

Available online at [www.sciencedirect.com](http://www.sciencedirect.com)

# Resuscitation

journal homepage: [www.elsevier.com/locate/resuscitation](http://www.elsevier.com/locate/resuscitation)EUROPEAN  
RESUSCITATION  
COUNCIL

## Clinical paper

# Intraosseous versus intravenous access in patients with out-of-hospital cardiac arrest: Insights from the resuscitation outcomes consortium continuous chest compression trial



**Purav Mody<sup>a,\*</sup>, Siobhan P. Brown<sup>b</sup>, Peter J. Kudenchuk<sup>c</sup>, Paul S. Chan<sup>d,e</sup>, Rohan Khera<sup>a</sup>, Colby Ayers<sup>a</sup>, Ambarish Pandey<sup>a</sup>, Karl B. Kern<sup>f</sup>, James A. de Lemos<sup>a</sup>, Mark S. Link<sup>a</sup>, Ahamed H. Idris<sup>g</sup>**

<sup>a</sup> Division of Cardiology, Department of Internal Medicine, UT Southwestern Medical Center, Dallas, TX, United States

<sup>b</sup> Department of Biostatistics, University of Washington, Seattle, WA, United States

<sup>c</sup> Division of Cardiology, Department of Medicine, University of Washington and King County Emergency Medical Services, Public Health-Seattle & King County, WA, United States

<sup>d</sup> Mid America Heart Institute, Saint Luke's Hospital of Kansas City, Kansas City, MO, United States

<sup>e</sup> Division of Cardiology, Department of Internal Medicine, University of Missouri-Kansas City, MO, United States

<sup>f</sup> University of Arizona, Sarver Heart Center, Tucson, AZ, United States

<sup>g</sup> Department of Emergency Medicine, UT Southwestern Medical Center, Dallas, TX, United States

## Abstract

**Aim:** To examine outcomes associated with intraosseous access route attempt for delivery of medications during out-of-hospital cardiac arrest (OHCA) resuscitation.

**Methods:** Using data from the Continuous Chest Compression trial, we examined rates of survival to hospital discharge, sustained return of spontaneous circulation (ROSC), and survival with favorable neurological function among patients with intraosseous and intravenous access attempts after adjusting for age, sex, initial rhythm, bystander cardiopulmonary resuscitation, public location, witnessed status, EMS response and trial randomization cluster.

**Results:** Among 19,731 patients, intraosseous access was attempted in 3068 patients and intravenous access in 16,663 patients respectively. Patients in whom intraosseous access was attempted were younger, more often female, and had marginally faster times to initial access and to initial drug administration. Unadjusted outcomes were significantly lower in patients with attempted intraosseous access compared with intravenous access: (4.6% vs. 5.7%,  $p = 0.01$ ) for survival to discharge, (17.9% vs. 23.5%,  $p < 0.001$ ) for sustained ROSC and (2.8% vs. 4.2%,  $p < 0.001$ ) for survival with favorable neurological function. After adjustment, there were no differences in hospital survival (OR, 0.88, 95% CI 0.72–1.09,  $p = 0.24$ ) or survival with favorable neurological function (OR, 0.87, 95% CI 0.67–1.12,  $p = 0.29$ ) in patients with intraosseous access attempt (vs. intravenous access). However, intraosseous access continued to associate with lower rates of sustained ROSC (OR, 0.80, 95% CI 0.71 – 0.89,  $p < 0.001$ ).

\* Corresponding author at: UT Southwestern Medical Center, 5323 Harry Hines Blvd. Dallas, 75390-8830, TX United States.  
E-mail address: [Purav.Mody@outlook.com](mailto:Purav.Mody@outlook.com) (P. Mody).

<https://doi.org/10.1016/j.resuscitation.2018.10.031>

Received 24 July 2018; Received in revised form 27 October 2018; Accepted 29 October 2018

0300-9572/© 2018 Elsevier B.V. All rights reserved.

**Conclusions:** Among patients with OHCA, intraosseous access attempt was associated with worse ROSC rates but no difference in survival. Further studies are necessary to elucidate the optimal access route among OHCA patients.

**Keywords:** Out of hospital cardiac arrest, Clinical outcomes, Advanced life support drugs

## Introduction

Out of hospital cardiac arrest (OHCA) occurs in over 350,000 persons each year in the United States.<sup>1</sup> Despite multiple advances,<sup>2–4</sup> overall survival rates remain low at approximately 10%, highlighting a critical need to identify additional opportunities for further improvement.<sup>1</sup>

Current cardiac arrest guidelines recommend pharmacological therapy when patients fail to immediately respond to CPR and defibrillation.<sup>5,6</sup> These guidelines recommend establishment of intraosseous access for drug administration as a reasonable alternative if intravenous access is not readily available for administration of critical drugs.<sup>6</sup> The rationale is that intraosseous access can be achieved quickly without the time required to successfully cannulate a suitable vein amidst cardiovascular collapse and could facilitate more rapid delivery of resuscitation medications and fluids.<sup>7</sup> However, data on the effectiveness of drug administration through the intraosseous route are limited. Previous studies on intraosseous access as a route of drug administration have included animal models of cardiac arrest,<sup>8,9</sup> pediatric patients in hypovolemic states<sup>10,11</sup> or human subjects who were hemodynamically stable.<sup>12</sup> Observational studies comparing intraosseous access with intravenous access have reported mixed results on survival,<sup>13–15</sup> were small in size<sup>13,15</sup> and often lacked specific time data regarding important resuscitation events<sup>14</sup>. Determining if intraosseous access during resuscitation from OHCA is associated with higher survival has potentially important implications in guiding cardiac arrest guideline recommendations and training.

Using data from the Resuscitation Outcomes Consortium's Continuous Chest Compression (CCC) trial, we compared rates of survival to hospital discharge from OHCA based on whether

parenteral access was attempted through an intraosseous or an intravenous route.

## Methods

### Data source

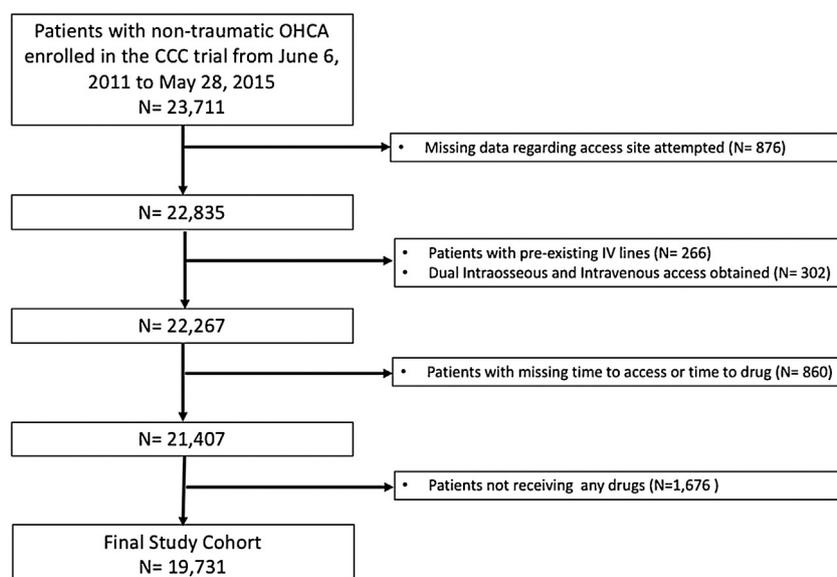
The CCC dataset was obtained from the National Institute of Health's Biologic Specimen and Data Repository Information Coordinating Center website (<https://biolincc.nhlbi.nih.gov/home/>). The detailed study design, baseline characteristics, and primary results of the CCC trial have been previously reported.<sup>16,17</sup>

### Study cohort

The trial included 23,711 adults with non-trauma-related OHCA who received chest compressions performed by providers from participating EMS agencies. Patients with missing data on access route (n=876), pre-existing access prior to arrest (n=266), use of both intravenous and intraosseous access for administration of drugs (n=302), missing time of successful access (n=860), and not receiving any drugs (n=1676) were excluded. Our final study cohort comprised 19,731 patients with available access information through which drugs were administered. (Fig. 1). This study was approved by the institutional review board at UT Southwestern.

### Study definitions

Information about baseline patient characteristics and outcomes were recorded throughout the trial.<sup>17</sup> The data collected included



**Fig. 1 – Derivation of study cohort.**

**OHCA: Out-of-hospital cardiac arrest; CCC: Continuous Chest Compression.**

participant demographics, initial EMS recorded cardiac arrest rhythm including shockable rhythms (ventricular tachycardia, ventricular fibrillation) and non-shockable rhythms (asystole, pulseless electrical activity, AED advised “no-shock”), witnessed status, use of bystander CPR, location of the arrest, CPR quality metrics, type of access attempted and successfully obtained (intraosseous or intravenous), drug doses, volume of fluid administered as well as the time of important resuscitation events such as arrival of EMS service at site of the arrest, successful placement of initial access (intraosseous or intravenous) and administration of initial drug relative to the initial 9-1-1 call.

For our primary analysis, we defined patients with intraosseous access attempt as those in whom EMS services initially attempted intraosseous access. This included patients where the initial attempted intraosseous access was successful as well as patients with failed initial intraosseous access attempt and successful subsequent intravenous access attempt. Similarly, we defined patients with intravenous access attempt as those in whom EMS services initially attempted intravenous access, which included patients with initial successful intravenous attempt as well as patients with failed initial intravenous attempt and successful subsequent intraosseous access attempt (Supplemental Figure 1). This was determined based on information recorded within the trial case report forms that included separate data fields for the type of access route attempted (intraosseous or intravenous access) as well as success of the attempted route.

We derived additional study variables from other timed resuscitation events. These included the EMS response interval (defined as the interval from initial 9-1-1 call to arrival of the first EMS vehicle on site), initial access interval (defined as the interval from arrival of first EMS vehicle on site to successful placement of an intraosseous or intravenous access) and initial drug administration interval (defined as the interval from arrival of first EMS vehicle on site to administration of initial drug) (Supplement Figure 2).

## Outcomes

The primary study outcome was survival to hospital discharge. Additionally, we examined rates of sustained return of spontaneous circulation (ROSC) and survival with favorable neurological function. Sustained ROSC was defined as the presence of ROSC on arrival to a hospital. Favorable neurological function was defined as a Modified Rankin score of  $\leq 3$ , which denotes survival with no more than moderate neurological disability with the ability to walk without assistance.

## Statistical analyses

Baseline characteristics between patients with attempted intraosseous and intravenous access were compared using chi-square tests for categorical variables and a Student's *t*-test or Wilcoxon-Mann-Whitney test for continuous variables.

To examine the relationship between attempted access (intraosseous or intravenous) and survival to hospital discharge, we constructed a mixed effects logistic regression model. In this model we included the trial randomization cluster as a random effect and patient level covariates as fixed effects.<sup>2–4,17–19</sup> These included age, sex, initial EMS-recorded cardiac arrest rhythm (shockable or non-shockable), witnessed arrest status, bystander CPR before EMS arrival, episode location (public or not), and EMS response

interval. We tested for interactions between attempted access type and initial presenting cardiac arrest rhythm (shockable or non-shockable) and witnessed status (witnessed or unwitnessed arrest). Separate mixed effects logistic regression models were constructed for sustained ROSC and survival with favorable neurological function.

To further account for the nonrandom selection of access route for patients with OHCA, we then performed a matched propensity-score analysis. The propensity score was defined as the conditional probability of receiving an initial intraosseous access attempt given the individual's covariate data. To estimate these scores, we constructed a multivariable logistic regression with intraosseous access as the dependent variable and conditioned on age, sex, initial EMS-recorded rhythm (shockable or non-shockable), witness status, bystander CPR, episode location (public or not), and EMS response time interval. The C-statistic was calculated for the propensity model. Once generated, patients were matched 1 to 1 on their propensity score within each randomization cluster (to account for variation in outcome across site) with a caliper width of no more than 0.2 times the standard deviation of the logit of the propensity score.<sup>20</sup> The success of matching was examined by comparing standardized differences in the distribution of the covariates between the two treatment strategies; a difference of  $<10\%$  between the two groups was considered acceptable.<sup>21</sup> After confirming the groups were similar, survival outcomes were evaluated using conditional logistic regression adjusting for age, sex, initial EMS-recorded rhythm (shockable or non-shockable), witness status, bystander CPR, episode location (public or not), and EMS response interval to ensure that the analysis was conducted within matched patient sets.

We performed a number of sensitivity analyses to check the robustness of our findings. First, we separately added initial access interval and initial drug administration interval separately to the primary multivariable model to examine the effect of time differences in obtaining access and drug administration as a possible mediator of outcome differences across the two groups. Second, we added in-hospital procedures such as coronary angiography and therapeutic hypothermia to the primary multivariable model. Third, we restricted our primary analysis to the cohort of patients in whom the initial intended access route attempt was successful (i.e. initial successful intraosseous and intravenous access attempt only with exclusion of patients in whom initial attempted intraosseous or intravenous access was not successful). Finally, we compared baseline characteristics and outcomes among patients based on eventual successful access route irrespective of the initial attempted access route.

All analyses were performed using SAS University edition 3.6 (SAS Institute Inc., Cary, North Carolina). Statistical tests were 2-sided, and a *p*-value below 0.05 was considered statistically significant.

## Results

### Patient characteristics

Of 19,731 patients, 3068 (15.5%) underwent attempted intraosseous access and 16,663 (84.4%) underwent attempted intravenous access. Intraosseous and intravenous access was successfully achieved in 2975 (96.9%) and 15,485 (92.9%) patients in each group, respectively. Baseline demographic and clinical characteristics of

**Table 1 – Baseline demographic and clinical characteristics of the study population<sup>\*</sup>.**

Clinical Characteristics	Overall Cohort			After Propensity Score Matching <sup>†</sup>		
	Initially attempted intraosseous access (N = 3068)	Initially attempted intravenous access (N = 16,663)	P-Value <sup>‡</sup>	Initially attempted intraosseous access (N = 2279)	Initially attempted intraosseous access (N = 2279)	Standardized Difference, %
<b>Pre-Access characteristics</b>						
Age, years	65 (53.0, 77.0)	68.0 (5670, 81.0)	<0.001	66.0 (54.0, 77.0)	64.0 (52.0, 78.0)	6.1
Male sex, %	56.8	66.4	<0.001	56.5	60.1	6
Bystander CPR, %	43.0	46.5	<0.001	41.3	39.2	4
Witnessed, %	37.0	43.0	<0.001	35.8	39.6	6.1
Initial Shockable rhythm, %	17.4	23.3	<0.001	17.3	19.6	5.9
Public location, %	11.1	14.5	<0.001	10.4	11.2	2.2
Chest compression fraction <sup>§</sup>	0.85 (0.77, 0.90)	0.85 (0.78, 0.90)	0.6	0.86 (0.79, 0.91)	0.85 (0.78, 0.90)	3.2
EMS response time interval, minutes	5.0 (3.9, 6.5)	5.5 (4.3, 7.0)	<0.001	4.8 (3.7, 6.0)	4.6 (3.5, 6.0)	6.6
<b>Post-access characteristics</b>						
Amount of fluids administered, ml	500 (250, 1000)	500 (250, 800)	0.6	500 (250, 1000)	500 (300, 1000)	–
Epinephrine dose, mg <sup>  </sup>	3.0 (3.0, 5.0)	3.0 (3.0, 4.0)	0.04	3.0 (2.0, 4.0)	3.0 (2.0, 4.0)	–
Initial access time interval, minutes	8.9 (6.3, 12.2)	9.0 (6.5, 12.6)	0.01	9.1 (6.6, 13.0)	8.0 (6.0, 11.0)	–
Initial drug administration time interval, minutes	10.6 (7.9, 14.3)	10.8 (8.0, 14.3)	0.03	11.0 (8.0, 14.9)	10.0 (7.5, 13.2)	–
<b>In-Hospital procedures<sup>#</sup></b>						
Therapeutic hypothermia, %	49.7	57.7	<0.001	49.0	55.0	–
Coronary angiography within 24 hours of ED arrival, %	20.5	26.8	0.001	21.4	23.5	–

<sup>\*</sup> Continuous variables are reported as median with interquartile range and categorical measures as percentages.

<sup>†</sup> Propensity score matched cohort was derived based on matching for characteristics prior to obtaining access.

<sup>‡</sup> Chi-square tests were used for categorical variables and a Student's *t*-test or Wilcoxon-Mann-Whitney tests were used for continuous variables.

<sup>§</sup> The chest-compression fraction is the proportion of each minute during which compressions were given.

<sup>||</sup> Values are for patients who received epinephrine.

<sup>#</sup> Values are for patients admitted as inpatient to the hospital.

patients from the two groups are compared in Table 1. Overall, patients with attempted intraosseous access were younger, more often female, less frequently received bystander CPR, and had a lower proportion of witnessed arrests and arrests with an initial shockable rhythm compared with patients with attempted intravenous access. Patients with attempted intraosseous access less commonly underwent in-hospital procedures such as therapeutic hypothermia and coronary angiography. Additionally, patients with attempted intraosseous access had slightly shorter EMS response intervals and times in establishing initial access (median [interquartile range], 8.9 [6.3, 12.2] vs. 9.0 [6.5, 12.6] minutes;  $p=0.01$ ) and to initial drug administration (10.6 [7.9, 14.3] vs. 10.8 [8.0, 14.3] minutes;  $p=0.03$ ). Baseline data on patients with unsuccessful initially attempted intraosseous and intravenous access are presented in Supplemental Table 1. In general, patients with failed initially attempted intraosseous and intravenous access had longer initial access intervals and initial drug administration intervals with worse outcomes compared with patients with successful initially attempted intraosseous and intravenous access (Supplemental Table 1). Finally, baseline data on patients based on ultimately success access route are presented in Supplemental Table 2.

### Clinical outcomes

Unadjusted rate of survival to hospital discharge was lower in patients receiving attempted intraosseous access compared with attempted intravenous access (4.6% vs. 5.7%,  $p=0.01$ ). However, after adjustment for age, sex, initial cardiac arrest rhythm, bystander

cardiopulmonary resuscitation, public location, witnessed status and EMS response time interval, attempted intraosseous access was no longer associated with decreased survival (adjusted OR, 0.88, 95% CI 0.72–1.09,  $p=0.24$ ), nor with favorable neurological status at discharge (unadjusted rate: 2.8% vs. 4.2%; adjusted OR, 0.87, 95% CI 0.67–1.12,  $p=0.29$ ). (Table 2). However, attempted intraosseous access was associated with lower rates of sustained ROSC (unadjusted rate: 17.9% vs. 23.5%, adjusted OR, 0.80, 95% CI 0.71–0.89,  $p<0.001$ ). There were no interactions between attempted access and initial rhythm or witnessed status for any of the outcomes (Supplemental Figures 3a–3c).

A propensity model was constructed for the propensity for intraosseous access and had a c-statistic of 0.61. We successfully matched 2279 patients with attempted intraosseous access with 2279 patients with attempted intravenous access using propensity score-matching. Baseline variables were well-balanced across the two groups after matching and are presented in Table 1. The rates of survival to hospital discharge (4.6% vs. 5.9%) and sustained ROSC (18.2% vs. 22.5%,  $p<0.001$ ) were significantly lower in the attempted intraosseous group compared with attempted intravenous group with no difference in rates of survival with favorable neurological function (3.0% vs. 3.6%) in the propensity matched analysis. In the matched cohort, the adjusted odds of survival to hospital discharge were not significantly different between the two groups (Table 2).

The results of our sensitivity analyses largely mirrored our primary analysis. Additional adjustment for initial access interval, initial drug administration interval or in-hospital procedures did not meaningfully change model results (Table 3). On restricting the study cohort to

**Table 2 – Association between intraosseous access and survival outcomes after OHCA, after multivariable adjustment and propensity score matching.**

Outcome	Initially attempted intraosseous access (N = 3068)	Initially attempted intravenous access (N = 16,663)	Adjusted OR (95% CI) for intraosseous access	P value <sup>†</sup>
<b>Primary study cohort (N = 22,267)</b>				
Survival to hospital discharge	142/3068 (4.6%)	955/16663 (5.7%)	0.88 (0.72– 1.09)	0.24
Sustained ROSC	551/3068 (17.9%)	3920/16663 (23.5%)	0.80 (0.71– 0.89)	<0.001
Survivable with favorable neurological function	86/3068 (2.8%)	706/16663 (4.2%)	0.87 (0.67– 1.12)	0.29
<b>Propensity Score Matched Cohort</b>				
	<b>Initially attempted intraosseous access (n = 2279)</b>	<b>Initially attempted intravenous access (n = 2279)</b>		
Survival to hospital discharge, %	105/2279 (4.6%)	135/2279 (5.9%)	0.85 (0.59– 1.22)	0.38
Sustained ROSC, %	415/2279 (18.2%)	514/2279 (22.5%)	0.72 (0.61– 0.85)	<0.001
Survived with favorable neurological function, %	69/2279 (3.0%)	82/2279 (3.6%)	0.95 (0.55– 1.63)	0.85

<sup>†</sup> For comparison of adjusted outcomes between intraosseous and intravenous access groups.

patients with initial successful access only, intraosseous access was associated with significantly lower rates of sustained ROSC only but not with survival to hospital discharge or survival with favorable neurological status (Table 3). In contrast, on comparing outcomes based on eventual successful access, patients receiving successful intraosseous access eventually had significantly lower rates of sustained ROSC (unadjusted rate: 17.6% vs. 18.9%; adjusted OR 0.73, 95% CI 0.66– 0.81,  $p < 0.001$ ), survival to hospital discharge (unadjusted rate: 4.2% vs. 5.9%; adjusted OR 0.77, 95% CI 0.63– 0.93,  $p = 0.005$ ) and survival with favorable neurological function discharge (unadjusted rate: 2.5% vs. 4.4%; adjusted OR 0.73, 95% CI 0.58– 0.93,  $p < 0.01$ ) compared with eventual successful intravenous access.

## Discussion

In a large, contemporary cohort of patients with OHCA, intraosseous access was attempted in 1 in 7 patients with OHCA. Despite marginally shorter vascular access and drug administration times, a strategy of

initial intraosseous access attempt compared with intravenous access attempt was not associated with any differences in overall survival or survival with favorable neurological function but was associated with lower rates of sustained ROSC. Collectively, our findings highlight the need for additional studies to evaluate the effectiveness of intraosseous access during acute resuscitations for OHCA.

National level data on the use of intraosseous access as a route for administration drugs and fluids in OHCA in the United States are currently lacking. The rates of intraosseous access have ranged from 5% of OHCA in the ROC PRIMED study cohort from 2007 to 2009<sup>14</sup> to 20% in recent times<sup>22</sup> indicative of the increasing popularity of this access site in recent times. Despite their increasing popularity, few studies have examined the effectiveness of intraosseous access as a route of administration of drugs during cardiac arrest with conflicting results. Similar to our study results, Feinstein et al. demonstrated significantly decreased rates of sustained ROSC but no difference in survival to hospital discharge among OHCA patients receiving intraosseous access at the tibial site in Seattle and King County.<sup>13</sup> In their study, intraosseous access was obtained as access after failure of initial intravenous attempts, suggesting these patients were

**Table 3 – Multivariable models examining the association of intraosseous access attempt (compared with intravenous access) and outcomes.**

Multivariable Models	Odds ratios (95% C.I.) comparing initially attempted intraosseous access with initially attempted intravenous access		
	Sustained ROSC	Survival to discharge	Survival with favorable neurological function
<b>Primary Study Cohort (N = 19,731)</b>			
Base model <sup>†</sup>	0.80 (0.71– 0.89)	0.88 (0.72– 1.09)	0.87 (0.67– 1.12)
Base model + initial access time interval	0.81 (0.72– 0.91)	0.92 (0.75– 1.14)	0.91 (0.70– 1.18)
Base model + initial drug administration time interval	0.80 (0.72– 0.90)	0.90 (0.73– 1.11)	0.88 (0.68– 1.14)
Base model + in-hospital procedures	0.85 (0.75– 0.97)	1.00 (0.80– 1.25)	0.95 (0.72– 1.26)
<b>Restricted Study Cohort (N = 18,460)<sup>‡</sup></b>			
Base model <sup>†</sup>	0.78 (0.69– 0.87)	0.87 (0.70– 1.07)	0.84 (0.65– 1.09)
Base model + initial access time interval	0.80 (0.71– 0.90)	0.92 (0.74– 1.14)	0.88 (0.68– 1.15)
Base model + initial drug administration time interval	0.79 (0.70– 0.89)	0.89 (0.72– 1.10)	0.85 (0.65– 1.11)

<sup>†</sup> Mixed effects logistic regression model was constructed with fitting of patient characteristics (age, sex, witnessed status, initial presenting cardiac arrest rhythm, bystander CPR, location of the arrest, EMS response time interval) as fixed effects and the trial randomization cluster as random effect.

<sup>‡</sup> Restricted study cohort includes patients with initially successful intraosseous and intravenous access only.

different from those with successful initial intravenous attempts. In contrast, Kawano et al. only included patients with initially successful access and reported lower rates of ROSC, survival to hospital discharge and survival with favorable neurological function in 660 patients receiving intraosseous access.<sup>14</sup> However, the non-contemporary nature of the study period (2007–2009), the lack of time data regarding important resuscitation events such as time of initial access and/or initial drug administration, as well as low overall use of intraosseous access route in their study cohort (~5%) potentially limits the generalizability of their findings.

Our study extends the findings of these prior studies of intraosseous vascular access during acute OHCA resuscitation. First, by analyzing this question in a large, contemporary data set, we were able to look at interactions across several subgroups, increasing the generalizability of our study findings. Second, with use of detailed time data of important resuscitation events, we were further able to establish that these results were not due to differences in times to vascular access or drug administration in the intraosseous group. On the contrary, we found that patients with attempted intraosseous access had marginally faster times to access and drug administration. Third, we examined the association of intraosseous access and survival outcomes in multiple ways—by initial access attempt (irrespective of success) and by successful initial access attempt. The similar findings in the two analyses support the robustness of our conclusion of no difference in survival with initial intraosseous vascular access attempt. Finally, on analyzing our study cohort based on ultimately successful access (initial or subsequent attempt), we observed worse outcomes with successful intraosseous access compared with successful intravenous access (initial or subsequent). However, a third of patients with successful intraosseous access received it after failed initial intravenous attempt leading to significant delays in obtaining access and subsequent drug administration (Supplemental Table 1) potentially contributing to significantly worse outcomes.<sup>23,24</sup> Additionally, failure to obtain initial intravenous access successfully could be secondary to high risk features such as obesity, or other existing comorbidities that may have influenced outcomes irrespective of the type of access subsequently obtained.

Interestingly, in our study, we noted worse outcomes for patients with failed initial access attempt leading to switch to alternative access route (intravenous or intraosseous) compared with patients with successful initial access attempt (intravenous or intraosseous). It is unclear if these worse outcomes are secondary to decreased biological efficacy from the access site ultimately used for drug administration, delays in administration of drugs, or from differences among patients with successful and failed attempts. It is plausible that delays in drug administration may play a role given the existence of prior studies demonstrating worsening survival with every minute delay in epinephrine administration.<sup>23,24</sup> However, given there was no difference in survival outcomes when drugs were administered intraosseous or intravenous in a timely manner in our primary analysis, the worse outcomes in patients with failed initial access attempt are likely secondary to increased drug administration times or unmeasured patient level factors.

Our study has several limitations. First, given the observational design of our study we cannot infer causality regarding the association between intraosseous access and lower rates of sustained ROSC. Second, we did not have information on the site of intraosseous insertion which may affect outcomes given potentially different pharmacokinetic drug profiles administered through different intraosseous sites. Third, we cannot exclude residual confounding, related

to unmeasured high-risk factors that may lead EMS providers to select the intraosseous site. However, we attempted to perform as robust of a comparison as possible between the two arms by conducting propensity-score matching and by stratifying patients based on key prognostic variables in addition to multivariable adjustment. Nevertheless, we lacked patient level variables such as body mass index or comorbidities such as existing cardiovascular disease that could have influenced our study outcomes and would not have been accounted for in our multivariable and propensity score analyses. Fourth, in patients that required switch to alternate access route after failed initial access route attempt, our strategy of attributing outcomes to the initially attempted access dilutes the impact of the access route ultimately obtained on outcomes. However, we performed additional analysis attributing outcomes to the ultimately successful access and present the results of this strategy as a sensitivity analysis. Finally, our findings may not be generalizable to children wherein vascular access can be far more difficult than adults. Nor do our findings suggest that intraosseous access should not be attempted as rescue access if initial attempts at intravenous access are unsuccessful.

---

## Conclusion

In a large, contemporary cohort of OHCA arrest patients, we found that despite marginally faster access and drug administration times, there was no difference in overall survival from OHCA with an initial intraosseous access strategy compared with initial intravenous access. However, intraosseous access was associated with lower rates of sustained ROSC. Future randomized studies are needed to elucidate the optimal route of access for administration of drugs in patients with OHCA.

---

## Funding

Dr. Chan is supported by a grant from National Heart Lung and Blood Institute (1R01HL123980). The sponsor was not involved in the study design, in the collection, analysis and interpretation of data; in the writing of the manuscript; and in the decision to submit the manuscript for publication

---

## Conflicts of interest

None of the authors have any conflicts of interest to disclose

---

## Acknowledgements

We thank the nurse coordinators, research personnel, and especially the paramedic prehospital care providers across the ROC, whose enthusiasm, professionalism, and dedication to advancing patient care and gaining new knowledge to save lives were the foundation for this endeavor.

---

## Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.resuscitation.2018.10.031>.

## REFERENCES

1. Chan PS, McNally B, Tang F, Kellermann A. Recent trends in survival from out-of-hospital cardiac arrest in the United States. *Circulation* 2014;130:1876–82.
2. Hansen CM, Kragholm K, Granger CB, et al. The role of bystanders, first responders, and emergency medical service providers in timely defibrillation and related outcomes after out-of-hospital cardiac arrest: results from a statewide registry. *Resuscitation* 2015;96:303–9.
3. Hasselqvist-Ax I, Riva G, Herlitz J, et al. Early cardiopulmonary resuscitation in out-of-hospital cardiac arrest. *N Engl J Med* 2015;372:2307–15.
4. Wissenberg M, Lippert FK, Folke F, et al. Association of national initiatives to improve cardiac arrest management with rates of bystander intervention and patient survival after out-of-hospital cardiac arrest. *JAMA* 2013;310:1377–84.
5. Link MS, Berkow LC, Kudenchuk PJ, et al. Part 7: adult advanced cardiovascular life support: 2015 American heart association guidelines update for cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation* 2015;132:S444–64.
6. Neumar RW, Otto CW, Link MS, et al. Part 8: adult advanced cardiovascular life support: 2010 American Heart Association Guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation* 2010;122:S729–67.
7. 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.
8. Mader TJ, Kellogg AR, Walterscheid JK, Lodding CC, Sherman LD. A randomized comparison of cardiocerebral and cardiopulmonary resuscitation using a swine model of prolonged ventricular fibrillation. *Resuscitation* 2010;81:596–602.
9. Johnson D, Garcia-Blanco J, Burgert J, et al. Effects of humeral intraosseous versus intravenous epinephrine on pharmacokinetics and return of spontaneous circulation in a porcine cardiac arrest model: a randomized control trial. *Ann Med Surg (Lond)* 2015;4:306–10.
10. Guy J, Haley K, Zuspan SJ. Use of intraosseous infusion in the pediatric trauma patient. *J Pediatr Surg* 1993;28:158–61.
11. Ellemunter H, Simma B, Trawoger R, Maurer H. Intraosseous lines in preterm and full term neonates. *Arch Dis Child Fetal Neonatal Ed* 1999;80:F74–75.
12. Von Hoff DD, Kuhn JG, Burris 3rd HA, Miller LJ. Does intraosseous equal intravenous? A pharmacokinetic study. *Am J Emerg Med* 2008;26:31–8.
13. Feinstein BA, Stubbs BA, Rea T, Kudenchuk PJ. Intraosseous compared to intravenous drug resuscitation in out-of-hospital cardiac arrest. *Resuscitation* 2017;117:91–6.
14. Kawano T, Grunau B, Scheuermeyer FX, et al. Intraosseous vascular access is associated with lower survival and neurologic recovery among patients with out-of-Hospital cardiac arrest. *Ann Emerg Med* 2018;71:588–96.
15. Clemency B, Tanaka K, May P, et al. Intravenous vs. Intraosseous access and return of spontaneous circulation during out of hospital cardiac arrest. *Am J Emerg Med* 2017;35:222–6.
16. Brown SP, Wang H, Aufderheide TP, et al. A randomized trial of continuous versus interrupted chest compressions in out-of-hospital cardiac arrest: rationale for and design of the Resuscitation Outcomes Consortium Continuous Chest Compressions Trial. *Am Heart J* 2015;169:334–41 e335.
17. Nichol G, Leroux B, Wang H, et al. Trial of continuous or interrupted chest compressions during CPR. *N Engl J Med* 2015;373:2203–14.
18. Soholm H, Hassager C, Lippert F, et al. Factors associated with successful resuscitation after out-of-Hospital cardiac arrest and temporal trends in survival and comorbidity. *Ann Emerg Med* 2015;65:523–31 e522.
19. Roth R, Stewart RD, Rogers K, Cannon GM. Out-of-hospital cardiac arrest: factors associated with survival. *Ann Emerg Med* 1984;13:237–43.
20. Austin PC. Optimal caliper widths for propensity-score matching when estimating differences in means and differences in proportions in observational studies. *Pharm Stat* 2011;10:150–61.
21. Austin PC. An introduction to propensity score methods for reducing the effects of confounding in observational studies. *Multivariate Behav Res* 2011;46:399–424.
22. 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.
23. Ewy GA, Bobrow BJ, Chikani V, Sanders AB, Otto CW, Spaite DW, et al. The time dependent association of adrenaline administration and survival from out-of-hospital cardiac arrest. *Resuscitation* 2015;96:180–5.
24. Hansen M, Schmicker RH, Newgard CD, Grunau B, Scheuermeyer F, Cheskes S, et al. Time to epinephrine administration and survival from nonshockable out-of-Hospital cardiac arrest among children and adults. *Circulation* 2018;137:2032–40.