ORIGINAL ARTICLE

Intraosseous or Intravenous Vascular Access for Out-of-Hospital Cardiac Arrest

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ABSTRACT

BACKGROUND

Out-of-hospital cardiac arrest is a leading cause of death worldwide. Establishing vascular access is critical for administering guideline-recommended drugs during cardiopulmonary resuscitation. Both the intraosseous route and the intravenous route are used routinely, but their comparative effectiveness remains unclear.

METHODS

We conducted a randomized clinical trial to compare the effectiveness of initial attempts at intraosseous or intravenous vascular access in adults who had nontraumatic out-of-hospital cardiac arrest. The primary outcome was a sustained return of spontaneous circulation. Key secondary outcomes were survival at 30 days and survival at 30 days with a favorable neurologic outcome, defined by a score of 0 to 3 on the modified Rankin scale (scores range from 0 to 6, with higher scores indicating greater disability).

RESULTS

Among 1506 patients who underwent randomization, 1479 were included in the primary analysis (731 in the intraosseous-access group and 748 in the intravenous-access group). The successful establishment of vascular access within two attempts occurred in 669 patients (92%) assigned to the intraosseous-access group and in 595 patients (80%) assigned to the intravenous-access group. Sustained return of spontaneous circulation occurred in 221 patients (30%) in the intraosseous-access group and in 214 patients (29%) in the intravenous-access group (risk ratio, 1.06; 95% confidence interval [CI], 0.90 to 1.24; P=0.49). At 30 days, 85 patients (12%) in the intraosseous-access group and 75 patients (10%) in the intravenous-access group were alive (risk ratio, 1.16; 95% CI, 0.87 to 1.56); a favorable neurologic outcome at 30 days occurred in 67 patients (9%) and 59 patients (8%), respectively (risk ratio, 1.16; 95% CI, 0.83 to 1.62). Prespecified adverse events were uncommon.

CONCLUSIONS

There was no significant difference in sustained return of spontaneous circulation between initial intraosseous and intravenous vascular access in adults who had out-of-hospital cardiac arrest. (Funded by the Novo Nordisk Foundation and others; IVIO EU Clinical Trials Register number, 2022-500744-38-00; ClinicalTrials.gov number, NCT05205031.)

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Out-of-hospital cardiac arrest is common and is associated with high mortality. An estimated 4 million such events occur worldwide each year, including approximately 5000 in Denmark.[1,2] Only an estimated 14% of patients in Denmark survive for 30 days or longer.[2]

International guidelines recommend the use of epinephrine in patients who have cardiac arrest with a nonshockable rhythm (asystole or pulseless electrical activity) and epinephrine in combination with amiodarone or lidocaine in patients with a refractory shockable rhythm (refractory ventricular fibrillation or pulseless ventricular tachycardia).[3,4] To enable the administration of these drugs, it is necessary to establish vascular access during advanced life support.[3,4] Both intravenous and intraosseous vascular access are routinely attempted for this purpose during out-of-hospital cardiac arrest.[5-7]

International guidelines recommend the use of intravenous access for initial attempts at vascular access, albeit with a very low certainty of evidence.[3,8-10] We therefore designed the Intravenous vs. Intraosseous Vascular Access during Out-of-Hospital Cardiac Arrest (IVIO) trial.[11] The objective of the trial was to determine whether the effectiveness of initial attempts at intraosseous vascular access or intravenous vascular access during out-of-hospital cardiac arrest would differ with respect to the return of spontaneous circulation.

METHODS

TRIAL DESIGN AND OVERSIGHT

This investigator-initiated, randomized, parallel-group superiority trial was conducted through emergency medical service agencies in all five regions of Denmark, covering 5.9 million inhabitants. Cardiac arrests in Denmark are generally attended by a primary ambulance unit and a physician-manned unit.[12] The physician may terminate resuscitation on scene.

The trial was approved by the relevant ethics committee and the Danish Medicines Agency. The trial was first approved under the European Union (EU) Clinical Trials Directive 2001/20/EC[13] and was subsequently approved on July 4, 2022, for transition to the EU Clinical Trials Regulation No. 536/2014.[14]

A steering committee designed the trial and wrote the protocol, which is available with the full text of this article at NEJM.org. Minor discrepancies between the protocol and the current report (primarily related to statistical reporting) are described in the Supplementary Appendix, available at NEJM.org. Data analyses were performed by the first and twelfth authors who, along with the last author, vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol. The first draft of the manuscript was written by the first and last authors. An independent data monitoring committee oversaw safety for the trial and reviewed data after approximately 50, 200, 400, and 800 patients were enrolled. The trial had no prespecified stopping criteria for harm, futility, or efficacy.

PATIENTS

Patients 18 years of age or older were eligible for inclusion in the trial if vascular access was indicated during an out-of-hospital cardiac arrest. Exclusion criteria were a suspected traumatic cause of the cardiac arrest, functioning vascular access already in place at the time of possible randomization, and previous enrollment in the trial.

Under the EU Clinical Trials Directive, oral consent from a physician who was not involved in the trial was required before a patient could be enrolled. This requirement was waived after transition to the EU Clinical Trials Regulation. For incapacitated survivors, written informed consent was obtained from a close relative and a physician who was not involved in the trial. Patients who regained capacity were approached for written informed consent as quickly as possible.

RANDOMIZATION AND INTERVENTION

When a patient met the eligibility criteria, the responsible on-site clinician performed the randomization by opening an opaque, sealed envelope. Patients were randomly assigned in a 1:1 ratio to undergo intraosseous vascular access (EZ-IO, Teleflex) or intravenous vascular access (Venflon Pro Safety, Becton Dickinson). Patients assigned to undergo intraosseous access were further randomly assigned in a 1:1 ratio to humeral or tibial intraosseous vascular access. The main comparison in the trial was between intravenous and intraosseous vascular access; humeral and tibial access were evaluated as a secondary comparison.

The intervention consisted of initial attempts to establish the assigned vascular access during the cardiac arrest. After two failed attempts, the method used for any further attempts was at the clinician's discretion. One attempt was defined by skin penetration, and successful vascular access was determined on the basis of clinical judgment. The elapsed times to successful vascular access and to epinephrine administration were reported by the clinicians. At two trial sites, patients in whom intraosseous access was successfully established underwent computed tomography (CT) of the access area if CT was already clinically indicated.

All the involved clinicians received an online training module and additional practical training if they were not already proficient in intraosseous access. Both the on-site clinicians and the in-hospital clinicians were aware of the trial-group assignments after randomization, whereas patients and surrogates were not informed of the assignments. Outcome assessors who conducted follow-up interviews were also unaware of the trial-group assignments.

OUTCOMES

The primary outcome was a sustained return of spontaneous circulation, which was defined as a palpable pulse or other signs of circulation with no further use of chest compressions for at least 20 minutes. Key secondary outcomes were survival at 30 days and survival at 30 days with a favorable neurologic outcome, which was defined by a score of 0 to 3 on the modified Rankin scale (scores range from 0 to 6, with higher scores indicating greater disability).[15]

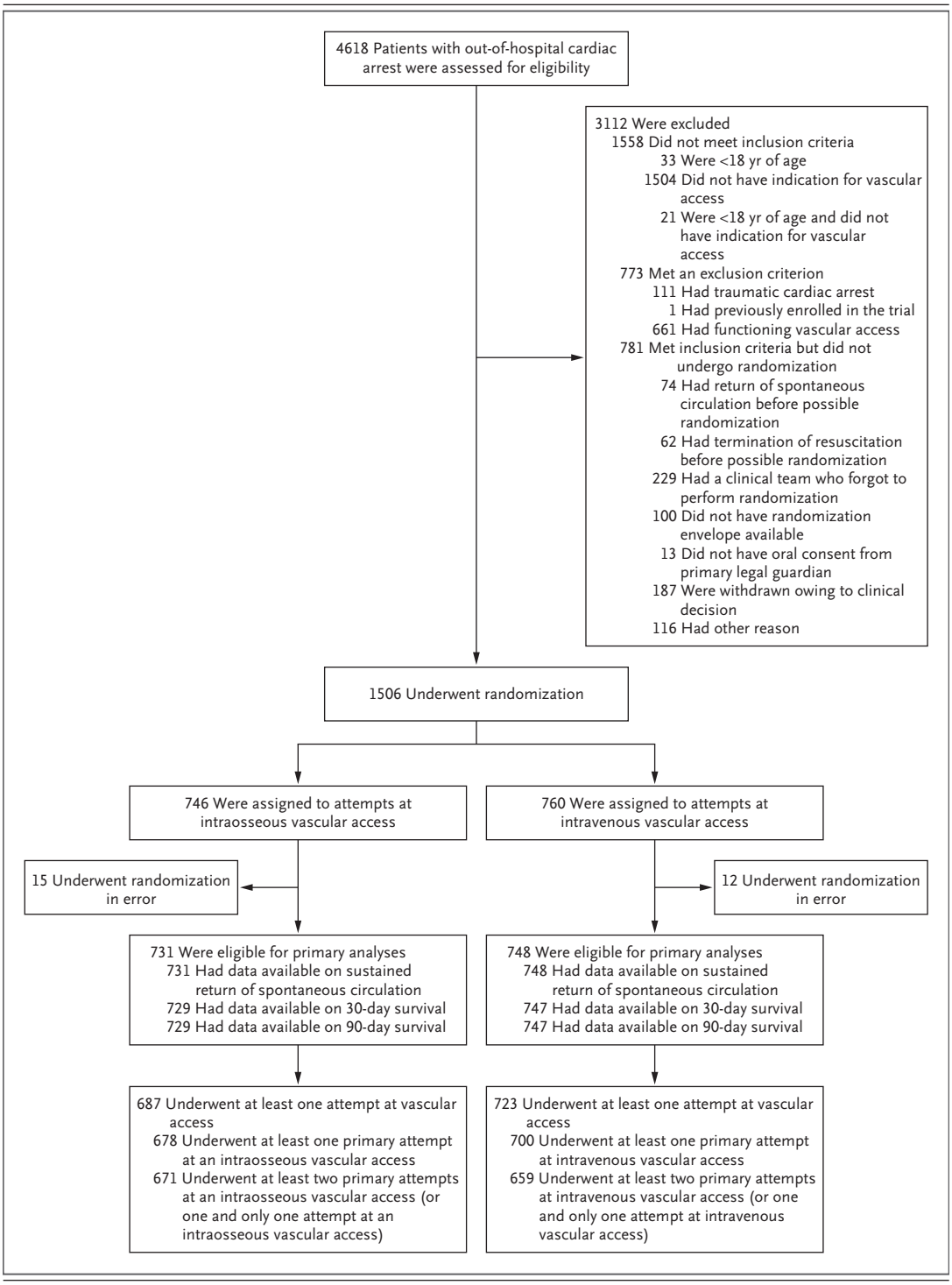
Other outcomes included health-related quality of life among survivors at 30 days, as assessed by the EuroQol Group 5-Dimension 5-Level questionnaire (EQ-5D-5L).[16] Results of the EQ-5D-5L are reported both as the patient-assessed numerical score and as the indexed value on the basis of Danish data.[17] Numerical scores on the EQ-5D-5L range from 0 to 100, with higher scores indicating better health-related quality of life. Survival, neurologic outcome, and health-related quality of life were also assessed at 90 days, 180 days, and 1 year. The current report includes 30-day and 90-day outcome results; collection of longer-term data is ongoing. Prespecified adverse events that occurred were recorded; details are provided in the protocol.

STATISTICAL ANALYSIS

The sample size was based on the assumption that 30% of the patients in one group and 38% of those in the other group would have sustained return of spontaneous circulation, corresponding to a risk ratio of 1.27. We calculated that a sample of 1470 patients would provide the trial with 90% power to detect a significant difference between the two groups at an alpha level of 0.05, using a chi-square test. Analyses were performed in the modified intention-to-treat population, which included only patients who had undergone randomization and, at the time of randomization, met all the inclusion criteria and none of the exclusion criteria.[18] Categorical data are presented as numbers and percentages, with differences between groups expressed as risk ratios and risk differences with 95% confidence intervals.[19] Continuous data are reported as means with standard deviations or as medians with interquartile ranges. Between-group differences in continuous outcomes are presented as mean differences with 95% confidence intervals, derived from a generalized linear model with robust standard errors.

Three sensitivity analyses for the primary and key secondary outcomes were performed. In the first analysis, a modified Poisson regression model was used to estimate risk ratios that were adjusted for important prognostic factors, including age, whether the cardiac arrest had been witnessed, whether early cardiopulmonary resuscitation had been initiated by a bystander or by emergency medical services, and the initial rhythm. A second adjusted analysis excluded patients who had undergone randomization but did not undergo any attempts at vascular access. A third adjusted analysis excluded patients who underwent either no attempts at vascular access or any attempt at vascular access that was discordant with the trial-group assignment in the first two attempts. We also assessed the effect of the vascular-access method on the primary outcome in prespecified subgroups that were defined according to the initial rhythm, whether the cardiac arrest had been witnessed, whether cardiopulmonary resuscitation had been initiated by a bystander, and sex.

Two-sided P values, which were calculated with the use of Fisher's exact test, were planned to be provided for the primary and key secondary outcomes on the basis of hierarchical testing. Be-



cause the potential for a type I error is not well defined when multiple secondary analyses are performed, analyses for other outcomes should be considered exploratory. The widths of the 95% confidence intervals have not been adjusted for multiplicity, so the intervals should not be used in place of hypothesis testing. Analyses were performed with the use of Stata software, version 18.0 (StataCorp), and SAS software, version 9.4 (SAS Institute).

Figure 1 (facing page). Screening, Randomization, and Adherence to the Intervention.

When patients met the inclusion criteria but did not undergo randomization, the clinical decisions for not performing randomization included the following: the on-site clinician prioritized a specific type of vascular access, the participating trial personnel had other tasks that were prioritized, and the physical environment compromised the placement of the device used for vascular access. "Other" reasons for not performing randomization when patients met the inclusion criteria included the following: no participating trial personnel attended the cardiac arrest, a misunderstanding regarding the trial protocol occurred, and miscommunication among on-site personnel occurred. Exclusions that occurred after randomization (because patients had undergone randomization in error) were prespecified in the protocol; patients were excluded if they either did not meet the inclusion criteria or met an exclusion criterion at the time of randomization. The reasons for exclusion after randomization were as follows: was not in cardiac arrest at the time of randomization (2 patients in the intraosseous-access group and 1 patient in the intravenous-access group), was 17 years of age at the time of cardiac arrest (2 patients in the intravenous-access group), had traumatic cardiac arrest (4 patients in the intraosseous-access group and 4 patients in the intravenous-access group), had previously enrolled in the trial (1 patient in the intravenous-access group), and already had functioning vascular access (9 patients in the intraosseous-access group and 4 patients in the intravenous-access group). Crossover information for within-intraosseous access (humeral to tibial access or tibial to humeral access) is described in Figure S9.

RESULTS

PATIENT CHARACTERISTICS

The trial was started in the Central Denmark Region on March 1, 2022; the sites from the other four regions were added successively beginning on February 15, 2023 (Table S1 in the Supplementary Appendix). From March 1, 2022, through May 5, 2024, a total of 4618 patients with out-of-hospital cardiac arrests were screened. Among 1506 patients who had undergone randomization, 1479 were eligible for inclusion in the primary analysis; 731 were randomly assigned to undergo intraosseous vascular access and 748 to undergo intravenous vascular access (Fig. 1). No data for the primary outcome were missing, but 2 patients in the intraosseous-access group and 1 patient in the intravenous-access group were lost to follow-up for the 30-day and 90-day survival evaluations.

Demographic, clinical, and event characteristics of the patients at baseline are shown in Table 1 and Table S2. The mean (±SD) age of the patients was 69±15 years, and 70% were men. Most of the cardiac arrests occurred at home (in 81% of patients) and with an initial nonshockable rhythm (in 77%). The representativeness of the trial population relative to the general U.S. and Danish populations of patients with out-of-hospital cardiac arrest is described in Table S3. The chest-compression fraction (the percentage of time chest compressions are administered during a cardiac arrest) and frequency (the number of chest compressions administered per minute) are detailed in Figures S1 and S2. Data on the interventions used during and after cardiac arrest are provided in Tables S4 and S5.

ADHERENCE AND PROCEDURAL OUTCOMES

A total of 44 patients (6%) assigned to intraosseous access and 25 patients (3%) assigned to intravenous access never underwent any attempt at vascular access during the cardiac arrest (Fig. 1) owing to early termination of resuscitation (in 78% of the patients) or an early return of spontaneous circulation (in 22%). An additional 16 patients (2%) in the intraosseous-access group and an additional 64 patients (9%) in the intravenous-access group underwent attempts that were discordant with the trial-group assignment in the first two attempts (Fig. 1).

The incidence of successful establishment of vascular access on the first or second attempt was 92% in the intraosseous-access group and 80% in the intravenous-access group (Table 2). The time to the first successful vascular access was similar in the two groups, as was the time to the first dose of epinephrine (Table 2, Table S6, and Figs. S3, S4, and S5). The incidence of displacement (which was defined as nonfunctional primary vascular access at the time of hospital admission, transfer to a helicopter unit, or termination of resuscitation), as assessed by the clinician, was low and similar in the two groups (Table S7).

PRIMARY AND KEY SECONDARY OUTCOMES

A sustained return of spontaneous circulation (the primary outcome) occurred in 221 patients (30%) in the intraosseous-access group and in 214 patients (29%) in the intravenous-access group, resulting in a risk ratio of 1.06 (95% confidence interval [CI], 0.90 to 1.24; P=0.49) (Ta-

Table 1. Demographic and Event Characteristics at Baseline According to Trial-Group Assignment.*

Characteristic	Intraosseous Access (N=731)	Intravenous Access (N=748)
Age — yr	69±15	70±14
Male sex — no. (%)	517 (71)	516 (69)
Body-mass index†	27±6	27±6
Location of cardiac arrest — no. (%)		
Home	589 (81)	608 (81)
Public area	142 (19)	140 (19)
Witness of cardiac arrest — no. (%)		
Bystander	383 (52)	391 (52)
Emergency medical services	38 (5)	29 (4)
Unwitnessed	310 (42)	328 (44)
Bystander-initiated CPR — no. (%)‡	585 (84)	594 (83)
Bystander-initiated use of AED — no. (%)‡		
AED shock administered	85 (12)	83 (12)
AED attached but no shock administered	126 (18)	124 (17)
No record of AED attached	482 (70)	512 (71)
Median response time, first unit on scene (IQR) — min	7 (5–10)	6 (4–10)
Initial rhythm — no. (%)§		
Shockable	159 (22)	183 (25)
Ventricular fibrillation	144 (20)	164 (22)
Pulseless ventricular tachycardia	14 (2)	17 (2)
Shockable, only AED available	1 (<1)	2 (<1)
Nonshockable	569 (78)	562 (75)
Pulseless electrical activity	171 (23)	188 (25)
Asystole	398 (55)	373 (50)
Nonshockable, only AED available	0	1 (<1)
Presumed cause of cardiac arrest — no. (%)		
Medical, cardiac	127 (17)	117 (16)
Medical, noncardiac	89 (12)	96 (13)
Drug overdose	13 (2)	12 (2)
Drowning	4 (1)	4 (1)
External asphyxia	22 (3)	20 (3)
Unknown or not recorded¶	474 (65)	494 (66)
Other	2 (<1)	5 (1)

* Plus–minus values are means ±SD. AED denotes automated external defibrillator, CPR cardiopulmonary resuscitation, and IQR interquartile range.
† The body-mass index is the weight in kilograms divided by the square of the height in meters. Data were missing in 367 patients (183 in the intraosseous-access group and 184 in the intravenous-access group).
‡ Emergency medical services–witnessed cardiac arrests (in 67 patients) were excluded from the denominator.
§ In cases in which manual defibrillator data were available, initial rhythm was based on electrocardiographic analysis of those data. In cases in which such data were not available, initial rhythm was based on the first manually assessed rhythm during the cardiac arrest, as determined by the clinician and entered in the patient's medical record. AED rhythms were selected only when there was no manually assessed rhythm during the cardiac arrest. Six patients (3 in the intraosseous-access group and 3 in the intravenous-access group) were not assessed for initial rhythm before randomization and then had sustained return of spontaneous circulation at the first rhythm assessment after randomization; these patients were excluded from the denominator.
¶ In the literature, causes of cardiac arrest that are unknown or not recorded are often referred to as "presumed cardiac" causes.

Table 2. Procedural Outcomes.

Outcome	Intraosseous Access	Intravenous Access
According to trial-group assignment		
No. of patients	731	748
Successful vascular access on first attempt — no. (%)	623 (85)	456 (61)
Successful vascular access on first or second attempt — no. (%)	669 (92)	595 (80)
Median time from first unit arrival on scene to successful vascular access (IQR) — min*	6 (4–10)	6 (4–10)
Median time to first successful vascular access (IQR) — min*†	14 (10–17)	14 (10–18)
Epinephrine administered during the cardiac arrest — no. (%)	615 (84)	621 (83)
Median time to first dose of epinephrine (IQR) — min†‡	15 (12–19)	15 (12–20)
Including only patients who underwent any attempts at vascular access§		
No. of patients	687	723
Successful vascular access on first attempt — no. (%)	623 (91)	456 (63)
Successful vascular access on first or second attempt — no. (%)	669 (97)	595 (82)
Median time from first unit arrival on scene to successful vascular access (IQR) — min¶	6 (4–10)	6 (4–10)
Median time to first successful vascular access (IQR) — min†¶	14 (10–17)	14 (10–18)
Epinephrine administered during the cardiac arrest — no. (%)	615 (90)	621 (86)
Median time to first dose of epinephrine (IQR) — min†‡	15 (12–19)	15 (12–20)
Including only patients who underwent attempts at vascular access according to trial-group assignment‖		
No. of patients	671	659
Successful vascular access on first attempt — no. (%)	618 (92)	435 (66)
Successful vascular access on first or second attempt — no. (%)	657 (98)	537 (81)
Median time from first unit arrival on scene to successful vascular access (IQR) — min**	6 (4–10)	6 (4–10)
Median time to first successful vascular access (IQR) — min†**	14 (10–17)	13 (10–17)
Epinephrine administered during the cardiac arrest — no. (%)	601 (90)	560 (85)
Median time to first dose of epinephrine (IQR) — min†‡	15 (12–19)	15 (12–19)

* A total of 49 patients in the intraosseous-access group and 48 patients in the intravenous-access group did not undergo a successful vascular access during cardiac arrest and were excluded from this analysis.
† The "time to first successful vascular access" and the "time to first dose of epinephrine" were calculated beginning at the time of cardiac arrest notification (i.e., the time of the emergency call or the time of the cardiac arrest, whichever came last).
‡ This analysis included only patients who received epinephrine during cardiac arrest.
§ A total of 44 patients in the intraosseous-access group and 25 patients in the intravenous-access group did not undergo any attempt at vascular access and were excluded from these analyses.
¶ A total of 5 patients in the intraosseous-access group and 23 patients in the intravenous-access group did not undergo a successful vascular access during cardiac arrest and were excluded from this analysis.
‖ In addition to patients who did not undergo any attempt at vascular access (44 in the intraosseous-access group and 25 in the intravenous-access group), patients who underwent any attempt at vascular access that was discordant with the trial-group assignment in the first two attempts (16 in the intraosseous-access group and 64 in the intravenous-access group) were excluded from these analyses.
** A total of 5 patients in the intraosseous-access group and 23 patients in the intravenous-access group did not undergo a successful vascular access during cardiac arrest and were excluded from this analysis.

ble 3). Similar results were observed in the analysis of any return of spontaneous circulation and in the analysis of a return of spontaneous circulation at the time of hospital arrival (Table S8). The effect of the vascular-access method on the primary outcome was consistent across the prespecified subgroups (Fig. 2), and the results of the sensitivity analyses were consistent with those of the main analysis (Tables S9 and S10).

At 30 days, 85 patients (12%) in the intraosseous-access group and 75 patients (10%) in the intravenous-access group were alive (risk ratio,

Table 3. Outcomes According to Trial-Group Assignment.*

Outcome	Intraosseous Access (N=731)	Intravenous Access (N=748)	Risk Ratio (95% CI)	Difference (95% CI)
Primary outcome: sustained return of spontaneous circulation — no. (%)	221 (30)	214 (29)	1.06 (0.90 to 1.24)†	1.6 (–3.0 to 6.3)†‡
30-Day outcomes				
Survival — no. (%)§	85 (12)	75 (10)	1.16 (0.87 to 1.56)	1.6 (–1.6 to 4.8)‡
Survival with a favorable neurologic outcome — no. (%)¶	67 (9)	59 (8)	1.16 (0.83 to 1.62)	1.3 (–1.6 to 4.2)‡
EQ-5D-5L score, as assessed by the patient‖	68±20	64±21	—	4 (–2 to 11)**
EQ-5D-5L score, index value‖	63±31	63±26	—	0 (–9 to 9)**
90-Day outcomes				
Survival — no. (%)††	82 (11)	71 (10)	1.18 (0.88 to 1.60)	1.7 (–1.4 to 4.9)‡
Survival with a favorable neurologic outcome — no. (%)¶	75 (10)	64 (9)	1.20 (0.88 to 1.65)	1.7 (–1.3 to 4.8)‡
EQ-5D-5L score, as assessed by the patient‖	78±19	74±20	—	3 (–3 to 10)**
EQ-5D-5L score, index value‖	82±24	81±23	—	1 (–6 to 9)**

* Plus–minus values are means ±SD. The widths of the 95% confidence intervals have not been adjusted for multiplicity; therefore, the intervals should not be used in place of hypothesis testing.

† P=0.49. Because the P value is above 0.05, no additional P values were calculated for key secondary outcomes (i.e., survival at 30 days and survival at 30 days with a favorable neurologic outcome).

‡ The risk difference between the groups is shown in percentage points.

§ A total of 2 of 731 patients (<1%) in the intraosseous-access group and 1 of 748 patients (<1%) in the intravenous-access group were lost to follow-up.

¶ This outcome was defined by a score of 0 to 3 on the modified Rankin scale (scores range from 0 to 6, with higher scores indicating greater disability). At 30 days, 3 of 731 patients (<1%) in the intraosseous-access group and 2 of 748 patients (<1%) in the intravenous-access group were lost to follow-up. At 90 days, 4 of 731 patients (<1%) in the intraosseous-access group and 2 of 748 patients (<1%) in the intravenous-access group were lost to follow-up.

‖ The results of the EuroQol Group 5-Dimension 5-Level questionnaire (EQ-5D-5L) are reported both as the patient-assessed numerical score and as the indexed value on the basis of Danish data. The numerical score is reported on a scale ranging from 0 to 100, with higher scores indicating better health-related quality of life. The index value can be negative. These analyses included only patients who survived to the specific time point. At 30 days, 3 of 731 patients (<1%) in the intraosseous-access group and 2 of 748 patients (<1%) in the intravenous-access group were lost to follow-up. At 90 days, 4 of 731 patients (<1%) in the intraosseous-access group and 2 of 748 patients (<1%) in the intravenous-access group were lost to follow-up.

** The mean difference between the groups is shown.

†† A total of 2 of 731 patients (<1%) in the intraosseous-access group and 1 of 748 patients (<1%) in the intravenous-access group were lost to follow-up.

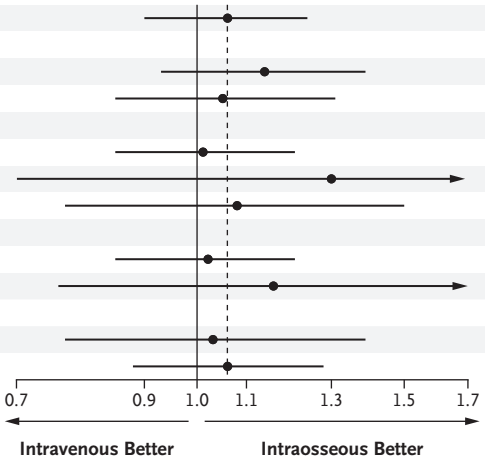
1.16; 95% CI, 0.87 to 1.56) (Table 3). The number of patients who were alive at 30 days and had a favorable neurologic outcome was 67 in the intraosseous-access group and 59 in the intravenous-access group (9% and 8%, respectively; risk ratio, 1.16; 95% CI, 0.83 to 1.62) (Table 3). The effect of the vascular-access method on these outcomes was consistent across the prespecified subgroups (Fig. S6 and S7), and the results of the sensitivity analyses were similar to those of the main analyses.

ADDITIONAL OUTCOMES

A total of 82 patients (11%) in the intraosseous-access group and 71 patients (10%) in the intravenous-access group were alive at 90 days (risk ratio, 1.18; 95% CI, 0.88 to 1.60) (Table 3). A Kaplan–Meier curve for 90-day survival is provided in Figure S8. The number of patients who were alive at 90 days and had a favorable neurologic outcome was 75 in the intraosseous-access group and 64 in the intravenous-access group (10% and 9%, respectively; risk ratio, 1.20; 95% CI, 0.88 to 1.65) (Table 3). Details on the neurologic outcomes are provided in Table S11. EQ-5D-5L scores among the survivors are shown in Table 3 and Table S12. Details on discharge disposition (e.g., discharge to home or to a rehabilitation facility) and the cause of death are provided in Table S13, and data on organ dysfunction and

A Risk Ratio for Sustained Return of Spontaneous Circulation

Subgroup	Intraosseous	Intravenous	Risk Ratio (95% CI)
	no. of events/total no. (%)		
Overall	221/731 (30)	214/748 (29)	1.06 (0.90 to 1.24)
Initial rhythm			
Shockable	90/159 (57)	91/183 (50)	1.14 (0.93 to 1.39)
Nonshockable	128/569 (22)	120/562 (21)	1.05 (0.85 to 1.31)
Witness of cardiac arrest			
Bystander	147/383 (38)	148/391 (38)	1.01 (0.85 to 1.21)
EMS	17/38 (45)	10/29 (34)	1.30 (0.72 to 2.44)
Unwitnessed	57/310 (18)	56/328 (17)	1.08 (0.77 to 1.50)
Bystander CPR			
Yes	173/585 (30)	173/594 (29)	1.02 (0.85 to 1.21)
No	31/108 (29)	31/125 (25)	1.16 (0.76 to 1.77)
Sex			
Female	61/214 (29)	64/232 (28)	1.03 (0.77 to 1.39)
Male	160/517 (31)	150/516 (29)	1.06 (0.88 to 1.28)



B Risk Difference for Sustained Return of Spontaneous Circulation

Subgroup	Intraosseous	Intravenous	Risk Difference (95% CI)
	no. of events/total no. (%)		
Overall	221/731 (30)	214/748 (29)	1.6 (–3.0 to 6.3)
Initial rhythm			
Shockable	90/159 (57)	91/183 (50)	6.9 (–3.7 to 17.0)
Nonshockable	128/569 (22)	120/562 (21)	1.1 (–3.7 to 6.0)
Witness of cardiac arrest			
Bystander	147/383 (38)	148/391 (38)	0.5 (–6.3 to 7.4)
EMS	17/38 (45)	10/29 (34)	10.0 (–14.0 to 33.0)
Unwitnessed	57/310 (18)	56/328 (17)	1.3 (–4.6 to 7.3)
Bystander CPR			
Yes	173/585 (30)	173/594 (29)	0.4 (–4.8 to 5.6)
No	31/108 (29)	31/125 (25)	3.9 (–7.5 to 15.0)
Sex			
Female	61/214 (29)	64/232 (28)	0.9 (–7.4 to 9.3)
Male	160/517 (31)	150/516 (29)	1.9 (–3.7 to 7.5)

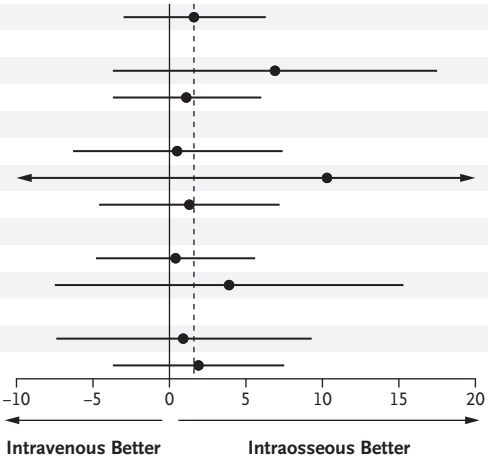


Figure 2. Subgroup Analyses of Sustained Return of Spontaneous Circulation.

The vertical solid lines indicate no difference between the groups, and the vertical dashed lines indicate the overall effect estimates of the primary outcome analysis. The x axis for the risk ratios is logarithmic. The risk difference between the groups is shown in percentage points. The arrows on the confidence interval bars indicate that the upper or lower boundary of the confidence interval is off the scale. The widths of the 95% confidence intervals have not been adjusted for multiplicity, and therefore, the intervals should not be used in place of hypothesis testing. Six patients (3 in the intraosseous-access group and 3 in the intravenous-access group) were not assessed for initial rhythm before randomization and then had sustained return of spontaneous circulation at the first rhythm assessment after randomization; these patients were excluded from the denominator. Emergency medical services (EMS)–witnessed cardiac arrests (in 67 patients) were excluded from the analyses of bystander cardiopulmonary resuscitation (CPR).

laboratory test results obtained after a return of spontaneous circulation are provided in Table S14.

SAFETY

The prespecified adverse events were uncommon and were limited to extravasation, bradyarrhythmia, and ventricular tachyarrhythmia (Table S15). No other prespecified adverse events (i.e., compartment syndrome, osteomyelitis, humeral or tibial traumatic bone fracture, or vascular-access–related inflammation, necrosis, or phlebitis) were reported in any patient.

COMPARISON OF HUMERAL AND TIBIAL INTRAOSSEOUS ACCESS

Among the 731 patients in the intraosseous-access group, 361 were randomly assigned to undergo humeral vascular access and 370 to undergo tibial vascular access. Demographic, clinical, and event characteristics of the patients at baseline are provided in Tables S16 and S17. Adherence to the assigned access method is detailed in Figure S9. A summary of interventions that were used at the time of cardiac arrest is provided in Table S18.

Time-related procedural outcomes are provided in Tables S19 and S20. The incidence of successful establishment of vascular access on the first or second attempt was 90% among the patients who underwent humeral access and 93% among those who underwent tibial access. The incidence of displacement, as assessed by the clinician, was 5% and 1%, respectively (Table S21).

A sustained return of spontaneous circulation occurred in 108 patients (30%) in the humeral-access group and in 113 patients (31%) in the tibial-access group (risk ratio, 0.98; 95% CI, 0.79 to 1.22). Results for the 30-day and 90-day outcomes are provided in Table S22.

CT scans were obtained in 32 patients who underwent humeral access and in 35 of those who underwent tibial access. The catheter was considered to be correctly positioned in the bone marrow in 23 patients (71%) in the humeral-access group and in all 35 patients (100%) in the tibial-access group (Tables S23 and S24). Half the patients in the humeral-access group had catheters that were bent at the time of CT as compared with 11% of the patients in the tibial-access group.

DISCUSSION

This randomized clinical trial showed no significant difference in sustained return of spontaneous circulation between the group that was assigned to undergo intraosseous vascular access and the group that was assigned to undergo intravenous vascular access during out-of-hospital cardiac arrest. Survival at 30 days and survival at 30 days with a favorable neurologic outcome were also similar in the two groups.

Current guidelines suggest the use of intravenous access for initial attempts at vascular access during cardiac arrest.[3,8] Despite this recommendation, the use of intraosseous access is increasing.[7,20] Intravenous access can be challenging to establish during cardiac arrest, whereas intraosseous access is perceived as an easier and faster method.[21] However, animal models of cardiac arrest have shown slightly longer times to reach peak drug concentrations in the central circulation with intraosseous drug administration than with intravenous administration.[22] The pharmacokinetics of intraosseous drug administration in cardiac arrest in humans remain unclear, and in previous randomized trials of drugs used for cardiac arrest, the intravenous route has primarily been used.[23,24]

A systematic review of observational studies showed that patients who received medication by an intraosseous route during cardiac arrest had worse outcomes than those who receive medication intravenously.[9] Any causal interpretation of these results is challenging owing to confounding and to "resuscitation time bias" (i.e., the intraosseous route is often used later during a cardiac arrest than the intravenous route, which could result in bias when the routes are compared).[9,25] Clinical-trial data comparing intravenous vascular access with intraosseous vascular access during cardiac arrest are limited.[9]

A recent cluster-randomized trial conducted in Taiwan did not show any substantial differences in clinical outcomes between clusters that were assigned to undergo intraosseous access and those that were assigned to undergo intravenous access.[26] However, interpretation of those results is limited by problems with the randomization process, an inability to conceal the trial-group assignment, and a difference between the two groups in the number of patients who were excluded after randomization.[26] Furthermore, the incidence of successful prehospital vascular access on the first or second attempt in the intravenous-access group in that trial (58%) was lower than that described in another previous trial[21] and in the current trial (80%).

In the current trial, despite a difference between the groups in the incidence of successful establishment of vascular access, the time to the first successful vascular access and the time to the first dose of epinephrine were both similar in the two groups. These results may explain the similar clinical outcomes of the groups, and they suggest that the effects of drugs given during cardiac arrest probably do not depend substantially on the route of administration. Given the very large effect of epinephrine on short-term

outcomes among patients who have cardiac arrest,[21] any important difference in the return of spontaneous circulation stemming from differences in the pharmacokinetics of intraosseous administration as compared with those of intravenous administration would most likely have been detected in the current trial.

The findings of this trial should be interpreted in the context of some limitations. First, the trial was powered for the analysis of sustained return of spontaneous circulation — not for the more patient-centered long-term outcomes (i.e., those at 30 or 90 days). Such outcomes require very large sample sizes to detect between-group differences that are presumed to be relatively small. Return of spontaneous circulation is more proximately and directly linked to the specific mechanism of the drugs used during cardiac arrest. Second, treating clinicians were aware of the trial-group assignments after randomization. Third, some patients who had undergone randomization never underwent an attempt at vascular access, and some crossed over to the group to which they had not been assigned. Results from sensitivity analyses addressing these issues supported the main results. Fourth, the trial was not powered for the comparison of humeral and tibial intraosseous access. Still, the narrow confidence interval for sustained return of spontaneous circulation suggests that a large difference in this outcome is unlikely. Fifth, generalizability may be limited on the basis of variability in the experience of the operator and in the type of vascular-access device.

In this randomized clinical trial, there was no significant difference in sustained return of spontaneous circulation between intraosseous and intravenous vascular access in adults who had out-of-hospital cardiac arrest.

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