Improving Use of Targeted Temperature Management After Out-of-Hospital Cardiac Arrest: A Stepped Wedge Cluster Randomized Controlled Trial

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Rationale: International guidelines recommend use of targeted temperature management following resuscitation from out-of-hospital cardiac arrest. This treatment, however, is often neglected or delayed.
Objective: To determine whether multifaceted quality improvement interventions would increase the proportion of eligible patients receiving successful targeted temperature management.
Setting: A network of 6 regional emergency medical services systems and 32 academic and community hospitals serving a population of 8.8 million people providing post arrest care to out-of-hospital cardiac arrest.
Interventions: Comparing interventions improve the implementation of targeted temperature management post out-of-hospital cardiac arrest through passive (education, generic protocol, order set, local champions) versus additional active quality improvement interventions (nurse specialist providing site-specific interventions, monthly audit-feedback, network educational events, internet blog) versus no intervention (baseline standard of care).
Measurements and Main Results: The primary process outcome was proportion of eligible patients receiving successful targeted temperature management, defined as a target temperature of 32-34°C within 6 hours of emergency department arrival. Secondary clinical outcomes included survival and neurological outcome at hospital discharge. Four thousand three hundred seventeen out-of-hospital cardiac arrests were transported to hospital; 1,737 (40%) achieved spontaneous circulation, and 934 (22%) were eligible for targeted temperature management. After accounting for secular trends, patients admitted during the passive quality improvement phase were more likely to achieve successful targeted temperature management compared with those admitted during the baseline period (25.7% passive vs 9.0% baseline; odds ratio, 2.76; 95% CI, 1.76–4.32; $p < 0.001$). Active quality improvement interventions conferred no additional improvements in rates of successful targeted temperature management (26.9% active vs 25.7% passive; odds ratio, 0.96; 95% CI, 0.63–1.45; $p = 0.84$). Despite a significant increase in rates of successful targeted temperature management, survival to hospital discharge was unchanged.
Conclusion: Simple quality improvement interventions significantly increased the rates of achieving successful targeted temperature management following out-of-hospital cardiac arrest in a large network of hospitals but did not improve clinical outcomes. (*Crit Care Med* 2015; XX:00–00)

Key Words: cluster randomized trial; critical care; emergency medicine; knowledge translation; out-of-hospital cardiac arrest; quality improvement; targeted temperature management; therapeutic hypothermia

Despite advances, the overall survival rate from out-of-hospital cardiac arrest (OHCA) remains between 3% and 16% (1). Previous randomized controlled trials (RCTs) have shown that therapeutic hypothermia, or targeted temperature management (TTM), improves survival and neurological outcomes in patients with ventricular fibrillation (VF) OHCA (2–4). This therapy involves cooling patients post cardiac arrest in the early postarrest period. The American Heart Association, the International Liaison Committee on Resuscitation, and other national and international agencies have recommended the use of TTM in all eligible comatose cardiac arrest survivors following resuscitation (5, 6). Although a recent large trial showed that using TTM to achieve a goal of 32–34°C did not confer additional benefit compared to TTM to achieve normothermia (36°C) (7, 8), experts still recommend that TTM be instituted following cardiac arrest to prevent hyperthermia (9, 10).

Despite these recommendations, several surveys and observational studies suggest that the adoption of TTM for eligible patients remains low (11–15). Prior research suggests that two main factors contribute to the poor uptake of TTM by clinicians: 1) lack of familiarity and availability of implementable TTM protocols and 2) availability of equipment, equipment costs, and high workload demands for providers (16). Other barriers identified were variable nursing awareness, variable staff uptake, lack of agreement with supporting evidence, lack of collaboration between the ICU and emergency department (ED), lack of interprofessional education, and challenges inherent in applying an intervention infrequently.

To overcome these challenges, we conducted a stepped wedge cluster-randomized pragmatic trial to evaluate a two-part (passive phase followed by active phase) multifaceted quality improvement (QI) intervention delivered to a network of hospitals in Ontario, Canada. We posited that a low-cost passive QI intervention would increase the timely delivery of TTM in patients surviving to hospital admission after OHCA compared with the preceding baseline period and that a second, active QI intervention would lead to further improvements. Our primary objective was to evaluate the comparative effectiveness of these different QI interventions; a secondary objective was to evaluate the impact of improved use of TTM on patient outcomes. We therefore hypothesized that patients admitted to hospitals receiving these QI interventions would be more likely to receive TTM and achieve the target temperature sooner than patients admitted to control hospitals.

METHODS

Study Design

A detailed description of our methods has been published (17). Randomization occurred at the level of the hospital rather than the patient to minimize contamination of our interventions, which targeted groups of clinicians (18). We chose a stepped wedge cluster RCT design, which has practical advantages over the traditional parallel cluster RCT because it allows for staggered implementation of the intervention, thereby decreasing the workload for the coordinating team. The stepped wedge cluster RCT design also avoids allocating hospitals to a control group for the duration of study, which can be undesirable in a QI trial. Finally, it may increase study power compared to a parallel cluster RCT (19).

After a baseline period lasting at least 7 months, each hospital was randomized to one of four stepped wedges to allow for staggered implementation of the interventions (passive and active phases) and temporal control by hospitals for comparison (20). The design was pragmatic, as it evaluated the

effectiveness of QI interventions that were designed to target diverse clinicians from different specialties and to be feasible in a wide range of facilities (21).

Participating Hospitals

The 37 hospitals in the Strategies for Post Arrest Care (SPARC) network were eligible for the study, representing all destination hospitals for six regional Emergency Medical Services (EMS) systems and serving a population of 8.8 million. The participating hospitals' baseline performance data were collected for at least 7 months prior to randomization. These academic and community hospitals were of variable size (range, 20–570 staffed hospital beds; range, 0–44 staffed ICU beds). The research ethics boards of all participating hospitals approved the study, waiving the requirement for obtaining individual patient consent.

Randomization and Study Flow

Eligible hospitals in the SPARC network were those that received patients resuscitated after OHCA from one of six participating EMS. Based on initial expressions of intent from hospitals, we randomly allocated all 37 hospitals into four wedges using a computerized randomization scheme, with stratification by ICU size (< 10 beds vs ≥ 10 beds). Four randomized hospitals could not participate in the trial because two EMS that routinely transported patients to these hospitals were unable to contribute complete, high-quality, timely, prehospital data, and one randomized hospital could not participate because its research ethics board did not approve the trial. Since no data were available from these five randomized but nonparticipating hospitals, we conducted a modified intention-to-treat analysis in the 32 remaining hospitals (**Fig. 1**). The QI interventions were applied in a stepwise

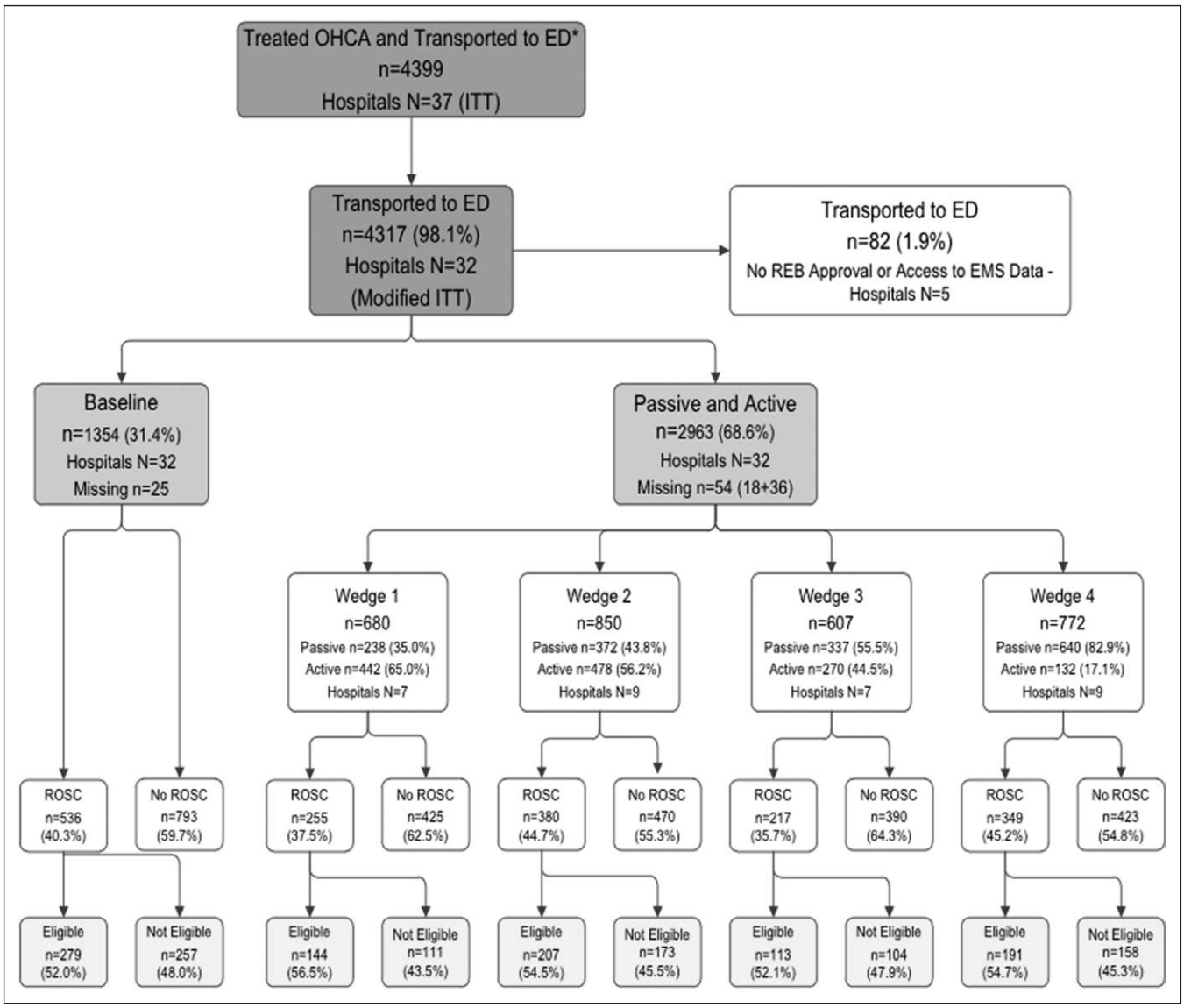

Figure 1. Consort diagram describing study flow of hospitals and patients. Passive refers to passive quality improvement (QI) intervention phase. Active refers to active QI intervention phase. See text for description of eligibility criteria for targeted temperature management. *Episode dates between September 1, 2007, and April 30, 2010; no obvious cause of out-of-hospital cardiac arrest (OHCA); age 18 yr old or older. ED = emergency department, EMS = Emergency Medical Services, ITT = intention to treat, REB = research ethics board, ROSC = return of spontaneous circulation.

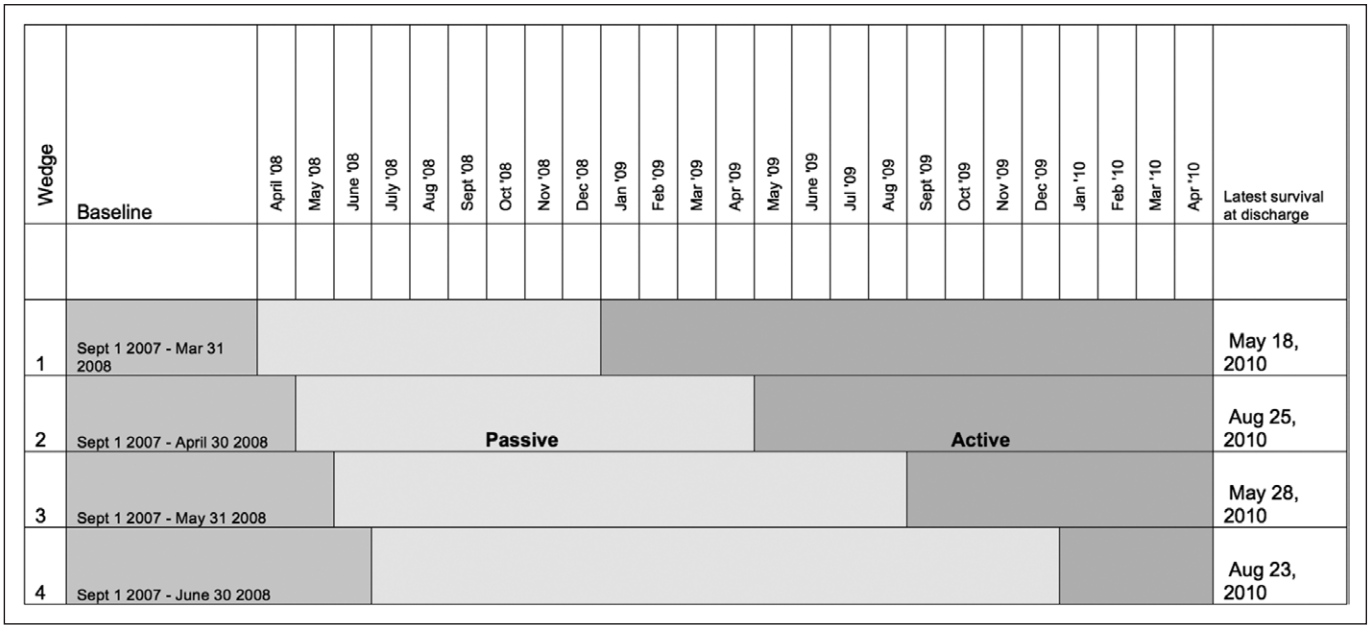

Figure 2. Study phases (baseline, passive quality improvement [QI] intervention, active QI intervention) according to stepped wedge allocation.

manner over four wedges: following at least 7 months of a baseline period, the sites received the passive QI intervention for at least 9 months, followed by the active QI intervention for at least 4 months (**Fig. 2**). The four wedges differed only in the dates of transition from preintervention to passive intervention and from passive to active interventions. All 32 hospitals received both the passive and active interventions by the end of the trial and were included in the final modified intention-to-treat analyses.

Passive Intervention

The passive QI intervention was a generic approach that included a site visit and didactic-style presentation about TTM to nursing and physician staff in the hospitals' EDs, coronary care units (CCUs) (if present), and ICUs and identified nurse and physician "TTM champions" for each site. In addition, all hospitals received a TTM protocol and access to Internet resources including generic order sets for implementing TTM (available at http://www.sparcnetwork.ca).

Active Intervention

The active QI intervention was designed to address site-specific barriers using two key strategies: 1) local detailing by a clinical nurse specialist to identify and address barriers to implementing TTM and to suggest site-specific interventions; and 2) audit and feedback using monthly reports of site-specific data compared with anonymous performance data from other sites receiving the active intervention. In addition, active sites were provided with invitations to network educational events (in-person and video-conferenced) and access to a real-time internet blog which was used to answer questions about TTM and to foster dialogue across sites and with content experts. The cost of this intervention was CAD$12,000 per participating hospital.

Inclusion and Exclusion Criteria

Patients were included in the analysis if they were eligible for TTM according to the following criteria: age greater than 18 years, nontraumatic cardiac arrest, sustained return of spontaneous circulation (palpable pulse for > 20 min), and Glasgow Coma Scale score below 10. Patients were deemed ineligible for cooling and excluded if they had active hemorrhage or intracranial bleeding, a written valid do-not-resuscitate order, or died or had life support withdrawn during the first 6 hours after ED arrival (even if TTM had been initiated).

Sample Size

During the year prior to the onset of the trial, 339 OHCA patients eligible for cooling were admitted to participating hospitals (mean 10 OHCA patients per hospital per year). Of these 339 eligible patients, only 34 cases (10%) were cooled to reach the target temperature within 6 hours of hospital arrival (intracluster correlation coefficient, 0.09). Assuming that a similar number of patients would be admitted during each year of the trial, we anticipated that we would have greater than 90% power (two-tailed type I error probability, 0.05) to detect an absolute increase of at least 30% during each study phase in the proportion of patients that were successfully cooled to reach the targeted temperature within 6 hours of hospital arrival.

Data Collection

All consecutive OHCA patients who were treated by participating EMS and transported to a participating hospital were identified and entered into a dataset containing demographic information in addition to data pertaining to patient and arrest characteristics, including the Utstein predictors, treatment information, and vital status at hospital arrival (22). The data variables, response options, and agreement statistics on key outcomes in this dataset have been published (23). Once

patients were identified as potentially eligible for TTM, trained research staff, who were blinded to intervention phase allocation, abstracted data related to TTM, other elements of in-hospital postarrest care, and clinical outcomes from hospital charts. All patient data were kept anonymous and stored in accordance with local privacy regulations.

Outcomes

The primary endpoint used to evaluate effectiveness of the multifaceted QI interventions was the proportion of eligible patients after OHCA that achieved the target temperature of 32–34°C within 6 hours of ED arrival (hereafter referred to as "successful TTM"). We chose this time window because it represented a feasible process endpoint for our QI study that would capture more efficient and timely delivery of TTM. The primary outcome of the study was the adjusted (for clustering) odds ratio (OR) of achieving successful TTM during the active QI intervention phase compared with the passive QI intervention phase and during the passive intervention phase compared with the baseline period. The adjusted OR is the recommended measure of effect for the stepped wedge study design to account for the time-dependent nature of the intervention and clustering of patients within centers (20). Secondary outcomes were the ORs (comparing active vs passive and passive vs baseline) of eligible patients ever (yes/no) receiving TTM, receiving TTM within 6 hours of ED arrival, surviving to discharge (with and without adjustment for Utstein outcome predictors), and surviving with good neurological outcome at hospital discharge (defined as a Modified Rankin Score of 0, 1, or 2). We also measured the time elapsed until the target temperature was achieved among those receiving TTM and the proportion of ineligible patients that received TTM during each QI intervention phase.

Analysis

Data were analyzed using SAS version 9.1 (SAS Institute, Cary, NC) and R version 2.15.3 (R Foundation for Statistical Computing, Vienna, Austria) (24). All tests were two-sided with p value less than or equal to 0.05 denoting statistical significance. The unit of analysis for the comparisons was the individual patient. The OR for the primary outcome of achieving successful TTM in the active QI intervention phase versus the passive QI intervention phase, and in the passive QI intervention phase versus the baseline period, was calculated using a generalized estimating equation (GEE) approach (logit link) to account for the hierarchical nature (clustering within centers) of the data. The R package GEE pack (1.1–6) was used to fit these models (25). We used a time-dependent variable to denote the change in intervention status (i.e., from baseline to passive to active intervention QI phases) as determined by the stepped wedge design. We included time as an independent variable in all models to account for the possibility that TTM might be improving across study phases due to secular trends since failure to include such time effects can bias estimates of effect sizes (20). ORs for all secondary outcomes were calculated in a similar manner where appropriate.

RESULTS

Thirty-two participating hospitals completed the study and were included in the modified intention-to-treat analysis. In total, 4,317 OHCA patients were transported to these hospitals, 1,737 (40%) achieved return of spontaneous circulation, and 934 (22%) were eligible for TTM. Figure 1 shows the overall flow of patients through each phase and wedge of the trial. There was a similar distribution of patient and in-hospital characteristics across study phases (**Table 1**). All 32 participating hospitals received all components of the passive intervention, including a didactic lecture and TTM protocol and order set. Similarly, all participating 32 hospitals received the active QI intervention, local detailing and implementation of site-specific interventions by a clinical nurse specialist, monthly comparative audit and feedback of performance data, and network educational events. However, the real-time internet blog was seldom used by clinicians.

Primary Outcome

Eligible patients admitted during the passive QI intervention phase were more than twice as likely to achieve successful TTM by reaching the target temperature within 6 hours (91/354; 25.7%) than during the baseline period (25/279; 9.0%; OR, 2.76; 95% CI, 1.76–4.32; $p < 0.00001$) (**Fig. 3**). Characteristics of patients receiving successful TTM are shown in Table A1 (Supplemental Digital Content 1, http://links.lww.com/CCM/B165). During the active QI intervention phase, there was no additional increase in rates of successful TTM compared to what had already been achieved during the passive QI intervention phase (81/301; 26.9%; OR, 0.96; 95% CI, 0.63–1.45; $p = 0.84$) (**Table 2**).

Secondary Outcomes

The rates of ever having TTM started in eligible patients were not influenced by the QI interventions (Table 2), ranging from 53% during the baseline period to 66% during the passive QI intervention ($p = 0.70$) and 63% during the active QI intervention ($p = 0.41$). Most other aspects of postarrest care were similar across study phases, although vasopressor use increased during both the passive and active QI intervention phases compared with baseline (**Table 3**). The rates of delivering TTM to patients who had absolute contraindications remained rare (5–6% of patients) during both intervention and baseline phases.

Among patients receiving TTM (**Table 4**), the mean (SD) time to achieve the target temperature was shorter during the passive QI intervention phase (7.9 hr [5.3]) or active QI intervention phase (7.9 hr [5.7]) than during the baseline period (9.8 hr [5.8]; $p = 0.006$). The mean (SD) duration of cooling during the baseline (20.5 hr [10.1]), passive intervention (21.7 hr [9.3]), and active intervention (21.7 hr [9.5]) phases was similar ($p = 0.46$). More patients were cooled with cold saline during the passive (38/235; 16%) and active (45/190; 24%) QI intervention phases than during the baseline period (20/149; 13%; $p = 0.03$).

Rates of short-term survival, survival to hospital discharge, and survival with good neurological outcome (Modified

TABLE 1. Characteristics of Patients Meeting Eligibility Criteria for Targeted Temperature Management

Characteristics	Baseline (*n* = 279)	Passive (*n* = 354)	Active (*n* = 301)
Patient characteristics			
Age—mean (SD), yr	64.8 ± 14.9	63.7 ± 16.4	65.0 ± 15.5
Male, *n* (%)	187 (67)	242 (68)	197 (65)
Public arrest, *n* (%)	95 (34)	101 (29)	75 (25)
Bystander witnessed, *n* (%)	167 (60)	208 (59)	176 (58)
Public access defibrillator applied, *n* (%)	14 (5)	13 (4)	11 (4)
Initial rhythm VF/VT, *n* (%)	154 (55)	197 (56)	149 (50)
Bystander witnessed and VF/VT rhythm, *n* (%)	108 (39)	139 (39)	107 (36)
Response time—mean (SD), min	6.1 ± 2.4	6.2 ± 2.3	6.3 ± 2.5
Total GCS score recorded post return of spontaneous circulation and within 6 hour of emergency department arrival			
Total GCS mean score (SD)	3.7 ± 1.6	3.6 ± 1.5	3.4 ± 1.2
Total GCS median (interquartile range)	3 (3,3)	3 (3,3)	3 (3,3)
Median (interquartile range)	3 (3, 3)	3 (3, 3)	3 (3, 3)
Hospital characteristics			
Academic hospital, *n* (%)	64 (23)	78 (22)	75 (25)
Large hospitals, *n* (%)	199 (71)	228 (64)	244 (81)
Small to medium hospitals, *n* (%)	80 (29)	126 (36)	57 (19)
ICU ≥ 10 beds, *n* (%)	233 (84)	294 (83)	212 (70)

VF = ventricular fibrillation, VT = ventricular tachycardia, GCS = Glasgow Coma Scale.
[a]GCS is the highest documented score after the last sustained return of spontaneous circulation defined as palpable pulse in any vessel for at least 20 min.

Rankin Scale of 1 or 2) at hospital discharge were similar across all study phases (Table 2). Only 14% of the patients (43/312) who died during the 6-hour target window (and who were therefore excluded from the primary analysis) were treated with TTM. Throughout the study, rates of subsequent withdrawal of life support among patients receiving TTM were similar (Table 4).

Temporal Trends During the Trial

We tested for temporal trends and potential effect modifications with time. There were no effect modifications with time for the primary or secondary study outcomes during the passive or active QI intervention phases. A temporal trend over all three phases of the trial for increasing rates of successful TTM was not significant (OR, 1.27 per year; 95% CI, 0.85–1.91); however, we detected a temporal trend for an increasing rate of initiating (ever) any TTM in eligible patients across all study phases (OR, 1.35 per year; 95% CI, 1.03–1.82; $p = 0.05$). During long-term follow-up of the 32 participating study sites, we observed no decay in rates of successful TTM following completion of the trial: for example, in the period spanning January 1, 2011, to December 31, 2011, 351 of 440 patients (79.8%) received TTM and 329 of 440 (74.8%) achieved the target temperature within 6 hours.

DISCUSSION

We conducted a stepped wedge cluster randomized trial in a network of 32 academic and community hospitals to evaluate multifaceted QI interventions that aimed to increase the rate of successfully applying TTM in patients admitted to hospital after OHCA. Surprisingly, the introduction of the simple passive QI intervention, namely, education, TTM protocols, and generic order set, and recruitment of local champions more than doubled the likelihood that eligible patients would successfully be cooled to the target temperature within 6 hours of ED arrival. The other important finding was that the introduction of the more intensive active QI intervention that involved local detailing to target hospital-specific barriers and monthly audit-feedback of comparative performance data did not yield incremental gains beyond what had already been achieved by the passive QI intervention.

Our passive QI intervention used generic protocols and order sets, as well as recruitment and of local nursing and physician champions, in each of the participating units (ED, ICU, and CCU). During this phase, we observed increased use of several treatments that can accelerate cooling, for example, neuromuscular blockers and infusion of cold saline. It is not possible from our data to differentiate which of these components had the most impact, but our results reinforce the premise that simple

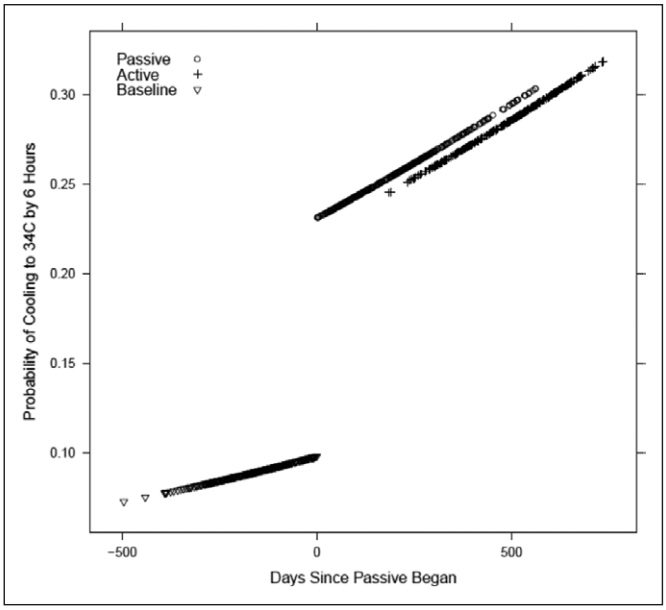

Figure 3. Probability of achieving targeted temperature management of 34°C by 6 hr. This graph shows the predicted probability of individual patients achieving targeted temperature management (TTM) of 34°C by 6 hr after emergency department arrival. *x*-axis shows time during the study, with day 0 representing start of the passive quality improvement (QI) intervention; negative values denote baseline period. *y*-axis shows predicted probability (based on generalized estimating equation model) of achieving the target temperature of 34°C (successful TTM) within 6 hr. The graph shows that the overall likelihood of receiving successful TTM increased during the passive QI intervention phase compared with the baseline period, but was unchanged during the active QI intervention phase. The graph also shows that a nonsignificant temporal trend led to increases in rates of successful TTM during the baseline period and throughout the study.

QI interventions linked with local champions charged with the responsibility to implement locally can be an effective strategy. The best available evidence during the planning of our study suggested that the multifaceted, tailored approaches for changing clinician behavior used in our active intervention phase would have more impact on changing behaviors than simple interventions (26–28). The failure of the more costly and time-intensive active QI intervention to confer additional benefit beyond what had been achieved with the passive intervention is therefore surprising and suggests that these approaches to QI may not be cost-effective for this care practice.

Implementation science is based on the premise that simply publishing guidelines and evidence-based reviews is insufficient to change processes of care. Some experts have suggested that our patterns of interpreting knowledge and modifying behavior stem from "mindlines" rather than guidelines (29). These mindlines are collectively reinforced, internalized tacit guidelines, which are informed by an awareness of the scientific literature but are mainly influenced by our own experiences, interactions with colleagues, patients, and discussions with credible spokespersons. These influences are in turn mediated by organizational needs and limitations and iteratively affected by a range of informal interactions with others in their community. Our own collaborative network by design sought to build on this collective wisdom and leverage credible spokespersons to influence these mindlines in order to improve rates of successful TTM. The odds of initiating TTM increased over time across each of the three phases of the trial suggesting that such mindlines were altered during the course of the study, possibly due to external factors and influences.

A number of previous large-scale QI trials targeting increased rates of TTM for eligible cardiac arrest patients have been successful; however, randomized trials are rare (30, 31). Indeed, many large-scale QI or knowledge translation initiatives in critically ill patients have used before-after study designs and are therefore vulnerable to confounding due to secular trends (32–34). A trial that randomized individual patients was infeasible for our study question because the interventions targeted groups of clinicians rather than individual providers or patients. The stepped wedge cluster randomized trial design offered several advantages: 1) it allowed us to target such groups of clinicians yet analyze patients as the unit of analysis; 2) it provided a control group of hospitals to monitor the effectiveness of our intervention and to account for secular improvements over time; 3) it ensured that all hospitals received the QI intervention by the end of the study; and 4) it provided practical advantages to our study team because hospitals were randomized to implement the intervention in a staggered manner rather than all at once. Considering these advantages, other investigators planning evaluations of large-scale interventions that pose minimal risk of harm may find this design appealing.

The time required for any intervention to change behavior and improve adherence to a protocol remains uncertain. Our time intervals between wedges for both interventions were restricted to a minimum of 4 months by funding as the active QI intervention was expensive. We chose a separation of at least 7 months between the baseline period and passive QI intervention phase and 9 months between the passive and active QI intervention phases, but our stepped wedge allocation schedule resulted in an increasing time interval spent in the passive phase for later wedges of hospitals (Fig. 2). It is therefore possible that the relative lack of effect of the active compared to passive QI interventions were related to the longer time intervals that hospitals spent in the passive phase compared to active phase, and more time was needed for our active QI interventions to exert their effects.

The lack of survival benefit associated with increased rates of successful TTM in our trial was not anticipated given the magnitude of benefit demonstrated for in-hospital cooling of patients in prior randomized trials. A linear relationship between TTM application by healthcare providers and increased survival has previously been suggested, for example, 100% adoption would result in an estimated 2,298 additional lives saved per year in the United States (35). Unfortunately, adoption of TTM in our trial was incomplete; the highest (66%) rate of starting TTM in eligible patients occurred during the passive QI phase of our trial, and we therefore lacked power to detect survival differences similar to the magnitude observed in previous RCTs (2, 3). In addition, previous RCTs of TTM have often restricted enrollment to patients presenting with VF or ventricular tachycardia (VT) as their initial rhythm

TABLE 2. Primary and Secondary Outcomes Across All Three Phases of the Trial

Outcomes	Baseline ($n = 279$)	Passive ($n = 354$)	Active ($n = 301$)	OR, Passive Versus Baseline[a] (95% CI; p)	OR, Active Versus Passive[a] (95% CI; p)
Primary outcome					
TTM reaching 32–34°C within 6 hr, *n* (%)	25 (9.0)	91 (25.7)	81 (26.9)	2.76 (1.76–4.32; $p < 0.001$)	0.96 (0.63–1.45; $p = 0.84$)
Secondary outcomes - TTM					
TTM started (ever), *n* (%)	149 (53.4)	235 (66.3)	190 (63.1)	1.09 (0.69–1.72; $p = 0.70$)	0.84 (0.55–1.27; $p = 0.41$)
TTM started in emergency department, *n* (%)	71 (25.4)	111 (31.4)	97 (32.2)	0.75 (0.42–1.34; $p = 0.32$)	0.68 (0.42–1.12; $p = 0.13$)
Secondary outcomes - survival					
Survival at 24 hr, *n* (%)	244 (87.4)	314 (88.7)	260 (86.4)	1.40 (0.58–3.35; $p = 0.45$)	0.96 (0.57–1.61; $p = 0.87$)
Survival at 72 hr, *n* (%)	192 (68.8)	242 (68.4)	203 (67.4)	1.64 (0.96–2.80; $p = 0.07$)	1.45 (0.95–2.21; $p = 0.09$)
Survival to hospital discharge, *n* (%)	108 (38.7)	122 (34.5)	99 (32.9)	0.92 (0.57–1.49; $p = 0.74$)	1.04 (0.74–1.46; $p = 0.81$)
Survival to hospital discharge—patients presenting with shockable rhythms, *n* (%)	85/154 (55.2)	98/197 (49.7)	69/149 (46.3)	0.75 (0.43–1.32; $p = 0.32$)	0.83 (0.51–1.37; $p = 0.47$)
Secondary outcome - functional survival					
Good neurologic outcome[b] at hospital discharge, *n* (%)	35/236 (14.8)	64/321 (19.9)	44/258 (17.1)	1.07 (0.48–2.43; $p = 0.86$)	0.71 (0.38–1.34; $p = 0.29$)

OR = odds ratio, TTM = targeted temperature management.

[a]ORs adjusted for clustering (hospitals) and time since start of study (see text for details).

[b]Good neurological outcome defined as Modified Rankin Score of 0, 1, or 2; denominators represent patients from whom data were available.

TABLE 3. Cointerventions Among Patients Eligible for Targeted Temperature Management

Cointerventions	Baseline ($n = 279$)	Passive ($n = 354$)	Active ($n = 301$)
Fibrinolytics during first 24 hr, *n* (%)	15 (5)	27 (8)	23 (8)
PCI during hospitalization, *n* (%)	20 (7)	38 (11)	36 (12)
PCI during first 24 hr, *n* (%)	15/20 (75)	29/38 (76)	29/36 (81)
Vasopressors during first 6 hr, *n* (%)[a]	133 (48)	208 (59)	178 (59)
Neuromuscular blockers during first 6 hr, *n* (%)[b]	68 (24)	142 (40)	117 (39)
DNR order or withdrawal of life support during first 24 hr, *n* (%)	23 (8)	25 (7)	29 (10)
DNR order or withdrawal of life support during first 7 d, *n* (%)	73 (26)	111 (31)	87 (29)

PCI = percutaneous coronary intervention, DNR = do not resuscitate.

[a]$p = 0.007$ for comparison (chi-square) across baseline, passive, and active phases.

[b]$p < 0.0001$ for comparison (chi-square) across baseline, passive, and active phases.

(2, 3). Although our trial impacted on hundreds of patients, our effective sample size was further reduced after adjusting for the effects of clustering of these patients within hospitals. In addition, the decision to start TTM was not randomly assigned at the level of the individual patient, and thus, the decision to start TTM may also have been influenced by clinical factors resulting in treatment selection bias that could obscure any improvements in survival. The direction of this bias is difficult to predict, but it is plausible that patients who did not receive TTM were deemed to be improving by the healthcare team, for example, showing signs of neurological recovery, and thus, the clinician made a decision to not start TTM. If true, this also reinforces that clinical judgment outside of protocols and guidelines is still important in the complex milieu of clinical

TABLE 4. Cointerventions in Eligible Patients Who Received Targeted Temperature Management

Characteristics	Baseline (*n* = 149)	Passive (*n* = 235)	Active (*n* = 190)
Cooling technique			
Cold saline, *n* (%)[a]	20 (13)	38 (16)	45 (24)
Ice packs, *n* (%)	85 (57)	152 (65)	129 (68)
Cooling blanket (%)	91 (61)	132 (56)	117 (62)
Cooling catheter (%)	3 (2.0)	1 (0.4)	2 (1.0)
Immersion (%)	3 (2)	11 (5)	6 (3)
Other (%)	4 (3)	16 (7)	5 (3)
Within the first 6 hr			
Neuromuscular blockers during first 6 hr, *n* (%)	64 (43)	128 (54)	104 (54)
Vasopressors during first 6 hr, *n* (%)[b]	71 (48)	140 (60)	114 (60)
Highest GCS score recorded post return of spontaneous circulation and within 6 hr of ED arrival—GCS motor—mean (SD)	*n* = 88 1.6 ± 1.1	*n* = 144 1.6 ± 1.2	*n* = 135 1.4 ± 1.1
Time to target temperature of 34°C (mean SD hr)[c]	*n* = 106 9.8 ± 5.8	*n* = 195 7.9 ± 5.3	*n* = 164 7.9 ± 5.7
Time to target temperature of 34°C within 6 hr of ED arrival for patients with successful TTM (mean SD hr)	*n* = 25 3.8 ± 1.6	*n* = 91 3.8 ± 1.4	*n* = 81 3.6 ± 1.4
Within 24 hr			
Last GCS score recorded between 6 and 24 hr after first ED arrival	*n* = 31 2.0 ± 1.6	*n* = 77 1.8 ± 1.5	*n* = 112 1.5 ± 1.3
GCS motor—mean (SD)	1 (1, 3)	1 (1, 1)	1 (1, 1)
GCS motor—median (interquartile range)	*n* = 123	*n* = 212	*n* = 179
Duration of TTM, mean (SD), hr	20.5 ± 10.1	21.7 ± 9.3	21.7 ± 9.5
At 72 hr			
Death due to withdrawal of life-sustaining therapy (%)—died within 72 hr	15 (10)	27 (11)	24 (13)
Death due to withdrawal of life-sustaining therapy (%)—died after 72 hr	38 (26)	65 (28)	49 (26)

GCS = Glasgow Coma Scale, ED = emergency department, TTM = targeted temperature management.
[a]$p = 0.03$ for comparison (chi-square) across baseline, passive, and active phases.
[b]$p = 0.04$ for comparison (chi-square) across baseline, passive, and active phases.
[c]$p = 0.006$ for comparison (chi-square) across baseline, passive, and active phases.

care. Finally, it is possible that the patients who were deemed most likely to benefit from TTM were already being targeted at the start of the trial, thereby minimizing the potential for any incremental survival benefit from greater adoption.

Our implementation trial targeted all patients after OHCA regardless of initial rhythm based on current guideline recommendations (5, 6), but whether TTM also leads to improved survival for these patients presenting with non-VF or non-VT is less clear. However, our subgroup analysis of those eligible patients presenting with VF or VT still showed no difference in survival. Another potential explanation is that the target temperature goal of 32–34°C within 6 hours does not afford the same magnitude of survival advantage when pragmatically applied to eligible patients and with incomplete penetration. Indeed, the mean time to achieve target temperature was only 2 hours faster during the passive and active QI intervention phases compared with the baseline period, and this difference may have been insufficient to lead to changes in clinical outcomes. It is also possible that patients in our study who did not receive TTM may still have received aggressive temperature management to maintain normothermia, and this may have decreased the relative efficacy of TTM in our study. Indeed, a recent large trial showed that using TTM to achieve a goal of 32–34°C did not confer additional benefit compared with TTM to achieve and maintain normothermia (36°C) (7, 8). Our study sheds light on the importance of evaluating the

large-scale and pragmatic implementation of interventions in order to evaluate whether the benefits reported by randomized trials can be realized (36).

CONCLUSIONS

Our stepped wedge cluster randomized trial conducted in a network of 32 community and academic hospitals providing care to a population of 8.8 million people demonstrated that a simple passive QI intervention including education, generic protocol and order set, and recruitment of local champions more than doubled the rate of achieving successful TTM, but did not improve clinical outcomes. The more expensive active QI intervention did not confer additional gains beyond what had already been achieved.

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