ORIGINAL ARTICLE

A Randomized Trial of Drug Route in Out-of-Hospital Cardiac Arrest

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ABSTRACT

BACKGROUND

In patients with out-of-hospital cardiac arrest, the effectiveness of drugs such as epinephrine is highly time-dependent. An intraosseous route of drug administration may enable more rapid drug administration than an intravenous route; however, its effect on clinical outcomes is uncertain.

METHODS

We conducted a multicenter, open-label, randomized trial across 11 emergency medical systems in the United Kingdom that involved adults in cardiac arrest for whom vascular access for drug administration was needed. Patients were randomly assigned to receive treatment from paramedics by means of an intraosseous-first or intravenous-first vascular access strategy. The primary outcome was survival at 30 days. Key secondary outcomes included any return of spontaneous circulation and favorable neurologic function at hospital discharge (defined by a score of 3 or less on the modified Rankin scale, on which scores range from 0 to 6, with higher scores indicating greater disability). No adjustment for multiplicity was made.

RESULTS

A total of 6082 patients were assigned to a trial group: 3040 to the intraosseous group and 3042 to the intravenous group. At 30 days, 137 of 3030 patients (4.5%) in the intraosseous group and 155 of 3034 (5.1%) in the intravenous group were alive (adjusted odds ratio, 0.94; 95% confidence interval [CI], 0.68 to 1.32; P=0.74). At the time of hospital discharge, a favorable neurologic outcome was observed in 80 of 2994 patients (2.7%) in the intraosseous group and in 85 of 2986 (2.8%) in the intravenous group (adjusted odds ratio, 0.91; 95% CI, 0.57 to 1.47); a return of spontaneous circulation at any time occurred in 1092 of 3031 patients (36.0%) and in 1186 of 3035 patients (39.1%), respectively (adjusted odds ratio, 0.86; 95% CI, 0.76 to 0.97). During the trial, one adverse event, which occurred in the intraosseous group, was reported.

CONCLUSIONS

Among adults with out-of-hospital cardiac arrest requiring drug therapy, the use of an intraosseous-first vascular access strategy did not result in higher 30-day survival than an intravenous-first strategy. (Funded by the National Institute for Health and Care Research; PARAMEDIC-3 ISRCTN Registry number, ISRCTN14223494.)

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*A complete list of the PARAMEDIC-3 collaborators is provided in the Supplementary Appendix, available at NEJM.org.

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Previous trials have explored the clinical effectiveness of medications commonly used in patients with out-of-hospital cardiac arrest.[1,2] The effects of such medications are highly time-dependent, which suggests that earlier drug administration may improve clinical outcomes.[3,4] Securing intravenous access in patients with out-of-hospital cardiac arrest is challenging because of environmental factors, such as poor lighting, and patient factors. In previous trials, the time from the emergency call to drug administration has ranged from 16 to 21 minutes.[1,2,5]

In observational studies and one small randomized trial, the intraosseous route facilitated a more rapid drug administration than the intravenous route, particularly when the proximal tibial site was used.[6,7] Observational studies comparing intraosseous and intravenous drug administration in patients with cardiac arrest have shown similar or worse outcomes among patients receiving drugs by an intraosseous route, but results of these studies are challenging to interpret because intraosseous access is typically attempted after an attempt at intravenous access has failed; such delays may lead to findings that are confounded by resuscitation time bias.[8-10] International resuscitation guidelines recommend peripheral intravenous access as the primary vascular access route[11,12]; however, studies have shown that the use of intraosseous access has increased (up to 60%) in some systems.[5,13-15]

Given ongoing uncertainty about the more effective route of drug administration in adults with cardiac arrest, the International Liaison Committee on Resuscitation highlighted the urgent need for randomized trials to evaluate the clinical effectiveness of the intraosseous access route.[16] In response, we conducted the PARAMEDIC-3 trial to determine the clinical effectiveness of an intraosseous-first strategy, as compared with an intravenous-first strategy, in adults with out-of-hospital cardiac arrest.

METHODS

TRIAL DESIGN AND OVERSIGHT

From November 2021 through July 2024, we conducted a pragmatic, open-label, randomized trial across 11 emergency medical systems (10 National Health Service ambulance services and one standalone air ambulance service) in the United Kingdom. The trial protocol, developed by the trial investigators, has been published previously and is available, together with the statistical analysis plan, with the full text of this article at NEJM.org.[17] The trial protocol was approved by the South Central–Oxford C Research Ethics Committee and the Health Research Authority Confidentiality Advisory Group. Owing to the time-critical nature of the treatment of cardiac arrest, and in accordance with local legislation, the Research Ethics Committee approved a process in which initial enrollment occurred without the consent of participants (details can be found in the Supplementary Appendix, available at NEJM.org). Written informed consent for ongoing data collection was subsequently sought after resuscitation from patients who survived or, if the patient lacked capacity, a legal representative.

The trial was funded by the National Institute for Health and Care Research (NIHR) Health Technology Assessment Programme, which had no role in the trial design, in the collection or analysis of the data, or in the preparation of the manuscript. The legal sponsor of the trial was the University of Warwick, and the trial was coordinated by the Warwick Clinical Trials Unit. An independent trial steering committee and data monitoring and ethics committee provided oversight, and the trial was conducted in accordance with the Good Clinical Practice guidelines of the International Council for Harmonisation, local regulations, and the principles of the Declaration of Helsinki. The trial statisticians had full access to all the data and assume responsibility for the integrity of the data, the completeness and accuracy of the data, and the fidelity of the trial to the protocol. The first author drafted an earlier version of the manuscript, which all the authors reviewed and approved to submit for publication. There were no confidentiality agreements between the sponsor and authors. We report here results of the analysis of the primary outcome, prehospital outcomes, neurologic function at hospital discharge, and hospital length of stay. Data on 3-month and 6-month follow-up, as well as outcomes related to health economics, quality of life, intraosseous access site, and length of stay in a critical care unit are not reported here.

PATIENT POPULATION

Adult patients (≥18 years of age) who had had an out-of-hospital cardiac arrest and who required

vascular access for drug administration during ongoing cardiopulmonary resuscitation (CPR) by trial-trained paramedics were eligible for inclusion in the trial. Exclusion criteria included a known or apparent pregnancy.

RANDOMIZATION AND TREATMENT

In this trial, paramedics from participating emergency medical systems performed resuscitation in accordance with current resuscitation guidelines (see the Supplementary Appendix). In the United Kingdom, paramedics are trained to administer advanced life support, including training in manual defibrillation, advanced airway management, drug therapy, and vascular access. Resuscitation may be terminated by paramedics in accordance with recognized criteria. Obtaining intravenous and intraosseous access are core skills for paramedics in the United Kingdom; therefore, additional training was not required for their participation in the trial.

Patients undergoing resuscitation who required vascular access were randomly assigned in a 1:1 ratio to receive treatment from paramedics according to an intraosseous-first or intravenous-first access strategy. Trial-group assignments were sealed in sequentially numbered, tamper-proof, opaque envelopes. This system ensured that the randomization process did not delay time-critical interventions. The randomization sequence, created by the trial statisticians, was stratified according to site. Envelopes were prepared at the Warwick Clinical Trials Unit before distribution to the sites. To ensure concealment of the assignments, paramedics opened envelopes only after they had confirmed patient eligibility for inclusion in the trial. Patients were considered by investigators to have undergone randomization at the point at which the envelope was opened.

The randomly assigned access route determined the initial strategy used for vascular access. If the paramedic could not obtain vascular access by means of the initially assigned route within two attempts, the route of subsequent vascular access attempts was determined by the treating paramedic. The anatomical location of both intraosseous and intravenous cannulae was decided by the treating paramedic. Once vascular access was obtained, it was expected that all cardiac arrest drugs would be given by that route.

The assigned vascular access route was used until spontaneous circulation returned, resuscitation was terminated, the cannula was dislodged, or the patient arrived at the hospital. Once patients were transferred to the hospital, treatment was determined by the hospital's clinical team, informed by international guidelines.[11] Data were collected at each site in accordance with standardized international definitions.[18]

OUTCOMES

The primary outcome was survival at 30 days. The secondary outcomes were any return of spontaneous circulation after randomization; sustained return of spontaneous circulation at the time of transfer of care to medical staff at the receiving hospital; survival at hospital discharge, 3 months, and 6 months; the time to return of spontaneous circulation; length of stay in the hospital or critical care unit; neurologic function (as measured by the modified Rankin scale) at hospital discharge, 3 months, and 6 months; and health-related quality of life (as measured by the EuroQol 5-Dimension 5-Level [EQ-5D-5L] questionnaire) at 3 months and 6 months. The modified Rankin scale is a 7-point scale, with scores ranging from 0 (no symptoms) to 6 (death); a score of 3 or less represents a favorable neurologic outcome.[19] Adverse events and serious adverse events were recorded until hospital discharge. The open-label nature of the trial meant that the outcome assessors were aware of the group assignments.

STATISTICAL ANALYSIS

We planned to recruit 15,000 patients. On the basis of the PARAMEDIC-2 trial data, we estimated that a sample size of 14,972 patients would provide the trial with 90% power to detect a difference of 1 percentage point (3.2% vs. 4.2%) in 30-day survival between the intraosseous group and intravenous group, at a two-sided significance level of 5%.[1] The variables used in the sample-size calculation are described in the protocol. Two formal interim analyses (when 10% and 50% of data had been collected) were planned to assess efficacy or harm during the trial. The O'Brien–Fleming alpha-spending function was used to develop stopping boundaries to control the type 1 error rate.[20]

All analyses were performed according to an intention-to-treat approach.[21] Categorical outcomes, including the primary outcome, were ana-

lyzed with the use of logistic-regression models, and results are presented as odds ratios with 95% confidence intervals. The primary analysis was the adjusted analysis, with adjustments made for age, sex, witness status, bystander CPR, initial cardiac rhythm, time from emergency call to drug administration, and cause of cardiac arrest. In order to mitigate any causal association between time of drug administration and outcome, we performed two post hoc sensitivity analyses — one in which time to drug administration was replaced with response time and one in which time to drug administration was removed. To address the potential overestimation of odds ratios, we report risk differences as a post hoc analysis. Continuous outcomes were analyzed with the use of linear regression models, and time-to-event outcomes were analyzed with the use of Cox regression models. There was no indication of violation of the proportional-hazards assumption, which was assessed with the use of the Kolmogorov-type supremum test. To prevent multiplicity in hypothesis testing, only the primary outcome was assessed with the use of statistical tests.

For the primary outcome, an estimand framework[22] was specified for two intercurrent events as sensitivity analyses: discontinuation of treatment before initiation of the assigned treatment and treatment crossover, as assessed by means of inverse-probability of censoring weighted methods.[23] Crossover was defined as the use of the nonrandomized drug route before the completion of two unsuccessful attempts at establishing vascular access with the use of the randomized route. We imputed missing data using multiple imputation by chained equations and tipping-point analyses.[24] The sensitivity of the primary outcome results was tested with the use of the fragility index.[25] The Kaplan–Meier curve was plotted for survival at 30 days.

Prespecified subgroup analyses included subgroups defined according to age, sex, witness status, bystander CPR, initial cardiac rhythm, time from emergency call to ambulance arrival, and cause of cardiac arrest. Logistic-regression models were fitted for both continuous and categorical subgroup variables. No adjustments were made for multiple hypothesis tests. Data management and analysis were performed with the use of SAS software, version 9.4.

RESULTS

RECRUITMENT

Recruitment was slower than anticipated and was stopped prematurely at the end of the funded recruitment period (July 1, 2024), when 6096 participants had been recruited and before the second formal interim analysis was performed. The trial data were masked to the trial investigators when the decision to stop recruitment was made. The decision to stop recruitment was supported by the independent trial steering committee and agreed to by the sponsor.

PATIENTS AND INTERVENTIONS

From November 2021 through July 2024, a total of 10,723 patients were screened for eligibility; 6096 of these patients underwent randomization, including 14 patients who underwent randomization in error. The remaining 6082 patients were assigned to a trial group — 3040 to the intraosseous group and 3042 to the intravenous group (Fig. 1).

The characteristics of the patients were balanced at baseline (Table 1). The representativeness of trial participants relative to the broader population of people who have out-of-hospital cardiac arrest is summarized in the Supplementary Appendix. The various time intervals and interventions are summarized in Table 2. The median time from the emergency call to epinephrine administration was 24.0 minutes (interquartile range, 19.0 to 30.0). Crossover from the initial randomized strategy occurred in 528 patients (8.7%).

PRIMARY AND SECONDARY OUTCOMES

Data for the primary outcome were available for 3030 patients (99.7%) in the intraosseous group and 3034 patients (99.7%) in the intravenous group. At 30 days, 137 of 3030 patients (4.5%) in the intraosseous group and 155 of 3034 (5.1%) in the intravenous group were alive (adjusted odds ratio, 0.94; 95% confidence interval [CI], 0.68 to 1.32; P=0.74). The results were similar in the unadjusted analysis.

Among those who survived until hospital discharge, a favorable neurologic outcome was observed in 80 of 2994 patients (2.7%) in the intraosseous group and in 85 of 2986 patients (2.8%) in the intravenous group (adjusted odds ratio, 0.91;

95% CI, 0.57 to 1.47). A return of spontaneous circulation at any time was observed in 1092 of 3031 patients (36.0%) in the intraosseous group and in 1186 of 3035 patients (39.1%) in the intravenous group (adjusted odds ratio, 0.86; 95% CI, 0.76 to 0.97). Results for other secondary outcomes, including sustained return of spontaneous circulation, are shown in Table 3. The results for the primary outcome were consistent across prespecified subgroups (Fig. 2 and Fig. S5 in the Supplementary Appendix) and in sensitivity analyses (Tables S10 through S13 and Fig. S7).

ADVERSE EVENTS

One adverse event, ongoing mild leg pain during certain activities, was reported by a patient in the intraosseous group (Table 3 and Tables S14 through S16). The event was not considered by investigators to be serious.

DISCUSSION

In this trial, the use of an intraosseous-first strategy for vascular access and drug administration did not result in significantly higher 30-day sur-

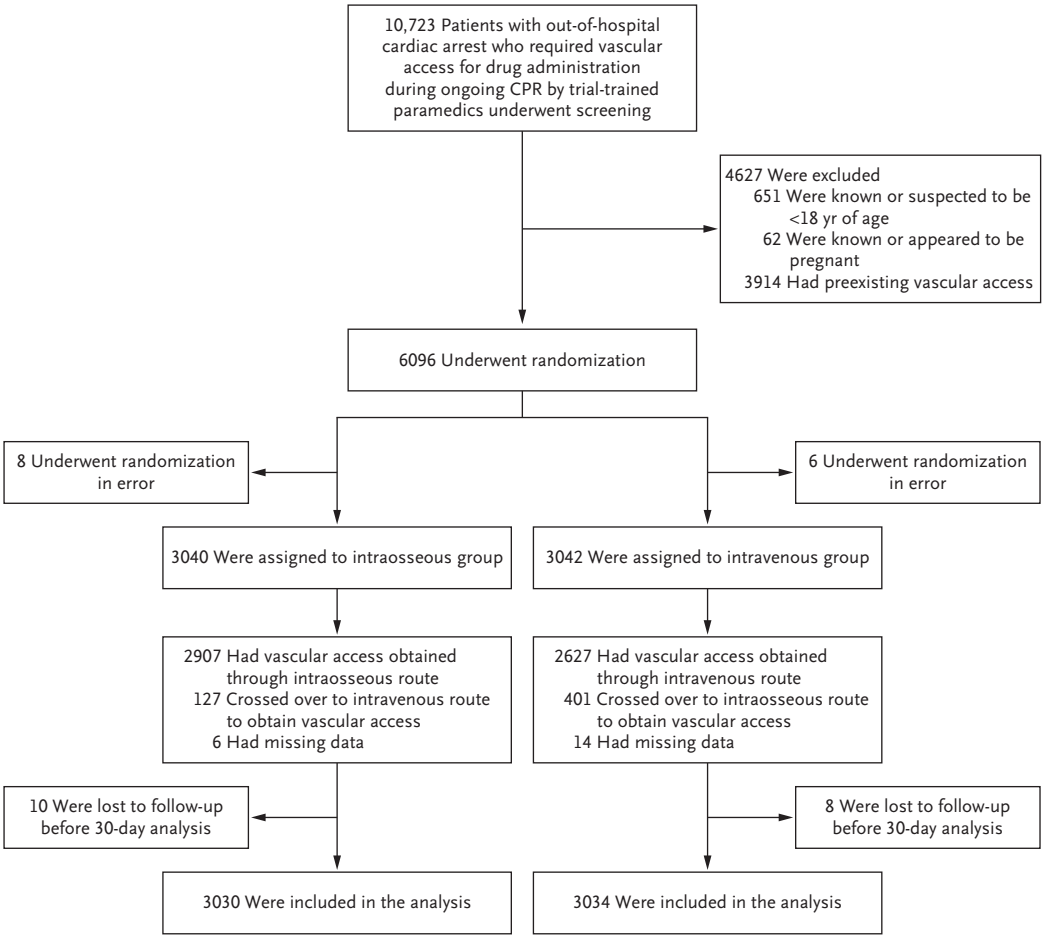

Figure 1. Screening, Enrollment, Randomization, and Inclusion in Analysis.

A total of 3914 patients were excluded from the trial owing to preexisting vascular access, which most likely occurred when a paramedic who was not trained in the trial protocol arrived on scene and secured vascular access before the arrival of a trial-trained paramedic. Crossover was defined as the use of the nonrandomized drug route before the completion of two unsuccessful attempts at establishing vascular access with the use of the randomized route. CPR denotes cardiopulmonary resuscitation.

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Intraosseous Route (N = 3040)	Intravenous Route (N = 3042)	Total (N = 6082)
Age			
No. of patients with data	2991	2992	5983
Mean — yr	67.8±16.3	68.3±15.9	68.1±16.1
Sex — no. (%)			
Male	1941 (63.8)	1951 (64.1)	3892 (64.0)
Female	1063 (35.0)	1048 (34.5)	2111 (34.7)
Missing data	36 (1.2)	43 (1.4)	79 (1.3)
Location of cardiac arrest — no. (%)†			
Home	2392 (78.7)	2422 (79.6)	4814 (79.2)
Industrial building or workplace	54 (1.8)	47 (1.5)	101 (1.7)
Sport or recreation event	24 (0.8)	27 (0.9)	51 (0.8)
Street or highway	245 (8.1)	242 (8.0)	487 (8.0)
Public building	99 (3.3)	96 (3.2)	195 (3.2)
Assisted living or nursing home	111 (3.7)	92 (3.0)	203 (3.3)
Educational institution	0	1 (<0.1)	1 (<0.1)
Others	98 (3.2)	103 (3.4)	201 (3.3)
Missing data	17 (0.6)	12 (0.4)	29 (0.5)
Initial cardiac rhythm — no. (%)			
Shockable	564 (18.6)	634 (20.8)	1198 (19.7)
Ventricular fibrillation	499 (16.4)	571 (18.8)	1070 (17.6)
Pulseless ventricular tachycardia	12 (0.4)	17 (0.6)	29 (0.5)
Not otherwise identified with AED	53 (1.7)	46 (1.5)	99 (1.6)
Nonshockable	2414 (79.4)	2358 (77.5)	4772 (78.5)
Asystole	1689 (55.6)	1638 (53.8)	3327 (54.7)
Pulseless electrical activity	681 (22.4)	656 (21.6)	1337 (22.0)
Not otherwise identified with AED	44 (1.4)	64 (2.1)	108 (1.8)
Missing data	62 (2.0)	50 (1.6)	112 (1.8)
Initial cause of cardiac arrest — no. (%)			
Medical cause	2484 (81.7)	2480 (81.5)	4964 (81.6)
Traumatic cause	48 (1.6)	38 (1.2)	86 (1.4)
Drowning	8 (0.3)	7 (0.2)	15 (0.2)
Drug overdose	57 (1.9)	67 (2.2)	124 (2.0)
Asphyxia	86 (2.8)	87 (2.9)	173 (2.8)
Electrocution	2 (0.1)	1 (<0.1)	3 (<0.1)
Missing data	355 (11.7)	362 (11.9)	717 (11.8)
Witness of cardiac arrest — no. (%)			
No witness	1164 (38.3)	1109 (36.5)	2273 (37.4)
EMS	194 (6.4)	183 (6.0)	377 (6.2)
Bystander	1645 (54.1)	1703 (56.0)	3348 (55.0)
Missing data	37 (1.2)	47 (1.5)	84 (1.4)

Table 1. (Continued.)

Characteristic	Intraosseous Route (N = 3040)	Intravenous Route (N = 3042)	Total (N = 6082)
Bystander CPR performed — no. (%)			
Yes	2089 (68.7)	2145 (70.5)	4234 (69.6)
No	701 (23.1)	670 (22.0)	1371 (22.5)
Not applicable: EMS witnessed	193 (6.3)	181 (6.0)	374 (6.1)
Missing data	6 (0.2)	7 (0.2)	13 (0.2)
Public access defibrillator used — no. (%)			
Yes	251 (8.3)	238 (7.8)	489 (8.0)
No	2638 (86.8)	2674 (87.9)	5312 (87.3)
Not applicable: EMS witnessed	109 (3.6)	100 (3.3)	209 (3.4)
Missing data	42 (1.4)	30 (1.0)	72 (1.2)

* AED denotes automated external defibrillator, CPR cardiopulmonary resuscitation, and EMS emergency medical services.
† Data were recorded in accordance with the Utstein style.

vival than an intravenous-first strategy among adults with out-of-hospital cardiac arrest. There was no apparent between-group difference in the percentage of patients with a favorable neurologic outcome at hospital discharge. The percentage of patients with a return of spontaneous circulation appeared to be lower among patients in the intraosseous group than among those in the intravenous group.

The trial hypothesis was that the intraosseous-first strategy would facilitate a more rapid administration of epinephrine, which would improve 30-day survival by reducing the time to a return of spontaneous circulation, thereby minimizing the hypoxic–ischemic damage — the main cause of death after cardiac arrest.[26] This hypothesis was formed on the basis of previous studies, which have shown a reduced time to drug administration in patients for whom initial vascular access attempts were made through the intraosseous route, particularly when the proximal tibial route was chosen.[6,7] In contrast to these previous studies, this trial showed that an intraosseous-first strategy did not reduce the time to drug administration.

Despite similarities in the time to drug administration, the percentage of patients with a return of spontaneous circulation appeared to be lower in the intraosseous group than in the intravenous group, a finding that suggests that drug efficacy was influenced by the route of administration. There are several potential explanations for this finding. First, intraosseous cannulae might be incorrectly positioned, which leads to suboptimal drug absorption. Although we were unable to assess this variable in our trial, the results of previous studies suggest that intraosseous cannulae are prone to both inadequate placement and dislodgement.[6,27] Second, peak drug concentration and the time to peak drug concentration with the use of the intraosseous route may be inferior to those with the intravenous route, even when the intraosseous cannula is successfully placed. Studies in animals have suggested that an intraosseous route with proximal humerus placement may result in a faster time to peak drug concentration than a peripheral intravenous route and that an intraosseous route with proximal tibial placement may be slower than a peripheral intravenous route.[9] However, this potential advantage of the proximal humerus site, as compared with the proximal tibial site, may be offset by lower success rates, higher dislodgement rates, and longer time to successful placement.[6] Third, it has been postulated that delivery of lipophilic drugs, such as amiodarone, to the central circulation is less effective when the intraosseous route is used than when the intravenous route is used.[28]

The results of this trial build on the recently published VICTOR (Venous Injection Compared to Intraosseous Injection during Resuscitation of Patients with Out-of-Hospital Cardiac Arrest) trial, a cluster-randomized trial conducted in Taiwan,

Table 2. Time Intervals between Key Events and Event Characteristics.*

Variable	Intraosseous Route (N = 3040)	Intravenous Route (N = 3042)	Total (N = 6082)
Time from emergency call to arrival of EMS on scene			
No. of patients with data	3026	3031	6057
Median (IQR) — min†	8.0 (5.0–12.0)	8.0 (5.0–12.0)	8.0 (5.0–12.0)
Time from arrival of EMS on scene to vascular access			
No. of patients with data	2870	2857	5727
Median (IQR) — min	12.0 (9.0–16.0)	12.0 (9.0–17.0)	12.0 (9.0–17.0)
Time from arrival of EMS on scene to drug administration			
No. of patients with data	2847	2811	5658
Median (IQR) — min	14.0 (11.0–19.0)	15.0 (11.0–20.0)	14.0 (11.0–19.0)
Time from emergency call to vascular access			
No. of patients with data	2874	2867	5741
Median (IQR) — min†	21.0 (17.0–27.0)	22.0 (17.0–28.0)	21.0 (17.0–27.0)
Time from emergency call to drug administration			
No. of patients with data	2857	2826	5683
Median (IQR) — min†	24.0 (19.0–30.0)	24.0 (20.0–31.0)	24.0 (19.0–30.0)
Time from arrival of EMS on scene to EMS transportation			
No. of patients with data	992	1107	2099
Median (IQR) — min	56.0 (42.0–71.5)	55.0 (43.0–70.0)	55.0 (42.0–71.0)
Time from emergency call to hospital arrival			
No. of patients with data	1009	1121	2130
Median (IQR) — min	78.0 (62.0–99.0)	78.0 (64.0–97.0)	78.0 (63.0–98.0)
Site of first successful vascular access			
Intraosseous access — no. (%)‡	2871 (94.4)	992 (32.6)	3863 (63.5)
Proximal humerus	519 (17.1)	160 (5.3)	679 (11.2)
Proximal tibial	2233 (73.5)	780 (25.6)	3013 (49.5)
Other	119 (3.9)	52 (1.7)	171 (2.8)
Intravenous access — no. (%)‡	107 (3.5)	1964 (64.6)	2071 (34.1)
Central	3 (0.1)	41 (1.3)	44 (0.7)
Peripheral	99 (3.3)	1857 (61.0)	1956 (32.2)
Other	5 (0.2)	66 (2.2)	71 (1.2)
Epinephrine			
Administered — no. (%)	2866 (94.3)	2836 (93.2)	5702 (93.8)
Median dose (IQR) — mg	5.0 (3.1–8.0)	5.0 (3.0–8.0)	5.0 (3.0–8.0)
Amiodarone administered — no. (%)	480 (15.8)	524 (17.2)	1004 (16.5)
Median no. of defibrillator shocks (IQR)	3.0 (1.0–6.0)	3.0 (1.0–6.0)	3.0 (1.0–6.0)
Supraglottic airway — no. (%)			
Yes	2765 (91.0)	2747 (90.3)	5512 (90.6)
No	220 (7.2)	237 (7.8)	457 (7.5)

Table 2. (Continued.)

Variable	Intraosseous Route (N = 3040)	Intravenous Route (N = 3042)	Total (N = 6082)
Tracheal tube — no. (%)			
Yes	648 (21.3)	613 (20.2)	1261 (20.7)
No	2318 (76.2)	2364 (77.7)	4682 (77.0)
Transported to hospital — no. (%)			
Yes	1024 (33.7)	1136 (37.3)	2160 (35.5)
No	2016 (66.3)	1906 (62.7)	3922 (64.5)

* IQR denotes interquartile range.
† Among cardiac arrests that were witnessed by paramedics, the interval between the emergency call and the cardiac arrest event was recorded as 0 minutes.
‡ Of the 107 patients in the intraosseous group who received intravenous access as their first successful vascular access, 88 were categorized as crossover patients. Of the 992 patients in the intravenous group who received intraosseous access as their first successful vascular access, 369 were categorized as crossover patients. Crossover was defined as the use of the nonrandomized drug route before the completion of two unsuccessful attempts at the randomized route.

in which 1771 adult patients with out-of-hospital cardiac arrest were randomly assigned to either intraosseous access in a proximal humerus or intravenous access in an upper limb.[29] The VICTOR trial showed that the intraosseous route did not result in an increased rate of survival at hospital discharge or a reduction in the time to drug administration, findings that are consistent with those in this trial.

In this trial, the overall median time from the emergency call to drug administration was 24 minutes, and survival at 30 days was 4.8%. The time to drug administration is similar to that seen in the VICTOR trial and only slightly longer than that in other randomized trials of drug interventions for cardiac arrest (range, 16 to 21 minutes).[1,2,5,29] The overall 30-day survival in the United Kingdom is similar to that in other regions, including parts of North America, Europe, and Asia.[30] The target population in this trial was patients with cardiac arrest who required drug therapy; therefore, patients in whom initial resuscitation attempts were successful and who had the best outcomes were ineligible for the trial.[1]

Recruitment was terminated before the planned sample size was reached because of lower-than-anticipated numbers of enrolled patients, so the trial is underpowered to detect a 1% difference between groups for the primary outcome. Trial investigators, who were unaware of the trial data, made the decision to terminate recruitment, which coincided with the end of the funded recruitment period. Subsequent analyses show that when this decision was made, effect estimates for the primary outcome were stable, which makes it unlikely that continuing to the original sample size would have materially influenced trial findings (Figs. S8 and S9).

In addition to the sample size, this trial has several other limitations. We did not collect information on resuscitation quality because of the pragmatic nature of the trial and the challenges of collecting such data. We did not create a protocol for or collect information on hospital-based postresuscitation care, although we would expect this care to be consistent between groups in accordance with the adoption of international guidelines in the United Kingdom.[31] The nature of the trial precluded blinding of the route of vascular access to prehospital care providers, but this is unlikely to have introduced performance bias because of the nature of cardiopulmonary resuscitation, which typically follows a standard protocol, particularly with respect to the decision to terminate resuscitation attempts.

Our prespecified adjusted analyses included the time to drug administration as a covariate, which was hypothesized as a potential mediator of the effect of the intervention. The absence of a time difference and the results of sensitivity analy-

Table 3. Primary and Secondary Outcomes.

Outcome	Intraosseous Route	Intravenous Route	Risk or Mean Difference (95% CI)*		Treatment Effect (95% CI)†	
			Unadjusted	Adjusted‡	Unadjusted	Adjusted
Primary outcome						
Survival at 30 days — no./total no. (%)	137/3030 (4.5)	155/3034 (5.1)	−0.6 (−1.7 to 0.5)	−0.2 (−1.1 to 0.8)	0.88 (0.70 to 1.11)	0.94 (0.68 to 1.32)§
Secondary outcomes						
Return of spontaneous circulation at any time — no./total no. (%)	1092/3031 (36.0)	1186/3035 (39.1)	−3.0 (−5.5 to −0.6)	−3.2 (−5.9 to −0.6)	0.88 (0.79 to 0.97)	0.86 (0.76 to 0.97)
Median time to return of spontaneous circulation (IQR) — min	33.0 (24.0 to 43.0)	32.0 (24.0 to 43.0)	0.76 (−1.06 to 2.58)	0.45 (−0.82 to 1.72)	0.90 (0.82 to 0.98)¶	0.89 (0.81 to 0.98)¶
Sustained return of spontaneous circulation at hospital handover — no./total no. (%)	654/3016 (21.7)	744/3023 (24.6)	−2.9 (−5.1 to −0.8)	−2.6 (−4.8 to −0.3)	0.85 (0.75 to 0.96)	0.85 (0.74 to 0.98)
Survival to hospital discharge — no./total no. (%)	112/3012 (3.7)	120/3012 (4.0)	−0.3 (−1.2 to 0.7)	0.0 (−0.9 to 0.8)	0.93 (0.72 to 1.21)	1.00 (0.68 to 1.46)
Median length of hospital stay (IQR) — days						
Patients who survived	18 (11.0 to 32.0)	16 (7.0 to 31.0)	3.12 (−4.70 to 10.94)	7.68 (−4.39 to 19.75)		
Patients who died	0 (0.0 to 0.0)	0 (0.0 to 0.0)	−0.23 (−0.48 to 0.02)	−0.18 (−0.45 to 0.10)		
Score on modified Rankin scale at hospital discharge — no./total no. (%)‖						
0–3: Favorable outcome	80/2994 (2.7)	85/2986 (2.8)	−0.2 (−1.0 to 0.7)	−0.1 (−0.8 to 0.6)	0.94 (0.69 to 1.28)	0.91 (0.57 to 1.47)
4–6: Unfavorable outcome	2914/2994 (97.3)	2901/2986 (97.2)				
Adverse events						
Any adverse event — no. per 1000 patients/total no. (%)	1/3040 (0.33)	0/3042 (0)			1.01 (0.86 to 1.18)**	
Serious adverse event — no. per 1000 patients/total no. (%)	0/3040 (0)	0/3042 (0)				

* Outcomes are reported as risk differences, except for the median time to return of spontaneous circulation and the median length of hospital stay (including participants who survived and those who died), which are reported as the mean difference. The mean difference and the risk difference (post hoc test) are for the intraosseous group as compared with the intravenous group. Risk differences are reported since odds ratios may overestimate the magnitude of treatment effect. Confidence interval widths have not been adjusted for multiplicity and may not be used in place of hypothesis testing.

† The hazard ratio is reported for the median time to return of spontaneous circulation. The incidence risk ratio (IRR) is reported for adverse events. The risk of an adverse event was assessed with the use of Poisson regression and the IRR is reported. No comparison analysis was performed for serious adverse events. All other treatment differences are reported as odds ratios. Treatment differences are adjusted for age, sex, witness status (EMS vs. bystander), bystander CPR performed (yes or no), initial cardiac rhythm (shockable vs. nonshockable), time from emergency call to drug administration, cause of cardiac arrest (medical vs. nonmedical). Confidence interval widths have not been adjusted for multiplicity and may not be used in place of hypothesis testing.

‡ The adjusted risk difference was estimated with the use of the margins macro in SAS software, version 9.4 (https://support.sas.com/kb/63/038.html).

§ P=0.74 for the between-group comparison in the primary analysis.

¶ The cause-specific hazard function was used to estimate the hazard ratio of return of spontaneous circulation. Death before any return of spontaneous circulation was considered to be a competing risk. The proportional hazard assumption was not violated for unadjusted or adjusted analyses.

‖ The modified Rankin scale is a 7-point scale, with scores ranging from 0 (no symptoms) to 6 (death). A score of 0, 1, 2, or 3 is categorized as a favorable neurologic outcome.[19]

** P=0.97 for the between-group comparison.

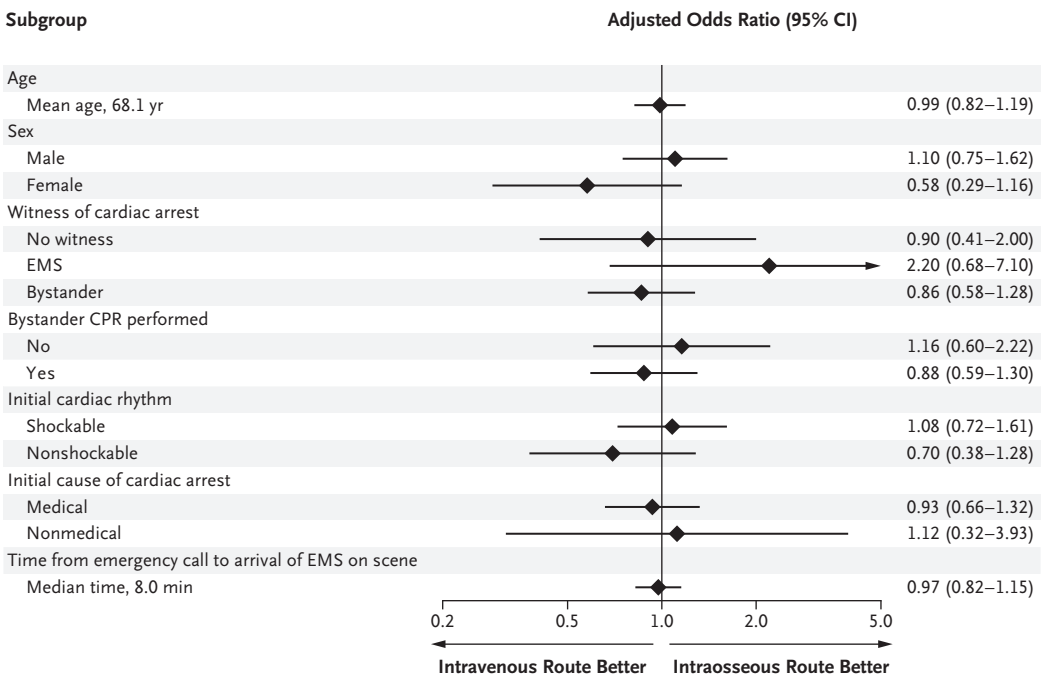

Figure 2. Subgroup Analyses of the Primary Outcome.

Shown are the odds ratios for 30-day survival (the primary outcome) in the prespecified subgroups defined according to age, sex, witness status, performance of bystander CPR, initial cardiac rhythm, initial cause of cardiac arrest, and time from emergency call to arrival of EMS on scene, where applicable. The widths of the confidence intervals have not been adjusted for multiplicity and should not be used in place of hypothesis testing.

ses suggest that this did not materially influence the trial findings. The main reason that patients who underwent screening were excluded from randomization was preexisting vascular access, which most likely occurred when a paramedic who was not trained for the trial arrived on scene and secured vascular access before the arrival of a trial-trained paramedic. It is unlikely that this introduced selection bias or influenced the generalizability of our findings since ambulance resources are allocated from a central control room on the basis of availability and location. In contrast to other trials, we did not specify the anatomical location of intraosseous cannulae in the protocol[29,32]; instead, paramedics selected the anatomical location of vascular access on the basis of personal preference and patient characteristics, informed by the available evidence.

In this trial involving adults with out-of-hospital cardiac arrest requiring drug therapy, the use of an intraosseous-first strategy did not result in higher 30-day survival than an intravenous-first strategy.

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APPENDIX

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REFERENCES

1. Perkins GD, Ji C, Deakin CD, et al. A randomized trial of epinephrine in out-of-hospital cardiac arrest. N Engl J Med 2018;379:711-21.

2. Kudenchuk PJ, Brown SP, Daya M, et al. Amiodarone, lidocaine, or placebo in out-of-hospital cardiac arrest. N Engl J Med 2016;374:1711-22.

3. Perkins GD, Kenna C, Ji C, et al. The influence of time to adrenaline administration in the Paramedic 2 randomised controlled trial. Intensive Care Med 2020;46:426-36.

4. Rahimi M, Dorian P, Cheskes S, Lebovic G, Lin S. Effect of time to treatment with antiarrhythmic drugs on return of spontaneous circulation in shock-refractory out-of-hospital cardiac arrest. J Am Heart Assoc 2022;11(6):e023958.

5. Vallentin MF, Granfeldt A, Meilandt C, et al. Effect of intravenous or intraosseous calcium vs saline on return of spontaneous circulation in adults with out-of-hospital cardiac arrest: a randomized clinical trial. JAMA 2021;326:2268-76.

6. Reades R, Studnek JR, Vandeventer S, Garrett J. Intraosseous versus intravenous vascular access during out-of-hospital cardiac arrest: a randomized controlled trial. Ann Emerg Med 2011;58:509-16.

7. Ross EM, Mapp J, Kharod C, Wampler DA, Velasquez C, Miramontes DA. Time to epinephrine in out-of-hospital cardiac arrest: a retrospective analysis of intraosseous versus intravenous access. Am J Disaster Med 2016;11:119-23.

8. Granfeldt A, Avis SR, Lind PC, et al. Intravenous vs. intraosseous administration of drugs during cardiac arrest: a systematic review. Resuscitation 2020;149:150-7.

9. Hooper A, Nolan JP, Rees N, Walker A, Perkins GD, Couper K. Drug routes in out-of-hospital cardiac arrest: a summary of current evidence. Resuscitation 2022;181:70-8.

10. Hsieh Y-L, Wu M-C, Wolfshohl J, et al. Intraosseous versus intravenous vascular access during cardiopulmonary resuscitation for out-of-hospital cardiac arrest: a systematic review and meta-analysis of observational studies. Scand J Trauma Resusc Emerg Med 2021;29:44.

11. Soar J, Böttiger BW, Carli P, et al. European Resuscitation Council guidelines 2021: adult advanced life support. Resuscitation 2021;161:115-51.

12. Panchal AR, Bartos JA, Cabañas JG, et al. Adult basic and advanced life support: 2020 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. Circulation 2020;142:Suppl 2:S366-S468.

13. Brebner C, Asamoah-Boaheng M, Zaidel B, et al. The association of intravenous vs. humeral-intraosseous vascular access with patient outcomes in adult out-of-hospital cardiac arrests. Resuscitation 2024;202:110360.

14. Agostinucci J-M, Alhéritière A, Metzger J, et al. Evolution of the use of intraosseous vascular access in prehospital advanced cardiopulmonary resuscitation: the IOVA-CPR study. Int J Nurs Pract 2024;30(5):13244.

15. Vadeyar S, Buckle A, Hooper A, et al. Trends in use of intraosseous and intravenous access in out-of-hospital cardiac arrest across English ambulance services: a registry-based, cohort study. Resuscitation 2023;191:109951.

16. Soar J, Berg KM, Andersen LW, et al. Adult advanced life support: 2020 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science with treatment recommendations. Resuscitation 2020;156:A80-A119.

17. Couper K, Ji C, Lall R, et al. Route of drug administration in out-of-hospital cardiac arrest: a protocol for a randomised controlled trial (PARAMEDIC-3). Resusc Plus 2023;17:100544.

18. Perkins GD, Jacobs IG, Nadkarni VM, et al. Cardiac arrest and cardiopulmonary resuscitation outcome reports: update of the Utstein Resuscitation Registry templates for out-of-hospital cardiac arrest: a statement for healthcare professionals from a task force of the International Liaison Committee on Resuscitation (American Heart Association, European Resuscitation Council, Australian and New Zealand Council on Resuscitation, Heart and Stroke Foundation of Canada, InterAmerican Heart Foundation, Resuscitation Council of Southern Africa, Resuscitation Council of Asia); and the American Heart Association Emergency Cardiovascular Care Committee and the Council on Cardiopulmonary, Critical Care, Perioperative and Resuscitation. Resuscitation 2015;96:328-40.

19. Haywood K, Whitehead L, Nadkarni VM, et al. COSCA (Core Outcome Set for Cardiac Arrest) in adults: an advisory statement from the International Liaison Committee on Resuscitation. Resuscitation 2018;127:147-63.

20. O'Brien PC, Fleming TR. A multiple testing procedure for clinical trials. Biometrics 1979;35:549-56.

21. McCoy CE. Understanding the intention-to-treat principle in randomized controlled trials. West J Emerg Med 2017;18:1075-8.

22. European Medicines Agency. ICH E9 (R1) addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials. Step 5. February 2020 (https://www.ema.europa.eu/en/documents/scientific-guideline/ich-e9-r1-addendum-estimands-sensitivity-analysis-clinical-trials-guideline-statistical-principles_en.pdf).
23. Rimawi M, Hilsenbeck SG. Making sense of clinical trial data: is inverse probability of censoring weighted analysis the answer to crossover bias? J Clin Oncol 2012;30:453-8.
24. Sui Y, Bu X, Duan Y, Li Y, Wang X. Application of tipping point analysis in clinical trials using the multiple imputation procedure in SAS. Baltimore: PharmaSUG, 2023 (https://www.pharmasug.org/proceedings/2023/SD/PharmaSUG-2023-SD-069.pdf).
25. Khan MS, Ochani RK, Shaikh A, et al. Fragility index in cardiovascular randomized controlled trials. Circ Cardiovasc Qual Outcomes 2019;12(12):e005755.
26. Perkins GD, Neumar R, Hsu CH, et al. Improving outcomes after post-cardiac arrest brain injury: a scientific statement from the International Liaison Committee on Resuscitation. Resuscitation 2024;201:110196.
27. Berger D, Petrie A, Lubin JS. The ability of paramedics to accurately locate correct anatomical sites for intraosseous needle insertion. Cureus 2023;15(1):e33355.
28. Daya MR, Leroux BG, Dorian P, et al. Survival after intravenous versus intraosseous amiodarone, lidocaine, or placebo in out-of-hospital shock-refractory cardiac arrest. Circulation 2020;141:188-98.
29. Ko Y-C, Lin H-Y, Huang EP-C, et al. Intraosseous versus intravenous vascular access in upper extremity among adults with out-of-hospital cardiac arrest: cluster randomised clinical trial (VICTOR trial). BMJ 2024;386:e079878.
30. Nishiyama C, Kiguchi T, Okubo M, et al. Three-year trends in out-of-hospital cardiac arrest across the world: second report from the International Liaison Committee on Resuscitation (ILCOR). Resuscitation 2023;186:109757.
31. Nolan JP, Sandroni C, Böttiger BW, et al. European Resuscitation Council and European Society of Intensive Care Medicine guidelines 2021: post-resuscitation care. Intensive Care Med 2021;47:369-421.
32. Meilandt C, Fink Vallentin M, Blumensaadt Winther K, et al. Intravenous vs. intraosseous vascular access during out-of-hospital cardiac arrest — protocol for a randomised clinical trial. Resusc Plus 2023;15:100428.