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Early Extracorporeal CPR for Refractory Out-of-Hospital Cardiac Arrest

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ABSTRACT

BACKGROUND

Extracorporeal cardiopulmonary resuscitation (CPR) restores perfusion and oxygenation in a patient who does not have spontaneous circulation. The evidence with regard to the effect of extracorporeal CPR on survival with a favorable neurologic outcome in refractory out-of-hospital cardiac arrest is inconclusive.

METHODS

In this multicenter, randomized, controlled trial conducted in the Netherlands, we assigned patients with an out-of-hospital cardiac arrest to receive extracorporeal CPR or conventional CPR (standard advanced cardiac life support). Eligible patients were between 18 and 70 years of age, had received bystander CPR, had an initial ventricular arrhythmia, and did not have a return of spontaneous circulation within 15 minutes after CPR had been initiated. The primary outcome was survival with a favorable neurologic outcome, defined as a Cerebral Performance Category score of 1 or 2 (range, 1 to 5, with higher scores indicating more severe disability) at 30 days. Analyses were performed on an intention-to-treat basis.

RESULTS

Of the 160 patients who underwent randomization, 70 were assigned to receive extracorporeal CPR and 64 to receive conventional CPR; 26 patients who did not meet the inclusion criteria at hospital admission were excluded. At 30 days, 14 patients (20%) in the extracorporeal-CPR group were alive with a favorable neurologic outcome, as compared with 10 patients (16%) in the conventional-CPR group (odds ratio, 1.4; 95% confidence interval, 0.5 to 3.5; P=0.52). The number of serious adverse events per patient was similar in the two groups.

CONCLUSIONS

In patients with refractory out-of-hospital cardiac arrest, extracorporeal CPR and conventional CPR had similar effects on survival with a favorable neurologic outcome. (Funded by the Netherlands Organization for Health Research and Development and Maquet Cardiopulmonary [Getinge]; INCEPTION ClinicalTrials.gov number, NCT03101787.)

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Ventricular arrhythmias are a major cause of out-of-hospital cardiac arrest.[1,2] Early initiation of basic life support with high-quality chest compressions and external defibrillation provides the best chance to restore spontaneous circulation.[3,4] However, when these measures fail and the cardiac arrest is refractory to medical interventions, the chance of survival with the use of conventional cardiopulmonary resuscitation (CPR; standard advanced cardiac life support) declines rapidly with time.[5]

When there is no return of spontaneous circulation after advanced life-support measures are taken, extracorporeal CPR (the addition of extracorporeal membrane oxygenation to standard advanced cardiac life support) can be initiated to restore perfusion with the goal of limiting hypoxic brain injury and allowing for the possible identification and treatment of the underlying cause of the cardiac arrest. However, evidence with regard to the effect of extracorporeal CPR on survival and neurologic outcomes in observational studies and randomized, controlled trials involving out-of-hospital cardiac arrest remains inconclusive.[6-12]

Two recent randomized, controlled trials ended prematurely, one owing to the superiority of extracorporeal CPR and one owing to futility of extracorporeal CPR in the prespecified interim analyses.[13,14] We conducted the INCEPTION (Early Initiation of Extracorporeal Life Support in Refractory Out-of-Hospital Cardiac Arrest) trial to assess extracorporeal CPR as compared with conventional CPR with regard to survival with a favorable neurologic outcome in patients with refractory out-of-hospital cardiac arrest and an initial ventricular arrhythmia.

Methods

Trial Design and Oversight

The INCEPTION trial was a multicenter, randomized, controlled trial conducted in the Netherlands. The trial rationale and design have been published previously.[15] The trial protocol (available with the full text of this article at NEJM.org) was designed by the authors and approved by the ethics committee of Maastricht University. Deferred consent was used, in accordance with Dutch legislation, and consent was waived when patients died before consent had been obtained. The consent process is described in the Supplementary Appendix, available at NEJM.org.

The sponsors (the Netherlands Organization for Health Research and Development and Maquet Cardiopulmonary [Getinge]) had no role in the trial design, site selection, data collection and analysis, monitoring, or writing of earlier drafts of the manuscript and had no access to the data. Members of the steering committee designed the trial, vouch for the fidelity of the trial to the protocol, and made the decision to submit the results for publication. The first author collected the data for the trial, which was monitored by representatives of the Clinical Trial Center Maastricht. All local principal investigators confirmed the data-gathering process at their sites. Data were analyzed by the first author and the trial statistician. The first draft of the manuscript was written by members of the writing committee, who vouch for the accuracy and completeness of the data. A data safety and monitoring committee oversaw the trial at regular predefined intervals. The committees are described in the Supplementary Appendix.

Trial Setting

From May 2017 through February 2021, patients were enrolled at 10 cardiosurgical centers served by 12 emergency medical services (EMS). Descriptions of the Dutch EMS system and cardiosurgical centers are provided in the Supplementary Appendix. EMS teams were qualified to administer advanced life support (according to European Resuscitation Council guidelines[16]), which was continued during intraarrest transport. EMS and hospital personnel did not adopt specific protocols but were informed of the purpose and design of the trial. All centers halted enrollment in the trial during the first outbreak of coronavirus disease 2019 (Fig. S1 in the Supplementary Appendix).

Patients

Eligible patients were 18 to 70 years of age and had a witnessed, refractory out-of-hospital cardiac arrest with an initial ventricular arrhythmia (either ventricular fibrillation or ventricular tachycardia diagnosed by the EMS team or a shockable rhythm detected by an automated external defibrillator). Basic life support had to be performed unless the arrest had been witnessed

by the EMS team that had initiated advanced cardiac life support. A cardiac arrest that persisted despite 15 minutes of advanced life support was considered refractory. Exclusion criteria were a return of spontaneous circulation with sustained hemodynamic recovery within 15 minutes, terminal heart failure (New York Heart Association class III or IV), severe pulmonary disease (grade III or IV on the Chronic Obstructive Pulmonary Disease Global Initiative for Obstructive Lung Disease criteria), disseminated oncologic disease, obvious or suspected pregnancy, bilateral femoral bypass surgery, known contraindications for extracorporeal CPR, known advance health-care directive prohibiting resuscitation or invasive ventilation, and expected time interval of more than 60 minutes between the initial cardiac arrest to the initiation of the cannulation procedure (Table S1). Other exclusion criteria were a known Cerebral Performance Category score of 3 or 4 (indicating severe neurologic disability or persistent vegetative state) before cardiac arrest and multi-injury trauma (Injury Severity Score >15 on a scale of 0 to 75, with higher scores indicating more severe injury).[17]

TRIAL RANDOMIZATION AND PROCEDURES

If the cardiac arrest persisted after at least 15 minutes of advanced life support, intraarrest transport to a hospital was initiated. During the transport, patient information was relayed to the receiving hospital. If information about exclusion criteria was lacking, randomization could nevertheless be performed to allow timely preparation for a possible extracorporeal CPR procedure. Patients underwent randomization in a 1:1 ratio with permuted-block randomization (in block sizes of 2, 4, and 6) stratified according to center with the use of a smartphone application (Randomizer, Medical University of Graz, Austria). In order to guarantee similar prehospital treatment in the two groups, EMS teams were unaware of the trial-group assignments.

After the patient arrived at the hospital, inclusion and exclusion criteria were reviewed and the patient could be excluded at that point. Patients in whom the actual time until the initiation of extracorporeal membrane oxygenation cannulation was more than 60 minutes after cardiac arrest were not excluded. If the stable return of spontaneous circulation occurred before extracorporeal CPR was initiated, extracorporeal CPR was not applied. Patients remained in the assigned group for the intention-to-treat analysis.

Extracorporeal CPR was performed with the use of Cardiohelp System and HLS Set Advanced 7.0 and 5.0 (Getinge) according to local institutional protocols (Table S2). Postresuscitation care, including targeted temperature management[18] and extracorporeal circulation management, was delivered according to current guidelines and institutional protocols. A multimodal neurologic assessment was conducted according to international guidelines, which included a clinical neurologic evaluation and, when indicated, an evaluation of somatosensory evoked potential, computed tomography, or electroencephalography.[19] Treatment decisions, including the withdrawal of therapy, were at the discretion of the medical team and were documented in the medical files.

The primary outcome was survival with a favorable neurologic outcome, defined as a Cerebral Performance Category score of 1 or 2 (normal or disabled but independent) at 30 days. The primary outcome was assessed by an independent neurologist who was unaware of the trial-group assignments during a nonstandardized inquiry that was completed by telephone or in person. Key secondary outcomes included the duration of CPR before return of circulation, the total duration of CPR, the duration of time in the intensive care unit, the duration of hospitalization, 30-day survival, 6-month survival, Cerebral Performance Category score 6 months after the out-of-hospital cardiac arrest, the reason for discontinuation of treatment, and the duration of mechanical ventilation (Table S3).

STATISTICAL ANALYSIS

We hypothesized that 30-day survival with a favorable neurologic outcome would increase from 8% to 30% with the use of extracorporeal CPR.[15] We estimated that 49 patients per group would give the trial 80% power to detect such a difference with the use of an uncorrected two-sided chi-square test with a significance level of 0.05. Accounting for 10% discontinuation, we estimated that the enrollment of 55 patients per group would be necessary.

The trial had an adaptive design that allowed for an adjustment in sample size on the basis of

a preplanned interim analysis after 40 patients had undergone randomization. The investigators were unaware of the trial-group assignments during the interim analysis. The data and safety monitoring committee did not recommend adjustment of the sample size on the basis of between-group differences. After 70 patients had been enrolled, 6 of 27 patients (22%) in the extracorporeal-CPR group had not received the assigned procedure owing to a return of spontaneous circulation. In agreement with the data and safety monitoring committee, we recalculated the sample size to 134 patients in order to reach the originally estimated number of 49 patients in the extracorporeal-CPR group. The database was locked on December 17, 2021.

Analyses were performed on an intention-to-treat basis. Categorical data are summarized as numbers and percentages. Continuous variables were calculated as means (±SD) for normally distributed data and otherwise as median and interquartile range. We used a logistic mixed model with correction for the stratification variable (cardiosurgical center) to analyze survival with a Cerebral Performance Category score of 1 or 2 at 30 days, 3 months, and 6 months. Centers with 10 or fewer enrolled patients were grouped. Odds ratios are reported as effect estimates with 95% confidence intervals. For the primary outcome, we also calculated a risk ratio with 95% confidence intervals using the same model but with a log-linear relation instead of a logit link. Because the statistical analysis plan did not specify correction for multiplicity when we tested for secondary or other outcomes, results are reported as point estimates and 95% confidence intervals. The widths of the confidence intervals have not been adjusted for multiplicity, so the intervals should not be used in place of a hypothesis test. Owing to the interim analysis, the alpha level for the primary outcome was adjusted on the basis of the O'Brien and Fleming stopping rule, which resulted in an alpha level of 0.005 for the interim analysis and 0.048 for the final analysis.[20]

RESULTS

PATIENTS

A total of 160 patients were randomly assigned to receive extracorporeal CPR or conventional CPR; 26 of the patients who underwent randomization did not meet the inclusion criteria at hospital admission and were excluded. The final trial population was composed of 70 patients in the extracorporeal-CPR group and 64 patients in the conventional-CPR group (Fig. 1). A screening log was kept at 5 of the 10 trial centers and included data for 113 of the 160 patients who underwent randomization (71%). Of the 2107 patients who had undergone screening at the five centers that kept logs, 1994 patients (95%) were excluded (Fig. S2). Consent was waived for 87 patients, proxy consent was obtained for 20 patients, and 27 patients provided informed consent themselves. No patients or legal representatives withdrew consent for the use of data, but 1 patient in the conventional-CPR group declined further participation before the 30-day follow-up.

The characteristics of the patients at baseline are shown in Table 1. The mean (±SD) age of the patients was 54±12 years in the extracorporeal-CPR group and 57±10 years in the conventional-CPR group; 90% and 89% of patients in the two groups, respectively, were men. A history of previous cardiovascular disease, the presence of cardiovascular risk factors, prehospital treatment, and occurrence of prehospital return of spontaneous circulation were mostly well balanced between the groups (Table 1 and Table S4). The mean time from the start of the cardiac arrest (witnessed by EMS personnel or by the person who made the emergency call) to the arrival of an ambulance was 8±4 minutes in both groups. Randomization occurred before hospital arrival in 44 patients (63%) in the extracorporeal-CPR group and in 42 patients (66%) in the conventional-CPR group (Table 2). The mean time between the cardiac arrest and the arrival of the patient at the emergency department was 36±12 minutes in the extracorporeal-CPR group and 38±11 minutes in the conventional-CPR group.

TREATMENT

Extracorporeal CPR was not initiated in 18 patients in the extracorporeal-CPR group (Tables 2 and 3). Cannulation and circulation were successful in 46 of 52 patients (88%) who had undergone extracorporeal-CPR procedures (66% of the patients in the extracorporeal-CPR group). Extracorporeal membrane oxygenation was un-

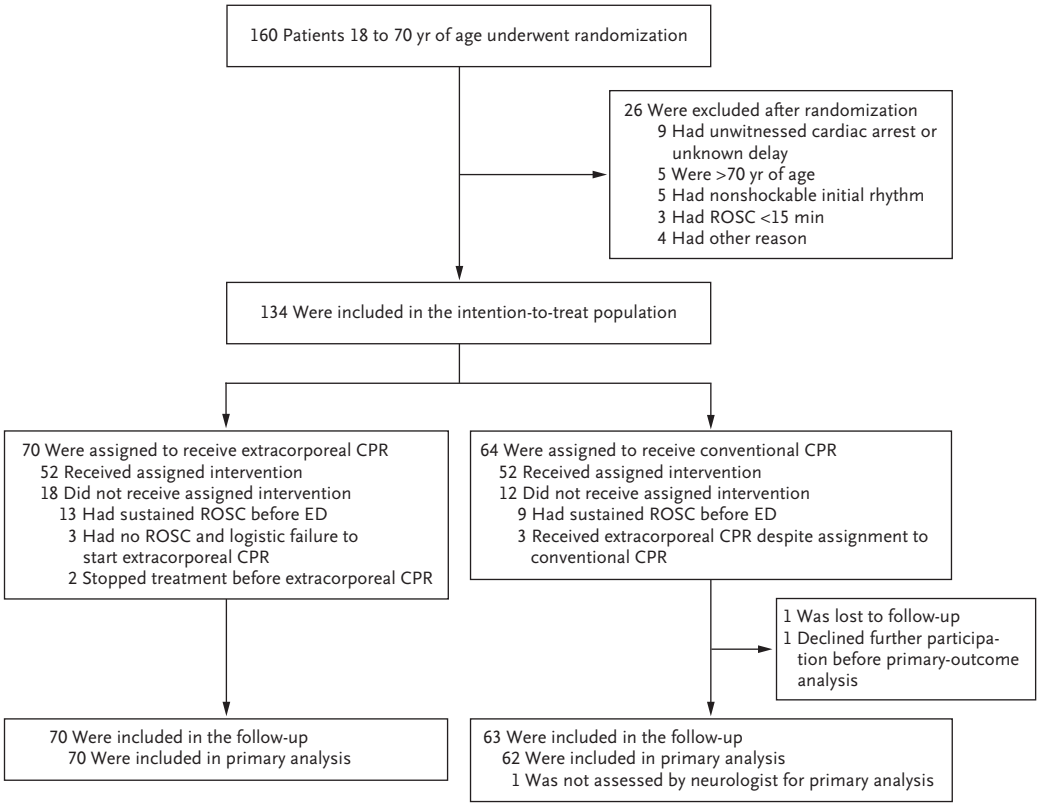

Figure 1. Randomization, Intervention, and Follow-up.

If the cardiac arrest persisted after at least 15 minutes of advanced life support, intraarrest transport was initiated. During transport, patient information was relayed to the receiving hospital. If information about exclusion criteria was lacking, randomization could still be performed to allow timely preparation for a possible extracorporeal–cardiopulmonary resuscitation (CPR) procedure. After hospital arrival, inclusion and exclusion criteria were reviewed, and the patient could be excluded at this point. Patients in whom the interval between cardiac arrest and the initiation of extracorporeal membrane oxygenation was more than 60 minutes were not excluded. ED denotes emergency department, and ROSC return of spontaneous circulation.

successful in 6 patients, owing to procedural complications in 5 patients and failure to establish sufficient extracorporeal membrane oxygenation flow in 1 patient. In the conventional-CPR group, crossover to extracorporeal membrane oxygenation CPR occurred in 3 patients. Cannulation was successful in all 3 patients. Concurrent prehospital and in-hospital treatments are shown in Tables S4 and S5.

The stable return of spontaneous circulation occurred in 18 patients (26%) in the extracorporeal-CPR group and in 20 patients (31%) in the conventional-CPR group. The mean interval between the emergency call and the return of spontaneous circulation was 43±20 minutes in the conventional-CPR group and 49±19 minutes in the extracorporeal-CPR group.

OUTCOMES

One patient in the conventional-CPR group was not assessed by an independent neurologist at 30 days, and 1 patient in the conventional-CPR group withdrew from the trial before 30 days. Data for the primary outcome were available for 62 patients (97%) in the conventional-CPR group and for all the patients in the extracorporeal-CPR group. At 30 days, survival with a Cerebral Performance Category score of 1 or 2 had occurred in 14 of the 70 patients (20%) in the extracorporeal-CPR group and in 10 of the 62 patients

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Extracorporeal CPR (N=70)	Conventional CPR (N=64)
Age — yr	54±12	57±10
Male sex — no. (%)	63 (90)	57 (89)
Primary shockable rhythm — no. (%)	69 (99)	63 (98)
Arrest occurred at home — no. (%)	31 (44)	24 (38)
Witnessed arrest — no. (%)	68 (97)	63 (98)
CPR started ≤5 min after arrest — no. (%)	69 (99)	61 (95)
Total no. of defibrillations	8±5	9±6
Transport distance — no. of patients (km)	68 (17±10)	63 (16±11)
Cause of arrest — no. (%)		
Acute myocardial infarction	51 (73)	52 (81)
Secondary arrhythmia	11 (16)	11 (17)
Pulmonary embolus	1 (1)	0
Metabolic or electrolyte	1 (1)	0
Neurologic	0	1 (2)
Intoxication	1 (1)	0
Other†	5 (7)	0
Medical history — no./total no. (%)		
Acute coronary syndrome	10/61 (16)	10/55 (18)
Coronary artery disease	7/61 (12)	6/53 (11)
PCI	5/62 (8)	5/53 (9)
CABG	2/62 (3)	4/54 (7)
Chronic heart failure	4/62 (6)	2/54 (4)
Cerebrovascular accident	3/61 (5)	9/54 (17)
Peripheral artery disease	2/61 (3)	4/54 (7)
Diabetes mellitus	10/62 (16)	6/54 (11)
Hypertension	24/44 (55)	15/33 (45)
Hypercholesterolemia	10/32 (31)	15/31 (48)
Current smoker	20/35 (57)	18/33 (55)

* Plus–minus values are means ±SD. Percentages may not total 100 because of rounding. CABG denotes coronary-artery bypass grafting, CPR cardiopulmonary resuscitation, and PCI percutaneous coronary intervention.
† Causes were unknown (in 3 patients) or were associated with a genetic mutation or cardiac sarcoidosis (in 1 patient each).

with data (16%) in the conventional-CPR group (odds ratio 1.4; 95% confidence interval, 0.5 to 3.5; P=0.52) (Table 4 and Fig. S3). Extracorporeal CPR was associated with a higher proportion of patients who survived until admission to the intensive care unit than conventional CPR; a similar proportion of patients in the two groups survived until hospital discharge (Table 3 and Fig. S4). Survival with a favorable neurologic outcome at 6 months was similar in the two groups (Table 4).

Reasons for discontinuation of treatment are shown in Table 3. In the extracorporeal-CPR group, the main reason for discontinuation was a neurologically unfavorable prognosis (in 24 of 56 patients [43%]); in the conventional-CPR group, the main reason for discontinuation was a lack of further treatment options (in 78% of the patients). There was no appreciable relationship between discontinuation of treatment and either the cardiosurgical center or the time to establishment of extracorporeal membrane oxygenation flow. The mean number of serious adverse events per patient was 1.4±0.9 in the extracorporeal-CPR group and 1.0±0.6 in the conventional-CPR group (Table S6).

DISCUSSION

In this multicenter, randomized, controlled trial, the use of extracorporeal or conventional CPR in refractory out-of-hospital cardiac arrest owing to ventricular arrhythmias resulted in a similar percentage of 30-day survival with a favorable neurologic outcome.

A previous randomized, controlled trial that compared extracorporeal CPR with conventional CPR in out-of-hospital cardiac arrest owing to ventricular arrhythmias was the ARREST (Advanced Reperfusion Strategies for Refractory Cardiac Arrest) trial,[13] a single-center trial that enrolled 30 patients and applied highly standardized treatment procedures. The ARREST trial was terminated early because of superiority of the intervention: survival to discharge occurred in 6 of 14 patients (43%) in the group that received extracorporeal CPR as compared with 1 of 15 patients (7%) in the group that received standard advanced cardiac life support. A single-center study in Prague, Czech Republic, involving patients with out-of-hospital cardiac arrest assigned patients to receive continued advanced life support at the scene of the cardiac arrest or to receive a multimodal, hyperinvasive resuscitation bundle that included intraarrest transport and the use of mechanical chest compression devices, immediate invasive assessment and treatment of the problem underlying the cardiac arrest, and the option of extracorporeal CPR.[21]

Table 2. Intervals between Events.*

Interval	Extracorporeal CPR (N=70)	Conventional CPR (N=64)	Treatment Effect (95% CI)†
Start of arrest to EMS arrival — no. of patients (min)	69 (8±4)	63 (8±4)	0.0 (–1.3 to 1.3)
Start of arrest to start of EMS transport to hospital — no. of patients (min)	67 (21±9)	55 (25±9)	–4.1 (–7.2 to –0.9)
Start of arrest to randomization — no. of patients (min)	70 (32±10)	64 (34±12)	–2.4 (–6.1 to 1.4)
Randomization before arrival at emergency department — no. (%)	44 (63)	42 (66)	0.9 (0.4 to 1.8)‡
Start of arrest to arrival at emergency department — no. of patients (min)	70 (36±12)	64 (38±11)	–2.1 (–6.0 to 1.7)
Start of arrest to ROSC — no. of patients (min)	17 (43±20)	19 (49±19)	–6.4 (–19.8 to 7.0)
Start of arrest to start of cannulation — no. of patients (min)	51 (58±13)	2§	
Hospital arrival to start of cannulation			
No. of patients	51	2§	
Median interval (IQR) — min	16 (11 to 22)	NA	
Start of arrest to start of ECLS flow			
No. of patients	44	2§	
Median interval (IQR) — min	74 (63 to 87)	NA	
Cannulation			
No. of patients	43	2§	
Median duration (IQR) — min	20 (11 to 25)	NA	

* Plus–minus values are means ±SD. Start of arrest includes arrests witnessed by emergency medical services (EMS) providers. CI denotes confidence interval, ECLS extracorporeal life support, IQR interquartile range, ROSC return of spontaneous circulation, and NA not applicable.
† The widths of the confidence intervals have not been adjusted for multiplicity and so should not be used in place of a hypothesis test.
‡ This value is an odds ratio.
§ The number of patients (2) was too small to calculate the treatment effect.

In the Prague trial, which was stopped early for futility, 32% of the patients in the intervention group survived with a favorable neurologic outcome at 6 months as compared with 22% of the patients in the control group. However, 27% of the patients in the intervention group and 44% in the control group had sustained spontaneous circulation at admission. Our trial had similar results, with 26% of the patients in the intervention group and 31% in the control group regaining spontaneous circulation without extracorporeal CPR. This result differs from that in the ARREST trial, in which return of spontaneous circulation without extracorporeal CPR occurred in 2 out of 30 patients and 3-month survival occurred only in patients who were assigned to the extracorporeal-CPR group. However, the ARREST trial and the current trial used a similar prehospital strategy. Regardless of the cause of these diverging outcomes, the potential efficacy of extracorporeal CPR might have been more difficult to substantiate in the presence of a high percentage of success with conventional CPR in the target population. In addition, we note that the 95% confidence interval for the primary outcome in the present trial is very wide.

In our trial, the median interval between hospital admission and the initiation of cannulation was 16 minutes, and the median interval between the start of cannulation and the start of extracorporeal membrane oxygenation flow was 20 minutes. These median intervals are longer than those in both the ARREST trial and the Prague study and reflect differences in such factors as team experience, logistics, and caseload. The caseload per site was higher in the ARREST trial and the Prague study than in our multicenter trial, a finding that reflects the experience at hospitals in large metropolitan areas. Our screening log shows that less than 2% of all eligible patients were missed for inclusion, although screening logs were only kept at 5 of the

Table 3. Clinical Outcomes.*

Outcome	Extracorporeal CPR (N=70)	Conventional CPR (N=64)	Odds Ratio (95% CI)†
Initiation of extracorporeal CPR — no. (%)	52 (74)	3 (5)	0.02 (0.0 to 0.6)
Cannulation and circulation successful	46 (66)	3 (5)	
Cannulation or circulation failed	6 (9)	0	
Patient died before ICU admission	2 (3)	0	
No initiation of extracorporeal CPR — no. (%)	18 (26)	61 (95)	58.7 (16.4 to 210.7)
Logistic failure	3 (4)	0	
Cessation of treatment	2 (3)	NA	
Stable ROSC	13 (19)	NA	
Randomly assigned to conventional CPR	NA	61 (100)	
ROSC — no./total no. (%)	18/70 (26)	20/64 (31)	1.3 (0.6 to 2.8)
ROSC before emergency department arrival	10/18 (56)	9/20 (45)	
ROSC after emergency department arrival	8/18 (44)	11/20 (55)	
Intermittent ROSC during resuscitation — no. (%)	27 (39)	22 (34)	0.8 (0.4 to 1.7)
Extracorporeal CPR performed in emergency department (vs. cardiac catheterization laboratory) — no. (%)	39 (56)	1 (2)	1.5 (0.1 to 18.0)
PCI — no. (%)	34 (49)	14 (22)	0.3 (0.2 to 0.6)
Admitted to ICU — no. (%)	57 (81)	23 (36)	0.1 (0.1 to 0.3)
Decannulation			
No. of patients	45	2‡	NA
Median interval from arrest to decannulation (IQR) — hr	26 (9–53)	NA	NA
ICU stay		4 (1–9)	
No. of patients	58	24	
Median duration (IQR) — days	1 (1–4)	4 (1–9)	NA§
Hospitalization			
No. of patients	55	23	
Median duration (IQR) — days	2 (2–14)	18 (2–30)	NA§
Death after ICU admission			
No. of patients	44	10	
Interval from arrest to death — days	3±6	5±6	−1.5 (−5.8 to 2.8)
Survived to ICU discharge — no. (%)	14 (20)	15 (23)	1.2 (0.5 to 2.8)
Survived to hospital discharge — no. (%)	14 (20)	13 (20)	1.0 (0.4 to 2.4)
Discontinued treatment — no./total no. (%)	56/70 (80)	51/64 (80)	1.0 (0.4 to 2.3)
Neurologically unfavorable	24/56 (43)	4/51 (8)	
Multiple organ failure	15/56 (27)	7/51 (14)	
Cannulation or ECLS failure	8/56 (14)	0	
No more treatment options	5/56 (9)	40/51 (78)	
Other	4/56 (7)	0	

* Plus–minus values are means ±SD. Percentages may not total 100 because of rounding. The widths of the confidence intervals have not been adjusted for multiplicity and so should not be used in place of a hypothesis test. ICU denotes intensive care unit.
† The widths of the confidence intervals have not been adjusted for multiplicity and so should not be used in place of a hypothesis test.
‡ The number of patients (2) was too small to calculate the treatment effect.
§ Parametric tests did not provide treatment effects with confidence intervals.

Table 4. Survival with Favorable Neurologic Outcome.*

Outcome	Extracorporeal CPR (N=70)	Conventional CPR (N=63)†	Odds Ratio (95% CI)	P Value	Risk Ratio (95% CI)
Primary outcome: 30-day survival with favorable neurologic outcome — no./total no. (%)	14/70 (20)	10/62 (16)‡	1.4 (0.5–3.5)	0.52	1.05 (0.97–1.13)
Secondary outcomes — no./total no. (%)					
3-month survival with favorable neurologic outcome	12/68 (18)	9/63 (14)	1.5 (0.6–3.8)		
6-month survival with favorable neurologic outcome	14/70 (20)	10/63 (16)	1.3 (0.5–3.3)		

* The widths of the confidence intervals have not been adjusted for multiplicity and so should not be used in place of a hypothesis test. A favorable neurologic outcome was defined as a Cerebral Performance Category score of 1 or 2 (normal performance or mild disability with independence) on a scale of 1 to 5, with higher scores indicating more severe disability.
† One patient was not assessed by an independent neurologist and thus was excluded from the primary analysis.
‡ One patient withdrew from the trial before 30 days.

10 participating centers. Therefore, outside of large metropolitan areas, obtaining broad and regular experience with extracorporeal CPR may be difficult.

Our trial had a pragmatic design, so EMS providers did not adopt specific protocols, and intraarrest transport was already common practice at the time of our trial. However, the EMS teams were aware of the trial, which might have prompted them to proceed to intraarrest transport earlier than usual. In a trial conducted in the United States, Grunau et al. found a negative association between intraarrest transport and outcome in out-of-hospital cardiac arrest.[22] However, in a Dutch trial, investigators found that shorter on-scene time was associated with a better outcome in patients who underwent intraarrest transport.[23] A standardized trial protocol for extracorporeal CPR was not specified, and each site relied on routines that had already been established at that site. We found no center-specific effect that might have affected outcomes. In our trial, 90% of the patients were male, which can mostly be ascribed to the male-to-female ratio of patients in the Netherlands affected by cardiac arrest caused by ventricular arrhythmia (80:20). Some of the inclusion criteria, however, may have skewed the male-to-female ratio even further (Table S7).[24]

Our trial has several limitations. First, early randomization led to a considerable number of patients who had a return of spontaneous circulation between random assignment and hospital arrival. Second, early randomization also led to some screen failures and postrandomization exclusions. The actual time-to-cannulation was not used as a postrandomization exclusion criterion, since it only applied to one group. No between-group differences in variables at baseline were apparent. Third, masking of treatment assignments was impossible, leading to crossovers by three patients, all of whom died despite receiving extracorporeal CPR. The lack of standardization of protocols for extracorporeal CPR may be viewed as a limitation, but this may also increase the generalizability of the resuscitation procedures and extracorporeal CPR.

The potential of extracorporeal CPR in an appropriate setting may seem evident. However, our findings suggest that the reproduction of such superior results is not self-evident when extracorporeal CPR is pragmatically implemented, even in cardiosurgical centers where providers are experienced in its use. Centers that provide extracorporeal CPR or are in the process of implementing the approach should critically assess their logistics and subsequently evaluate the efficacy of the procedure. Future research should address indications and outcome predictors.

In this multicenter, pragmatic, randomized trial, extracorporeal CPR and conventional CPR had similar effects on survival with a favorable neurologic outcome at 30 days in patients with refractory out-of-hospital cardiac arrest caused by an initial ventricular arrhythmia.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

APPENDIX

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