Statewide Regionalization of Postarrest Care for Out-of-Hospital Cardiac Arrest: Association With Survival and Neurologic Outcome

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Study objective: For out-of-hospital cardiac arrest, authoritative, evidence-based recommendations have been made for regionalization of postarrest care. However, system-wide implementation of these guidelines has not been evaluated. Our hypothesis is that statewide regionalization of postarrest interventions, combined with emergency medical services (EMS) triage bypass, is associated with improved survival and neurologic outcome.

Methods: This was a prospective before-after observational study comparing patients admitted to cardiac receiving centers before implementation of the interventions ("before") versus those admitted after ("after"). In December 2007, the Arizona Department of Health Services began officially recognizing cardiac receiving centers according to commitment to provide specified postarrest care. Subsequently, the State EMS Council approved protocols allowing preferential EMS transport to these centers. Participants were adults (≥18 years) experiencing out-of-hospital cardiac arrest of presumed cardiac cause who were transported to a cardiac receiving center. Interventions included (1) implementation of postarrest care at cardiac receiving centers focusing on provision of therapeutic hypothermia and coronary angiography or percutaneous coronary interventions (catheterization/PCI); and (2) implementation of EMS bypass triage protocols. Main outcomes included discharged alive from the hospital and cerebral performance category score at discharge.

Results: During the study (December 1, 2007, to December 31, 2010), 31 hospitals were recognized as cardiac receiving centers statewide. Four hundred forty patients were transported to cardiac receiving centers before and 1,737 after. Provision of therapeutic hypothermia among patients with return of spontaneous circulation increased from 0% (before: 0/145; 95% confidence interval [CI] 0% to 2.5%) to 44.0% (after: 300/682; 95% CI 40.2, 47.8). The post return of spontaneous circulation catheterization PCI rate increased from 11.7% (17/145; 95% CI 7.0, 18.1) before to 30.7% (210/684; 95% CI 27.3, 34.3) after. All-rhythm survival increased from 8.9% (39/440) to 14.4% (250/1,734; adjusted odds ratio [aOR]=2.22; 95% CI 1.47 to 3.34). Survival with favorable neurologic outcome (cerebral performance category score=1 or 2) increased from 5.9% (26/439) to 8.9% (153/1,727; aOR=2.26 [95% CI 1.37, 3.73]). For witnessed shockable rhythms, survival increased from 21.4% (21/98) to 39.2% (115/293; aOR=2.96 [95% CI 1.63, 5.38]) and cerebral performance category score=1 or 2 increased from 19.4% (19/98) to 29.8% (87/292; aOR=2.12 [95% CI 1.14, 3.93]).

Conclusion: Implementation of a statewide system of cardiac receiving centers and EMS bypass was independently associated with increased overall survival and favorable neurologic outcome. In addition, these outcomes improved among patients with witnessed shockable rhythms. [Ann Emerg Med. 2014;64:496-506.]

Please see page 497 for the Editor's Capsule Summary of this article.

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INTRODUCTION

Background

For decades, out-of-hospital cardiac arrest has been a major focus of emergency medical services (EMS) systems, and several bystander and EMS interventions have been shown to improve outcomes.[1-10] In contrast, inhospital postarrest care of out-of-hospital cardiac arrest has historically received little attention. The consensus was that, if a patient was not "saved" in the field, the likelihood that hospital care would make any significant difference was very low.[11,12] However, in the late 1990s, major interest in postarrest care was sparked by observational studies showing a potential effect of inhospital interventions, even in

†Arizona Cardiac Receiving Center Consortium participants are listed in the Appendix.

Editor's Capsule Summary

What is already known on this topic

Expert postarrest care improves out-of-hospital cardiac arrest outcomes.

What question this study addressed

Does regionalization of postarrest care improve out-of-hospital cardiac arrest outcomes?

What this study adds to our knowledge

In this before-after analysis, a statewide strategy of EMS bypass to specialized postarrest care centers resulted in improved neurologically intact out-of-hospital cardiac arrest survival.

How this is relevant to clinical practice

If the results can be replicated, communities should consider out-of-hospital cardiac arrest care regionalization strategies.

some patients with major neurologic deficits.[13-16] There is an increasing amount of literature and consensus that specialized postarrest care, including therapeutic hypothermia and targeted temperature management, improves out-of-hospital cardiac arrest outcomes.[17-19] In response, international recommendations for the use of therapeutic hypothermia were published.[20-22] There is also an increasing amount of literature reporting that a wide range of interventions, combined with standardized comprehensive critical care, may improve outcome.[15,23-38]

Importance

The literature showing that inhospital care significantly influences outcomes after out-of-hospital cardiac arrest has resulted in discussions in support of regionalizing postarrest care through EMS triage to specialized centers[39-42] and ultimately led to the American Heart Association policy statement on regionalization.[43] However, direct evidence for the effect of widespread, multisystem regionalization on patient outcomes is lacking.

Goals of This Investigation

In 2004, the Arizona Department of Health Services developed a statewide partnership with EMS agencies and researchers focusing on out-of-hospital cardiac arrest. The net effect was improvement in bystander and EMS care that led to a tripling of survival statewide.[7,44,45] In 2007, this partnership established criteria for a statewide network of specialized cardiac receiving centers that could provide therapeutic hypothermia, prompt percutaneous coronary interventions, and other guideline-based postarrest critical care. In 2008, protocols were developed allowing EMS to bypass local hospitals to preferentially transport patients to cardiac receiving centers.

The goal for this study was to evaluate whether statewide regionalization of postarrest interventions, combined with EMS triage, would be associated with improved survival and neurologic outcome. Here we report the outcomes of this effort.

MATERIALS AND METHODS

Study Design

This was a prospective, multicenter, multisystem, before-after observational cohort analysis comparing outcomes in patients admitted to cardiac receiving centers during the period before implementation versus those admitted to the same hospitals after implementation.

Setting

Arizona had 6.4 million residents in 2010 (http://quickfacts.census.gov/qfd/states/04000.html), with 62 licensed acute care hospitals. The Arizona Department of Health Services establishes EMS protocols, scope of practice, and provider certification. EMS crew configuration, vehicle deployment, dispatch, and response intervals vary widely across the state.[46]

There are 19,428 licensed out-of-hospital providers statewide (basic EMTs [12,901], EMT-intermediate-99 [39], and paramedics [6,488]). In the majority of locations, paramedics perform field resuscitation attempts and transport postarrest patients to cardiac receiving centers. At this analysis, 31 hospitals and 120 EMS agencies, responding to approximately 80% of the state's population, participated in the state-sponsored Save Hearts in Arizona Registry and Education (SHARE) program. SHARE provided the data collection and infrastructure for this study and has been previously described in detail.[7,44,46]

Data Collection and Processing and Methods of Measurement

Since 2004, more than 13,000 out-of-hospital cardiac arrests have been entered into the SHARE database. EMS data are obtained from the patient care reports and outcomes are obtained either directly from the hospitals or from the State Office of Vital Records. SHARE includes an Utstein-style out-of-hospital cardiac arrest EMS database linked with inhospital postarrest care and outcome data. Data collected from participating EMS systems and hospitals are manually entered into an Access 2007 (Microsoft, Redmond, WA) database by an experienced team of trained data coordinators who link and abstract the information. Consistent with Utstein methodology, every out-of-hospital cardiac arrest in which EMS documents an attempted resuscitation is included. Data are cross-referenced between first responding fire department-based EMS, private ambulance transport companies, and the cardiac receiving center database. For this effort, a data tool was developed to collect patient information for all out-of-hospital cardiac arrest patients brought to cardiac receiving centers (Appendix E1, available online at http://www.annemergmed.com). The data forms were completed by cardiac receiving center clinical personnel on patient discharge or death. Each individual completing data forms was trained in person and each form was reviewed by a study data coordinator for completeness and accuracy before entry into the database. Any inconsistencies were addressed in follow-up by examining the hospital medical record. A detailed description of the processes of data linkage, collection, and abstraction has been reported previously.[46]

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

Selection of Participants

The study population was composed of all adults (≥18 years) who (1) had an out-of-hospital cardiac arrest of presumed cardiac cause before the arrival of EMS[46] during the study period; and (2) were transported by EMS directly to a cardiac receiving center (before and after designation; details below). Exclusion criteria were patients younger than 18 years, patients declared dead at the scene, transfers from another hospital, and arrests of presumed noncardiac cause.

Interventions

In 2007, the Arizona Department of Health Services established the Arizona Cardiac Receiving Center Consortium. It was initiated with guidance from key physician, hospital, and EMS stakeholders. The consortium determined that official recognition as a cardiac receiving center required continuous institutional ability and commitment to provide therapeutic hypothermia, coronary angiography, and percutaneous coronary interventions to appropriate patients who had return of spontaneous circulation after an arrest. In addition, cardiac receiving centers were encouraged to provide other American Heart Association guideline–based care.[22,43] Although the International Liaison Committee on Resuscitation/American Heart Association guidelines have recommended therapeutic hypothermia for adults experiencing an out-of-hospital arrest with a shockable rhythm,[20-22,47] some hospitals elected to provide therapeutic hypothermia for patients with all rhythms of arrest who achieve return of spontaneous circulation and remain comatose. The first cardiac receiving centers were officially recognized by the Arizona Department of Health Services in December 2007.

In May 2008, the State EMS Council approved a protocol allowing EMS personnel to bypass local hospitals to transport all out-of-hospital cardiac arrest patients to cardiac receiving centers as long as the estimated increase in transport interval was less than 15 minutes.

All cases in this analysis occurred between January 1, 2007, and December 31, 2010. Each cardiac receiving center was required to provide data for out-of-hospital cardiac arrest patients beginning approximately 6 months before their cardiac receiving center recognition. Because implementation was not simultaneous at the cardiac receiving centers, the start dates for inclusion in the program varied among centers. Cases were divided into 2 study phases for each cardiac receiving center according to the date of first use of guideline therapy that included therapeutic hypothermia ("before" and "after"). The start dates for the after phase ranged from December 14, 2007, to November 25, 2010. Because program implementation was continuous, we included all cardiac receiving centers that implemented before December 31, 2010, which prevented the potential bias of including only "mature" cardiac receiving centers according to some arbitrary minimum time in the after phase.

The first use of therapeutic hypothermia by each hospital was chosen as the index date for the start of the after phase for 2 reasons: First, administrative recognition as a cardiac receiving center could occur either before or after actual implementation of guideline therapy, and our main goal was to evaluate changes in outcomes after clinical implementation. Given the site-specific variations in the timing and process of cardiac receiving center recognition, we believe the best identifier of actual clinical implementation is the first use of therapeutic hypothermia. Second, therapeutic hypothermia was never used at the hospitals before this program.[48] Thus, this provided unambiguous evidence that implementation had occurred.

Outcome Measures

The primary outcome measure was survival to hospital discharge. Secondary outcome was favorable neurologic outcome (cerebral performance category score of 1 or 2) at discharge.[9,10,49]

Primary Data Analysis

Continuous variables are presented as mean and SD for variables that are normally distributed and median with interquartile range for nonparametric data. Proportions and absolute difference between proportions, along with 95% confidence intervals (CIs), are presented where appropriate. All P values are 2-tailed, and the a priori α level for significance was .05.

The study hypothesis was tested by calculating adjusted odds ratios (aORs) for outcomes, using hierarchic multivariable logistic regression (considered significant if 95% CIs did not cross unity), treating hospitals, and EMS agencies as nested clusters. The primary analysis included only cases with complete data for all relevant variables used for multivariable regression analysis. A secondary sensitivity analysis, using all cases (even those excluded in the primary analysis), was conducted with missing data accounted for, using multiple imputation to assess the potential for bias that might have been introduced by excluding missing data from the primary analysis.

Previously known and potential confounders were included in initial models, and model development proceeded by purposeful forward selection. The primary independent variable (before versus after) was included in all models. On the basis of univariate association with outcomes, covariates were added to the models in a stepwise fashion, with those with lowest *P* values added first. Covariates were included in the final model if they were significantly associated with outcomes (likelihood ratio test $P \leq .05$) or judged to be a significant confounder of the relationship between outcomes and the before-after periods (ie, inclusion of the confounder changed the regression coefficient for before-after by at least 10% or published data showed evidence of confounding). The Hosmer-Lemeshow goodness-of-fit statistic was calculated for each final model, accounting for fixed and random effects combined. In addition, regression diagnostic statistics (Pregibon Δ-β and Hosmer-Lemeshow $\Delta\ \chi^2$ and Δ-D influence, Pregibon leverage, and Pearson residuals) were calculated to investigate overly influential covariate patterns representing potentially miscoded cases. Variable coding was checked and cases with high diagnostic statistics (representing the top 5 covariate patterns for each statistic above) were excluded one at a time. The analysis was then repeated and the change in the regression coefficient for our main study risk factor (before versus after) assessed. A change of 20% or more in the regression coefficient was considered significant and warranted case exclusion and model reassessment. We also calculated the area under the receiver operating characteristic curve for each final model as a measure of model discrimination.

To test for potentially confounding secular trends in outcomes, a time component was included in multivariable analyses. In addition, we examined outcomes across years (2007 to 2010) in the before period, using Fisher's exact test and a test for trend in proportions across years.

Subgroup analyses were conducted for survival and neurologic outcomes by initial rhythm[46] (ventricular fibrillation or tachycardia, asystole, pulseless electrical activity) and for bystander-witnessed ventricular fibrillation or ventricular tachycardia, using logistic regression.

We also compared the rate of out-of-hospital cardiac arrest patients (number of cases per 30 days) transported to cardiac receiving centers between the before and after phases to assess the influence of bypass protocols on case volume at the cardiac receiving centers, using random effects Poisson regression, with hospitals as the cluster.

Multiple imputation was used to address missing values for all independent variables, using the chained equations method,[50-52] and all multivariable logistic regression analyses were repeated with the imputed data as a sensitivity analysis.

RESULTS

Thirty-one hospitals, serving approximately 80% of the state's population, were designated as cardiac receiving centers between December 2007 and November 2010. The median length of the before phase was 6 months (interquartile range 4 to 11); and of the after phase, 18 months (interquartile range 10 to 27). Detailed patient and event characteristics for before and after are shown in Table 1. The results of the final regression models for all-rhythms survival and neurologic outcome are shown in Tables 2 and 3.

Fifty-five EMS agencies transported out-of-hospital cardiac arrest patients to cardiac receiving centers, 440 patients before and 1,737 after. Three cases (0.1%) were excluded from the survival analysis because of missing survival data and 11 (0.5%) from neurologic outcome analysis because of missing neurologic outcome data. The primary logistic regression analysis included a total of 1,947 cases with complete data for survival to hospital discharge (230 excluded; 10.4%) and 1,943 cases with complete data for favorable neurologic outcome (223 excluded; 10.3%). The secondary sensitivity analysis included all cases with outcomes (N=2,174 for survival; N=2,166 for neurologic outcome).

There were 145 patients with return of spontaneous circulation in the before cohort and 684 in the after. Patients with return of spontaneous circulation who remained comatose after arrival at the hospital were clinically eligible for therapeutic hypothermia. However, information about neurologic status on arrival at cardiac receiving centers was not available. Despite this, we were able to determine the most conservative rates of therapeutic hypothermia provision by calculating the proportion of all patients with return of spontaneous circulation (the "potentially eligible" group) who were cooled. The provision of therapeutic hypothermia in this cohort (all patients with return of spontaneous circulation) increased from 0% (0/145; 95% CI 0% to 2.5%) before to 44.0% after (300/682; 95% CI 40.2% to 47.8%) (Table 1). Thus, even a "worst-case" comparison reveals a significant increase in the provision of this guideline therapy after cardiac receiving center implementation.

The rate of potentially eligible patients (all return of spontaneous circulation) taken to coronary angiography increased from 11.7% (17/145; 95% CI 7.0% to 18.1%; before) to 30.7% (210/684; 95% CI 27.3% to 34.3%) after implementation (Table 1).

As expected, out-of-hospital cardiac arrest patients were transported to cardiac receiving centers at a higher rate during the after phase (mean=3.17 cases/30 days) compared with the before phase (1.98 cases/30 days). The adjusted incidence rate ratio of patients going to cardiac receiving centers after versus before was 1.60 (1.30, 1.98), representing a 60% increase in the rate of patients taken to cardiac receiving centers after. The proportion of patients who achieved out-of-hospital return of spontaneous circulation was similar in the 2 study periods (before=25.3% [95% CI 21.3, 29.6]; after=24.1% [95% CI 22.1, 26.2]).

All-rhythm survival increased from 8.9% before to 14.4% after (aOR=2.22; 95% CI 1.47 to 3.34) (Table 2, Figure). Favorable neurologic survival improved from 5.9% to 8.9% (aOR 2.26; 95% CI 1.37 to 3.73) (Table 3, Figure). Among patients with bystander-witnessed ventricular fibrillation or ventricular tachycardia, survival increased from 21.4% to 39.2% (aOR 2.96; 95% CI 1.63 to 5.38) (Table 1, Figure) and favorable neurologic survival increased from 19.4% to 29.8% (aOR 2.12; 95% CI 1.14 to 3.93) (Table 1, Figure). The Figure shows a forest plot of aORs for both survival and

Table 1. Characteristics of study population stratified by before (pre) versus after (post) cardiac arrest protocol implementation by cardiac receiving centers.

	Pre (N=440)			Post (N=1,737)		
Characteristic	**n/N**	**% (95% CI)**	**Missing n**	**n/N**	**% (95% CI)**	**Missing n**
Male sex	280/440	63.6 (58.9–68.1)	0	1,132/1,731	65.4 (63.1–67.6)	6
Age, mean (95% CI), y	440	63.9 (62.4–65.4)	0	1,728	63.0 (62.2–63.8)	9
Age, y			0			9
≥80	75/440	17.0 (13.6–20.9)		306/1,728	17.7 (15.9–19.6)	
60–79	192/440	43.6 (38.9–48.4)		744/1,728	43.1 (40.7–45.4)	
18–59	173/440	39.3 (34.7–44.1)		678/1,728	39.2 (36.9–41.6)	
Witnessed arrest	215/429	50.1 (45.3–54.9)	11	671/1,640	40.9 (38.5–43.3)	97
Initial rhythm on EMS arrival			9			76
VF/VT	147/431	34.1 (29.6–38.7)		468/1,661	28.2 (26.0–30.4)	
Asystole	168/431	39.0 (34.3–43.8)		815/1,661	49.1 (46.6–51.5)	
PEA	113/431	26.2 (22.1–30.6)		342/1,661	20.6 (18.7–22.6)	
Other, non-VF/VT rhythms	3/431	0.7 (0.1–2.0)		36/1,661	2.2 (1.5–3.0)	
Location of OHCA			10			114
Residential	298/430	69.3 (64.7–73.6)		1,157/1,623	71.3 (69.0–73.5)	
Medical facility	39/430	9.1 (6.5–12.2)		195/1,623	12.0 (10.5–13.7)	
Public	93/430	21.6 (17.8–25.8)		271/1,623	16.7 (14.9–18.6)	
Provision of bystander CPR	207/428	48.4 (43.5–53.2)	12	811/1,632	49.7 (47.2–52.1)	105
EMS use of MICR	182/430	42.3 (37.6–47.2)	10	1,061/1,652	64.2 (61.9–66.5)	85
Response interval, median (IQR), min	429	5 (4–6)	11	1,623	5 (4–7)	114
Intubated before ED arrival	308/433	71.1 (66.6–75.4)	7	1,185/1,715	69.2 (66.8–71.3)	22
Any out-of-hospital ROSC	111/439	25.3 (21.3–29.6)	1	418/1,735	24.1 (22.1–26.2)	2
Any ROSC (out-of-hospital or posthospital)	145/440	33.0 (28.6–37.6)	0	684/1,737	39.4 (37.1–41.7)	0
Went to catheterization laboratory						
All patients	17/440	3.9 (2.3–6.1)	0	210/1,737	12.1 (10.6–13.7)	0
Patients with any ROSC	17/145	11.7 (7.0–18.1)	0	210/684	30.7 (27.3–343)	0
Received therapeutic hypothermia						
All patients	0/440	0 (0–0.8)	0	300/1,735	17.3 (15.5–19.2)	2
Patients with any ROSC	0/145	0 (0–2.5)	0	300/682	44.0 (40.2–47.8)	2
Survival to hospital discharge						
All rhythms	39/440	8.9 (6.4–11.9)	0	250/1,734	14.4 (12.8–16.2)	3
Witnessed arrests with VF/VT	21/98	21.4 (13.8–30.9)	12	115/293	39.2 (33.6–45.1)	106
Any ROSC	39/145	26.9 (19.9–34.9)	0	250/681	36.7 (33.1–40.5)	3
Positive neurologic outcome (cerebral performance category score=1 or 2) at discharge						
All rhythms	26/439	5.9 (3.9–8.6)	1	153/1,727	8.9 (7.6–10.3)	10
Witnessed arrest with VF/VT	19/98	19.4 (12.1–28.6)	12	87/292	29.8 (24.6–35.4)	107
Any ROSC	26/144	18.1 (12.1–25.3)	1	153/674	22.7 (19.6–26.1)	10

VF, Ventricular fibrillation; *VT*, ventricular tachycardia; *PEA*, pulseless electrical activity; *OHCA*, out-of-hospital cardiac arrest; *MICR*, minimally interrupted cardiac resuscitation; *IQR*, interquartile range; *ROSC*, return of spontaneous circulation.

neurologic outcomes for all rhythms and in several patient subgroups.

Final logistic regression models for all-rhythms survival and positive neurologic outcome (primary analysis) had adequate fit according to the Hosmer-Lemeshow goodness-of-fit test (Tables 2 and 3), and the area under the receiver operating characteristic was greater than 0.8 for both outcomes (Tables 2 and 3). There were 40 cases representing potential outliers according to diagnostic statistics for both survival and positive neurologic outcomes. For survival, the largest change in the regression coefficient for before versus after, after removal of potential outliers, was 4.3%, well below our 20% threshold. For favorable neurologic outcome, the largest change in the regression coefficient for before versus after was 6.9%, also below the threshold. Thus, all cases were retained in the final analysis.

To control for potential secular trends occurring independently of implementation, a time component (year) was included in the analysis. aORs did not significantly change for any variable (no aOR changed by more than 5%) and time was not significantly associated with outcomes (survival aOR=0.95, 95% CI 0.75 to 1.20; neurologic outcome aOR=1.07, 95% CI 0.79 to 1.44). Neither survival nor neurologic outcome varied significantly across years in the before period (survival: Fisher's exact test P=.91, test for trend P=.86; positive neurologic outcome: Fisher's exact test P=.18, test for trend P=.74).

The proportion of cases with missing variables was low (highest proportion of missing data was 5.8% for arrest location) (Table 1). The secondary sensitivity analysis showed that logistic regression results using imputed data for cases with missing

Table 2. Logistic regression analyses for survival to hospital discharge.

Characteristic	Survival (N=2,174), n/N	%	Primary Analysis (Cases With Complete Data Only, N=1,947)				Secondary Analysis (Multiple Imputation Data Set, N=2,174)	
			Crude OR*	95% CI	aOR*†	95% CI	aOR*‡	95% CI
Total	289/2174	13.3	NA	NA	NA	NA	NA	NA
Study phase								
Before	39/440	8.9	[Referent]		[Referent]		[Referent]	
After	250/1,734	14.4	1.69	1.18–2.43	2.22	1.47–3.34	2.34	1.57–3.50
Witnessed arrest								
No	89/1,182	7.5	[Referent]		[Referent]		[Referent]	
Yes	180/884	20.4	3.20	2.43–4.21	2.13	1.55–2.92	2.11	1.55–2.86
Initial VF/VT								
No	89/1,475	6.0	[Referent]		[Referent]		[Referent]	
Yes	182/614	29.6	6.75	5.1–8.94	5.57	4.04–7.68	5.34	3.93–7.25
OHCA location								
Residential	140/1,455	9.6	[Referent]		[Referent]		[Referent]	
Medical facility	33/231	14.3	1.57	1.04–2.35	2.09	1.27–3.44	2.36	1.47–3.80
Public	88/364	24.2	2.99	2.23–4.03	1.92	1.35–2.74	1.87	1.33–2.64
Age, y								
≥80	25/381	6.6	[Referent]		[Referent]		[Referent]	
60–79	118/935	12.6	2.05	1.3–3.22	1.72	1.05–2.84	1.83	1.14–2.93
18–59	144/849	17.0	2.94	1.88–4.61	2.72	1.65–4.50	3.02	1.88–4.86
Bystander CPR								
No	119/1,042	11.4	[Referent]		[Referent]		[Referent]	
Yes	147/1,015	14.5	1.32	1.01–1.71	0.92	0.68–1.25	0.90	0.65–1.24
EMS response interval/min			0.93	0.87–0.98	0.95	0.90–1.01	0.95	0.89–1.01
EMS use of MICR								
No	105/836	12.6	[Referent]		[Referent]		[Referent]	
Yes	163/1,243	13.1	0.97	0.74–1.28	0.96	0.69–1.32	0.81	0.59–1.11
Sex								
Female	89/757	11.8	[Referent]		[Referent]		[Referent]	
Male	200/1,411	14.2	1.24	0.94–1.62	0.89	0.64–1.23	0.85	0.63–1.16

OR, Odds ratio; *NA*, not applicable.
*Hierarchic logistic regression (random-effects variables: EMS agencies nested within hospitals).
†Adjusted for all other variables with reported aORs in the table. Hosmer-Lemeshow goodness of fit, $P=.81$; area under the receiver operating characteristics curve=0.805 (95% CI 0.775 to 0.834).
‡Variables included to generate multiple imputation data set: imputed variables (regression method) were witnessed arrest, provision of bystander CPR, EMS use of MICR, sex, use of therapeutic hypothermia (logistic regression), age (linear regression, variable categorized after imputation), location of OHCA, rhythm on EMS arrival (multinomial logistic regression), and EMS response interval (negative binomial regression); nonimputed covariates were use of catheterization laboratory, incident year, ROSC at any point (out-of-hospital or inhospital), EMS agency, hospital, and survival.

covariates matched those of the primary analysis that included only cases with complete data, indicating minimal bias from analyzing only cases with no missing data (ie, nonimputed data) for the effect of regionalization on outcomes (Tables 2 and 3).

LIMITATIONS

This study was not randomized. Thus, we can show only associations between outcomes and the intervention and cannot prove causal relationships. Randomization is theoretically the best design to assess the effect of regionalization. However, because regionalization includes a "bundle" (eg, therapeutic hypothermia, continuous catheterization/PCI availability, comprehensive critical care, EMS bypass), we believe that randomization is not feasible.

Another approach is to randomize agencies and hospitals. However, even if these organizations would be willing to be randomized to not provide guideline-based care, the agency and hospital randomization interactions would create inherent nonalignment (ie, agencies randomized to perform triage might be paired with nonimplementing hospitals and areas with implementing hospitals might have EMS agencies that were not randomized to triage patients to cardiac receiving centers). This study has many of the attributes of the Ontario Prehospital Advanced Life Support study that evaluated the effect of implementing bundles of care for various conditions across a vast and diverse geography and included many EMS systems and hospitals.[8-10,53-55]

Only 2 specific inhospital interventions were documented (therapeutic hypothermia and catheterization/PCI). Because the sites were encouraged to provide other guideline-based treatments as well,[43,56] interventions that are part of comprehensive postarrest critical care may have affected outcomes. For example, this factor could potentially account for the fact that inhospital return of spontaneous circulation occurred more frequently in the after than the before cohort. Thus, we are unable to identify the relative influence of the individual interventions or combinations of

Table 3. Logistic regression analyses for favorable neurologic outcome on hospital discharge.

Characteristic	FNO* (N=2,166), n/N	%	Primary Analysis (Cases With Complete Data Only, N=1,943)				Secondary Analysis (Multiple Imputation Data Set, N=2,166)	
			Crude OR†	95% CI	aOR†‡	95% CI	aOR†§	95% CI
Total	179/2,166	8.3	NA	NA	NA	NA	NA	NA
Study phase								
Before	26/439	5.9	[Referent]		[Referent]		[Referent]	
After	153/1,727	8.9	1.55	1.00–2.40	2.26	1.37–3.73	2.51	1.52–4.13
Witnessed arrest								
No	36/1,179	3.1	[Referent]		[Referent]		[Referent]	
Yes	132/882	15.0	5.86	3.81–8.18	3.70	2.39–5.72	3.49	2.29–5.31
VF/VT								
No	40/1,470	2.7	[Referent]		[Referent]		[Referent]	
Yes	128/613	20.9	9.53	6.56–13.83	6.48	4.24–9.90	6.20	4.16–9.25
OHCA location								
Residential	78/1,451	5.4	[Referent]		[Referent]		[Referent]	
Medical facility	15/231	6.5	1.24	0.69–3.22	1.38	0.67–2.85	1.80	0.91–3.55
Public	71/363	19.6	4.60	3.20–6.60	2.47	1.63–3.80	2.59	1.71–3.91
Age, y								
≥80	11/379	2.9	[Referent]		[Referent]		[Referent]	
60–79	66/934	7.1	2.52	1.31–4.86	1.99	0.98–4.02	2.02	1.05–3.90
18–59	100/844	11.8	4.62	2.43–8.76	4.17	2.08–8.38	4.33	2.25–8.33
Bystander CPR								
No	73/1,039	7.0	[Referent]		[Referent]		[Referent]	
Yes	94/1,013	9.3	1.39	1.01–1.92	0.93	0.63–1.36	0.89	0.61–1.31
EMS response interval/min			0.91	0.84–0.98	0.94	0.87–1.01	0.94	0.87–1.01
EMS use of MICR								
No	69/834	8.3	[Referent]		[Referent]		[Referent]	
Yes	99/1,240	8.0	0.90	0.64–1.25	0.86	0.57–1.28	0.70	0.47–1.04
Sex								
Female	55/753	7.3	[Referent]		[Referent]		[Referent]	
Male	124/1,407	8.8	1.24	0.89–1.73	0.72	0.48–1.09	0.71	0.48–1.06

FNO, Favorable neurologic outcome.

*Cerebral performance category score=1 or 2.

†Hierarchical logistic regression (random-effects variables: EMS agencies nested within hospitals).

‡Adjusted for all other variables with reported aORs in table. Hosmer-Lemeshow goodness of fit, P=.23; area under the receiver operating characteristics curve=0.861 (95% CI 0.831 to 0.890).

§Variables included in multiple imputation model: imputed variables (regression method) were witnessed arrest, provision of bystander CPR, EMS use of MICR, sex, use of therapeutic hypothermia (logistic regression), age (linear regression, variable categorized after imputation), location of OHCA, rhythm on EMS arrival (multinomial logistic regression), and EMS response interval (negative binomial regression); nonimputed covariates were use of catheterization laboratory, incident year, ROSC at any time (out-of-hospital or inhospital), EMS agency, hospital, and FNO.

interventions. This is true of any study that evaluates the impact of a "bundle." However, the results are still meaningful because the intention of the guidelines is to implement as much of the evidence-based bundle as possible.

Because true regionalization was the intent of this effort, it included a change in the EMS systems' transport protocols. We were aware that the after phase could have a higher proportion of out-of-hospital patients with return of spontaneous circulation arriving at cardiac receiving centers (more likely to survive than patients without return of spontaneous circulation) and this could "artificially" improve the cardiac receiving center survival rates. However, this did not happen. The proportions of out-of-hospital return of spontaneous circulation among out-of-hospital cardiac arrest patients transported to cardiac receiving centers were similar before (25.3%) and after (24.1%).

Some of the changes in outcome might be due to secular trends. To help mitigate this potential, a short preimplementation (before) period (≈6 months) was chosen for establishing baseline data at each hospital for comparison to the after period. Furthermore, we included a time component in our models (which was not significant) to control for potential secular trends. In addition, we analyzed outcomes across years for the before period and found no trend of improvement that could have accounted for our findings of improved survival and positive neurologic outcome in the after period.

Given that this is an observational study, it is not unexpected that sampling error or variation could result in demographic differences between periods or that bias of some kind could result in differences. There were no identifiable differences in patient age, sex, location of arrest, EMS response interval, or provision of bystander cardiopulmonary resuscitation (CPR). However, patients in the after period did have a lower proportion of witnessed arrests, a lower proportion of shockable rhythms on EMS arrival, and a higher proportion of EMS use of minimally

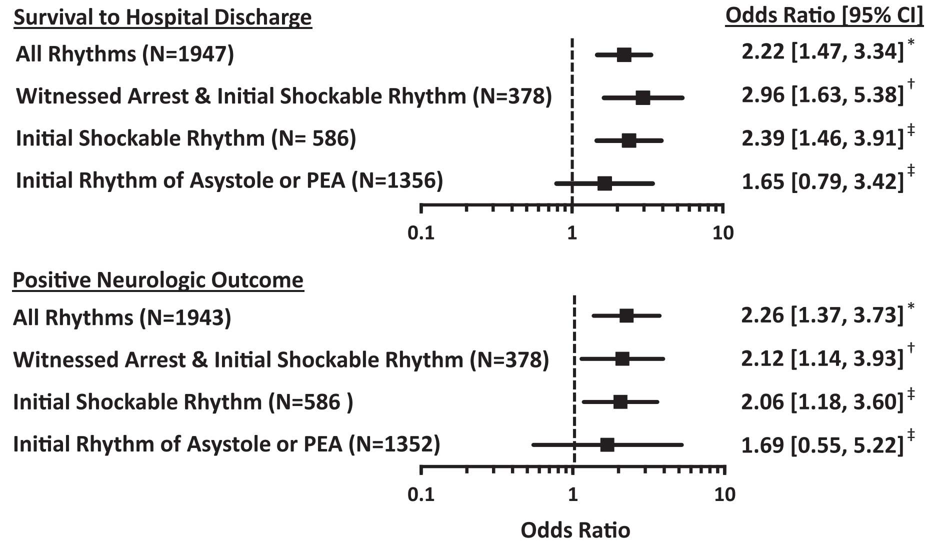

Figure. Comparison of outcomes for the after intervention period versus the before intervention period. Forest plots showing aOR for survival and survival with favorable functional outcome for the after intervention period versus the before intervention period (OR >1 favors the after period) for the entire study population (all rhythms) and several subgroups. *OR adjusted for the following: age, sex, EMS response interval, witnessed arrest, initial rhythm on EMS arrival, bystander CPR provision, location of OHCA, and EMS use of MICR. †OR adjusted for the following: age, sex, EMS response interval, bystander CPR provision, location of OHCA, and EMS use of MICR. ‡OR adjusted for the following: age, sex, EMS response interval, witnessed arrest, bystander CPR, location of OHCA, and EMS use of MICR.

interrupted cardiac resuscitation. The fact that EMS use of minimally interrupted cardiac resuscitation is higher in the postperiod is most likely a reflection of ongoing practice in Arizona as more EMS systems use minimally interrupted cardiac resuscitation over time. We have included this variable in our multivariable analysis to ensure that its influence on outcomes is accounted for (ie, controlled for) in our models so that the underlying effect of our main independent variable (before versus after period) can be accurately measured.

Finally, we are unable to prove that the EMS triage protocol actually led to preferential transport of patients to cardiac receiving centers. With scores of EMS agencies involved, logistic issues preclude us from knowing when the bypass protocol was invoked versus when the closest cardiac receiving center was also the closest "general hospital" (and would have received the patient whether it was a cardiac receiving center or not). However, the fact that there was a 60% increase in the rate at which out-of-hospital cardiac arrest patients were taken to cardiac receiving centers after implementation is consistent with the intent of the officially established triage protocols and with the concept of regionalization.

DISCUSSION

Implementation of this regionalized system of care was associated with improvement in overall survival (aOR=2.22), survival among patients with witnessed ventricular fibrillation or ventricular tachycardia (aOR=2.96), and the odds of favorable neurologic outcome for both the all-rhythm cohort (aOR=2.26) and those with witnessed ventricular fibrillation or ventricular tachycardia (aOR=2.12; Figure). In addition, although not statistically significant, the rates of both survival and favorable neurologic outcome increased in patients with nonshockable rhythms as well (Figure). The American Heart Association policy statement on regionalization recommends triaging patients with return of spontaneous circulation to cardiac receiving centers regardless of presenting rhythm.[43] Although our findings strongly support regionalization for patients with shockable rhythms, they also suggest that this recommendation is reasonable for patients with nonshockable rhythms.

To our knowledge, this is the first statewide report showing an association between improved outcomes and regionalization. This effort involved 55 EMS agencies and 31 hospitals of widely varying size (case numbers per agency/cardiac receiving center ranged from 1 to 197), representing a vast array of organizational and demographic characteristics. Despite these variations, we found significant improvements in outcomes even after controlling for various confounders and independent risk factors, as well as the effects of cluster sampling by hospitals and EMS agencies. Previous investigations were smaller, generally reported implementation in 1 or 2 major regional hospitals with close linkages between the investigators and the clinical care, and did not include officially approved, system-wide EMS triage.[13,14,23,25,26,43,57-60] For instance, Engdahl et al[25] evaluated the inhospital care provided in 2 hospitals in Göteborg, Sweden, and found an association between improved outcome and receiving care at the hospital providing higher rates of specified postarrest interventions. However, EMS did not preferentially triage patients to a specified hospital. Thus, this was not a regionalized approach to out-of-hospital cardiac arrest care because EMS was agnostic to destination hospital.

The concept of regionalization in health care has been described as "the direction of patients with select medical conditions to specially skilled, experienced, and equipped treatment centers."[60] This statewide effort was aimed at implementing both aspects of regionalization: guideline-based inhospital care and EMS triage.[43,60] We did not have data on the patients who were transported to noncardiac receiving centers, and thus we are ultimately unable to completely assess the effect of redirecting patients within the system. However, our findings are consistent with the intent of regionalization. First, we predicted that the implementation of the EMS triage protocols would significantly increase the rate of out-of-hospital cardiac arrest patients arriving at cardiac receiving centers compared with the preprogram rates. Indeed, the number of arrest patients arriving at cardiac receiving centers increased by 60% after protocol implementation. Second, this effort was associated with significant increases in use of guideline therapies at the cardiac receiving centers. Among potentially eligible patients, provision of therapeutic hypothermia increased from 0% to 44.0% and coronary angiography (with or without percutaneous coronary intervention) increased from 11.7% to 30.7%.

The literature has discussed a potential association between outcomes and the volume of patients cared for by cardiac receiving centers.[43,61] In our study, individual hospital volume ranged from 14 to 197 and overall survival varied widely among hospitals. However, when cardiac receiving centers were stratified by number of patients (<50, 50 to 100, and 101 to 197), there were no statistical differences across these groups in overall survivorship (15.3% [95% CI 12.3% to 18.7%] versus 13.2% [95% CI 10.1% to 16.7%] versus 12.5% [95% CI 10.7% to 14.5%], respectively). In addition, when the number of patients cared for at a given cardiac receiving center was added into the final LR model for survival, it had no effect on the OR for survival (regression coefficient changed by less than 5%) for after versus before and it was not significantly associated with survival. This is consistent with previous findings from the Cardiac Arrest Registry to Enhance Survival that showed no association between cardiac receiving center patient volume and outcome.[61]

Although our study does not prove that regionalization of EMS and inhospital care caused the doubling of survival, we believe our findings support the concept of widespread regionalization for the following reasons: First, bypass of local hospitals to take patients to cardiac receiving centers is likely safe. Our large preimplementation evaluations of transport time intervals and distance (in Arizona and Ontario, Canada) identified no association between longer transport intervals and higher mortality.[39,40] Second, there is widespread and growing evidence for a positive effect of intentional, guideline-based, postarrest, inhospital care. This strongly supports the theoretical plausibility for regionalization.[13-15,17-19,23,25-27,29,31,32,38,43,57-59,62] Third, our regionalization program was implemented across a vast demography in a wide variety of local systems and hospitals. This finding is particularly meaningful because the health care system in Arizona is decentralized—the "lead agency" can coordinate and collaborate, but does not mandate changes in care. Thus, it appears that an EMS jurisdiction can lead effective implementation of out-of-hospital cardiac arrest regionalization even if it does not have authority to require the necessary organizations to participate. This may mean that the "transportability" of regionalization to other EMS jurisdictions has the potential for success through a collaborative process even if they do not possess "control" of the system. Fourth, our findings are consistent with the nationally vetted recommendations for implementation of regionalized systems of care.[43]

In summary, implementation of a voluntary, statewide specialty hospital recognition program and EMS bypass protocols directing postarrest patients to these centers was independently associated with improvements in overall survival and the likelihood of favorable neurologic survival. In addition, survival from bystander-witnessed shockable rhythms improved, as did the rate of favorable neurologic outcome in this subgroup.

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REFERENCES

1. Eisenberg MS, Bergner L, Hallstrom A. Cardiac resuscitation in the community. Importance of rapid provision and implications for program planning. *JAMA*. 1979;241:1905-1907.
2. Cummins RO, Ornato JP, Thies WH, et al. Improving survival from sudden cardiac arrest: the "chain of survival" concept. A statement for health professionals from the Advanced Cardiac Life Support Subcommittee and the Emergency Cardiac Care Committee, American Heart Association. *Circulation*. 1991;83:1832-1847.
3. Nichol G, Stiell IG, Laupacis A, et al. A cumulative meta-analysis of the effectiveness of defibrillator-capable emergency medical services for victims of out-of-hospital cardiac arrest. *Ann Emerg Med*. 1999;34:517-525.
4. Spaite DW, Hanlon T, Criss EA, et al. Prehospital cardiac arrest: the impact of witnessed collapse and bystander CPR in a metropolitan EMS system with short response times. *Ann Emerg Med*. 1990;19:1264-1269.
5. Eisenberg MS, Horwood BT, Cummins RO, et al. Cardiac arrest and resuscitation: a tale of 29 cities. *Ann Emerg Med*. 1990;19:179-186.
6. Valenzuela TD, Roe DJ, Nichol G, et al. Outcomes of rapid defibrillation by security officers after cardiac arrest in casinos. *N Engl J Med*. 2000;343:1206-1209.
7. Bobrow BJ, Spaite DW, Berg RA, et al. Chest compression–only CPR by lay rescuers and survival from out-of-hospital cardiac arrest. *JAMA*. 2010;304:1447-1454.
8. Stiell I, Nichol G, Wells G, et al. Health-related quality of life is better for cardiac arrest survivors who received citizen cardiopulmonary resuscitation. *Circulation*. 2003;108:1939-1944.
9. Stiell IG, Wells GA, Field B, et al. Advanced cardiac life support in out-of-hospital cardiac arrest. *N Engl J Med*. 2004;351:647-656.
10. Stiell IG, Wells GA, Field BJ, et al. Improved out-of-hospital cardiac arrest survival through the inexpensive optimization of an existing defibrillation program: OPALS study phase II. Ontario Prehospital Advanced Life Support. *JAMA*. 1999;281:1175-1181.
11. Sasson C, Rogers MA, Dahl J, et al. Predictors of survival from out-of-hospital cardiac arrest: a systematic review and meta-analysis. *Circ Cardiovasc Qual Outcomes*. 2010;3:63-81.
12. Kellermann AL, Staves DR, Hackman BB. In-hospital resuscitation following unsuccessful prehospital advanced cardiac life support: "heroic efforts" or an exercise in futility? *Ann Emerg Med*. 1988;17:589-594.
13. Bernard SA, Jones BM, Horne MK. Clinical trial of induced hypothermia in comatose survivors of out-of-hospital cardiac arrest. *Ann Emerg Med*. 1997;30:146-153.
14. Yanagawa Y, Ishihara S, Norio H, et al. Preliminary clinical outcome study of mild resuscitative hypothermia after out-of-hospital cardiopulmonary arrest. *Resuscitation*. 1998;39:61-66.
15. Nagao K, Hayashi N, Kanmatsuse K, et al. Cardiopulmonary cerebral resuscitation using emergency cardiopulmonary bypass, coronary reperfusion therapy and mild hypothermia in patients with cardiac arrest outside the hospital. *J Am Coll Cardiol*. 2000;36:776-783.
16. Zeiner A, Holzer M, Sterz F, et al. Mild resuscitative hypothermia to improve neurological outcome after cardiac arrest. A clinical feasibility trial. Hypothermia After Cardiac Arrest (HACA) Study Group. *Stroke*. 2000;31:86-94.
17. Hypothermia after Cardiac Arrest Study Group. Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. *N Engl J Med*. 2002;346:549-556.
18. Bernard SA, Gray TW, Buist MD, et al. Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. *N Engl J Med*. 2002;346:557-563.
19. Nielsen N, Wetterslev J, Cronberg T, et al. Targeted temperature management at 33 degrees C versus 36 degrees C after cardiac arrest. *N Engl J Med*. 2013;369:2197-2206.
20. Nolan JP, Morley PT, Hoek TL, et al. Therapeutic hypothermia after cardiac arrest. An advisory statement by the Advancement Life support Task Force of the International Liaison Committee on Resuscitation. *Resuscitation*. 2003;57:231-235.
21. Nolan JP, Morley PT, Vanden Hoek TL, et al. Therapeutic hypothermia after cardiac arrest: an advisory statement by the Advanced Life Support Task Force of the International Liaison Committee on Resuscitation. *Circulation*. 2003;108:118-121.
22. Resuscitation-International Liaison Committee on Resuscitation. Postresuscitation support: consensus guidelines from ILCOR on emergency cardiac care and CPR. *Circulation*. 2005;112:IV 84-8, 136-8.
23. Herlitz J, Castren M, Friberg H, et al. Post resuscitation care—what are the therapeutic alternatives and what do we know? *Resuscitation*. 2006;69:15-22.
24. Langhelle A, Tyvold SS, Lexow K, et al. In-hospital factors associated with improved outcome after out-of-hospital cardiac arrest. A comparison between four regions in Norway. *Resuscitation*. 2003;56:247-263.
25. Engdahl J, Abrahamsson P, Bang A, et al. Is hospital care of major importance for outcome after out-of-hospital cardiac arrest? experience acquired from patients with out-of-hospital cardiac arrest resuscitated by the same emergency medical service and admitted to one of two hospitals over a 16-year period in the municipality of Goteborg. *Resuscitation*. 2000;43:201-211.
26. Borger van der Burg AE, Bax JJ, Boersma E, et al. Impact of percutaneous coronary intervention or coronary artery bypass grafting on outcome after nonfatal cardiac arrest outside the hospital. *Am J Cardiol*. 2003;91:785-789.
27. Spaulding CM, Joly LM, Rosenberg A, et al. Immediate coronary angiography in survivors of out-of-hospital cardiac arrest. *N Engl J Med*. 1997;336:1629-1633.
28. Sunde K, Pytte M, Jacobsen D, et al. Implementation of a standardised treatment protocol for post resuscitation care after out-of-hospital cardiac arrest. *Resuscitation*. 2007;73:29-39.
29. Huang L, Weil MH, Tang WC, et al. Comparison between dobutamine and levosimendan for management of postresuscitation myocardial dysfunction. *Crit Care Med*. 2005;33:487-491.
30. Ruiz-Bailen M, Aguayo de Hoyos E, Ruiz-Navarro S, et al. Reversible myocardial dysfunction after cardiopulmonary resuscitation. *Resuscitation*. 2005;66:175-181.
31. Balan IS, Fiskum G, Hazelton J, et al. Oximetry-guided reoxygenation improves neurological outcome after experimental cardiac arrest. *Stroke*. 2006;37:3008-3013.
32. Sung K, Lee YT, Park PW, et al. Improved survival after cardiac arrest using emergent autopriming percutaneous cardiopulmonary support. *Ann Thorac Surg*. 2006;82:651-656.
33. Nichol G, Karmy-Jones R, Salerno C, et al. Systematic review of percutaneous cardiopulmonary bypass for cardiac arrest or cardiogenic shock states. *Resuscitation*. 2006;70:381-394.
34. Oksanen T, Skrifvars MB, Varpula T, et al. Strict versus moderate glucose control after resuscitation from ventricular fibrillation. *Intensive Care Med*. 2007;33:2093-2100.
35. Aufderheide TP, Sigurdsson G, Pirrallo RG, et al. Hyperventilation-induced hypotension during cardiopulmonary resuscitation. *Circulation*. 2004;109:1960-1965.

36. Hosmane VR, Mustafa NG, Reddy VK, et al. Survival and neurologic recovery in patients with ST-segment elevation myocardial infarction resuscitated from cardiac arrest. *J Am Coll Cardiol*. 2009;53: 409-415.
37. Lettieri C, Savonitto S, De Servi S, et al. Emergency percutaneous coronary intervention in patients with ST-elevation myocardial infarction complicated by out-of-hospital cardiac arrest: early and medium-term outcome. *Am Heart J*. 2009;157:569-575.e1.
38. Grasner JT, Meybohm P, Caliebe A, et al. Postresuscitation care with mild therapeutic hypothermia and coronary intervention after out-of-hospital cardiopulmonary resuscitation: a prospective registry analysis. *Crit Care*. 2011;15:R61.
39. Spaite DW, Bobrow BJ, Vadeboncoeur TF, et al. The impact of prehospital transport interval on survival in out-of-hospital cardiac arrest: implications for regionalization of post-resuscitation care. *Resuscitation*. 2008;79:61-66.
40. Spaite DW, Stiell IG, Bobrow BJ, et al. Effect of transport interval on out-of-hospital cardiac arrest survival in the OPALS study: implications for triaging patients to specialized cardiac arrest centers. *Ann Emerg Med*. 2009;54:248-255.
41. Lurie KG, Idris A, Holcomb JB. Level 1 cardiac arrest centers: learning from the trauma surgeons. *Acad Emerg Med*. 2005;12:79-80.
42. Davis DP, Fisher R, Aguilar S, et al. The feasibility of a regional cardiac arrest receiving system. *Resuscitation*. 2007;74:44-51.
43. Nichol G, Aufderheide TP, Eigel B, et al. Regional systems of care for out-of-hospital cardiac arrest: a policy statement from the American Heart Association. *Circulation*. 2010;121:709-729.
44. Bobrow BJ, Clark LL, Ewy GA, et al. Minimally interrupted cardiac resuscitation by emergency medical services for out-of-hospital cardiac arrest. *JAMA*. 2008;299:1158-1165.
45. Bobrow BJ, Spaite DW, Geyer B, et al. The impact of a statewide, comprehensive system of care on survival from out-of-hospital cardiac arrest. *Circulation*. 2010;122:A36.
46. Bobrow BJ, Vadeboncoeur TF, Clark L, et al. Establishing Arizona's statewide cardiac arrest reporting and educational network. *Prehosp Emerg Care*. 2008;12:381-387.
47. Therapeutic hypothermia after cardiac arrest. ILCOR Advisory Statement, October 2002. *CJEM*. 2005;7:129.
48. Snyder Q, Hiller KM, Bogert J, et al. Use of therapeutic hypothermia in comatose survivors of out-of-hospital cardiac arrest in Arizona emergency departments. *West J Emerg Med*. 2008;9:62-63.
49. Stiell IG, Wells GA, Spaite DW, et al. The Ontario Prehospital Advanced Life Support (OPALS) study: rationale and methodology for cardiac arrest patients. *Ann Emerg Med*. 1998;32:180-190.
50. White IR, Royston P, Wood AM. Multiple imputation using chained equations: issues and guidance for practice. *Stat Med*. 2011;30:377-399.
51. White IR, Royston P, Wood AM. Multiple imputation using chained equations: Issues and guidance for practice. *Stat Med*. 2011;30:377-399.
52. Rubin DB. Multiple imputation after 18+ years. *J Am Stat Assoc*. 1996;91:473-489.
53. Stiell IG, Wells GA, Spaite DW, et al. The Ontario Prehospital Advanced Life Support (OPALS) study part II: rationale and methodology for trauma and respiratory distress patients. OPALS Study Group. *Ann Emerg Med*. 1999;34:256-262.
54. Stiell IG, Nesbitt LP, Pickett W, et al. The OPALS Major Trauma study: impact of advanced life-support on survival and morbidity. *CMAJ*. 2008;178:1141-1152.
55. Stiell IG, Spaite DW, Field B, et al. Advanced life support for out-of-hospital respiratory distress. *N Engl J Med*. 2007;356:2156-2164.
56. Neumar RW, Nolan JP, Adrie C, et al. Post-cardiac arrest syndrome: epidemiology, pathophysiology, treatment, and prognostication. A consensus statement from the International Liaison Committee on Resuscitation (American Heart Association, Australian and New Zealand Council on Resuscitation, European Resuscitation Council, Heart and Stroke Foundation of Canada, InterAmerican Heart Foundation, Resuscitation Council of Asia, and the Resuscitation Council of Southern Africa); the American Heart Association Emergency Cardiovascular Care Committee; the Council on Cardiovascular Surgery and Anesthesia; the Council on Cardiopulmonary, Perioperative, and Critical Care; the Council on Clinical Cardiology; and the Stroke Council. *Circulation*. 2008;118:2452-2483.
57. Arrich J. Clinical application of mild therapeutic hypothermia after cardiac arrest. *Crit Care Med*. 2007;35:1041-1047.
58. Belliard G, Catez E, Charron C, et al. Efficacy of therapeutic hypothermia after out-of-hospital cardiac arrest due to ventricular fibrillation. *Resuscitation*. 2007;75:252-259.
59. Busch M, Soreide E, Lossius HM, et al. Rapid implementation of therapeutic hypothermia in comatose out-of-hospital cardiac arrest survivors. *Acta Anaesthesiol Scand*. 2006;50:1277-1283.
60. Wang HE, Yealy DM. Distribution of specialized care centers in the United States. *Ann Emerg Med*. 2012;60:632-637.e7.
61. Cudnik MT, Sasson C, Rea TD, et al. Increasing hospital volume is not associated with improved survival in out of hospital cardiac arrest of cardiac etiology. *Resuscitation*. 2012;83:862-868.
62. Oddo M, Schaller MD, Feihl F, et al. From evidence to clinical practice: effective implementation of therapeutic hypothermia to improve patient outcome after cardiac arrest. *Crit Care Med*. 2006;34: 1865-1873.

APPENDIX E1. SHARE cardiac receiving center data form.

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