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Association Between Therapeutic Hypothermia and Survival After In-Hospital Cardiac Arrest

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IMPORTANCE Therapeutic hypothermia is used for patients following both out-of-hospital and in-hospital cardiac arrest. However, randomized trials on its efficacy for the in-hospital setting do not exist, and comparative effectiveness data are limited.

OBJECTIVE To evaluate the association between therapeutic hypothermia and survival after in-hospital cardiac arrest.

DESIGN, SETTING, AND PATIENTS In this cohort study, within the national Get With the Guidelines–Resuscitation registry, 26 183 patients successfully resuscitated from an in-hospital cardiac arrest between March 1, 2002, and December 31, 2014, and either treated or not treated with hypothermia at 355 US hospitals were identified. Follow-up ended February 4, 2015.

EXPOSURE Induction of therapeutic hypothermia.

MAIN OUTCOMES AND MEASURES The primary outcome was survival to hospital discharge. The secondary outcome was favorable neurological survival, defined as a Cerebral Performance Category score of 1 or 2 (ie, without severe neurological disability). Comparisons were performed using a matched propensity score analysis and examined for all cardiac arrests and separately for nonshockable (asystole and pulseless electrical activity) and shockable (ventricular fibrillation and pulseless ventricular tachycardia) cardiac arrests.

RESULTS Overall, 1568 of 26 183 patients with in-hospital cardiac arrest (6.0%) were treated with therapeutic hypothermia; 1524 of these patients (mean [SD] age, 61.6 [16.2] years; 58.5% male) were matched by propensity score to 3714 non–hypothermia-treated patients (mean [SD] age, 62.2 [17.5] years; 57.1% male). After adjustment, therapeutic hypothermia was associated with lower in-hospital survival (27.4% vs 29.2%; relative risk [RR], 0.88 [95% CI, 0.80 to 0.97]; risk difference, −3.6% [95% CI, −6.3% to −0.9%]; $P = .01$), and this association was similar (interaction $P = .74$) for nonshockable cardiac arrest rhythms (22.2% vs 24.5%; RR, 0.87 [95% CI, 0.76 to 0.99]; risk difference, −3.2% [95% CI, −6.2% to −0.3%]) and shockable cardiac arrest rhythms (41.3% vs 44.1%; RR, 0.90 [95% CI, 0.77 to 1.05]; risk difference, −4.6% [95% CI, −10.9% to 1.7%]). Therapeutic hypothermia was also associated with lower rates of favorable neurological survival for the overall cohort (hypothermia-treated group, 17.0% [246 of 1443 patients]; non–hypothermia-treated group, 20.5% [725 of 3529 patients]; RR, 0.79 [95% CI, 0.69 to 0.90]; risk difference, −4.4% [95% CI, −6.8% to −2.0%]; $P < .001$) and for both rhythm types (interaction $P = .88$).

CONCLUSIONS AND RELEVANCE Among patients with in-hospital cardiac arrest, use of therapeutic hypothermia compared with usual care was associated with a lower likelihood of survival to hospital discharge and a lower likelihood of favorable neurological survival. These observational findings warrant a randomized clinical trial to assess efficacy of therapeutic hypothermia for in-hospital cardiac arrest.

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Supplemental content

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Therapeutic hypothermia, or targeted temperature management, is recommended for comatose patients following both out-of-hospital and in-hospital cardiac arrest.[1] Nevertheless, therapeutic hypothermia has only been shown to improve overall survival and rates of favorable neurological survival in patients with out-of-hospital cardiac arrest due to ventricular fibrillation.[2,3] Whether this treatment improves survival for patients with in-hospital cardiac arrest—in which response times, comorbidity burden, and cardiac arrest etiology differ markedly from the out-of-hospital setting—is unknown.

To our knowledge, there have been no randomized trials conducted in the in-hospital setting. Two small observational studies (comprising a total of 231 treated patients) have not shown a survival benefit,[4,5] and a third included only 42 treated patients with in-hospital cardiac arrest.[6] In addition, more than 80% of in-hospital cardiac arrests have initial rhythms of asystole or pulseless electrical activity (PEA), cardiac arrest rhythms for which the evidence base for therapeutic hypothermia is unclear, even for the out-of-hospital setting.[7] As in-hospital cardiac arrest affects approximately 200 000 individuals annually in the United States,[8] there is a need to understand whether therapeutic hypothermia is associated with improved survival for these patients.

To address this gap in knowledge, this study was designed to evaluate the association of hypothermia treatment with survival to hospital discharge and with favorable neurological survival at hospital discharge among patients with in-hospital cardiac arrest. Data were leveraged from the Get With the Guidelines (GWTG)–Resuscitation registry. In addition, by linking this registry with Medicare files, the association between hypothermia treatment and 1-year survival was evaluated.

Key Points

Question Is therapeutic hypothermia associated with better survival outcomes for patients with in-hospital cardiac arrest?

Findings In this cohort study using a US national registry, survival outcomes were compared for 26 183 patients who were treated vs not treated with therapeutic hypothermia after surviving an in-hospital cardiac arrest. Compared with untreated patients, those treated with therapeutic hypothermia had significantly lower rates of in-hospital survival (29.2% vs 27.4%, respectively), as well as lower rates of survival to discharge with favorable neurological status.

Meaning Therapeutic hypothermia was not associated with improved survival or better neurological outcomes and was potentially harmful. Current use of therapeutic hypothermia for in-hospital cardiac arrest may warrant reconsideration.

Methods

The institutional review board of Saint Luke's Mid America Heart Institute approved this study and waived the requirement for informed consent because data were deidentified.

Data Sources

The GWTG-Resuscitation registry is a large, prospective, national, quality improvement registry of in-hospital cardiac arrest sponsored by the American Heart Association. Its design has been previously described.[9] In brief, trained hospital personnel attempt to identify all patients without do-not-resuscitate orders with a cardiac arrest (defined as absence of a palpable central pulse, apnea, and unresponsiveness) who undergo cardiopulmonary resuscitation. Cases are identified by hospital research staff through multiple methods, including centralized collection of cardiac arrest flow sheets, reviews of hospital paging system logs, and routine checks of code carts and pharmacy tracer drug records.[9] Standardized Utstein-style definitions are used for all patient variables and outcomes to facilitate uniform reporting across hospitals.[10,11] Data accuracy in GWTG-Resuscitation is supported by certification of research staff, use of case-study methods for newly enrolled hospitals to enhance operational definition compliance prior to data acceptance, use of standardized software with data checks for completeness and accuracy, and a periodic reabstraction process, which has been demonstrated to have a mean error rate of 2.4%.[9]

For patients aged 65 years and older, GWTG-Resuscitation data have been previously linked with Medicare inpatient files.[12,13] For each linked patient, Medicare denominator and inpatient files were obtained. For this study, as newer years of Medicare files were available, the deterministic linkage was repeated for Medicare data through 2012. This linkage was successful in 66.5% of Medicare-eligible patients in GWTG-Resuscitation, similar to the prior rate of 68.6%.[13]

Study Population

The study included patients aged 18 years and older enrolled in GWTG-Resuscitation between March 1, 2002 (after publication of hypothermia trials for out-of-hospital cardiac arrest[2,3]), and December 31, 2014. As this study evaluated therapeutic hypothermia, only patients with return of spontaneous circulation after an index in-hospital cardiac arrest were included. For those aged 65 years and older, patients who were not linked to Medicare inpatient files (no unique match or enrolled after 2012) were excluded to enable examination of postdischarge survival. To ascertain that hypothermia was available at each hospital, patients from hospitals with no cases of therapeutic hypothermia were excluded. Moreover, only cases occurring after the first documented use of therapeutic hypothermia for in-hospital cardiac arrest at each hospital were included. As therapeutic hypothermia is considered in comatose patients, the cohort was restricted to patients on mechanical ventilation at the time of cardiac arrest (as documented by GWTG-Resuscitation) or after cardiac arrest (as documented by a Medicare *International Classification of Diseases, Ninth Revision, Clinical Modification* procedure code for mechanical ventilation [96.7X] among those aged ≥65 years). Patients with missing information on survival to discharge and comorbidities for model adjustment were excluded. Furthermore, patients with an initial out-of-hospital cardiac arrest followed by an in-hospital cardiac arrest were excluded.

Independent Variable and Study Outcomes

The independent exposure variable was active induction of therapeutic hypothermia, as documented within GWTG-Resuscitation. The primary outcome was in-hospital survival (ie, to hospital discharge). The secondary outcome was favorable neurological survival, defined as survival to hospital discharge with a Cerebral Performance Category score of 1 or 2 (ie, without severe neurological disability).[14] Additionally, among patients aged 65 years and older, cumulative survival (ie, area under the survival curve) over the first year and 1-year survival were examined using Medicare denominator files. The last follow-up date was February 4, 2015, for survival to discharge and favorable neurological survival and December 31, 2012, for 1-year outcomes.

Statistical Analysis

Baseline differences between patients treated and not treated with therapeutic hypothermia were evaluated using χ^2 tests for categorical variables and *t* tests for continuous variables.

To evaluate the association between therapeutic hypothermia treatment and survival outcomes, propensity score analyses were conducted. A multivariable logistic regression model was constructed to estimate a patient's likelihood of being treated with therapeutic hypothermia after in-hospital cardiac arrest. This model included the hospital site and the following variables from GWTG-Resuscitation: age, sex, self-identified race by patients or families (which is known to affect survival[15] and was categorized as white, black, and other), initial cardiac arrest rhythm (asystole, PEA, ventricular fibrillation, and pulseless ventricular tachycardia), location of cardiac arrest, comorbid conditions (prior heart failure or myocardial infarction, index admission heart failure or myocardial infarction, diabetes mellitus, baseline depression in central nervous system function, acute stroke, pneumonia, and metastatic or hematologic malignant neoplasm), medical conditions present within 24 hours of cardiac arrest (renal insufficiency, hepatic insufficiency, respiratory insufficiency, hypotension, septicemia, and metabolic or electrolyte abnormality), and interventions in place at the time of cardiac arrest (continuous intravenous vasopressor, implantable cardioverter-defibrillator, and hemodialysis). The model also adjusted for duration of acute cardiopulmonary resuscitation, the time of day (work hours [7:00 AM to 10:59 PM] vs after hours [11:00 PM to 6:59 AM]), and day of the week (weekday vs weekend) of the cardiac arrest.[16]

After deriving a propensity score for each patient, variable optimal matching for each hypothermia-treated patient was performed, with up to 4 controls without replacement for each treated patient, using an algorithm match with a caliper width no greater than 0.2 times the standard deviation of the logit of the propensity score.[17] Besides matching by propensity score, hypothermia-treated and non–hypothermia-treated patients were additionally matched on 3 other criteria: cardiac arrest within 365 days of the hypothermia-treated patient's cardiac arrest, initial cardiac arrest rhythm, and duration of acute cardiopulmonary resuscitation (in 5-minute categories [eg, 6-10 minutes, 11-15 minutes, 16-20 minutes]). Matched patients were compared to assess balance in covariates (ie, standardized differences for each covariate were <10%).[18] After confirming this, the associations between therapeutic hypothermia and survival to discharge and favorable neurological survival were assessed by constructing binomial models using a log link stratified by matched sets to estimate relative risks (RRs) as well as an identity link to estimate risk differences.[19]

Interaction analyses were conducted between therapeutic hypothermia and cardiac arrest rhythm to assess whether the association between therapeutic hypothermia and survival outcomes differed for patients with shockable (ventricular fibrillation and pulseless ventricular tachycardia) and nonshockable (asystole and PEA) cardiac arrest rhythms. For 1-year survival, a separate propensity score model was derived for patients aged 65 years and older. Cumulative survival over the first year was compared between the propensity score–matched patients. In addition, a binomial model using a log link stratified by matched sets assessed overall rates of 1-year survival.

Although use of a propensity score balances measured covariates between treatment groups, indication bias due to unmeasured confounding may exist. To address this, a sensitivity analysis was conducted whereby all patients who died within the first 24 hours were excluded. If there was indication bias against therapeutic hypothermia treatment (whereby sicker patients were more likely to receive therapeutic hypothermia), this analysis, from 24 hours onward, would result in a stronger survival benefit for therapeutic hypothermia treatment, as a greater proportion of patients treated with hypothermia would have died during the first 24 hours. This sensitivity analysis was conducted after deriving new propensity scores for this cohort and reperforming the previous analyses.

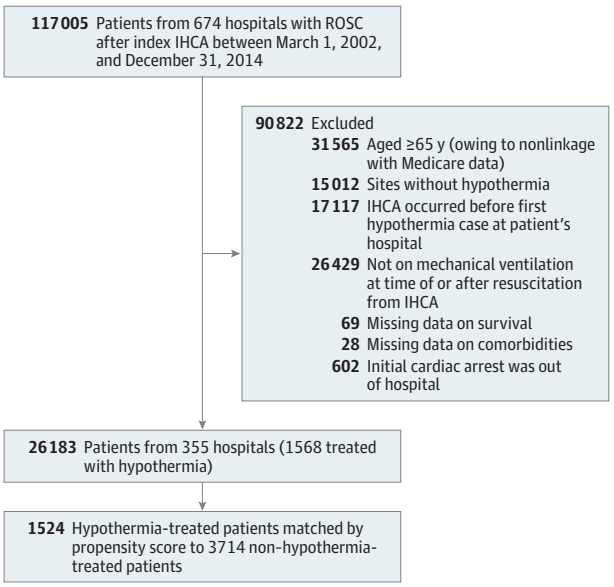
For each analysis, the null hypothesis was evaluated at a 2-sided significance level of .05, and 95% confidence intervals were calculated using robust standard errors. All analyses were performed using SAS version 9.2 (SAS Institute Inc) and R version 2.10.0 (R Foundation for Statistical Computing) statistical software.

Results

An initial 117 005 patients with in-hospital cardiac arrest with return of spontaneous circulation from 674 hospitals were identified (**Figure**). A total of 90 822 patients were excluded: 31 565 were not linked with Medicare data, 15 012 were from hospitals without hypothermia cases, 17 117 had an in-hospital cardiac arrest prior to the first patient treated with therapeutic hypothermia at their hospital, 26 429 were not on mechanical ventilation, 69 were missing data on survival, 28 were missing data on comorbidities, and 602 had an initial out-of-hospital cardiac arrest. The final cohort included 26 183 patients from 355 hospitals who were successfully resuscitated after in-hospital cardiac arrest.

Overall, 1568 patients (6.0%) were treated with therapeutic hypothermia. Patients treated with hypothermia were younger, less likely to have a cardiac arrest in the intensive care unit, and more likely to have an initial cardiac arrest rhythm

Figure. Derivation of the Study Cohort



IHCA indicates in-hospital cardiac arrest; ROSC, return of spontaneous circulation.

of ventricular fibrillation (**Table 1**). The duration of resuscitation before return of spontaneous circulation was similar between patients treated with and without hypothermia, but patients with therapeutic hypothermia initiated were more likely to have a myocardial infarction prior to their cardiac arrest and less likely to have hypotension, respiratory insufficiency, renal insufficiency, hepatic insufficiency, pneumonia, acute stroke, and a metastatic or hematologic malignant neoplasm at the time of their cardiac arrest.

The propensity score for the overall cohort had good discrimination (C statistic of 0.783) and led to the successful matching of 1524 patients treated with hypothermia (mean [SD] age, 61.6 [16.2] years; 58.5% male) to 3714 patients not treated with hypothermia (mean [SD] age, 62.2 [17.5] years; 57.1% male). The mean (SD) age of the propensity score–matched cohort was 62.0 (17.5) years, 57.5% were men, and 68.0% were white. Prior differences in age, sex, race, initial cardiac arrest rhythm, location of arrest, and comorbidities were well balanced after matching for the overall cohort (Table 1) and by rhythm type (eTable 1 in the Supplement). Temperature data (optional data element) were available for 364 matched patients treated with hypothermia (23.9%) and 607 not treated with hypothermia (16.3%). The median lowest achieved temperature was 33.1°C (interquartile range [IQR], 32.3°C-35.7°C) in hypothermia-treated patients (with 76 [20.9%] below the recommended nadir of 32°C) and 36.3°C (IQR, 35.6°C-36.8°C) in non-hypothermia-treated patients ($P < .001$).

Survival to Discharge

In the overall propensity score–matched cohort, 417 patients treated with therapeutic hypothermia (27.4%) survived to hospital discharge, as compared with 1084 non-hypothermia-treated patients (29.2%). Therapeutic hypothermia was associated with a lower likelihood of in-hospital survival (relative risk [RR], 0.88 [95% CI, 0.80 to 0.97]; risk difference, −3.6% [−6.3% to −0.9%]; $P = .01$), and this association was similar (interaction $P = .74$) for nonshockable cardiac arrest rhythms (22.2% vs 24.5%; RR, 0.87 [95% CI, 0.76 to 0.99]; risk difference, −3.2% [95% CI, −6.2% to −0.3%]) and shockable cardiac arrest rhythms (41.3% vs 44.1%; RR, 0.90 [95% CI, 0.77 to 1.05]; risk difference, −4.6% [95% CI, −10.9% to 1.7%]) (**Table 2**).

A lower proportion of patients in the hypothermia-treated group died during the first day than in the non-hypothermia-treated group (29.1% vs 45.0%, respectively; $P < .001$). In sensitivity analysis, wherein the study cohort was restricted to the 3124 propensity score–matched patients who survived the first 24 hours after cardiac arrest (59.6%), all associations between therapeutic hypothermia and survival persisted (eTable 2 in the Supplement). In addition, survival results were not due to higher rates of de novo do-not-resuscitate orders in the hypothermia group after achieving return of spontaneous circulation (eTable 3 in the Supplement).

Favorable Neurological Survival

Information on favorable neurological survival was missing for 81 hypothermia-treated patients (5.3%) and 185 non-hypothermia-treated patients (5.0%). After excluding these patients, therapeutic hypothermia was associated with a lower likelihood of favorable neurological survival for all rhythms (246 of 1443 hypothermia-treated patients [17.0%] vs 725 of 3529 non-hypothermia-treated patients [20.5%]; RR, 0.79 [95% CI, 0.69 to 0.90]; risk difference, −4.4% [95% CI, −6.8% to −2.0%]; $P < .001$), with similar patterns in patients with nonshockable and shockable rhythms (interaction $P = .88$) (Table 2). These results did not change when the analyses were restricted to propensity score–matched patients who survived the first 24 hours after cardiac arrest (eTable 2 in the Supplement).

One-Year Survival

Among 2741 propensity score–matched patients successfully linked to Medicare inpatient files, 706 patients treated with therapeutic hypothermia were matched to 2035 non-hypothermia-treated controls. Cumulative survival throughout the first year was similar between the 2 groups (mean, 2.21 months [95% CI, 1.89-2.53] vs 2.20 months [95% CI, 2.02-2.39], respectively; $P = .92$) (**Table 3** and eFigure in the Supplement). At 1 year, 100 hypothermia-treated patients (14.2%) and 286 non-hypothermia-treated patients (14.1%) were alive, and there were no differences in 1-year survival between the 2 groups overall (RR, 1.00 [95% CI, 0.96-1.03]; $P = .94$) and by rhythm type (Table 3).

Discussion

In a large national registry, treatment with therapeutic hypothermia was not associated with higher rates of survival to discharge or favorable neurological survival in patients with in-hospital cardiac arrest and was associated with potential harm. These associations were similar for both shockable and nonshockable cardiac arrest rhythms. When follow-up was

Table 1. Comparison of Hypothermia-Treated and Non–Hypothermia-Treated Patients Before and After Propensity Score Matching

Characteristic	Before Propensity Score Matching			After Propensity Score Matching[a]		
	Hypothermia (n = 1568)	No Hypothermia (n = 24 615)	*P* Value	Hypothermia (n = 1524)	No Hypothermia (n = 3714)	Standardized Difference, %
Demographics						
Age, mean (SD), y	61.5 (16.2)	63.9 (16.9)	<.001	61.6 (16.2)	62.2 (17.5)	3.2
Male, No. (%)	908 (57.9)	13 750 (55.9)	.11	892 (58.5)	2120 (57.1)	1.7
Race, No. (%)						
White	1044 (66.6)	17 184 (69.8)	.07	1015 (66.6)	2548 (68.6)	5.0
Black	377 (24.0)	5315 (21.6)		366 (24.0)	870 (23.4)	
Other	147 (9.4)	2116 (8.6)		143 (9.4)	296 (8.0)	
Cardiac arrest factors						
CPR duration, min						
Mean (SD)	16.5 (18.7)	16.3 (19.0)	.78	16.5 (18.7)	16.3 (18.8)	2.7
Median (IQR)	11.0 (8.0-22.0)	10.0 (8.0-21.0)	.09	11.0 (8.0-22.0)	11.0 (8.0-21.0)	NA[b]
Location of cardiac arrest, No. (%)						
Intensive care unit	852 (54.3)	15 908 (64.6)	<.001	830 (54.5)	2208 (59.5)	8.3
Telemetry unit	126 (8.0)	2495 (10.1)		126 (8.3)	330 (8.9)	
Nonmonitored hospital unit	152 (9.7)	2248 (9.1)		149 (9.8)	347 (9.3)	
Emergency department	254 (16.2)	2046 (8.3)		248 (16.3)	475 (12.8)	
Procedural area	165 (10.5)	1737 (7.1)		154 (10.1)	319 (8.6)	
Other	19 (1.2)	181 (0.7)		17 (1.1)	35 (0.9)	
Time of cardiac arrest, No. (%)						
Night, 11 PM to 6:59 AM	451 (28.8)	7693 (31.3)	.04	436 (28.6)	1101 (29.6)	1.3
Weekend	492 (31.4)	7846 (31.9)	.68	481 (31.6)	1171 (31.5)	0.1
Initial cardiac arrest rhythm, No. (%)						
Asystole	407 (26.0)	7016 (28.5)	<.001	397 (26.0)	1000 (26.9)	2.7
Pulseless electrical activity	735 (46.9)	12 785 (51.9)		715 (46.9)	1832 (49.3)	
Ventricular fibrillation	263 (16.8)	2548 (10.4)		254 (16.7)	500 (13.5)	
Pulseless ventricular tachycardia	163 (10.4)	2266 (9.2)		158 (10.4)	382 (10.3)	
Preexisting conditions, No. (%)						
Heart failure this admission	250 (15.9)	4423 (18.0)	.04	244 (16.0)	581 (15.6)	0.3
Heart failure prior to admission	310 (19.8)	5030 (20.4)	.53	304 (19.9)	717 (19.3)	1.5
MI this admission	346 (22.1)	3804 (15.5)	<.001	338 (22.2)	728 (19.6)	5.2
MI prior to admission	252 (16.1)	3600 (14.6)	.12	248 (16.3)	570 (15.3)	2.0
Hypotension[c]	494 (31.5)	8817 (35.8)	<.001	473 (31.0)	1239 (33.4)	3.9
Respiratory insufficiency[c]	818 (52.2)	13 828 (56.2)	.001	797 (52.3)	2015 (54.3)	2.3
Renal insufficiency[c]	514 (32.8)	9289 (37.7)	<.001	502 (32.9)	1248 (33.6)	0.7
Hepatic insufficiency[c]	106 (6.8)	2300 (9.3)	<.001	103 (6.8)	307 (8.3)	4.5
Metabolic or electrolyte abnormality[c]	310 (19.2)	5197 (21.1)	.07	291 (19.1)	740 (19.9)	1.3
Diabetes mellitus	475 (30.3)	7545 (30.7)	.77	462 (30.3)	1062 (28.6)	2.4
Baseline depression in CNS function	216 (13.8)	3341 (13.6)	.82	211 (13.8)	495 (13.3)	0.1
Major trauma	71 (4.5)	1702 (6.9)	<.001	68 (4.5)	215 (5.8)	5.4
Acute stroke	50 (3.2)	1125 (4.6)	.01	49 (3.2)	133 (3.6)	2.1
Pneumonia	227 (14.5)	4304 (17.5)	.002	225 (14.8)	607 (16.3)	5.0
Septicemia[c]	263 (16.8)	5404 (22.0)	<.001	258 (16.9)	716 (19.3)	4.6
Metastatic or hematologic malignant neoplasm	122 (7.8)	2784 (11.3)	<.001	119 (7.8)	355 (9.6)	5.5
Interventions in place at time of arrest, No. (%)						
Continuous intravenous vasopressor	572 (36.5)	9157 (37.2)	.57	554 (36.4)	1371 (36.9)	1.1
Dialysis or extracorporeal filtration	53 (3.4)	1144 (4.6)	.02	52 (3.4)	126 (3.4)	0.1
Preexisting ICD	31 (2.0)	444 (1.8)	.62	30 (2.0)	75 (2.0)	0.0

Abbreviations: CNS, central nervous system; CPR, cardiopulmonary resuscitation; ICD, implantable cardioverter-defibrillator; IQR, interquartile range; MI, myocardial infarction; NA, not applicable.

[a] Patient and cardiac arrest factors were well balanced (ie, standardized differences <10%) after propensity score matching.

[b] Standardized difference cannot be calculated for a comparison of medians.

[c] Conditions that were present within 24 hours of cardiac arrest.

Table 2. In-Hospital Outcomes and Model Results

Survival	Patients, No./Total No. (%)		Relative Risk With Hypothermia (95% CI)[a]	Risk Difference With Hypothermia, % (95% CI)[a,b]	*P* Value[c]	*P* Value for Interaction[d]
	Hypothermia	No Hypothermia				
Survival to discharge						
All cardiac arrests	417/1524 (27.4)	1084/3714 (29.2)	0.88 (0.80 to 0.97)	−3.6 (−6.3 to −0.9)	.01	
Nonshockable cardiac arrests	247/1112 (22.2)	695/2832 (24.5)	0.87 (0.76 to 0.99)	−3.2 (−6.2 to −0.3)		.74
Shockable cardiac arrests	170/412 (41.3)	389/882 (44.1)	0.90 (0.77 to 1.05)	−4.6 (−10.9 to 1.7)		
Favorable neurological survival[e]						
All cardiac arrests	246/1443 (17.0)	725/3529 (20.5)	0.79 (0.69 to 0.90)	−4.4 (−6.8 to −2.0)	<.001	
Nonshockable cardiac arrests	137/1054 (13.0)	446/2723 (16.4)	0.78 (0.64 to 0.93)	−3.7 (−6.2 to −1.1)		.88
Shockable cardiac arrests	109/389 (28.0)	279/806 (34.6)	0.79 (0.65 to 0.97)	−7.3 (−13.3 to −1.3)		

[a] Both relative risks and absolute risk differences are reported for propensity score–matched cohorts.

[b] Risk difference is calculated as the absolute survival rate with hypothermia treatment minus the rate with no hypothermia treatment.

[c] For comparison of outcomes in the overall cohort.

[d] Interaction between hypothermia and initial cardiac arrest rhythm tests whether the estimates of effect were different in the shockable and nonshockable rhythm subgroups.

[e] Survival to discharge with a Cerebral Performance Category score of 1 or 2. Information on neurological status was not available for 81 hypothermia-treated patients and 185 non–hypothermia-treated patients.

Table 3. One-Year Outcomes and Model Results[a]

Cardiac Arrests	Patients With 1-y Survival, No./Total No. (%)		Cumulative Survival in First Year, Mean (95% CI), mo			Alive at 1 y			
	Hypothermia	No Hypothermia	Hypothermia	No Hypothermia	*P* Value	Relative Risk With Hypothermia (95% CI)	Risk Difference With Hypothermia, % (95% CI)[b]	*P* Value[c]	*P* Value for Interaction[d]
All	100/706 (14.2)	286/2035 (14.1)	2.21 (1.89 to 2.53)	2.20 (2.02 to 2.39)	.92	1.00 (0.96 to 1.03)	−0.1 (−3.1 to 2.9)	.94	
Nonshockable	60/537 (11.2)	184/1587 (11.6)	1.83 (1.49 to 2.16)	1.84 (1.65 to 2.04)	.93	1.01 (0.97 to 1.04)	0.5 (−2.7 to 3.6)		.53
Shockable	40/169 (23.7)	102/448 (22.8)	3.44 (2.65 to 4.23)	3.44 (2.97 to 3.91)	.99	0.97 (0.88 to 107)	−2.2 (−9.7 to 5.4%)		

[a] Results reported for mean cumulative survival during the first year and whether patients were alive at 1 year. Cumulative 1-year survival quantifies the area under the survival curve during the first year of follow-up.

[b] Risk difference is calculated as the absolute survival rate with hypothermia treatment minus the rate with no hypothermia treatment.

[c] For comparison of outcomes in the overall cohort.

[d] Interaction between hypothermia and initial cardiac arrest rhythm tests whether the estimates of effect were different in the shockable and nonshockable rhythm subgroups.

extended to 1 year, there remained no survival advantage with therapeutic hypothermia treatment. Collectively, these findings do not support current use of therapeutic hypothermia for patients with in-hospital cardiac arrest.

To our knowledge, there are no randomized trials of therapeutic hypothermia for in-hospital cardiac arrest, and observational studies are scant and have been underpowered. Kory et al[4] found no difference in rates of survival to discharge between 17 hypothermia-treated patients (24%) and 16 non-hypothermia-treated patients (31%) (*P* = .62). An early study within GWTG-Resuscitation found no difference in rates of favorable neurological survival between 214 hypothermia-treated patients (18.7%) vs 8102 non–hypothermia-treated patients (20.1%), but that study involved few patients treated with hypothermia and did not restrict analyses to sites with hypothermia capability.[5] A more recent study[6] reported improved survival among 42 hypothermia-treated patients, but this study used a limited propensity score derived from 5 factors unrelated to in-hospital cardiac arrest.[20] The current study extends the findings of prior studies by including a large study sample, restricting the analyses to hospitals with therapeutic hypothermia capability, requiring all study patients to be on mechanical ventilation, using a robust propensity score, examining outcomes for both shockable and nonshockable cardiac arrest rhythms, and evaluating both in-hospital and 1-year survival.

A particular focus of this study was to assess whether unmeasured factors leading to indication bias (eg, initiating hypothermia in those with a worse prognosis) influenced study results. To address this, a sensitivity analysis that excluded patients who died within the first 24 hours after return of spontaneous circulation was conducted; it found that a lower proportion of patients treated with hypothermia died within the first day. This suggests that either therapeutic hypothermia was protective during the first 24 hours after return of spontaneous circulation but was not effective overall, or that any indication bias was in favor of patients treated with hypothermia.

Another potential concern is that GWTG-Resuscitation does not collect information on comatose status among patients resuscitated from an in-hospital cardiac arrest. To overcome this limitation, patients were required to be on mechanical ventilation at the time of, or after, cardiac arrest as a surrogate for comatose status. Given a mean duration of cardiopulmonary resuscitation of 16 minutes in both groups and

the additional requirement of mechanical ventilation, it is likely that only a few noncomatose patients were included in the study cohort, and any misclassification would be expected to be nondifferential. Nonetheless, potential indication bias and misclassification of comatose status further suggest that this study's findings warrant confirmation with a randomized clinical trial.

The finding that therapeutic hypothermia was not associated with better survival outcomes may raise questions about plausibility. However, clinical trials have found that therapeutic hypothermia leads to worse survival outcomes for other conditions, such as traumatic brain injury[21,22] and bacterial meningitis.[23] To date, the only randomized trials to examine therapeutic hypothermia vs no temperature management have been for out-of-hospital cardiac arrest.[2,3] In-hospital cardiac arrest is a different condition with faster response times (median times of <1 minute to cardiopulmonary resuscitation, 1 minute to first defibrillation,[24] and 3 minutes to first epinephrine dose[25]), potentially limiting the theorized benefit of therapeutic hypothermia to reduce free radical–mediated reperfusion injury from anoxic brain injury.[26] Moreover, 4 in 5 patients with in-hospital cardiac arrest have an initial rhythm of asystole or PEA, cardiac arrest rhythms for which randomized trials of therapeutic hypothermia do not exist. Additionally, although patients treated with hypothermia in this study achieved, on average, a median lowest temperature of 33.1°C, which is consistent with recent trials of therapeutic hypothermia,[27] 21% of patients treated with hypothermia achieved temperatures below the recommended nadir of 32°C. These factors may explain why therapeutic hypothermia for in-hospital cardiac arrest in this registry was not associated with improved short-term or long-term survival and was possibly harmful. Since therapeutic hypothermia is not without costs, national registries such as GWTG-Resuscitation have a unique opportunity to conduct low-cost, large-scale, pragmatic trials of therapeutic hypothermia treatment to establish its efficacy for in-hospital cardiac arrest.[28]

This study should be interpreted in the context of the following limitations. First, although data available in GWTG-Resuscitation enabled a propensity score analysis that adjusted for a number of key variables linked to survival after cardiac arrest, the possibility of residual confounding remains. Second, GWTG-Resuscitation did not collect detailed data on therapeutic hypothermia protocols and treatments for each patient; therefore, this study reflects outcomes of community implementation of hypothermia treatment. Moreover, the temperature data field was optional, so these data were not available for most patients. The possibility remains that the null findings for therapeutic hypothermia seen in this study may reflect poor implementation (eg, insufficient duration of hypothermia), even though the median lowest achieved temperature was 33.1°C among patients treated with hypothermia for whom temperature data were available. Also, since the Targeted Management Trial for out-of-hospital cardiac arrest was not published until December 2013[27] (a year before the study period ended), the proportion of non-hypothermia-treated patients with targeted temperature management of 36°C is likely small. Third, this study may have included some patients who were not comatose following cardiac arrest. Any misclassification would be expected to be nondifferential, but differential misclassification favoring the non-hypothermia-treated group could have influenced the study results. Fourth, results for favorable neurological survival should be interpreted with some caution as variability in assessing neurological status exists[29] and some patients were missing data on this outcome. Fifth, although GWTG-Resuscitation is a quality improvement registry that collects cardiac arrest data from a diverse population of US hospitals, findings may be different in nonparticipating hospitals.

Conclusions

Among patients with in-hospital cardiac arrest, use of therapeutic hypothermia compared with usual care was associated with a lower likelihood of survival to hospital discharge and a lower likelihood of favorable neurological survival. These observational findings warrant a randomized clinical trial to assess efficacy of therapeutic hypothermia for in-hospital cardiac arrest.

ARTICLE INFORMATION

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