Use of Therapeutic Hypothermia After In-Hospital Cardiac Arrest*

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***See also p. 1565.**

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Dr. Berg serves as chair for the Get WithThe Guidelines-Resuscitation Clinical Working Group. Dr. Mosesso has medical advisory board membership with OxySure Systems, Inc. Dr. Mosesso serves as the medical director and honorary board member for the Sudden Cardiac Arrest Association.The remaining authors have disclosed that they do not have any potential conflicts of interest.

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Objectives: Formal guidelines recommend that therapeutic hypothermia be considered after in-hospital cardiac arrest. The rate of therapeutic hypothermia use after in-hospital cardiac arrest and details about its implementation are unknown. We aimed to determine the use of therapeutic hypothermia for adult in-hospital cardiac arrest, whether use has increased over time, and to identify factors associated with its use.

Design: Multicenter, prospective cohort study.

Setting: A total of 538 hospitals participating in the Get With the Guidelines-Resuscitation database (2003–2009).

Patients: A total of 67,498 patients who had return of spontaneous circulation after in-hospital cardiac arrest.

Interventions: None.

Measurements and Main Results: The primary outcome was the initiation of therapeutic hypothermia. We measured the proportion of therapeutic hypothermia patients who achieved target temperature (32–34°C) and were overcooled. Of 67,498 patients, therapeutic hypothermia was initiated in 1,367 patients (2.0%). The target temperature (32–34°C) was not achieved in 44.3% of therapeutic hypothermia patients within 24 hours and 17.6% were overcooled. The use of therapeutic hypothermia increased from 0.7% in 2003 to 3.3% in 2009 ($p < 0.001$). We found that younger age ($p < 0.001$) and occurrence in a non-ICU location ($p < 0.001$), on a weekday ($p = 0.005$), and in a teaching hospital ($p = 0.001$) were associated with an increased likelihood of therapeutic hypothermia being initiated.

Conclusions: After in-hospital cardiac arrest, therapeutic hypothermia was used rarely. Once initiated, the target temperature was commonly not achieved. The frequency of use increased over time but remained low. Factors associated with therapeutic hypothermia use included patient age, time and location of occurrence, and type of hospital. (*Crit Care Med* 2013; 41:1385–1395)

Key Words: cardiac arrest; hypothermia; in-hospital cardiac arrest; knowledge translation; utilization

In the United States, approximately 210,000 in-hospital cardiac arrests (IHCA) occur annually, the rate appears to be increasing (1), and less than 20% of these patients will survive to hospital discharge (2, 3). In 2002, two landmark studies demonstrated that mild therapeutic hypothermia (TH) improved neurologic outcome and survival in comatose survivors of out-of-hospital cardiac arrest (OHCA) when the initial rhythm was ventricular fibrillation (VF) or pulseless ventricular tachycardia (VT) (4, 5).

In 2003, the International Liaison Committee on Resuscitation recommended the use of TH (32–34°C) for OHCA caused by VF/VT and consideration of its use after IHCA and arrests caused by other rhythms (6). Subsequent nonrandomized studies have suggested that the effectiveness of TH may apply more broadly (7–12), and investigators have advocated expanding the indications for its use (13). The 2010 American Heart Association (AHA) guidelines for postcardiac arrest care recommended that comatose adults with return of spontaneous circulation (ROSC) after OHCA caused by VF/VT receive TH (Class I) and that TH "may be considered" after IHCA and OHCA caused by nonshockable rhythms (Class IIb) (14).

The rate of TH use after IHCA and details about its implementation are unknown. Using data from the American Heart Association (AHA)'s Get With the Guidelines-Resuscitation (GWTG-R), formerly known as the National Registry of Cardiopulmonary Resuscitation (NRCPR), we examined the use of TH after IHCA and investigated whether use has increased over time. We hypothesized that TH is infrequently used, but that use has increased over time. Furthermore, we evaluated which patient- and hospital-level factors were associated with the use of TH. Results of this study were previously reported in abstract form (15).

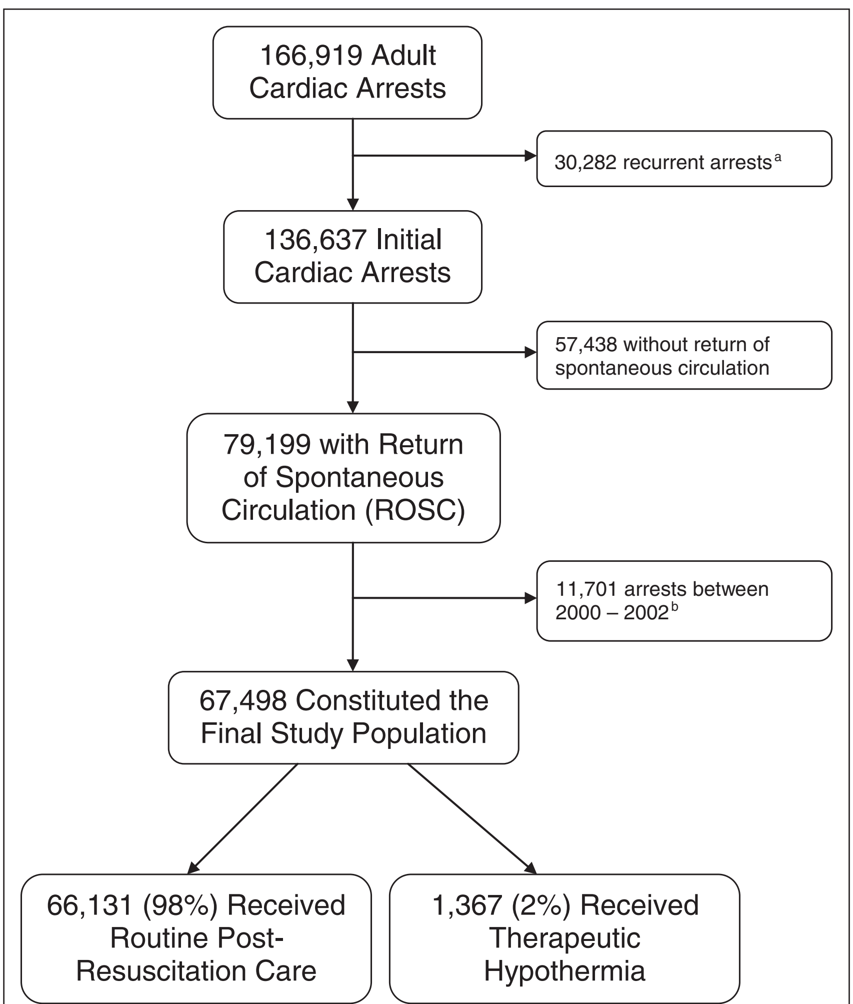

Figure 1. Flow diagram of study population. [a]Of 30,282 recurrent arrests, the initial arrest occurred out of hospital in 7,713 cases; therapeutic hypothermia (TH) was used in 5.0% (218 of 4,148) of subsequent in-hospital cardiac arrest cases with return of spontaneous circulation (ROSC). In those 22,569 instances of recurrent in-hospital cardiac arrests, TH was used in 2.1% of subsequent cases with ROSC (270 of 12,934).
[b]Data regarding the use of TH were missing in 99.7% of patients in 2000, 96.8% of patients in 2001, and 41.1% of patients in 2002; subjects from 2000 to 2002 were excluded.

MATERIALS AND METHODS

The study was approved by the GWTG-R Research Committee and the University of Pennsylvania's Office of Regulatory Affairs.

Study Population

We conducted a cohort study of the use of TH in patients with ROSC after IHCA using the GWTG-R database. The GWTG-R is a multicenter, voluntary, prospective registry of in-hospital resuscitation which began in 2000. We focused on the interval 2003–2009 as the landmark trials were published in 2002, and substantial data regarding TH use were missing in prior years. For patients with multiple arrests, we included the index IHCA case only (**Fig. 1**).

Patient and Hospital Characteristics

Detailed clinical information was obtained from the patient's record using the GWTG-R data collection form and standardized Utstein-style definitions (16). The details of the GWTG-R have been published previously (2, 17–19). We hypothesized a priori that patients with an initial cardiac rhythm of VF/VT, compared with those with asystole or pulseless electrical activity (PEA), would be more likely to receive TH (4, 5, 20, 21). Additional patient factors to be tested for an association with TH use included sociodemographics; admission source; coexisting conditions, including interventions in place prior to cardiac arrest (e.g., mechanical ventilation and vasoactive agents) and time (i.e., night or weekend) and duration of cardiopulmonary resuscitation (CPR) (categorized as less than or equal to 5 min, 6–60 min, and > 60 min); location; and cause of cardiac arrest. We categorized duration of CPR as 5 minutes or less, 6–60 minutes, and greater than 60 minutes based on published data for these categories in previous TH investigations (4, 5). Hospital-level data included geographic location, hospital size, and teaching status (19). We hypothesized that academic hospitals, as likely early adopters of new interventions, would be more likely to use TH (21).

Therapeutic Hypothermia

Since its inception, the GWTG-R case report form has included an option to document whether TH was initiated in patients who have ROSC. The response options include "yes" and "no/not documented." Beginning in 2004, lowest and highest patient temperatures during the initial 24 hours post-ROSC were recorded. The method of cooling was not recorded. To assess protocol adherence, we report the proportion of TH patients who achieved target temperature and were overcooled (< 32°C).

Statistical Analysis

We tested whether the frequency of TH use has increased over time using the nonparametric test for trend (22). We performed several sensitivity analyses. To ensure that our findings were not biased by varying hospital participation over time and/or hospitals that never used TH, we tested whether the frequency of use of TH has increased over time in the 112 hospitals contributing data for all years of the study period (2003–2009) and then tested whether the frequency of use of TH has increased over time after excluding the 21 hospitals that never used TH. Because of the recommendation to consider TH in comatose adults with ROSC after IHCA (6, 14) and because an objective assessment of consciousness post-ROSC was unavailable, we first repeated the analyses using the subgroup of patients who required intubation at the time of the arrest as a surrogate for coma and then repeated these analyses after excluding patients with a duration of CPR of 5 minutes or less (4, 5).

We examined the univariate association between patient characteristics, hospital factors, and TH initiation over the study interval using the chi-square statistic, Fisher's exact test, Student *t* test, or Wilcoxon's rank sum test, as appropriate. To test the independent association between patient and hospital factors and TH use, we created separate mixed-effects multivariable models including variables associated ($p < 0.20$) with the use of TH in univariate analyses (23) and adjusting for center-level random effects (24). We used variance inflation factors to assess for multicollinearity. In our primary analyses, we included initial cardiac rhythm and dropped the presence of VF/VT during the event because of collinearity between these variables. In secondary analyses, we replaced initial cardiac rhythm with the presence of VF/VT during the event to determine whether the presence of VF/VT at any time during the event was associated with the use of TH. We excluded variables with significant missing data (> 5%) from our models. Finally, we created a complete mixed-effects multivariable model incorporating patient and hospital factors that were found to be significantly associated with TH use in the separate models. We used Stata SE 10.0 software to perform statistical analyses (StataCorp, College Station, TX) and considered two-sided *p* values less than 0.05 to be significant.

RESULTS

Use of TH

From 2003 to 2009, 67,498 subjects at 538 hospitals had ROSC after an IHCA (Fig. 1); TH was initiated in 1,367 (2.0%) of these patients. The nadir temperature was significantly lower during the initial 24 hours in TH patients (median 33.4°C; interquartile range [IQR], 32.2–35.9 vs. 36.2°C; IQR, 35.6–36.8, in non-TH patients, $p < 0.001$). The target temperature was not achieved in 44.3% of TH patients within 24 hours of ROSC (median nadir temperature, 36.1°C, IQR, 35.2–36.7); 38.1% of patients achieved target temperature (median nadir temperature 32.8°C; IQR, 32.4–33.1); and 17.6% were overcooled (median nadir temperature, 31.2°C; IQR, 30.4–31.7). In the subset of patients intubated at the time of the event, TH was initiated in 2.3% of cases (822 of 36,292) and 2.35% of cases (746 of 31,804) when the analysis was limited further to those patients who received greater than 5 minutes of CPR.

The number of subjects reported to the registry at each center ranged from 1 to 1,153 (mean = 126) over the study period. Of 538 hospitals that participated at any time during the study period, TH was initiated in at least one patient in 52% of hospitals (282 of 538) and TH was not initiated in any patient in the remaining 48% of hospitals (256 of 538). Use of TH at the subject level varied significantly by hospital, ranging from 0% to 24% (TH initiated in 15 of 62 cases in one hospital with at least ten reported cases of IHCA). Of the 112 hospitals that reported data yearly throughout the entire study period, TH was initiated in at least one patient in 81% of hospitals (91 of 112).

Overall, 32.8% of the 67,498 subjects with ROSC survived to hospital discharge. Survival to hospital discharge varied significantly by hospital, ranging from 6% to 71% when limited to centers with at least ten reported cases of IHCA.

Use of TH Over Time

The rate of TH initiation increased from 0.7% to 3.3% (p for trend < 0.001) between 2003 and 2009 (**Fig. 2**). We found a similar pattern of increasing TH use, whether we limited our analyses to those 112 hospitals contributing data for all years of the study period (overall, 1.7%, ranging from 0.6% in 2003 to 3.0% in 2009; $p < 0.001$), limited our analyses further to 91 hospitals after excluding those 21 hospitals that never used TH (overall, 1.9%, ranging from 0.7% in 2003 to 3.2% in 2009, $p < 0.001$), or limited the primary analysis to the subset of patients intubated at the time of the event (overall, 2.3%, ranging from 0.5% in 2003 to 3.8% in 2009, $p < 0.001$).

Factors Associated With the Initiation of TH After IHCA

Baseline patient and hospital characteristics according to whether TH was initiated after IHCA are presented in **Tables 1 and 2**,

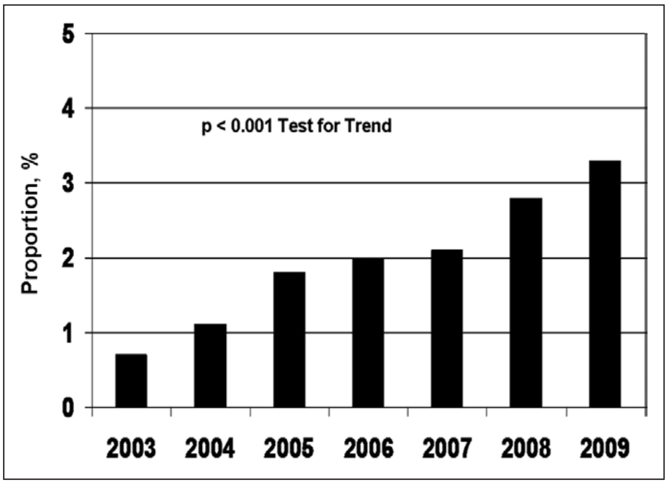

Figure 2. Use of therapeutic hypothermia (TH) over time. Proportion of patients with return of spontaneous circulation after cardiac arrest who received TH from 2003 to 2009.

respectively. **Table 3** summarizes the results of the multivariable analyses. In multivariable analyses limited to patient factors, we found that TH was more likely to be initiated in younger patients ($p < 0.001$), when the arrest occurred outside of the ICU setting ($p < 0.001$) and when the duration of CPR was 6–60 minutes, compared with less than or equal to 5 ($p < 0.001$), and in patients sustaining a cardiac arrest on weekdays vs. weekends ($p = 0.02$). Contrary to our hypothesis, TH was not more likely to be used in patients with VF/VT as the initial cardiac rhythm; however, TH was significantly less likely to be initiated when the initial cardiac rhythm was unknown. When we replaced the initial cardiac rhythm with the presence of VF/VT during the event in the patient factor model, we found a significant association between the presence of VF/VT during the event and the initiation of TH (OR, 1.15, 95% CI, 1.02, 1.29, $p = 0.02$). In multivariable analyses limited to hospital factors, patients were significantly more likely to receive TH when the event occurred in an academic teaching hospital vs. a nonteaching hospital ($p = 0.04$).

In multivariable analyses combining patient and hospital factors simultaneously, we found that younger age ($p < 0.001$) and occurrence in a non-ICU location ($p < 0.001$), on a weekday ($p = 0.005$), in a teaching hospital ($p = 0.001$), and duration of CPR ($p < 0.001$) were associated with an increased likelihood of TH being initiated. Initial cardiac rhythm was not associated with the use of TH, except that TH was significantly less likely to be initiated if the initial rhythm was unknown ($p = 0.007$). When the presence of VF/VT at any time during the event replaced initial cardiac rhythm in the model, we found a significant association between the presence of VF/VT during the event and the initiation of TH (OR, 1.13, 95% CI, 1.00, 1.27, $p = 0.048$).

DISCUSSION

Despite its potential to improve outcomes, we found that TH is rarely initiated after IHCA over the time period (2003–2009) studied. Once TH was initiated, the target temperature was commonly not achieved and overcooling was common. While the frequency of use has steadily increased, the use of TH remained low. Factors associated with TH use included patient age, time, location, and duration of arrest, and type of hospital.

Many patients who achieve ROSC following cardiac arrest exhibit a characteristic ischemia-reperfusion injury. TH is the only therapy associated with significant and important improvements in outcome in patients with OHCA due to VF (11, 25–33). However, it remains uncertain whether other patients benefit from TH. This is crucial to determine since the incidence of VF/VT OHCA appears to be declining (34), the incidence of IHCA appears to be increasing (1), and less than 25% of IHCA have VF/VT as the initial cardiac rhythm (35).

To date, no randomized controlled trial of TH has been conducted after IHCA. The data regarding the use of TH in nonshockable rhythms are conflicting, with several observational studies suggesting a benefit (7–12), while others suggest no benefit (27–29, 31–33). Potential explanations for these disparate findings include the heterogeneous etiology of arrests resulting in nonshockable rhythms, variable time to ROSC and to target temperature, and insufficient power to detect a difference.

Although IHCA cases have been included in several observational studies of TH (7, 8, 10, 12, 31), data regarding outcomes in the subgroup of IHCA cases that receive TH are extremely limited. In two small studies, there was no suggestion that TH was associated with improved outcomes compared with standard postresuscitation care after IHCA (8, 31). In contrast, a recent large multicenter study using the Dutch National Intensive Care Evaluation database demonstrated that the implementation of TH was associated with a significant mortality reduction when applied after OHCA and IHCA ($n = 5{,}317$; OR, 0.80; 95% CI, 0.64–0.98; $p = 0.029$) (10). When the analysis was limited to IHCA, the effect size was similar, but attenuated and no longer statistically significant, in part, due to the loss of statistical power ($n = 2{,}207$; OR, 0.84; 95% CI, 0.62–1.12; $p = 0.24$) (P. Pickkers, personal communication, September 2011).

In the face of uncertain risks, potential yet unproven benefits, and guidelines that recommend the consideration of its use after IHCA (6, 14), we found that 52% of 538 hospitals initiated TH after IHCA in at least one patient. When we limited our analysis to the 112 hospitals that contributed data throughout the study period, this figure reached 81%. These findings are consistent with the frequency of use of TH after cardiac arrest reported by physician and/or nurse respondents in recent survey studies (20, 21, 36, 37).

At the patient level, we found that TH was initiated in 2% of cases of IHCA. Although the frequency of use increased, use remained very low. Together, these findings suggest that hospitals have the ability to provide TH yet rarely implement TH after IHCA on a per-case basis. One plausible explanation for these findings is the lack of demonstrable benefit within this population from a trial, which is reflected in guideline recommendations to "consider" its use. If true, it is reasonable to assume

TABLE 1. Patient-Specific Characteristics According to Whether Therapeutic Hypothermia Was Initiated After Cardiac Arrest

Patient Characteristics	Standard Care (*n* = 66,131)	Hypothermia (*n* = 1,367)	*p*
Age, median (25% to 75%), yr	68 (56–78)	64 (52–75)	< 0.001
Gender (female), no. (%)	28,969 (43.8)	566 (41.4)	0.08
Race, no. (%)[a]			
White	45,994 (74.1)	900 (69.8)	0.001
Black	13,414 (21.6)	335 (26.0)	
Asian	1,016 (1.6)	26 (2.0)	
Other	1,681 (2.7)	28 (2.2)	
Admission source, no. (%)			
Home	49,498 (77.5)	1,065 (79.7)	0.03
Outside hospital transfer	7,105 (11.1)	127 (9.5)	
Extended care facility	6,447 (10.1)	119 (8.9)	
Other	833 (1.3)	25 (1.9)	
Admission CPC, no. (%)[a]			
CPC 1	29,233 (54.5)	613 (58.4)	< 0.001
CPC 2	15, 063 (28.1)	241 (23.0)	
CPC 3	6,657 (12.4)	120 (11.4)	
CPC 4	2,641 (4.9)	72 (6.9)	
CPC 5	5 (0.01)	3 (0.3)	
Initial rhythm, no. (%)			
Asystole	19,643 (29.7)	427 (31.2)	0.19
Pulseless electrical activity	26,653 (40.3)	531 (38.8)	
VF/VT	15,388 (23.3)	332 (24.3)	
Other/unknown	4,447 (6.7)	77 (5.6)	
VF/VT at any time during event, no. (%)	25,977 (39.3)	594 (43.4)	0.002
Event location, no. (%)			
Intensive care	31,251 (47.3)	518 (37.9)	< 0.001
Inpatient	21,490 (32.5)	459 (33.6)	
Emergency department	6,672 (10.1)	187 (13.7)	
Operating room/procedure area/other[b]	6,680 (10.1)	203 (14.8)	
Admitting diagnosis, no. (%)			
Medical, cardiac	22,532 (34.1)	431 (31.6)	0.017
Surgical, cardiac	5,325 (8.1)	135 (9.9)	
Noncardiac	38,227 (57.8)	800 (58.6)	

(Continued)

TABLE 1. (*Continued*). Patient-Specific Characteristics According to Whether Therapeutic Hypothermia Was Initiated After Cardiac Arrest

Patient Characteristics	Standard Care ($n = 66,131$)	Hypothermia ($n = 1,367$)	p
Coexisting medical conditions, no. (%)[a]			
Acute nonstroke neurologic disorder	4,852 (8.3)	102 (8.7)	0.60
Acute stroke	2,312 (4.0)	36 (3.1)	0.13
Baseline central nervous system deficit[c]	7,278 (12.5)	149 (12.8)	0.76
Congestive heart failure at admission	11,014 (18.8)	202 (17.3)	0.18
Congestive heart failure prior to admission	12,499 (21.4)	238 (20.4)	0.40
Diabetes mellitus	18,997 (32.5)	349 (29.9)	0.06
Hepatic insufficiency	4,532 (7.8)	101 (8.6)	0.26
Human immunodeficiency virus	228 (0.4)	8 (0.7)	0.15
Hypotension	16,649 (28.5)	310 (26.5)	0.14
Major trauma	2,180 (3.7)	46 (3.9)	0.71
Metastatic or hematologic malignancy	6,818 (11.7)	110 (9.4)	0.017
Metabolic or electrolyte derangement	10,040 (17.2)	207 (17.7)	0.63
Myocardial infarction at admission	10,792 (18.5)	202 (17.3)	0.30
Myocardial infarction prior to admission	9,934 (17.0)	170 (14.6)	0.027
Pneumonia	8,023 (13.7)	141 (12.1)	0.10
Renal insufficiency	20,202 (34.6)	399 (34.2)	0.77
Respiratory insufficiency	25,071 (42.9)	484 (41.4)	0.31
Sepsis	9,575 (16.4)	189 (16.2)	0.85
Interventions prior to cardiac arrest, no. (%)			
Dialysis[a]	2,470 (4.0)	44 (3.8)	0.66
Mechanical ventilation	19,563 (29.6)	389 (28.5)	0.37
Vasoactive agent	15,526 (25.2)	281 (23.9)	0.34
Cause of cardiac arrest, no. (%)[a]			
Acute coronary syndrome	5,437 (8.8)	101 (8.4)	0.61
Acute pneumothorax	306 (0.5)	10 (0.8)	0.10
Acute pulmonary edema	1,067 (1.7)	19 (1.6)	0.69
Acute pulmonary embolism	1,046 (1.7)	23 (1.9)	0.57
Acute respiratory insufficiency	23,709 (38.5)	496 (41.3)	0.05
Acute stroke	511 (0.8)	10 (0.8)	0.99
Arrhythmia	37,962 (61.6)	776 (64.6)	0.038
Conscious/Procedural sedation	614 (1.0)	23 (1.9)	0.002
Hypotension	23,898 (38.8)	445 (37.0)	0.21
Hypothermia	386 (0.6)	13 (1.1)	0.049
Inadequate or obstruction of invasive airway	823 (1.3)	18 (1.5)	0.63
Inadequate or obstruction of natural airway	2,241 (3.6)	61 (5.1)	0.009
Invasive airway displacement	200 (0.3)	4 (0.3)	0.80

(Continued)

TABLE 1. (*Continued*). Patient-Specific Characteristics According to Whether Therapeutic Hypothermia Was Initiated After Cardiac Arrest

Patient Characteristics	Standard Care ($n = 66,131$)	Hypothermia ($n = 1,367$)	p
Malfunction of device for assisted ventilation	12 (0.02)	0 (0)	1.00
Metabolic abnormality	7,779 (12.6)	180 (15.0)	0.02
Status epilepticus	240 (0.4)	4 (0.3)	0.75
Adverse drug effect	231 (0.4)	13 (1.1)	< 0.001
Drug overdose	228 (0.4)	5 (0.4)	0.80
Time of cardiac arrest, no. (%)			
Time of day, night (11 PM to 7 AM)	19,656 (30.1)	393 (29.2)	0.50
Weekend (11 PM Friday to 7 AM Monday)	19,659 (29.8)	362 (26.6)	0.009
Duration of CPR, median (25% to 75%), min	13 (6–25)	14 (7–25)	< 0.001
Category of CPR duration, min			
0–5	14,959 (23.6)	232 (17.7)	
6–60	46,254 (73.0)	1,038 (79.3)	< 0.001
> 60	2,193 (3.5)	39 (3.0)	

CPC = cerebral performance category; VF = ventricular fibrillation; VT = pulseless ventricular tachycardia; CPR = cardiopulmonary resuscitation.
Continuous data are presented as medians with interquartile ranges (25th, 75th percentile), and categorical data are presented as counts and percentiles.
[a]Data were missing in > 5% of the cohort; available data presented.
[b]Includes postanesthesia care unit, same-day surgery, and cardiac catheterization laboratory.
[c]Includes baseline motor, cognitive, and/or functional deficit.

TABLE 2. Hospital-Level Characteristics According to Whether Therapeutic Hypothermia Was Initiated After Cardiac Arrest

Hospital Characteristics[a]	Standard Care ($n = 63,138$)	Hypothermia ($n = 1,281$)	p
Hospital size, no. (%)			0.002
< 250 beds	11,855 (18.8)	199 (15.5)	
250–499 beds	26,363 (41.8)	525 (41.0)	
≥ 500 beds	24,920 (39.5)	557 (43.5)	
Academic status, no. (%)			<0.001
Academic	24,038 (38.1)	596 (46.5)	
Community	18,401 (29.1)	301 (23.5)	
Nonteaching	20,699 (32.8)	384 (30.0)	
Geographic region, no. (%)			0.021
Northeast	8,530 (13.5)	181 (14.1)	
Southeast	16,915 (26.8)	308 (24.0)	
Midwest	15,482 (24.5)	305 (23.8)	
Southwest	12,125 (19.2)	243 (19.0)	
West	10,086 (16.0)	244 (19.0)	

[a]Hospital characteristics available for 64,419 subjects (95.4% of cohort).

TABLE 3. Factors Associated With the Initiation of Therapeutic Hypothermia After Cardiac Arrest in Multivariable Analysis

	Adjusted Odds Ratio (95% Confidence Interval)	*p*
Patient factor model (*n* = 62,472)		
Age (per 10 yr increase)	0.89 (0.86–0.92)	< 0.001
Gender (male)[a]	1.08 (0.96–1.22)	0.17
Admission source		
Home	Reference	Reference
Outside hospital transfer	0.82 (0.68–1.01)	0.059
Extended care facility	0.95 (0.77–1.16)	0.60
Other	1.11 (0.70–1.74)	0.66
Initial rhythm		
Asystole	Reference	Reference
PEA	0.91 (0.80–1.05)	0.20
VF/VT	0.97 (0.82–1.14)	0.70
Unknown	0.71 (0.54–0.93)	0.01
Event location		
Intensive care	Reference	Reference
Inpatient	1.35 (1.17–1.55)	< 0.001
Emergency department	1.99 (1.65–2.41)	< 0.001
Operating room/ procedure area	1.76 (1.46–2.11)	< 0.001
Admitting diagnosis		
Medical, cardiac	Reference	Reference
Surgical, cardiac	1.22 (0.98–1.51)	0.08
Noncardiac	1.06 (0.93–1.21)	0.37
Timing of cardiac arrest (weekend)[b]	0.85 (0.75–0.97)	0.02
Duration of CPR, min		
0–5	Reference	Reference
6–60	1.51 (1.30–1.76)	< 0.001
> 60	1.07 (0.75–1.52)	0.70
Hospital factor model (*n* = 64,419)		
Hospital size		
< 250 beds	Reference	Reference
250–499 beds	1.32 (0.93–1.89)	0.12
≥ 500 beds	1.32 (0.83–2.09)	0.24
Academic status		
Nonteaching	Reference	Reference
Community	0.99 (0.69–1.42)	0.97
Academic	1.57 (1.02–2.41)	0.04
Geographic region		
Northeast	Reference	Reference
Southeast	0.75 (0.46–1.22)	0.24
Midwest	0.74 (0.45–1.21)	0.23
Southwest	0.79 (0.48–1.31)	0.37
West	1.10 (0.66–1.82)	0.71
Complete model (*n* = 61,766)		
Age (per 10 yr increase)	0.89 (0.86–0.93)	< 0.001
Initial rhythm		
Asystole	Reference	Reference
PEA	0.89 (0.77–1.02)	0.10
VF/VT	0.93 (0.79–1.09)	0.37
Unknown	0.68 (0.52–0.90)	0.007
Event location		
Intensive care	Reference	Reference
Inpatient	1.33 (1.16–1.53)	< 0.001
Emergency department	2.02 (1.67–2.44)	< 0.001
Operating room/ procedure area	1.81 (1.50–2.17)	< 0.001
Timing of cardiac arrest (weekend)[b]	0.82 (0.72–0.94)	0.005
Duration of CPR, min		
0–5	Reference	Reference
6–60	1.48 (1.27–1.73)	< 0.001
> 60	1.03 (0.72–1.48)	0.86
Academic status of hospital		
Nonteaching	Reference	Reference
Community	1.07 (0.74–1.52)	0.72
Academic	1.82 (1.26–2.63)	0.001

(Continued)

PEA = pulseless electrical activity; VF = ventricular fibrillation; VT = pulseless ventricular tachycardia; CPR = cardiopulmonary resuscitation.

[a]Gender was forced into the patient-factor model.

[b]Weekend was defined as 11 PM Friday to 7 AM Monday.

that this potentially beneficial therapy will rarely be used unless TH after IHCA is demonstrated to improve outcomes in high-quality observational studies or clinical trials. Additional explanations, drawn from survey research on the use of TH, include lack of an institutional TH protocol, lack of resources to implement TH, technical challenges, and initial attempts to use TH, which were unsatisfactory (20, 21, 36, 37).

When TH was initiated, we found that the target temperature was not achieved in 44% of patients and overcooling occurred in 18% of patients. These findings confirm prior work, including the HACA trial wherein 14% of patients could not achieve the target temperature (5), and a recent study demonstrating overcooling is common and potentially harmful (38). As the means of cooling were not recorded, we are unable to compare the effectiveness of different approaches (e.g., surface vs. endovascular cooling) to achieve target temperature. The optimal approach to effective cooling remains an active area of research. Further efforts, including the use of a TH protocol and iterative assessments of protocol adherence, are required to ensure the safe and effective implementation of TH.

We found that patient age and the location and duration of arrest were associated with TH initiation. In this observational study, we were unable to determine why these patients were more likely to receive TH. One plausible explanation is that these patients most closely approximated those patients included in the OHCA trials (4, 5). However, even among those patients identified as more likely to have TH initiated, use remained low. For example, TH was initiated in 2.1% of inpatient cases, in 2.7% of ED cases, and in 3.0% of procedural area cases. As recently as 2009, only 5.9% of patients received TH when the event occurred in the ED and the initial rhythm was VF/VT. Since GWTG-R is a registry of in-hospital resuscitation, this finding cannot be used as evidence that TH is underutilized after OHCA from VF/VT; however, it is a signal that warrants further investigation.

Contrary to our hypothesis and the results of recent survey studies (20, 21), we found no significant difference in the rate of TH use by initial cardiac rhythm. However, consistent with a recent single-center study (34), we found that when there was uncertainty regarding the initial rhythm, TH was less likely to be used. Finally, it appeared that TH was more likely to be initiated when VF/VT occurred at any time during the event. As recent evidence suggests, IHCA with an initial nonshockable rhythm that transitions to VF/VT is commonplace and outcomes are dismal (35). Future observational studies will need to account for this potential bias when assessing the effectiveness of TH.

Our findings that TH, an admittedly complex therapy, was less likely to be initiated on weekends and more likely to be initiated in teaching hospitals are consistent with prior research. In patients with myocardial infarction, weekend admission is associated with higher mortality, which appears to be mediated, in part, by the lower rate of invasive cardiac procedures (39). Similar to emergency procedures, TH relies on expertise, staffing, and ancillary support, all of which may be less readily available over the weekend. Alternatively, this finding could reflect differences in patients who arrest over the weekend or differences in cardiac arrest data tracking and reporting. Recently, it was found that survival rates are lower during weekends (2); whether increased use of TH would attenuate this apparent outcome disparity is unknown.

There are several limitations to our study. First, our study focused on the use of TH, not the outcomes associated with its use. Whether outcomes would have been improved had TH been used more frequently and implementation been more effective remains unknown. While we eagerly await high-quality studies examining whether TH is safe and effective after IHCA, our findings suggest that observational studies will be challenging given the rare use of TH in this population, the apparent selection bias, the potential for residual confounding after adjustment (e.g., glucose variability (40), time to defibrillation (18, 19), and duration of CPR (41)), the use of TH in patients who have poor outcomes (e.g., those who transition to VF/VT), the failure to implement TH effectively (e.g., inability to achieve target temperature), and significant variability in TH use and outcomes at the hospital level (19). Second, our designation of TH use relied on self-reporting by participating centers, and the clustering of "no" and "not documented" may have resulted in TH use being underreported. Further, our assessment of protocol adherence was limited to the ability to achieve target temperature; further investigation is required to ascertain whether target temperature was sustained once achieved. Third, our results may underestimate the true rate of appropriate use of TH since we were unable to exclude patients who were not comatose post-ROSC. Importantly, we cannot exclude the possibility that some patients had a relative or absolute contraindication to the use of TH (e.g., active hemorrhage and transitioning to comfort measures). However, when we analyzed the subset of patients on mechanical ventilation after IHCA or with a finite duration of CPR, as reasonable surrogates to assess for comatose state with precedent (31), we found a similar rate of TH use. Furthermore, even if we were to exclude half of the patients in whom TH was not initiated as having a contraindication based on a recent study (31), we estimate that TH would be initiated in approximately 4% of IHCA cases. Fourth, as a study based on a national registry, it is unclear how often TH is applied after IHCA internationally. Fifth, we did not include a penalty for multiple comparisons in our multivariable analyses; however, if we used a conservative significance level of 0.005, the factors associated with TH use would remain significant. Finally, we acknowledge that important factors (e.g., race) could not be examined in our multivariable analyses due to missing data.

In conclusion, our study revealed that despite formal recommendations "to consider" the use of TH after IHCA, during the time period of this study TH was used infrequently. While the frequency of use increased over time, use remained low. Our multicenter sample of United States hospitals suggests community equipoise for a clinical trial of TH after IHCA.

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APPENDIX

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