management protocol for out-of-hospital cardiac arrest patients who remain comatose and an evidence-based termination-of-resuscitation protocol that includes a 72-hour moratorium on termination of care for patients receiving targeted temperature management.

Study Design

This was a prospective, multicenter, observational cohort study of consecutive adult patients (≥18 years) with out-of-hospital cardiac arrest between January 1, 2008, and March 31, 2014, who were transported initially or transferred to a cardiac receiving center and treated with targeted temperature management. Cases were excluded if out-of-hospital resuscitation was not initiated, the cause of the arrest was presumed to be noncardiac (eg, known respiratory arrest, suicide, trauma, drowning, drug overdose), or the patient had a do-not-resuscitate order.

Data Collection and Processing and Methods of Measurement

Since 2004, more than 18,000 out-of-hospital cardiac arrests have been entered into the SHARE database. EMS data are obtained from the patient care reports, and outcomes are obtained either directly from the hospitals or from the State Office of Vital Records. SHARE includes an Utstein-style out-of-hospital cardiac arrest EMS database linked with inhospital postarrest care and outcome data. Consistent with Utstein methodology, each out-of-hospital cardiac arrest in which EMS attempts resuscitation is included. EMS data are cross-referenced between first responding fire department–based EMS agencies, private ambulance transport companies, and the cardiac receiving center database. To perform continuous quality improvement for in-hospital postarrest care at the cardiac receiving centers, a data tool was developed to collect inhospital patient information for all out-of-hospital cardiac arrest patients brought to a state department of health–recognized cardiac receiving center (Appendix E1, available online at http://www.annemergmed.com). The cardiac receiving center data included details on the method of targeted temperature management, the timing of initiation, duration, and any complication associated with targeted temperature management and its rewarming phase. It also included the final patient outcome, including the Cerebral Performance Category score.[12] The data forms were completed by cardiac receiving center clinical personnel using a secure Web-based data entry system. Each individual completing data forms was trained in person, and each form was secondarily reviewed by a SHARE data coordinator for completeness and accuracy before entry into the database. Any inconsistencies were addressed in follow-up by examining the hospital medical record.

SHARE is an Arizona Department of Health Services–sponsored public health initiative. As such, the attorney general has determined that the program is exempt from the requirements of the Health Insurance Portability and Accountability Act, which allows linkage of EMS and hospital data, tracking of out-of-hospital cardiac arrest events, and evaluation of efforts to improve resuscitation care. The University of Arizona Institutional Review Board and the Arizona Department of Health Services Human Subjects Review Board determined that, by virtue of being a public health initiative, neither the interventions nor their evaluation constitutes human subjects research and approved the publication of deidentified data.

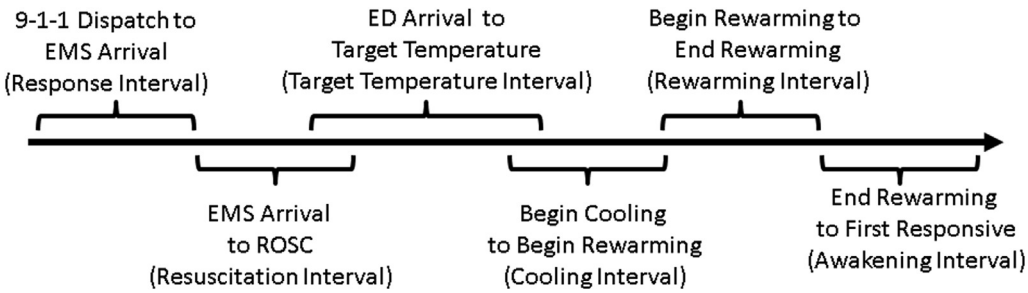

Figure 1. Resuscitation intervals. *ROSC*, Return of spontaneous circulation.

Selection of Participants

Patients included in the study experienced out-of-hospital cardiac arrest before the arrival of EMS, completed the cooling interval (Figure 1), survived to hospital discharge, and followed commands (Figure 2). "Awakening" was defined as the time when the patient first followed commands as determined by the treating providers. Data were stratified according to whether patients awakened before the point of 48 hours after rewarming ("early awakeners") or more than 48 hours after rewarming ("late awakeners").

Primary Data Analysis

To maximize the available subjects for analysis, multiple imputation was carried out in SAS (version 9.3; SAS Institute, Inc., Cary, NC) to impute missing data. Multiple imputation has been shown to generate less biased estimates with more statistical efficiency compared with alternative methods of handling incomplete data (eg, complete-case analysis, single imputation, missing indicator regression).[13,14] It involves 3 distinct phases: (1) the missing data are filled in m times to generate m complete data sets, (2) the m data sets are analyzed by using standard procedures, and (3) the results from the m complete data sets are combined for the inference. Multiple imputation procedure replaces each missing value with a set of plausible values that represent the uncertainty about the right value to impute instead of filling in a single value for each missing value. We used all the variables in Table 1 for multiple imputation. Twenty imputed data sets were generated and model fit diagnostics were evaluated. Missing data fit an arbitrary missing pattern, and we used the fully conditional specification method to impute data. Linear regression was used to impute all intervals (Figure 1). Logistic regression was used to impute categorical variables, witnessed arrest, bystander cardiopulmonary resuscitation (CPR), shockable rhythm, and ST-segment elevation myocardial infarction.

Descriptive statistics were used to describe the study population and are reported as proportion for categorical and binary data and as mean and standard deviation (SD) for continuous data. All analyses used the imputed data, accounting for variance across imputed data sets with Rubin's rules[15] (using Proc MI in SAS). Normalizing transformations were applied to the statistics estimated from each imputed data set before the Rubin's combination rules were applied. For binary outcomes, odds ratios (ORs) were obtained with the Mantel-Haenszel estimate of the common OR with 95% confidence interval (CI) to assess for any differences between early and late awakeners. Mean and 95% CI were calculated to evaluate intervals between the 2 groups. The probability of future awakening was assessed by life-table survival analysis. For the purpose of the survival analysis, an "event" was considered when a patient became responsive, and the time of awakening relative to the end of rewarming was considered the time at which the event occurred. Patients who died after rewarming were considered censored. The conditional probability of awakening (an estimate of the probability that a person will become responsive in the interval) and

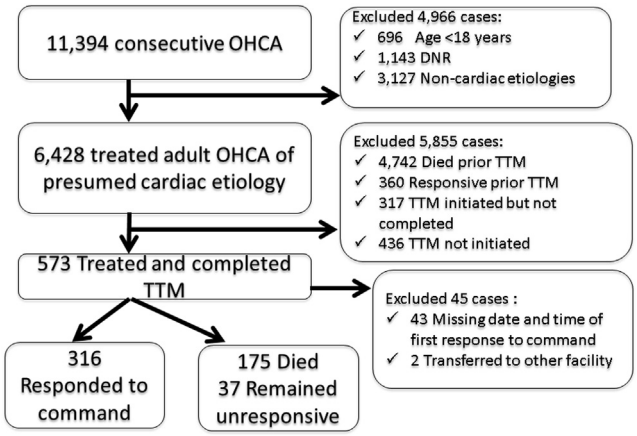

Figure 2. Diagram of the study cohort. *OHCA*, Out-of-hospital cardiac arrest; *DNR*, do not resuscitate; *TTM*, targeted temperature management.

Table 1. Demographics and event characteristics.

Demographics/Event Characteristics	N=528	
	No. (%)	Missing, No. (%)
Male	392 (74.2)	0
Age, mean (SD), y	60.3 (13.5)	0
Arrest witnessed	253 (65.4)	141 (26.7)
Arrest location home	239 (60.8)	135 (25.6)
Bystander CPR performed	192 (50.3)	151 (28.6)
Initial rhythm VF/VT	240 (61.5)	138 (26.1)
STEMI	161 (31.7)	20 (3.8)
GCS score, median (Q1, Q3)	3 (3, 3)	53 (10.0)
Response interval, mean (SD), min	5.3 (2.9)	145 (27.5)
Resuscitation interval, median (Q1, Q3), min	25 (15, 37)	207 (39.2)
Target temperature interval, mean (SD), h	7.7 (5.5)	53 (10.0)
Cooling interval, mean (SD), h	26.6 (5.9)	85 (16.1)
Rewarming interval, mean (SD), h	12.2 (8.4)	65 (12.3)
CPC scale		
All	522 (98.9)	6 (1.1)
1	223 (42.7)	
2	69 (13.2)	
3	13 (2.5)	
4	42 (8.1)	
5	175 (33.5)	

VF, Ventricular fibrillation; *VT*, ventricular tachycardia; *STEMI*, ST-segment elevation myocardial infarction; *GCS*, Glasgow Coma Scale; *Q1*, quartile 1; *Q3*, quartile 3; *CPC*, Cerebral Performance Category.

the cumulative probability of awakening (the probability of awakening from that point forward) were calculated. The log rank and Wilcoxon tests were used to assess the survival probability. Data were analyzed with SAS (version 9.3; SAS Institute, Inc.). $P<.05$ was considered statistically significant.

RESULTS

From January 1, 2008, to March 31, 2014, 11,394 consecutive out-of-hospital cardiac arrest patients were enrolled. Among 11,394 consecutive out-of-hospital cardiac arrests during the study period, 696 cases were excluded for aged younger than 18 years. There were 1,143 cases excluded for do-not-resuscitate orders, in which EMS providers did not attempt resuscitation, and 3,127 cases were excluded because of noncardiac causes. Of the 6,428 treated adult patients with out-of-hospital cardiac arrests of presumed cardiac cause, 573 completed the local targeted temperature management protocol and 316 became responsive, with a documented response to command time (Figure 2). Table 1 shows patient characteristics, along with the missing data for the 528 patients who completed targeted temperature management and were not excluded for missing time of first response to command. Median age was 60.3 years and 74.2% were male. Overall, 292 patients (55.3%) survived, with a Cerebral Performance Category score of 1 or 2.

Figure 3 is a histogram of the patients categorized by time to awakening. Data for the 35 patients who became responsive after the cooling interval (targeted temperature management completed) but before the end of rewarming are not shown. Among the 316 responders, 60 (19.0%) responded more than 48 hours after rewarming, and 48 (15.2%) became responsive more than 72 hours after rewarming. Eight patients woke up more than 7 days after rewarming, including 2 discharged with a Cerebral Performance Category score of 1 and 4 discharged with a score of 2. Table 2 shows a life-table survival analysis depicting the chances of a comatose victim's becoming responsive as time extends beyond the end of the rewarming interval. The cumulative probability of awakening among patients who were still comatose at the beginning of the third day after rewarming was 0.3345.

Table 3 shows the differences in patient characteristics between the 316 who completed targeted temperature management and became responsive and the 212 who completed it and either died or remained unresponsive. Patients who became responsive were more likely to have a witnessed arrest, an initial shockable rhythm, and an ST-segment elevation myocardial infarction. Table 4 shows the differences in patient characteristics between the early and late awakeners. The Mantel-Haenszel estimate of the common OR did not show significant differences with respect to out-of-hospital and inhospital data elements. The odds of good neurologic outcome were significantly higher in the early group (OR 2.93; 95% CI 1.09 to 7.93) compared with the late group.

LIMITATIONS

There are several limitations to this study. Bias is always possible in an observational study; however, the large study

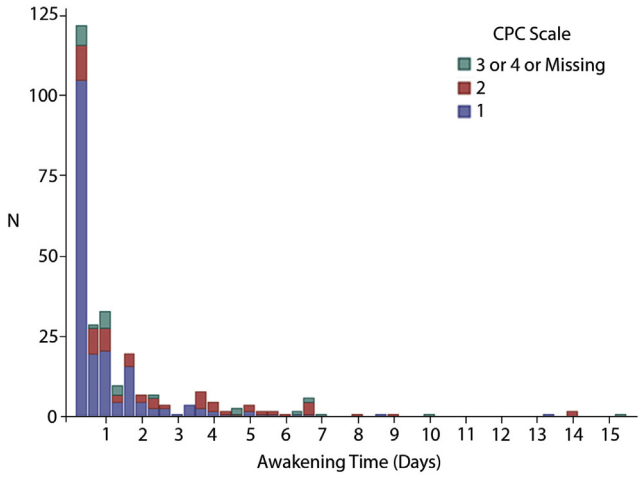

Figure 3. Cerebral Performance Category score histogram.

Table 2. Life-table survival estimate.

Interval, Days		Number Awakened	Number Died	Effective Sample Size	Conditional Probability of Awakening	Conditional Probability Standard Error	Cumulative Probability of Awakening
0	1	34	5	453.5	0.0750	0.0124	0.5447
1	2	150	41	396.5	0.3783	0.0244	0.2446
2	3	37	31	210.5	0.1758	0.0262	0.2850
3	4	12	29	143.5	0.0836	0.0231	0.3345
4	5	17	18	108.0	0.1574	0.0350	0.2870
5	6	9	14	75.0	0.1200	0.0375	0.2933
6	7	5	9	54.5	0.0917	0.0391	0.3119
7	8	9	8	41.0	0.2195	0.0646	0.1951
8	9	1	3	26.5	0.0377	0.0370	0.2642
9	10	2	4	22.0	0.0909	0.0613	0.2273
10	11	1	1	17.5	0.0571	0.0555	0.2286
11	12	0	2	15.0	0	0	0.2667
12	13	0	0	14.0	0	0	0.2857
13	14	0	1	13.5	0	0	0.2963
14	15	3	1	12.5	0.2400	0.1208	0.0800
15	16	0	0	9.0	0	0	0.1111
16	17	1	1	8.5	0.1176	0.1105	0
17	18	0	1	6.5	0	0	0
18	19	0	0	6.0	0	0	0
19	20	0	0	6.0	0	0	0
20	21	0	2	5.0	0	0	0
21	22	0	0	4.0	0	0	0
22	-	0	4	2.0	0	0	0

population represented, including numerous hospitals and EMS agencies, mitigates this risk. The fact that these data are derived from a mature statewide out-of-hospital cardiac arrest quality improvement program, which emphasizes high-quality CPR and includes cardiac receiving centers dedicated to postresuscitation care, might make the results less generalizable. To be a cardiac receiving center, a hospital has to have a targeted temperature management protocol for out-of-hospital cardiac arrest victims who remain comatose, which allows wide practice variation in inclusion and exclusion criteria for cooling, timing of cooling, and methods of cooling. This potential for practice variation might also have affected our results. One example is that we do not have data on the type, quantity, and duration of sedation used. Although the use of sedatives clearly has an influence on level of consciousness, we have no reason to believe that these 35 hospitals differ from other hospitals in their practice of sedation. The hospitals participating in this study have protocols not to prognosticate before 72 hours after the arrest. Institutions without such protocols might have fewer late survivors because of early prognostication and withdrawal of care.

Table 3. Differences in demographics and event variables.

	Responded to Command (n=316), %	Died/Unresponsive (n=212), %	Mantel-Haenszel Estimate of the Common OR (95% CI)
Male patient	74.4	74.1	1.02 (0.68–1.51)
Arrest witnessed	71.4	57.1	0.53 (0.35–0.80)
Arrest location home	57.9	64.4	0.76 (0.50–1.15)
Bystander CPR performed	55.3	46.5	0.70 (0.46–1.07)
Initial rhythm VF/VT	75.0	41.8	0.24 (0.16–0.37)
STEMI	38.0	22.0	0.46 (0.30–0.69)
	Mean (95% CI)	**Mean (95% CI)**	
Age, y	60.0 (58.6–61.4)	60.9 (58.9–62.8)	
Response interval, min	5.2 (4.8–5.6)	5.5 (5.0–6.1)	
Resuscitation interval, min	29.2 (25.5–32.8)	35.2 (31.6–38.8)	
Target temperature interval, h	8.2 (7.5–8.9)	7.2 (6.5–7.9)	
Cooling interval, h	26.7 (26.0–27.3)	26.6 (25.5–27.8)	
Rewarming interval, h	12.4 (11.3–13.4)	12.4 (11.1–13.6)	

Table 4. Differences in demographics and event variables between early and late awakeners.

Responded to Command (n=316)	Early (≤48 Hours), n=256, %	Late (>48 Hours), n=60, %	Mantel-Haenszel Estimate of the Common OR (95% CI)
Male patient	75.4	70.0	1.31 (0.71–2.44)
Arrest witnessed	72.5	66.7	0.76 (0.39–1.48)
Arrest location home	57.2	61.0	0.86 (0.46–1.64)
Bystander CPR performed	54.5	58.8	1.20 (0.60–2.38)
Initial rhythm VF/VT	75.4	73.4	0.91 (0.43–1.91)
STEMI	35.6	48.3	1.69 (0.96–2.98)
CPC score 1 or 2	95.6	88.1	2.93 (1.09–7.93)
	Mean (95% CI)	**Mean (95% CI)**	
Age, y	59.8 (58.1–61.4)	61.0 (58.0–64.0)	
Response interval, min	5.2 (4.8–5.6)	5.5 (4.5–6.4)	
Resuscitation interval, min	29.1 (25.3–32.9)	29.2 (22.0–37.0)	
Target temperature interval, h	8.1 (7.5–8.7)	8.7 (6.1–11.4)	
Cooling interval, h	26.5 (25.7–27.2)	27.6 (26.0–29.1)	
Rewarming interval, h	12.3 (11.1–13.5)	12.6 (10.7–14.5)	

Finally, we do not have inhospital serial physical examination and dedicated prognostication data. It is possible that this information would have provided clues about which patients were more or less likely to wake up after an extended coma.

DISCUSSION

In recent years, the use of targeted temperature management for comatose adult victims of out-of-hospital cardiac arrest has become standard of care.[16] However, there is enormous variability in the methods, the exact temperature and duration of targeted temperature management, and particularly in the timing of neurologic prognostication after out-of-hospital cardiac arrest.[17-21] In 2006, the American Academy of Neurology published a neurologic prognostication practice parameter for postarrest patients.[4] Unfortunately, the recommendations were based on literature from before the advent of targeted temperature management and have been shown to be ineffective with the use of targeted temperature management and its associated sedative and neuromuscular-blocking medications.[22] The 2010 American Heart Association guidelines emphasized that the most commonly used prognosticators of poor outcome after out-of-hospital cardiac arrest have less utility after targeted temperature management and that durations of observation greater than 72 hours after return of spontaneous circulation should be considered (Class 1, Level of Evidence C).[2]

Targeted temperature management is thought to improve outcomes from out-of-hospital cardiac arrest by providing neuroprotection. There is physiologic evidence that decreasing brain temperature reduces cerebral blood flow and cerebral oxygen consumption.[23] Additionally, targeted temperature management avoids the deleterious effects of postarrest hyperthermia.[16,24-26] These neuroprotective effects might allow delayed awakening by decreasing the degree of permanent brain injury. In the present study, 60 of 316 responsive survivors (19%) initially followed commands at least 48 hours after rewarming. Additionally, patients who were alive but comatose 48 hours after rewarming had a 33% chance of awakening. The cutoff of 48 hours after rewarming is similar to the 72 hours after return of spontaneous circulation recommended by the American Heart Association. Surprisingly, in our study, 8 victims (2.5%) became responsive more than a week after rewarming, 6 of whom were discharged with a good neurologic outcome (Cerebral Performance Category score 1 or 2). We found no reliable out-of-hospital– or hospital-based predictors of late awakening.

Our study design does not allow determination of causality for nearly 20% of responders becoming so after greater than 48 hours from cooling and 6 victims responding after more than a week with a Cerebral Performance Category score of 1 or 2. Whether this is because some combination of bystander CPR, high-quality professional CPR, and targeted temperature management itself preserved neurologic function or whether the sedative medications used during targeted temperature management protocols delayed responsiveness remains unknown. Perhaps a general optimization of care from the initial 911 call and advances in postresuscitation critical care are allowing victims to become responsive after prolonged coma. Regardless of the specific reason, the findings have implications for hospital-based physicians and researchers attempting to enhance neuroprognostication efforts while balancing the hopes for meaningful survival with use of resources. Perhaps more importantly, they provide evidence for the bedside emergency physician who is attempting to

respond to the questions of loved ones about the likelihood and timing of a meaningful recovery.

The previous literature is consistent with our findings. For 194 consecutive out-of-hospital cardiac arrest victims treated with targeted temperature management, Grossestreuer et al[27] reported that time to awakening after resuscitation was highly variable. Gold et al[28] evaluated 89 patients and concluded that after out-of-hospital cardiac arrest and targeted temperature management, arbitrary withdrawal of life support less than 48 hours after rewarming may prematurely terminate the life of many patients with the potential for full neurologic recovery. Our analysis differs from that of the previous studies by including a larger population from numerous (35) treating hospitals. Additionally, we compared out-of-hospital Utstein variables between early and late awakeners.

In conclusion, we found that a substantial proportion of adult out-of-hospital cardiac arrest victims treated with targeted temperature management awoke more than 48 hours after rewarming, with a good neurologic outcome. A remarkable number remained comatose for greater than 1 week and were discharged home with a Cerebral Performance Category score of 1 or 2. According to our findings, the avoidance of inappropriate early prognostication has the potential to save the lives of numerous patients with out-of-hospital cardiac arrest and should be a focus of future guidelines and education.

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Author contributions: All authors conceived and designed the study. TI, MM, and BJB supervised the data collection. TI, MM, VC, and BJB managed the data. TI, TFV, VC, DWS, and BJB provided statistical advice on study design and analyzed the data. TI drafted the article, and all authors contributed substantially to its revision. BJB takes responsibility for the paper as a whole.

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