

# Intraosseous versus intravenous access in pre-hospital cardiac arrest: Systematic Review

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Ενδοοστική έναντι ενδοφλέβιας πρόσβασης σε προνοσοκομειακή καρδιακή ανακοπή: Συστηματική ανασκόπηση

Περίληψη στο τέλος του άρθρου

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**Introduction:** Out-of-hospital cardiac arrest is a significant cause of mortality worldwide. The main concern is how to achieve the best outcomes for those patients, and this is a reason why intraosseous infusion has become again an alternative route of infusion in these patients, while its effectiveness is under investigation.

**Objective:** to investigate the efficacy of intraosseous infusion, in contrast to intravenous infusion, in prehospital cardiac arrest events, via a systematic review of literature.

**Material and Methods:** The international literature was searched through MEDLINE database via PubMed online platform, and Scopus database, until the 10th of July 2024. The search was made using the following keywords: «intraosseous», «intravenous», «pre-hospital», «out-of-hospital», «cardiac arrest», and «heart arrest». The inclusion criteria of this study were defined as follows: a) research study (randomized controlled trials, cohort studies, and retrospective studies using data from patient registries), b) Greek or English language, c) non-experimental (conducted on humans), d) adults >18 years old, and e) non-traumatic etiology of cardiac arrest. The manuscript is fully compliant with PRISMA guidelines

**Results:** From the literature search, 63 studies from the PubMed database and 64 from Scopus emerged for further evaluation. The final sample of this systematic review, based on the inclusion criteria, as defined, after the removal of duplicates, was 12 studies. The majority were cohort studies within the region of America. There was considerable heterogeneity in the characteristics of intraosseous and intravenous subgroups, as well as in the definition of «access route» by the researchers. This led to unclear results, with some showing the superiority of the intravenous

route, while others showed non-statistically significant differences in outcomes between the two routes of administration. However, the most recent published results show no statistically significant differences in outcomes, with the only meta-analysis that is published, highlight a possible superiority of intraosseous route of access if time to intervention is considered.

**Conclusions:** Intraosseous infusion in prehospital cardiac arrest appears to show no statistically significant difference, when compared to intravenous infusion, in terms of survival and good neurologic outcome. However, it is deemed necessary for further research, by conducting more studies and ideally, randomized clinical trials.

**Keywords:** *Cardiac arrest, Heart arrest, Intraosseous, Intravenous, Pre-Hospital, Out-of-hospital*

## Introduction

Out of Hospital Cardiac Arrest (OHCA) is a major public health problem, that the scientific community tries to manage in the best possible way, since it is the leading cause of mortality in Europe and the United States of America (USA).<sup>1</sup> According to the American Heart Association (AHA), survival from OHCA mainly relies on the "chain of survival", which is a therapeutic protocol including quick access to emergency care, cardiopulmonary resuscitation (CPR), defibrillation, and advanced care in case return of spontaneous circulation (ROSC) is succeeded.<sup>2</sup> Survival rates range from 2,5% to 10,5%,<sup>3</sup> an interval that is mainly due to modifications in the "chain of survival" among healthcare systems.<sup>2</sup>

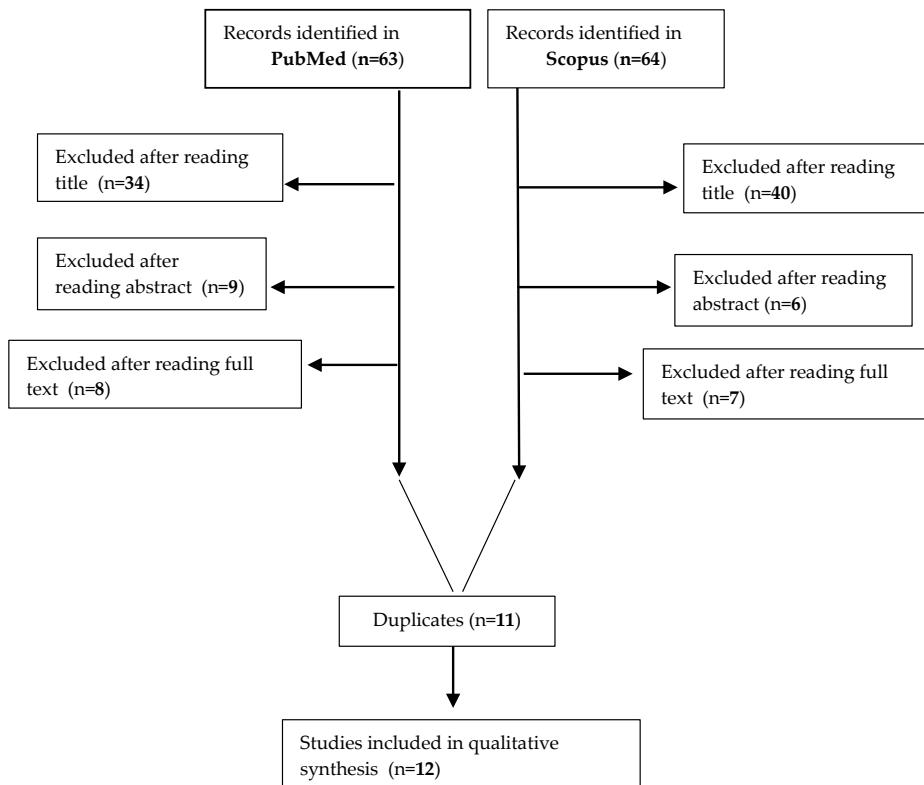
To improve survival rates, rapid activation of emergency care units is necessary and the time until the arrival of an ambulance should be decreased. Also, it is very important to increase the knowledge of CPR in the community, achieve quick access to defibrillation<sup>1</sup> and ensure fast access to the vascular system of the patient.<sup>3</sup> A new aspect that has evolved lately is "life-saving systems", in which smartphone alerting systems (SAS) is included. The use of SAS allows the first responders to notify about a possible OHCA patient, but also see the nearest automatic external defibrillator (AED) which can be used in bystander CPR.<sup>4</sup> The use of such "life-saving systems" is recommended in the 2021 guidelines of the European Resuscitation Council (ERC).<sup>5</sup> The intravenous (IV) route has been used since 1830 for fluid administration in patients who are in need of resuscitation.<sup>6</sup> In several cases, even experienced healthcare workers face difficulties in obtaining an IV line, especially in prehospi-

tal care.<sup>7</sup> In every emergency case, the most important thing for the health providers is knowing that the route of access being used is safe for administrating the necessary fluids/drugs within a reasonable time.<sup>8</sup> Such an example is the intraosseous (IO) route since it's an effective route of vascular access that can be achieved in a minimum period of time and has been used in many countries for prehospital resuscitation efforts, restoring fluid volume, and administrating drugs.

The IO route mainly evolved during World War II, in the 1940's, and it's only a few years since its massive use in prehospital care, as it provides a safe and easy-to-use route of vascular access.<sup>9</sup> It is the best alternative route the healthcare providers have until today for adults in out-of-hospital settings<sup>7</sup> and can also be used by specially trained nurses.<sup>10</sup> The use of the IO route can be expanded in non-urgent cases too as a temporary solution when difficulty in IV placement is faced,<sup>11</sup> since its placement is fast (approximately 1-2 minutes), with high success rates (>80%) even from inexperienced personnel.<sup>12</sup>

Even though IO access has been used for many years, it has rapidly evolved during the last decades, when its use has increased. This implies that devices used nowadays are more technologically advanced, healthcare professionals are better educated, and many cases have been treated via the IO route compared to the past. All these factors may have a key role in the outcomes of patients when treated by the IO route.

Many researchers have published studies related to the issue of this systematic review, most of which are in the last 10 years. Although most of the studies agree that the IO route is a useful alternative in case of difficult IV placement, some highlight that there is no signif-



**Figure 1:** Flow chart

ificant difference between these two routes and others that IO has even better outcomes. This review aimed to add new insights into the effectiveness of IO versus IV access in OHCA by evaluating their impact on critical outcomes like survival, ROSC, and neurological status. Also, it sought to clarify inconsistencies in existing research and determine whether IO access offers superior outcomes, contributing to improved resuscitation strategies in emergency care. Despite the availability of previous systematic reviews and meta-analyses,<sup>13,14</sup> the ongoing debate over the efficacy of IO versus IV vascular access in OHCA served as the main incentive to conduct the current systematic review, with the intent of adding updated information to the existing knowledge asset.

### Materials and Methods

The electronic databases MEDLINE (via PubMed online platform) and Scopus were methodically searched between April and June of 2024. Exclusive articles published until the 10<sup>th</sup> of July were evaluated. The keywords “intraosseous”, “intravenous”, “cardiac arrest”, “heart arrest”, “pre-hospital” and “out-of-hospital” were searched individually and combined. Data was extracted and the

validity was assessed by the writing team. The manuscript is fully compliant with PRISMA guidelines.<sup>15</sup>

Published studies were considered eligible if they were in English or Greek language and included only adults (>18 years old) who suffered from OHCA. Also, cardiac arrest shouldn't have had etiology related to trauma. Any study that did not meet these criteria was excluded from further analysis.

Initially, 63 studies were noticed in the MEDLINE database (via PubMed) and 64 studies in Scopus, with their title and abstract being carefully screened. A total of 74 studies were excluded after reading the title, 15 after reading the abstract and 15 more after reading the full text. When duplicates were excluded, 12 articles met the inclusion criteria of this study and were included in the article. Figure 1 presents the flow chart of the selection of the studies.

### Results

In total, 12 studies were included in the present systematic review. As presented in Table 1, some studies found that the IV route was superior to IO, other studies found non-statistically significant differences, and

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**Table 1.** Main characteristics of the studies & key results

Authors/Year	Country	Type	N	Intervention	Results
Clemency et al./2017 <sup>16</sup>	U.S.A	Retrospective chart review	1.310	IO: N=552 IV: N= 788	<ul style="list-style-type: none"> <li>IV access was used more as first access site (60.1% of the cases)</li> <li>IO access had higher success rates with the first try (94.8% vs 81.6%, <math>p&lt;0.01</math>)</li> <li>Non-statistical significance between two routes of access in ROSC at the time of arrival at ER (IO: 19.9% vs IV: 19.7%, <math>p=0.01</math>)</li> <li>The ROSC was higher when first attempt of vascular access was successful, no matter the route of access (OR=1.92, <math>p=0.02</math>)</li> </ul>
Feinstein et al./2017 <sup>17</sup>	U.S.A.	Retrospective cohort study	1.800	IO: N=275 IV: N=1.525	<ul style="list-style-type: none"> <li>Non-statistical significance in survival to arrival at ER (aOR=0.72, <math>p=0.06</math>) and to hospital discharge (aOR=0.81, <math>p=0.31</math>)</li> <li>ROSC was higher in the IV sub-group (aOR=0.67, <math>p=0.004</math>)</li> </ul>
Kawano et al./2018 <sup>18</sup>	U.S.A., Canada	Retrospective cohort study	13.155	IO: N=660 IV: N=12.495	<ul style="list-style-type: none"> <li>ROSC (aOR=0.66), survival (aOR=0.5) and good neurological outcome (aOR=0.29) were less likely to IO access</li> </ul>
Mody et al./2019 <sup>19</sup>	U.S.A., Canada	Retrospective cohort study	19.731	IO: N=3.068 IV: N=16.663	<ul style="list-style-type: none"> <li>Non-statistical significance in survival (OR=0.88, <math>p=0.24</math>) and good neurologic outcome (OR=0.87, <math>p=0.29</math>) between two routes</li> <li>ROSC rates were higher in IV subgroup (OR=0.8, <math>p&lt;0.001</math>)</li> <li>No matter the route of access, if the first attempt was unsuccessful the results were worse</li> </ul>
Nguyen et al./2019 <sup>20</sup>	U.S.A.	Retrospective cohort study	795	IO: N=342 IV: N=453	<ul style="list-style-type: none"> <li>IO access was associated with lower chances of ROSC (25.7% vs 45.1%, <math>p&lt;0.001</math>) and 26.6% vs 42.4% when time until ambulance arrival was calculated</li> </ul>

Baert et al./2020 <sup>21</sup>	France	Retrospective comparative multicenter study	28.856	IO: N=1.576 IV: N=27.280	<ul style="list-style-type: none"> <li>• IO route was associated with better results in neurological outcomes (85.2% vs 65.7%, p=0.082)</li> <li>• Non-statistical significance in survival at 30-days or at hospital discharge between two routes (IO: 1.8% vs IV: 2.4%, p=0.266)</li> <li>• IO subgroup was less likely to achieve ROSC (19.8% vs 25.3%, p&lt;0.001)</li> <li>• The authors do not discourage the use of intraosseous route, they recommend it</li> </ul>
Daya et al./2020 <sup>22</sup>	U.S.A., Canada	Prespecified analysis of a randomized placebo-controlled clinical trial	3.019	IO: N=661 IV: N=2.358	<ul style="list-style-type: none"> <li>• Amiodarone and lidocaine had better results when administered IV than placebo (survival: p=0.32 and good neurological outcomes: p=0.47)</li> <li>• Non-statistical significance between amiodarone and lidocaine IO administration and placebo</li> </ul>
Zhang et al./2020 <sup>23</sup>	U.S.A., Canada	Retrospective cohort study	35.733	IO: N=7.975 IV: N=27.758	<ul style="list-style-type: none"> <li>• IV seemed to have had better results in survival (aOR=1.43), ROSC (aOR=1.45) and neurological outcomes (aOR=1.8)</li> <li>• When both routes were used, non-statistically significant relationship was found in the studied results</li> </ul>
Hamam et al./2021 <sup>24</sup>	U.S.A.	Retrospective cohort study	6.896	IO: N=2.603 IV: N=4.293	<ul style="list-style-type: none"> <li>• Non-statistical significance in ROSC between two groups (aOR=0.85, p&lt;0.001)</li> <li>• IV subgroup had better results in survival (aOR=0.43, p&lt;0.001) and neurological outcomes (aOR=0.53, p&lt;0.001)</li> </ul>

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### Intraosseous versus intravenous access in pre-hospital cardiac arrest

Monaco et al./2023 <sup>25</sup>	Germany, Austria	Retrospective cohort study	37.106	IO: N=1.363 IV: N=29.688	<ul style="list-style-type: none"> <li>IV access had better results in survival to hospital arrival/24 hours and 30-day/hospital discharge, ROSC and neurological outcomes (<math>p&lt;0.01</math>)</li> </ul>
Nilsson et al./2023 <sup>26</sup>	Denmark	Retrospective cohort study	6.752	IO: N=773 IV: N=5.979	<ul style="list-style-type: none"> <li>IV access had better results in 7,30 and 90-day survival (<math>p=0.001</math>), as well as in ROSC (<math>p&lt;0.001</math>)</li> </ul>
Lee et al./2024 <sup>27</sup>	Taiwan	Retrospective cohort study	2.003	IO: N=401 IV: N=1.602	<ul style="list-style-type: none"> <li>Non-statistical significance in sustained ROSC for over 2 hours (<math>aOR=0.83</math>, <math>p=0.2086</math>) and good neurological outcomes (<math>aOR=0.96</math>, <math>p=0.9356</math>)</li> </ul>

some showed the superiority of IO access in patients' outcomes.

Clemency et al.<sup>16</sup> in their study published in 2017, wanted to evaluate the effect between the route of vascular access and ROSC on OHCA patients when the adrenaline was administered until they arrived at the emergency department. They searched in OHCA patients' database in New York, where annually over 260.000 cases are recorded. The search period was from November 2013 until April 2015. The median age of patients was 59.8 years old (y.o.) in the IO subgroup and 63 in the IV. Also, a higher percentage of men was included in the IV group, but no statistical significance existed in terms of unwitnessed cardiac arrest (CA) or bystander CPR.

Regarding ROSC, no significant difference was observed between the two routes ( $p=0.01$ ) while, regarding adrenaline administration, the IV route was selected as the first choice in 51.5%, with the OR being estimated at 0.86 for the same outcome. Also, another finding of this study was that no matter what the route of vascular access was, if the first attempt was successful the results were better.

In the most recently published study of this review (2024), Lee et al.<sup>27</sup> conducted a cohort study in Taiwan to compare outcomes between IO and IV access in OHCA patients. The study period was from January 1<sup>st</sup>, 2019, to December 31<sup>st</sup>, 2022. Almost 89% of the initial sample met the inclusion criteria. The access point was defined as the final route of access that patients were treated. In

the IV group, there were more male patients, with higher rates of witnessed arrest, but also more time for ambulance arrival. The results as presented show non-statistically significant differences in any studied outcome (ROSC and good neurologic condition).

Lee's study also analyzed the spots where IO and IV access were placed. The IO group was divided into tibial and humerus subgroups, while IV subgroups were upper and lower limb. Humerus IO access seemed to have 4.2% more chances for successful ROSC than tibial, while tibial access was more effective than upper limb IV placement (21.1% vs 20.7%) in ROSC. Regarding neurological condition, the humerus had better results than tibial access (2.6% vs 0.8%), while non-statistically significant differences were observed in humerus to upper IV comparison (2.6% vs 2.7%).

In 2018, Kawano et al.<sup>18</sup> published the results of their study, conducted from June 2007 to November 2009, when data were collected from OHCA patient databases in the U.S.A. and Canada. Patients whose access to their vascular system was impossible or it was accessed both intraosseously and intravenously were excluded from further analysis. Also, if successful access to IO or IV space was after failed attempts on the other route, these patients were excluded too.

In total, 75.4% of the cases identified in the beginning of the study met the inclusion criteria. The intraosseous route was used in 5% of the patients, while the remaining 95% were treated via the IV route. In the IO subgroup the proportions of unwitnessed CA and initial

non-shockable rhythms were higher, while the time to arrival of the paramedics was shorter. From 660 patients of the IO group, 158 achieved ROSC (23.9%), 25 survived to hospital discharge (3.8%) and 10 had good neurologic outcomes (1.5%), while the same percentages in IV group were 38.3% (4.783 patients), 10.3% (1.287 patients) and 7.6% (945 patients) respectively.

Nguyen et al.<sup>20</sup> in 2019 conducted a retrospective cohort study to find the most effective way of vascular access to administrate drugs in OHCA patients. Data was collected from Florida's OHCA database from January 2013 to December 2017. It is important to mention that for any patient treated from both IO and IV routes, the data included in the study refers to the first access point. The two groups had similar characteristics in terms of age, sex, time to ambulance arrival, and initial percent of shockable rhythms. The results of this study show that the intravenous route seems to have better outcomes regarding ROSC, no matter if time to ambulance arrival was estimated or not.

Daya et al.<sup>22</sup> in 2020, conducted a secondary analysis of a Randomized Controlled Trial (RCT) to see if the route of administrating drugs (amiodarone and lidocaine) affects the outcomes of the patients. The RCT's data were from 2012 until 2015. Every group (IO and IV) was divided into 3 subgroups. One that administered amiodarone, one with lidocaine, and one with a placebo was used. The results of this study show that the two antiarrhythmic drugs have a better effect on patients' outcomes when delivered via the IV route than placebo, but there is no statistical significance when administered intraosseously.

Zhang et al.<sup>23</sup> in the last study of 2020 had the objective to investigate any difference in patients' results when adrenaline is administered intravenously and intraosseously, in prehospital cardiac arrest. For this purpose, they conducted a retrospective cohort study, using data from U.S.A. and Canadian databases from April 1<sup>st</sup>, 2011, until June 30<sup>th</sup>, 2015. Patients over 89 y.o., with the route of access being unclear or both routes being used in resuscitation efforts, were excluded.

In the IV group there were more male patients, with higher median age than the IO group and higher rates of witnessed arrest and initial shockable rhythm. In the adjusted analysis of the data, IV access seemed to have better outcomes for the patients in every studied outcome. Writers conclude that adrenaline administration via the IV route is superior to the IO route, but from further analysis that they did, the use of both routes simul-

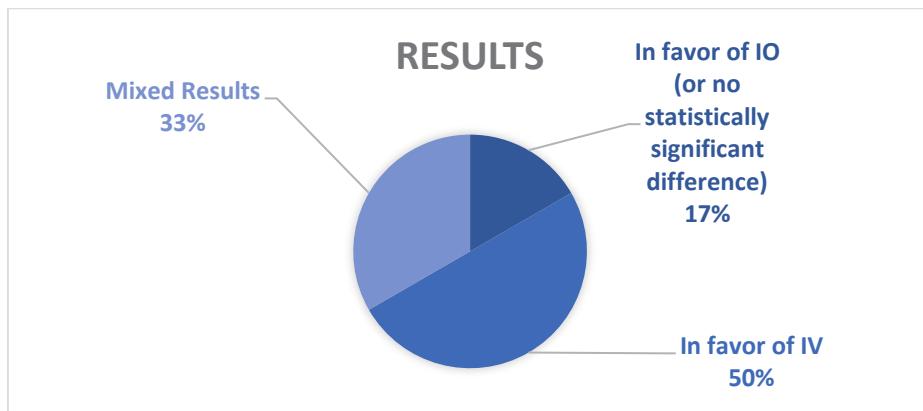
taneously did not have statistically significant difference in patients' outcomes.

A retrospective cohort study published its results in 2023, with study areas in Germany and Austria, conducted by Monaco et al.<sup>25</sup> The data presented refers to a time frame from 1989 to 2020 and were extracted from OHCA patient databases in these countries. Only 17.48% of the initial population met the inclusion criteria. The final sample was divided into four subgroups as follows: 1) IO group (1.363 patients), 2) IV group (29.688 patients), 3) IO followed by IV access group (4.827 patients) and 4) endotracheal followed by IV access group (276). In the 1<sup>st</sup> subgroup when compared to the 2<sup>nd</sup>, the median age was lower, but there were also lower rates in initial shockable rhythms, cardiac etiology arrest and witnessed arrest. The results of the study showed that IV access seems to have better upshots for the patients in every studied outcome ( $p<0.001$ ).

Nilsson et al.<sup>26</sup> in their cohort study (2023) in Denmark, tried to find which route (IO or IV) has better outcomes for OHCA patients. The study period was from January 1<sup>st</sup>, 2016, to December 31<sup>st</sup>, 2020. No clear inclusion criteria are mentioned, but cases that achieved ROSC before the paramedics arrived or the data presented were insufficient and excluded. The intraosseous group seemed to have worse results in every studied outcome, with mortality at 30-days aOR=2.02 ( $p=0.001$ ), no-ROSC aOR=1.51 ( $p<0.001$ ), mortality at 7-days aOR=1.94 ( $p=0.001$ ) and mortality at 90-days aOR=2.29 ( $p=0.001$ ). The only outcome that did not have a statistically significant difference was the "dead at scene" declaration, with aOR=1.28 ( $p=0.001$ ) in favor of IV access. In the results of this study, authors acknowledge the existence of confounding factors (such as unwitnessed arrests or initial shockable rhythms) that could alter the results of their study.

In the same year as Clemency, Feinstein et al.<sup>17</sup> published their study. In their cohort study, they focused on Washington DC, and more specifically on King's County. The data were collected between September 1<sup>st</sup>, 2012, and December 31<sup>st</sup>, 2014, from the local OHCA database. For the purpose of their study, the main route of access was designated as the one that was used for drug administration.

In the subgroup of IO access, there were more female patients, and it was more common for unwitnessed CA, non-cardiac etiology and non-shockable initial rhythm. Also, the time to ambulance arrival was significantly higher in IO group, with a median time at 18.4 minutes



**Graph 1:** Studies Results in chart pie

versus 16.3 minutes for IV group. In the analysis of the data, survival to hospital discharge and to arrival at emergency room didn't have statistically significant differences., but ROSC was more likely to sustain in the IV group.

Mody et al.<sup>19</sup> in their cohort study (2019) had as objective to compare results in prehospital cardiac arrest when IO and IV route are used. For the purposes of their study, they searched in OHCA patients' databases in the U.S.A. and Canada from 2011 to 2015. In IO group were added only patients that initially treated via this route and the first access attempt was successful. The same applies to the IV group.

The IO subgroup had higher success rates (96.9%) than the IV group (92.9%). In IO group the median age was lower, there were more women and unwitnessed cardiac arrest with initial non-shockable rhythm had a higher percentage than in IV subgroup, while bystander CPR was lower. Despite the existence of these confounding factors, the results of this study conclude that there is no statistically significant difference in terms of survival to hospital discharge and good neurologic condition at that time, even though ROSC is a little bit lower in this subgroup. The authors state that from their research time to achieve IO access is significantly lower than IV access and that if the first attempt isn't successful the outcomes are worse no matter the route of access.

One of the first studies that was conducted beyond the borders of the United States was the one from Baert et al.<sup>21</sup> in 2020. The study region was France and the national OHCA database was searched from July 1<sup>st</sup>, 2011, until June 1<sup>st</sup>, 2017. In the IO subgroup (5.5% of the studied population) the median age was lower, there were

more women, and the number of non-cardiac etiology arrests was higher, so the percentage of unwitnessed CA and bystander CPR.

The IO access in the initial results was found to have worse results in ROSC (19.7% vs 27.7%) and survival at 30 days or discharge (1.9% vs 3.8%), but better outcomes in good neurologic condition at discharge (81.8% vs 72.7%). In the adjusted analysis, the IO route continued to have worse outcomes in ROSC, but there were non-statistically significant differences in survival at 30 days, or hospital discharge and neurological outcomes continued to be better in this group.

In the last study of the current systematic review, Hamam et al.<sup>24</sup> in 2021 published another cohort study related to the topic. They searched OHCA databases from U.S.A. paramedic services from January 1<sup>st</sup>, 2015, to December 31<sup>st</sup>, 2017. In the intraosseous subgroup, the median age was lower, there was a higher proportion of female patients and unwitnessed cardiac arrests with initial non-shockable rhythm were higher too. The results of the adjusted analysis that was conducted, in which time to ambulance arrival was included, a non-statistically significant difference was found in terms of ROSC, but the IV subgroup had better outcomes in survival to hospital discharge and good neurological condition at the time of discharge.

## Discussion

This systematic review was conducted to investigate potential differences in key patient outcomes-survival, return of spontaneous circulation (ROSC), and neurological status when IO versus IV routes is used in OHCA. A total of 12 studies met the inclusion criteria of the re-

view, providing a comprehensive analysis of these critical outcomes.

Some studies showed the superiority of IV route in survival, ROSC and good neurologic condition,<sup>18,20,22,23,25,26</sup> others showed non-statistical significance between two routes in some of the studied outcomes,<sup>17,19,24</sup> while others in every outcome mentioned.<sup>16,27</sup> There was also one study with mixed results, that showed non-statistical significance in some outcomes and superiority in one outcome for IO and one for IV access.<sup>21</sup>

From the literature review as conducted, no RCT was found, only a secondary analysis of randomized controlled trials,<sup>18,22</sup> in which the authors recognize the existence of error, due to secondary research. The results of these studies showed better outcomes in ROSC, survival, and neurologic condition at discharge when the IV route was used, something that is in contrast with Lee's study<sup>27</sup> that no statistically significant differences were observed in ROSC and neurologic outcomes of the patients.

A major factor that heterogeneity could be attributed to is differences in the definition of "route of access" between the studies. For example, in Feinstein's study,<sup>17</sup> IO group consisted of those who were the final route of administration, while in Mody's study<sup>19</sup> in the IO group included those who were the first choice of access. This is recognized as a significant confounding factor by Granfeldt et al.<sup>13</sup> in their systematic review published in 2020. It is reasonable to think that when IO follows IV failed attempts, the victim has remained in an arrest state for a longer period, with the results being worse. It is bibliographically documented that the more a victim is in arrest state, the worse the outcomes are,<sup>28</sup> so it is not easy to be attributed to the route selected. This is also stated in Nguyen's study,<sup>20</sup> that since the criteria of route selection aren't clear, it is a logical assumption that the ones with difficult IV access may have a worse health status, with more comorbidities, affecting results as an independent factor.

Also, as presented in Table 1, most of the studies refer to data until 2015, with only two of them,<sup>24,27</sup> including exclusive data from 2015 and later. Both two studies showed non-statistically significant differences in ROSC, with Lee's study<sup>27</sup> finding the same for neurologic conditions too. These differences could be because these studies include data that comply with the most recent resuscitation guidelines and IO devices, as long as the fact that IO access has been used again in clinical practice for only the last 20 years.

Another important factor is that none of the studies except Lee's refer to access points. Selection of tibial bone in the IO route might have worse results than humerus bone if taken into consideration the fact that tibia is further away from central circulation than humerus. This is supported by Lee's study, in which IO access via the humerus has 4.2% more chances for ROSC than via tibial bone.

Also, Lee's study is the only one that refers to ambulance staffing, providing data about the median number of paramedics and EMTs (emergency medical technicians). As mentioned in their study, the number of ambulance staff seems to have a role in route selection, with paramedics being less than 2 favoring IV access (aOR 0.17), EMTs being more than 4 favoring IV access too (aOR 0.84), but when EMTs are less than 4, it is in favor of IO access (aOR 1.33). This would be interesting information to be included in the most recent studies published.

Another significant factor that may affect the way results are interpreted is the percentage of included cases, in contrast to the initial number of cases that appeared in database research. The lower this rate is, the higher the chances are for the study to contain significant errors. The studies with the lowest rate are those of Monaco et al. (17.48%) in 2023<sup>25</sup> and Nilsson's et al. (39.1%) in 2023 too.<sup>26</sup> Both studies showed the superiority of the IV route administration in every studied outcome. The study with the highest rate was Lee's et al. (89.9%) in 2024,<sup>27</sup> in which IO had non-statistically significant differences in all studied outcomes.

Results from Hsieh's et al.<sup>14</sup> the only published meta-analysis (2021), showed no significant differences between the two routes in survival to discharge and the neurologic condition of the patients. They found "time to drug administration" to be a significant confounding factor, which is not mentioned in all studies presented in the current review. Also, it is stated that the definition of "route of access" has a key role in results and their interpretation. Finally, if the time to intervention is taken into consideration, the patient's outcomes could be in favor of the IO route, as mentioned in this meta-analysis.

To our knowledge, there are only two more systematic reviews relative to the topic published,<sup>13,14</sup> one of them with a meta-analysis to have been conducted.<sup>14</sup> Our systematic review includes 6 more published studies than Granfeldt et al.,<sup>13</sup> and 4 more than Hsieh et al.,<sup>14</sup> thus presenting the most recent data regarding the studied topic. However, our study has several

limitations worth mentioning. The writing language of the searched studies was Greek and English, leading to miss any study written in other language and, the studied period was until June 30<sup>th</sup>, 2024, so any study published later than this date was not included. Furthermore, there was no RCT (randomized controlled trial), since none was published in the studied period. The time for ambulance arrival, the ambulance staffing, and team equipment were not mentioned in all included studies, thus we could not conclude. However, on October 31<sup>st</sup>, the first RCT related to this topic was published in NEJM (The New England Journal of Medicine),<sup>29</sup> with the results stating no statistically significant difference in OHCA patients' outcomes when the IO and IV routes were compared.

One more limitation is the amount of detail about the training and expertise of the Prehospital teams included in the referenced studies. This potential confounder relates to the level of experience and proficiency among emergency responders, which may affect the selection of the vascular access option and, subsequently, patient outcomes. More advanced teams may find greater success with a particular technique, not because the technique itself is inherently more effective, but because they are simply better at getting the technique to work for them. Also, in our attempt to achieve a PROSPERO ID for our study, this was not possible, since our study was completed at that time and since 2019 PROSPERO does not accept completed systematic reviews.

### Conclusions

The intraosseous route is documented as a safe and effective way to access the vascular system of OHCA patients, with less time than IV placement needed and higher success rates. In the last few years, the use of IO access has increased. This systematic review clearly shows that intraosseous access does not appear to have statistically significant differences in terms of survival, ROSC, and neurologic outcomes of OHCA victims, thus recommending its use in emergency cases.

Future research should examine variables such as ambulance response time, staffing levels, available equipment, team skills levels, and success rates of procedures since they significantly influence outcomes in out-of-hospital cardiac arrest settings. Moreover, including recent evidence like the RCT by Vallentin et al.,<sup>29</sup> while other factors can also be quite influential in future evaluations will be very beneficial for a better insight into the comparative effectiveness among the intraosseous as well as intravenous route. Finally, this highlights the urgent need for further randomized controlled trials to adequately inform whether IO access is at least as good or even better than IV access in the context of prehospital resuscitation.

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## ΠΕΡΙΛΗΨΗ

**Ενδοοστική έναντι ενδοφλέβιας πρόσβασης σε προνοσοκομειακή καρδιακή ανακοπή: Συστηματική ανασκόπηση**

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**Εισαγωγή:** Η καρδιακή ανακοπή που λαμβάνει χώρα εκτός νοσοκομειακών δομών, είναι μια σημαντική αιτία θνητότητας σε παγκόσμιο επίπεδο. Βασικό μέλημα είναι οι βέλτιστες δυνατές εκβάσεις των ασθενών αυτών, με την ενδοοστική έγχυση να έχει επανέλθει τα τελευταία χρόνια στο προσκήνιο, για χρήση σε προνοσοκομειακή καρδιακή ανακοπή, με την αποτελεσματικότητα της να είναι υπό διερεύνηση. **Σκοπός:** Η διερεύνηση μέσω συστηματικής ανασκόπησης της αποτελεσματικότητας της ενδοοστικής προσπέλασης, σε σύγκριση με την ενδοφλέβια, σε συμβάματα προνοσοκομειακής καρδιακής ανακοπής. **Υλικό και Μέθοδος:** Έγινε αναζήτηση της διεθνούς βιβλιογραφίας στις βάσεις δεδομένων PubMed και Scopus ως τις 10 Ιουλίου 2024. Η αναζήτηση έγινε με τις εξής λέξεις-κλειδιά: «intraosseous», «intravenous», «pre-hospital», «out-of-hospital», «cardiac arrest», «heart arrest». Τα κριτήρια ένταξης στη μελέτη ορίστηκαν ως εξής: α) ερευνητική μελέτη, β) γλώσσα συγγραφής ελληνικά ή αγγλικά, γ) μη πειραματική (διεξαγωγή σε ανθρώπους), δ) ενήλικες >18 ετών, ε) καρδιακή ανακοπή μη τραυματικής αιτιολογίας. Όσες μελέτες δεν πληρούσαν τα ανωτέρω κριτήρια, αποκλείστηκαν από περαιτέρω αξιολόγηση. **Αποτελέσματα:** Από την αναζήτηση της βιβλιογραφίας προέκυψαν προς αξιολόγηση 63 μελέτες από τη βάση δεδομένων PubMed και 64 από τη Scopus. Το τελικό δείγμα 65 της παρούσας ανασκόπησης με βάση τα κριτήρια ένταξης, όπως αυτά ορίστηκαν, έπειτα από αφαίρεση των διπλότυπων άρθρων, ήταν 12 μελέτες. Στην πλειοψηφία τους επρόκειτο για μελέτες κοόρτης, με τον πληθυσμό να βρίσκεται εντός της ηπείρου της Αμερικής. Υπήρχε σημαντική ανομοιογένεια ως προς τα χαρακτηριστικά των ομάδων της ενδοοστικής και ενδοφλέβιας προσπέλασης, καθώς και στον ορισμό της «οδού προσπέλασης» από τις ερευνητικές ομάδες. Αυτό οδήγησε σε ανομοιογενή αποτελέσματα μεταξύ τους, με ορισμένες να δείχνουν υπεροχή της ενδοφλέβιας οδού και άλλες μη στατιστικά σημαντικές διαφορές ως προς τις εκβάσεις μεταξύ των δύο οδών χορήγησης. Τα πλέον πρόσφατα δημοσιευμένα αποτελέσματα ωστόσο, δεν δείχνουν στατιστικά σημαντική διαφορά, με μετα-ανάλυση να τονίζει πιθανή υπεροχή της ενδοοστικής εάν συνυπολογιστεί ο χρόνος ως την παρέμβαση. **Συμπεράσματα:** Η ενδοοστική έγχυση σε προνοσοκομειακή καρδιακή ανακοπή φαίνεται να μην παρουσιάζει στατιστικά σημαντική διαφορά με την ενδοφλέβια, ως προς την επιβίωση και την καλή νευρολογική έκβαση. Ωστόσο, κρίνεται αναγκαία η περαιτέρω διερεύνηση του θέματος με διεξαγωγή περισσότερων μελετών και ιδανικά, τυχαιοποιημένων κλινικών δοκιμών.

**Λέξεις-κλειδιά:** Καρδιακή ανακοπή, Προνοσοκομειακή, Εξωνοσοκομειακή, Ενδοοστική, Ενδοφλέβια, έγχυση.

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## ΣΥΣΤΗΜΑΤΙΚΗ ΑΝΑΣΚΟΠΗΣΗ - SYSTEMATIC REVIEW

### Intraosseous versus intravenous access in pre-hospital cardiac arrest

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