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Early versus Later Rhythm Analysis in Patients with Out-of-Hospital Cardiac Arrest

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ABSTRACT

BACKGROUND

In a departure from the previous strategy of immediate defibrillation, the 2005 resuscitation guidelines from the American Heart Association–International Liaison Committee on Resuscitation suggested that emergency medical service (EMS) personnel could provide 2 minutes of cardiopulmonary resuscitation (CPR) before the first analysis of cardiac rhythm. We compared the strategy of a brief period of CPR with early analysis of rhythm with the strategy of a longer period of CPR with delayed analysis of rhythm.

METHODS

We conducted a cluster-randomized trial involving adults with out-of-hospital cardiac arrest at 10 Resuscitation Outcomes Consortium sites in the United States and Canada. Patients in the early-analysis group were assigned to receive 30 to 60 seconds of EMS-administered CPR and those in the later-analysis group were assigned to receive 180 seconds of CPR, before the initial electrocardiographic analysis. The primary outcome was survival to hospital discharge with satisfactory functional status (a modified Rankin scale score of ≤3, on a scale of 0 to 6, with higher scores indicating greater disability).

RESULTS

We included 9933 patients, of whom 5290 were assigned to early analysis of cardiac rhythm and 4643 to later analysis. A total of 273 patients (5.9%) in the later-analysis group and 310 patients (5.9%) in the early-analysis group met the criteria for the primary outcome, with a cluster-adjusted difference of −0.2 percentage points (95% confidence interval, −1.1 to 0.7; P=0.59). Analyses of the data with adjustment for confounding factors, as well as subgroup analyses, also showed no survival benefit for either study group.

CONCLUSIONS

Among patients who had an out-of-hospital cardiac arrest, we found no difference in the outcomes with a brief period, as compared with a longer period, of EMS-administered CPR before the first analysis of cardiac rhythm. (Funded by the National Heart, Lung, and Blood Institute and others; ROC PRIMED ClinicalTrials.gov number, NCT00394706.)

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Out-of-hospital cardiac arrest is a common and lethal problem, leading to an estimated 330,000 deaths each year in the United States and Canada.[1] Overall, the rate of survival to hospital discharge among patients with an out-of-hospital cardiac arrest who are treated by emergency medical services (EMS) personnel is low but varies greatly, with rates ranging from 3.0% to 16.3%.[1] This variation in the rate of survival can be attributed partly to local variations in the five key links in the chain of survival: rapid EMS access, early cardiopulmonary resuscitation (CPR), early defibrillation, early advanced cardiac life support, and effective care after resuscitation.[2-6] Concerted efforts by EMS personnel to strengthen these links have led to only a slight increase in survival rates in recent years.

The traditional approach to out-of-hospital cardiac arrest has been to emphasize early analysis of cardiac rhythm, with delivery of defibrillatory shocks, if indicated, as quickly as possible. It has been suggested, however, that many patients may benefit from a period of CPR before the first analysis of rhythm.[7] The 2005 resuscitation guidelines from the American Heart Association–International Liaison Committee on Resuscitation (AHA–ILCOR) departed from its previous "shock first" strategy by suggesting that responders could provide 2 minutes of CPR before analysis of cardiac rhythm.[3] These changes in the guidelines are supported by the findings of three clinical studies[8-10] but are not supported by two others,[11,12] and in the 2010 guidelines, the recommendation was modified to say that "there is inconsistent evidence to support or refute" such a delay in the analysis of cardiac rhythm.[13] Therefore, the preferred initial approach remains uncertain.[14] Our objective was to compare two approaches to the timing of CPR by EMS personnel — a brief period of manual chest compressions and ventilations with prompt initiation of rhythm analysis and defibrillation (early analysis) versus a longer period of compressions and ventilations before the first analysis of cardiac rhythm (later analysis).

METHODS

STUDY DESIGN AND OVERSIGHT

A detailed description of the methods has been published previously.[15] The Resuscitation Outcomes Consortium (ROC) is a clinical trial consortium comprising 10 U.S. and Canadian universities and their regional EMS systems.[16] The ROC investigators designed the Prehospital Resuscitation Impedance Valve and Early Versus Delayed Analysis (ROC PRIMED) trial to study two randomized comparisons.[15,17] The first comparison, in which early analysis of cardiac rhythm was compared with later rhythm analysis, is the subject of this article. The second, concurrent comparison, in which the use of an impedance threshold device (ITD) was compared with the use of a sham ITD, is reported elsewhere in this issue of the *Journal*.[18] Most patients were enrolled simultaneously in both the early-analysis-versus-later-analysis component and the active-ITD-versus-sham-ITD component of the ROC PRIMED trial, although the two components had slightly different eligibility criteria. Additional details are provided in the Supplementary Appendix, available with the full text of this article at NEJM.org.

The protocol was approved by the institutional review or research ethics boards at each participating site. The trial protocol, including the statistical analysis plan, is available at NEJM.org. All the authors vouch for the completeness and accuracy of the data and the analyses and for the fidelity of the study to the trial protocol.

STUDY SETTING AND POPULATION

The trial was conducted at 150 of the 260 EMS agencies participating in the ROC. The trial agencies were selected because they had the capability to provide advanced cardiac life-support interventions and to record CPR process measures and because they met prespecified quality criteria during an initial run-in phase.

We included all persons 18 years of age or older who had an out-of-hospital cardiac arrest that was not the result of trauma and who were treated with defibrillation, delivery of chest compressions, or both by EMS providers. Persons were excluded if the arrest was witnessed by EMS personnel; if they had a blunt, penetrating, or burn-related injury; if the arrest was due to exsanguination; if they were pregnant; if they were prisoners; if they had an "opt-out" bracelet, indicating that they wished to opt out of the study; if they had "do not attempt resuscitation" orders; if the rhythm analysis was performed by police or a lay responder; or if they received initial treatment by an EMS agency that was not in the ROC. Patients were not required to

provide informed consent; according to the regulations of the Food and Drug Administration and the Canadian Tri-Council agreement, this study qualified for exception from the requirements for informed consent because it involved research conducted during an emergency situation.

RANDOMIZATION

Each of the 10 participating ROC centers (or sites) was divided into approximately 20 subunits, designated as "clusters," according to EMS agency or geographic boundaries or according to defibrillator device, ambulance, station, or battalion. Randomization of clusters was stratified according to site. All episodes of cardiac arrest in a cluster were randomly assigned to one CPR strategy; after a set period of time, ranging from 3 to 12 months, all episodes in that cluster were then assigned to the other strategy. All the clusters were assigned to cross over to the other strategy one or more times during the study at fixed intervals; we estimated that approximately 100 patients would be included during each interval.

STUDY INTERVENTION

Patients in the early-analysis group were assigned to receive 30 to 60 seconds of chest compressions and ventilations (sufficient time to place defibrillator electrodes) before electrocardiographic (ECG) analysis, and those in the late-analysis group were assigned to receive 3 minutes of chest compressions and ventilations before ECG analysis. The assigned intervention was implemented by the first qualified EMS provider to arrive at the scene (defibrillation-capable firefighter, emergency medical technician, or paramedic). The start and stop times for CPR were recorded by the responders, and the information was supplemented by the recording of defibrillator time.

The training of participating EMS providers emphasized uninterrupted chest compressions except for required ventilations, with compressions and ventilations applied in a 30:2 ratio, and specified that advanced airway devices were to be placed with minimal interruptions to compressions. Every 6 months, the EMS providers underwent some retraining that included written reminders, slide presentations, and Web-based modules. All ROC sites implemented high-quality electronic monitoring of the CPR process with the use of defibrillator hardware and software. Adherence to the protocol-specified performance targets and to the requirements for data submission was monitored throughout the study by a study monitoring committee, which provided regular feedback to sites.

OUTCOME MEASURES

The primary outcome was survival to hospital discharge with satisfactory functional status, defined as a score of 3 or less on the modified Rankin scale.[19-21] This is a validated scale, ranging from 0 to 6, that is commonly used for measuring the performance of daily activities by people who have had a stroke. Lower scores represent better performance; scores of 4 or higher represent severe disability or death. Secondary outcomes were survival to discharge, survival to hospital admission, and return of spontaneous circulation at the time of arrival at the emergency department.

STATISTICAL ANALYSIS

We estimated that with enrollment of 13,239 patients who could be evaluated, the study would have 99.6% power to detect an improvement in the primary outcome from 5.4% with early analysis of heart rhythm to 7.4% with later analysis, assuming a group-sequential stopping rule at a two-sided alpha level of 0.05 with up to three interim analyses (O'Brien–Fleming boundaries).[22] This calculation took into consideration the concurrent ITD portion of the trial, which required the enrollment of 14,154 patients who could be evaluated, in order to have 90% power to detect a 25% difference in the outcome between the two groups in that trial.

Analyses of the primary and secondary effectiveness outcomes were performed on the basis of a modified intention-to-treat principle with data from eligible patients in whom the cardiac arrest was not due to drowning, strangulation, or electrocution and for whom the primary outcome was known. An independent data and safety monitoring board reviewed the data at prespecified intervals and used a group-sequential stopping rule. The primary analysis compared the outcomes between the groups with the use of the Wald statistic for the treatment group in a generalized linear mixed model.[23] The model included random effects for each of the clusters, accommodated the binary distribution of the outcome variable, and used a linear-link function to estimate an absolute difference in risk.

The between-group difference in the primary

outcome, adjusted for baseline characteristics, was calculated with the use of a multiple linear regression model, with robust standard errors to accommodate clustering and the binary distribution of the outcome. Analyses of binary secondary outcomes and subgroup analyses were performed with the use of generalized-estimating-equation models to estimate differences in risk.[24] Mean scores on the modified Rankin scale were compared between the two treatment groups with the use of a linear model.

We conducted further exploratory analyses of the data using kernel density estimators to estimate the distribution of time from the start of CPR to the actual analysis of cardiac rhythm, separately within treatment groups.[25] The association between the primary outcome and the time of cardiac-rhythm analysis was explored with the use of smoothing splines, and confidence intervals were computed with the use of the bootstrap method.[26,27]

RESULTS

ENROLLMENT AND RANDOMIZATION

The first site commenced the run-in phase in June 2007. All the sites stopped enrollment in November 2009, when the data and safety monitoring board recommended that the trial be stopped early because continuing recruitment was unlikely to change the outcome of the study. Of 13,460 patients screened, 10,365 were enrolled, and 10,153 underwent randomization. Of these, 195 were excluded from the data analysis when their cardiac arrest was confirmed to be due to drowning, strangulation, or electrocution, and 25 were excluded because the outcome with respect to the primary end point was unknown. Thus, 9933 patients were included in the primary data analysis (Fig. 1 in the Supplementary Appendix).

CHARACTERISTICS OF THE TWO STUDY GROUPS

The early-analysis group comprised more patients than the later-analysis group (5290 vs. 4643) owing to early termination of the trial. The two study groups were evenly balanced with respect to baseline characteristics except that there were small group imbalances in the distribution of patients across sites (Table 1); however, these would not have any appreciable effect on the results because of the cluster-crossover design, which yields treatment comparisons within clusters. Not all the scheduled cluster crossovers had occurred at the time of termination, although each cluster had crossed over at least once. The postrandomization characteristics of the patients in each group are provided in Table 2. The median time to the analysis of cardiac rhythm was 42 seconds (interquartile range, 27 to 80) in the early-analysis group and 180 seconds (interquartile range, 151 to 190) in the later-analysis group. A majority of patients in each group received rhythm analysis within the targeted range for that group: 68% of patients in the early-analysis group received analysis of cardiac rhythm within the targeted range of 0 to 60 seconds and 60% of patients in the later-analysis group received analysis of cardiac rhythm within the targeted range of 150 to 210 seconds (Fig. 2 in the Supplementary Appendix).

PRIMARY AND SECONDARY OUTCOMES

A total of 310 patients in the early-analysis group (5.9%) and 273 patients in the later-analysis group (5.9%) survived to hospital discharge with a modified Rankin score of 3 or less, with a cluster-adjusted difference between later cardiac analysis and early cardiac analysis of −0.2 percentage points (95% confidence interval [CI], −1.1 to 0.7; P=0.59) (Table 3). There was also no significant difference between the study groups with respect to any of the secondary outcomes. An analysis adjusted for potential confounders evaluated the effect of study group on survival and showed a difference of −0.3 percentage points (95% CI, −1.3 to 0.7) between later cardiac analysis and early cardiac analysis (P=0.61).

ADDITIONAL ANALYSES

We conducted a number of prespecified and post hoc subgroup analyses (Fig. 1) and found that the absence of significant differences in the rate of survival between the two study groups was consistent across subgroups. The relationship between the site-specific treatment effect and the site-specific probability of survival overall is shown in Figure 3 in the Supplementary Appendix.

When the outcomes were analyzed on an as-treated basis, the rates of survival with satisfactory functional status were 6.0% among the 3982 patients in whom the analysis of cardiac rhythm was performed between 0 and 60 seconds and 5.9%

Table 1. Baseline Characteristics of the Patients Included in the Primary Analysis.*

Characteristic	Early Analysis of Cardiac Rhythm (N=5290)	Later Analysis of Cardiac Rhythm (N=4643)
Age — yr†	66.7±16.6	66.7±16.6
Male sex — no./total no. (%)	3408/5289 (64.4)	2965/4643 (63.9)
Cause of cardiac arrest obvious — no./total no. (%)‡	110/5288 (2.1)	105/4643 (2.3)
Cardiac arrest occurring in public location — no. (%)	737 (13.9)	655 (14.1)
Cardiac arrest witnessed by bystander — no. (%)	2316 (43.8)	2029 (43.7)
CPR performed by bystander — no. (%)	2098 (39.7)	1904 (41.0)
Time from dispatch to first arrival of EMS — min§	6.0±3.7	6.0±5.9
Time from dispatch to first EMS arrival ≤4 min — no./total no. (%)	1060/5243 (20.2)	868/4601 (18.9)
Time from dispatch to first arrival of ALS providers — min¶	9.1±5.8	9.1±7.4
Treated with ALS — no. (%)	5105 (96.5)	4492 (96.7)
Site — no. (%)		
Alabama	40 (0.8)	60 (1.3)
Dallas	113 (2.1)	78 (1.7)
Milwaukee	408 (7.7)	354 (7.6)
Ottawa–OPALS‖	915 (17.3)	694 (14.9)
Pittsburgh	129 (2.4)	118 (2.5)
Portland, OR	334 (6.3)	314 (6.8)
San Diego, CA	206 (3.9)	218 (4.7)
King County, WA	672 (12.7)	642 (13.8)
Toronto	1873 (35.4)	1536 (33.1)
Vancouver, BC	600 (11.3)	629 (13.5)

* Plus–minus values are means ±SD. The distribution of sites differed significantly between the two groups (P<0.05). None of the other between-group differences were significant. ALS denotes advanced life support, CPR cardiopulmonary resuscitation, and EMS emergency medical services.

† The comparison with respect to age was based on 5279 patients in the early-analysis group and 4625 in the later-analysis group.

‡ Obvious causes included, but were not limited to, drug or chemical poisoning and mechanical suffocation (foreign body or hanging).

§ The comparison with respect to the time from dispatch to first arrival of EMS was based on 5243 patients in the early-analysis group and 4601 in the later-analysis group.

¶ The comparison with respect to the time from dispatch to first arrival of advanced life support was based only on the cases for which advanced life support was on the scene (5104 in the early-analysis group and 4490 in the later-analysis group).

‖ The Ottawa–Ontario Prehospital Advanced Life Support (OPALS) group is a group of 7 EMS services and 13 cities in Ontario.

among the 3115 patients in whom the analysis of cardiac rhythm was performed between 150 and 210 seconds (P=0.97). In an additional exploratory analysis, we evaluated the rate of survival as a function of the actual time to the first rhythm analysis, regardless of the study group (Fig. 2). The chance of survival with satisfactory functional status did not improve with increasing time to the first analysis of cardiac rhythm, and among patients with an initial rhythm of ventricular tachycardia or ventricular fibrillation who received CPR from a bystander, the rate of survival tended to decline with increasing time to the first rhythm analysis.

Table 2. Postrandomization Characteristics of the Patients Included in the Primary Analysis.*

Characteristic	Early Analysis of Cardiac Rhythm (N=5290)		Later Analysis of Cardiac Rhythm (N=4643)	
	No. of Patients with Data	Value	No. of Patients with Data	Value
Time to analysis of cardiac rhythm — sec	5132		4454	
Mean		71±175		171±84
Median		42		180
Interquartile range		27–80		151–190
First rhythm interpretation — no. (%)	5290		4643	
Ventricular tachycardia or ventricular fibrillation, shockable		1279 (24.2)		1153 (24.8)
Pulseless electrical activity		1043 (19.7)		891 (19.2)
Asystole		2450 (46.3)		2147 (46.2)
AED used, no shock advised, no rhythm strip available		477 (9.0)		403 (8.7)
Perfusing		6 (0.1)		12 (0.3)
Unknown or could not be determined		35 (0.7)		37 (0.8)
Receipt of shocks				
Any received — no. of patients (%)	5281	2078 (39.3)	4637	1856 (40.0)
Mean no. received	2075	3.2±2.7	1853	3.2±2.7
Intubation before arrival at hospital — no. (%)	5290		4643	
Attempted		4056 (76.7)		3595 (77.4)
Successful		3607 (68.2)		3225 (69.5)
CPR process measures up to 5 min or until intubation				
Pause before shock — sec	1324	17.6±12.5	1189	17.1±11.1
Pause after shock — sec	1380	8.4±7.1	1184	9.1±7.9
Compression rate — no./min	3236	107.2±18.9	2719	108.6±19.4
Compression depth — mm	2315	41.9±12.2	1875	42.2±11.4
CPR fraction†	3243	0.66±0.2	2722	0.71±0.2
Drugs administered before arrival at hospital				
Epinephrine — no. (%)	5258	4306 (81.9)	4625	3825 (82.7)
Dose of epinephrine — mg	4299	3.5±1.8	3820	3.7±2.0
Sodium bicarbonate — no. (%)	5257	961 (18.3)	4625	920 (19.9)
Atropine — no. (%)	5257	3597 (68.4)	4625	3132 (67.7)
Lidocaine — no. (%)	5257	531 (10.1)	4625	516 (11.2)
Amiodarone — no. (%)	5257	536 (10.2)	4625	475 (10.3)
Coenrollment in ITD component of trial — no. (%)	5290		4643	
Sham ITD		1872 (35.4)		1696 (36.5)
Real ITD		1925 (36.4)		1682 (36.2)
Not enrolled in ITD study		1493 (28.2)		1265 (27.2)
Hospital procedures — no. (%)‡	1312		1139	
Hypothermia		606 (46.2)		514 (45.1)
Coronary catheterization		407 (31.0)		345 (30.3)
Implantable cardioverter–defibrillator		130 (9.9)		108 (9.5)

* Plus–minus values are means ±SD. The following variables differed significantly between the two groups ($P<0.05$): time to analysis of cardiac rhythm, pause after shock, compression rate, cardiopulmonary resuscitation (CPR) fraction, dose of epinephrine, and use of sodium bicarbonate. None of the other between-group differences were significant. AED denotes automated external defibrillator, and ITD impedance threshold device.

† The CPR fraction is the proportion of each minute during which compressions are given.

‡ A total of 1312 patients in the early-analysis group and 1139 in the later-analysis group were admitted to the hospital.

Table 3. Outcomes for the Patients Included in the Primary Analysis.*

Outcome	Early Analysis of Cardiac Rhythm (N=5290)	Later Analysis of Cardiac Rhythm (N=4643)	Difference: Later Analysis – Early Analysis (95% CI)	P Value
Transported to hospital — no. (%)	2812 (53.2)	2468 (53.2)	0.0 (–2.7 to 2.7)	1.00
Pulse present on arrival at emergency department — no. (%)	1352 (25.6)	1218 (26.2)	0.7 (–1.0 to 2.4)	0.44
Survival to hospital admission — no. (%)	1303 (24.6)	1132 (24.4)	–0.3 (–1.6 to 1.1)	0.71
Survival to hospital discharge — no. (%)	427 (8.1)	372 (8.0)	–0.1 (–1.2 to 1.1)	0.92
Modified Rankin score — no. (%)†				
≤3‡	310 (5.9)	273 (5.9)	–0.2 (–1.1 to 0.7)	0.59
0	82 (1.6)	71 (1.5)		
1	117 (2.2)	100 (2.2)		
2	20 (0.4)	29 (0.6)		
3	91 (1.7)	73 (1.6)		
4	69 (1.3)	55 (1.2)		
5	48 (0.9)	44 (0.9)		
6	4863 (91.9)	4271 (92.0)		
Mean modified Rankin score	5.7±1.1	5.7±1.1	0.00 (–0.05 to 0.05)	0.98

* Plus–minus values are means ±SD.
† The modified Rankin scale is commonly used for measuring the performance of daily activities by people who have had a stroke. Scores range from 0 to 6, with lower scores representing better performance; a score of 6 indicates death.
‡ A modified Rankin score of 3 or less was a primary outcome. The between-group difference was adjusted for cluster randomization.

DISCUSSION

In this randomized trial, we tested the hypothesis that patients with an out-of-hospital cardiac arrest might benefit from the administration of CPR by EMS personnel for approximately 3 minutes before the first analysis of cardiac rhythm (with delivery of a defibrillator shock as appropriate). We found that there was no significant difference in the rate of survival with satisfactory functional status between the two EMS strategies of a brief period of CPR with early analysis of cardiac rhythm and a longer period of CPR with delayed analysis of rhythm. Subgroup and adjusted analyses also did not show any significant differences in the outcomes between the two study groups. We further explored the relationship between the rate of survival and the actual time to rhythm analysis and found that outcomes did not improve with increasing time to analysis. This finding suggests that there is no advantage of delaying the analysis of cardiac rhythm during EMS-administered CPR. Indeed, the data suggest that there may be a disadvantage of delaying the rhythm analysis in the subgroup of patients with a first rhythm of either ventricular tachycardia or ventricular fibrillation who have received CPR from a bystander. Overall, our data suggest that the administration of 2 minutes of CPR by EMS personnel before the first analysis of rhythm, which was suggested in the 2005 guidelines of the AHA–ILCOR, is unlikely to provide a greater benefit than CPR of shorter duration.

The hypothesis that a brief period of initial CPR before analysis of cardiac rhythm could be beneficial is based primarily on the concept that a few minutes of chest compressions may increase myocardial perfusion, thus improving the metabolic state of the cardiac myocytes and enhancing the likelihood of successful defibrillation.[7] Several studies in animals with experimentally induced ventricular fibrillation showed that the outcomes with delayed countershock after a period of chest compressions were better than the outcomes with earlier countershock,[21,28,29] whereas other studies failed to show a benefit of CPR before shock.[30,31] Five previous clinical studies also attempted to

Subgroup	Early Analysis	Later Analysis	Difference: Later Analysis – Early Analysis (95% CI)	P Value for Interaction
	no. of patients/total no. (%)			
mITT population	310/5290 (5.9)	273/4643 (5.9)	0.0 (–0.9 to 0.9)	
Prespecified subgroups				
First rhythm interpretation				0.16
VT or VF	248/1279 (19.4)	213/1153 (18.5)	–0.9 (–4.0 to 2.2)	
Pulseless electrical activity	25/1043 (2.4)	35/891 (3.9)	1.5 (0.0 to 3.1)	
Asystole	17/2450 (0.7)	10/2147 (0.5)	–0.2 (–0.7 to 2.0)	
Other	17/512 (3.3)	10/440 (2.3)	–1.0 (–3.0 to 1.3)	
Time to arrival of EMS				0.56
<4 min	66/875 (7.5)	59/712 (8.3)	0.7 (–1.9 to 3.4)	
≥4 min	241/4368 (5.5)	211/3889 (5.4)	–0.1 (–1.1 to 0.9)	
Bystander CPR				0.90
Given	181/2098 (8.6)	162/1904 (8.5)	–0.1 (–1.9 to 1.6)	
Not given or unknown	129/3192 (4.0)	111/2739 (4.1)	0.0 (–1.0 to 1.0)	
Exploratory subgroups				
Protocol-adherent, 1st vehicle				0.63
Yes	211/3488 (6.0)	170/2669 (6.4)	0.3 (–0.9 to 1.5)	
No	92/1644 (5.6)	97/1785 (5.4)	–0.2 (–1.7 to 1.4)	
Protocol-adherent, 1st CPR				0.81
Yes	214/3528 (6.1)	170/2697 (6.3)	0.2 (–1.0 to 1.4)	
No	89/1576 (5.6)	97/1719 (5.6)	0.0 (–1.6 to 1.6)	
Bystander-witnessed				0.90
Yes	242/2316 (10.4)	214/2029 (10.5)	0.1 (–1.7 to 1.9)	
No	68/2974 (2.3)	59/2614 (2.3)	0.0 (–0.8 to 0.8)	
ITD study group				0.11
Sham	104/1925 (5.4)	94/1682 (5.6)	0.2 (–1.3 to 1.7)	
Active	88/1872 (4.7)	98/1696 (5.8)	1.1 (–0.4 to 2.5)	
Not in ITD study	118/1493 (7.9)	81/1265 (6.4)	–1.5 (–3.4 to 0.4)	

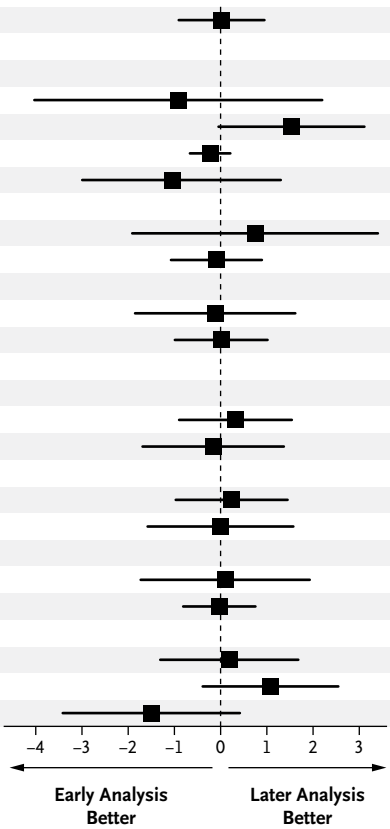

Figure 1. Subgroup Analyses of the Primary Outcome.

Shown are the results of analyses of the primary outcome (survival to hospital discharge with a score on the modified Rankin scale of ≤3, on a scale of 0 to 6, with higher scores indicating greater disability), according to prespecified subgroups and post hoc exploratory subgroups. The impedance threshold device (ITD) study group refers to a concurrent study (involving most of the patients who were enrolled in this study), in which the use of an active ITD during cardiopulmonary resuscitation (CPR) was compared with the use of a sham ITD. The abbreviation mITT denotes modified intention to treat, VF ventricular fibrillation, and VT ventricular tachycardia.

evaluate this issue, but all five had limitations involving the design or sample size, and none had findings that were definitive.[8-12] Cobb et al.,[8] in a before-and-after study, showed that the rate of survival increased after the implementation of a policy that required 90 seconds of CPR before analysis of cardiac rhythm when an automated external defibrillator was used. Wik et al.[9] conducted a randomized trial and found no significant difference between the outcomes after immediate defibrillation and those after 3 minutes of basic CPR before defibrillation, but the outcomes in a subgroup with response times exceeding 5 minutes were better after initial CPR than after immediate defibrillation. Randomized trials reported by Jacobs et al.[11] and Baker et al.[12] showed no significant difference in outcomes with early as compared with late defibrillation. Bradley et al.[10] performed an observational analysis and found that CPR by EMS personnel for 46 to 195 seconds before defibrillation was weakly associated with an improved rate of survival.

Given the complex clinical circumstances of out-of-hospital cardiac arrest, precise control of the time to the first analysis of cardiac rhythm is difficult to achieve. In our trial, the duration of CPR before the first analysis of rhythm did not fall within the assigned target for 36% of the patients. Although this observation raises the question of quality control in training and trial supervision,

the participating EMS agencies were high-functioning services with advanced-level paramedics; in addition, they had collected high-quality patient data before the start of the trial, and they made continuous efforts to reinforce performance targets. Thus, although implementation of the protocol was imperfect, it nonetheless represents the degree of precision with which such therapies are likely to be practiced in the clinical setting of out-of-hospital cardiac arrest. Furthermore, despite this limitation, there was very good separation between the two study groups in the duration of CPR, and a variety of data analyses confirmed the primary finding of no significant difference in the outcome between patients who had early rhythm analysis and those who had later rhythm analysis.

Our results indicate that in most cases, the outcome is similar with as few as 30 seconds and as many as 180 seconds of EMS-administered CPR before the analysis of cardiac rhythm. The exception is the case of cardiac arrest witnessed by EMS responders, which was not evaluated in this study and for which rapid defibrillation remains the standard of care.[13] Our results also do not address the strategy of immediate analysis of cardiac rhythm without any preceding CPR, since we deliberately insisted on some CPR for the early-analysis group, in the belief that good patient care required cardiopulmonary support while the defibrillator was being prepared.

Exploratory examination of our data suggests that a strategy of brief CPR and early analysis may be more appropriate than longer CPR and later analysis for patients who have received CPR from a bystander before the arrival of professional responders. Conversely, for patients who have not received CPR from a bystander, there is no approach that is clearly advantageous with respect to the time to analysis of rhythm. The 2010 guidelines of the AHA–ILCOR give little direction as to the preferred period of CPR before analysis of cardiac rhythm.[13] Each EMS system should consider its operational situation when deciding on its strategy for initial EMS-administered CPR. We believe that it is important to administer CPR for some period while the defibrillator pads are being applied and that compressions should be of high quality with minimal interruptions.

In conclusion, in a large clinical trial, we evaluated the timing of the analysis of cardiac rhythm during CPR in patients who had an out-of-hospital cardiac arrest that was not witnessed by EMS personnel. We found no difference in the outcome between the EMS strategy of a brief period of CPR before early rhythm analysis and that of a longer period of CPR before delayed rhythm analysis.

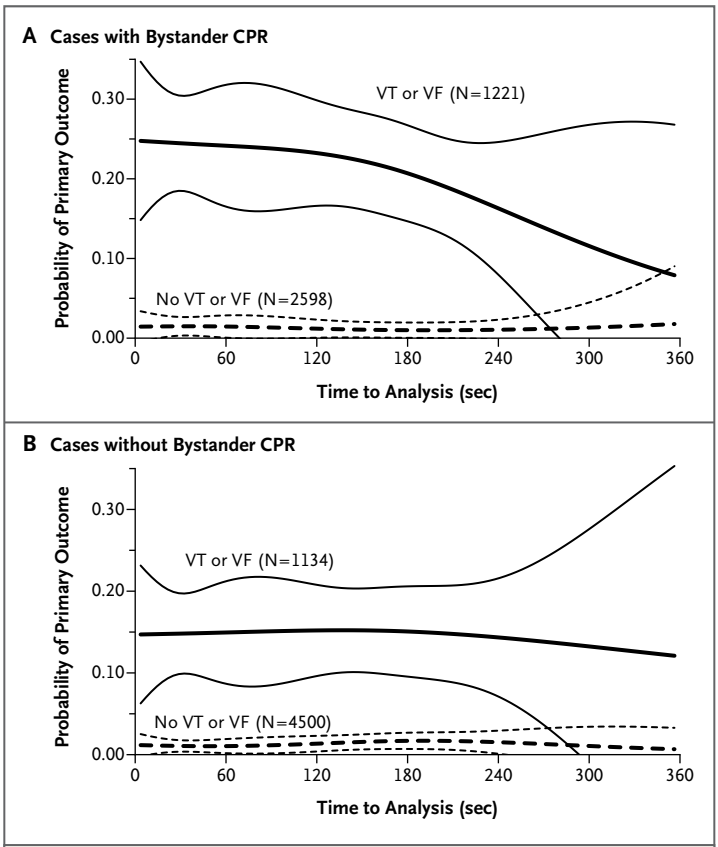

Figure 2. Rate of the Primary Outcome, According to Actual Time to Analysis of Cardiac Rhythm.

The primary outcome was survival to hospital discharge with a score on the modified Rankin scale of 3 or less. The rate of the primary outcome is shown according to the actual time to the analysis of cardiac rhythm, regardless of the study group, among patients who received cardiopulmonary resuscitation (CPR) from a bystander (Panel A) and among patients who did not receive CPR from a bystander (Panel B). In each panel, the rates are shown for patients in whom the first rhythm was ventricular fibrillation (VF) or ventricular tachycardia (VT) (thick solid lines, with 95% confidence intervals indicated by thin solid lines) and for patients in whom the first rhythm was neither VF nor VT (thick broken lines, with 95% confidence intervals indicated by thin broken lines).

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APPENDIX

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