

Decision Letter (JCQ-2025-0007)**From:****To:****CC:****BCC:****Subject:** Journal of Clinical Question - Decision on Manuscript ID JCQ-2025-0007**Body:** 05-Apr-2025

Dear Dr Zeng,

Manuscript ID JCQ-2025-0007 entitled "Intraosseous Versus Intravenous Drug Administration in Out-of-Hospital Cardiac Arrest: A Systematic Review and Meta-Analysis of Randomized Controlled Studies" which you submitted to the Journal of Clinical Question, has been reviewed. The comments of the reviewer(s) are included at the bottom of this letter.

The reviewer(s) have recommended publication, but also suggest some revisions to your manuscript. Therefore, I invite you to respond to the reviewer(s)' comments and revise your manuscript.

To submit your revised manuscript, follow the below steps.

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You will be unable to make your revisions on the originally submitted version of the manuscript. Instead, revise your manuscript using a word processing program and save it on your computer. Please also highlight the changes to your manuscript within the document by using the track changes mode in MS Word or by using bold or colored text.

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When submitting your revised manuscript, you will be able to respond to the comments made by the reviewer(s) in the space provided. You can use this space to document any changes you make to the original manuscript. In order to expedite the processing of the revised manuscript, please be as specific as possible in your response to the reviewer(s).

IMPORTANT: Your original files are available to you when you upload your revised manuscript. Please delete any redundant files before completing the submission.

Because we are trying to facilitate timely publication of manuscripts submitted to the Journal of Clinical Question, your revised manuscript should be uploaded as soon as possible. If it is not possible for you to submit your revision in a reasonable amount of time, we may have to consider your paper as a new submission.

Once again, thank you for submitting your manuscript to the Journal of Clinical Question and I look forward to receiving your revision.

Sincerely,
Professor EIC JCQ
Editor in Chief, Journal of Clinical Question
jqeic@gleampub.com

[Editor's Comments]
Associate Editor
Comments to the Author:
(There are no comments.)

[Reviewer(s)' Comments]
Reviewer: 1

Comments to the Author
Thank you for submitting this review.

Unfortunately, this review is fundamentally flawed.
The critical problem is that you have included two studies which did not meet your eligibility criteria. Vallentin 2021 was a randomised controlled trial which randomised patients to receive either calcium or placebo (it did not randomise the route of administration). Daya 2020 is a secondary analysis of the ALPS randomised controlled trial which randomised patients to amiodarone, lidocaine or placebo (it did not randomise route of administration). On this basis, all the analyses are incorrect and invalid.

The authors cite a recent systematic review (Couper et al- reference 19), but make no attempt to explain what this review adds to the literature.

The authors uploaded a review registration to OSF, but this was uploaded 15 days after the search (10th Feb v 25th Feb).

I could not see the full search strategy- lines 115-119 refer to some search terms, but this is obviously too superficial to be the full search strategy.

At several points, the authors suggest that IO access is quicker than IV without providing any supporting evidence. This is wrong- the three recent RCTs showed consistently that IO was not quicker than IV.

Reviewer: 2

Comments to the Author
Title: Intraosseous Versus Intravenous Drug Administration in Out-of-Hospital Cardiac Arrest: A Systematic Review and Meta-Analysis of Randomized Controlled Studies

The present study is trying to give a synoptic appraisal of the existing literature on drug administration during out-of-hospital cardiac arrest with respect to differences in clinical outcomes between intravenous and intraosseous application. The study is approaching this question by means of a systematic literature review, identifying 5 randomized controlled trials (RCTs) for further analysis. The authors document the methodological approach and the main findings in great detail, but there remain several major and minor aspects to clarify or adjust in order to improve the overall quality of the study.

Major points:

- In 2020, Granfeldt et al. published a systematic review in Resuscitation covering virtually the same research question: Granfeldt et al., "Intravenous vs. intraosseous administration of drugs during cardiac arrest: A systematic review", Resuscitation 2020, DOI: 10.1016/j.resuscitation.2020.02.025 [reference 29 of the present manuscript]. Granfeldt et al. included 10 observational studies and RCTs, only one of which has also been identified in the present study (Daya et al., Circulation, 2020) What is the substantial addition provided by the present review? Does it confirm, contradict or otherwise contribute to the findings of Granfeldt et al.? Why aren't all publications or at least all RCTs identified by Granfeldt et al. also included in the present study?

- The scope of the present seems too wide in two crucial ways:

- 1) It does not consider types of medications (namely catecholamines vs. antiarrhythmic drugs) when comparing access types. Due to the vastly differing half-life of different drugs, the different plasma times achievable through different access types might be highly relevant or rather negligible, making a pooled analysis questionable. Generally speaking, different drugs used during cardiopulmonary resuscitation show vastly differing pharmacodynamics and pharmacokinetics. Both could be substantially altered by different access routes in some drugs but not in others.
- 2) It does not differentiate between the locations of IO access (humeral, tibial, sternal). Due to differing plasma times and flow capacity of different IO sites, a pooled analysis potentially obscures clinically relevant benefits or risks behind the group average. While the differentiation between humeral and tibial intraosseous access locations might not be of equal importance for all resuscitative drugs, please also address the drugs implicitly underlying the comparisons, not only the access types as such.

Please explain why a meta-analysis pooling both drug type and IO access location from multiple studies seems worthwhile in terms of teasing out subtle differences of OHCA outcome beyond the established findings in the existing literature.

Please also discuss the relevance of the specific drugs for the comparison of access types.

Minor points:

- P4, line 72ff: "...advanced interventions such as supraglottic airways and endotracheal intubation, with recent evidence supporting the efficacy of supraglottic devices." The emphasis on "the efficacy of supraglottic" devices raises the question, of the relative efficacy compared to endotracheal airways. Do the authors want to merely mention an existing yet inferior alternative, do they want to claim non-inferiority or do they want to imply superiority of the supraglottic airway during OHCA? Please clarify the intended meaning.
- P5, line 90ff: "Another randomized trial reported...[18,19]" Please specify whether the trial cited is reference [18] or [19]. Please note that both 18 and 19 don't seem to fit the quote. [18] did not randomize for vascular access but for continuous vs. interrupted chest compressions. [19] is a meta study, not an RCT.
- P5, line 98ff: "These findings may influence emergency medical services (EMS) protocols" Reviews and pooled analyses are scientifically relevant and can be insightful. Yet one should in principle be very careful with direct practice changing recommendations. The study design is not equipped to yield such strong levels of evidence that EMS protocols should be amended based on its results.
- P8, line 131: Would it be possible to specify the access location for the IO group, presumably tibial or humeral?
- P9, line 148: "We also assessed the type of vasopressor used." Were any vasopressors other than adrenaline used in any of the included RCTs? Are the results of this subgroup analyses reported?
- P12, line 212: "reinforcing IV access as the preferred route due to its potential advantages in drug efficacy and pharmacokinetics" Please elaborate on these IV advantages in terms of efficacy and pharmacokinetics, especially since the final conclusion will again mention pharmacokinetic advantages of IV access as one of the study's central findings in P14, line 256.
- P12, line 216: "The consistency of these findings with previous studies underscores the ongoing debate" Wouldn't consistency across multiple studies rather settle a debate instead of invigorating it?
- Table 1: Please specify if "CPR" means "bystander CPR" before arrival of EMS personnel or any chest compressions at all. Is there a reason, the studies are abbreviated by the main author without reference to colleagues? Why e.g. "Couper 2025" instead of "Couper et al. 2025"? This applies to the majority of figures and tables.
- Table 2. Please make specify within the table whether the respective odd's ratios, while not significant, would favor the IO or the IV access.
- Figures 1–3 and S2–S3: Please clarify which side of the forest plots favors IO and which IV.
- Figure S1: There seem to be reports, records and studies included and excluded. Eventually there are 5 studies and 5 reports being included, yielding seemingly the inclusion of 10 publications which does not match the text body of the manuscript. Please use uniform language and revise the chart.
- Figures S5–S7: Please add explanatory caption and figure legend for data points.

Date Sent: 05-Apr-2025

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Author's Response to Decision Letter for (JCQ-2025-0007)**Intraosseous Versus Intravenous Drug Administration in Out-of-Hospital Cardiac Arrest: A Systematic Review and Meta-Analysis of Randomized Controlled Studies**

Response Letter

Dear Reviewers,
We would like to thank the reviewers for their valuable and constructive comments, which have greatly helped improve the quality of our manuscript. Below are our detailed responses to each comment, with corresponding revisions made in the manuscript.

Reviewer: 1

Comments1: Thank you for submitting this review. Unfortunately, this review is fundamentally flawed. The critical problem is that you have included two studies which did not meet your eligibility criteria. Vallentin 2021 was a randomised controlled trial which randomised patients to receive either calcium or placebo (it did not randomise the route of administration). Daya 2020 is a secondary analysis of the ALPS randomised controlled trial which randomised patients to amiodarone, lidocaine or placebo (it did not randomise route of administration). On this basis, all the analyses are incorrect and invalid.

Response: Thank you for your insightful comment. We acknowledge that the studies by Vallentin (2021) and Daya (2020) did not randomize patients based on the route of administration. These trials were primarily designed to compare specific medications with placebo in the context of OHCA. However, both studies provided subgroup analyses that identified differences between IO and IV administration.

As the reviewer rightly pointed out, it is essential to prioritize data derived from studies with direct comparisons between IO and IV routes. Nevertheless, we believe that incorporating all available evidence, including data from subgroup analyses, can enhance clinical decision-making. To address the differences in study design, we conducted subgroup analyses by separating studies into direct and indirect comparison groups for each outcome. During the peer-review process, we also included another relevant RCT by Nolan (2020), which also involved an indirect comparison between IO and IV administration.¹

Comment 2: The authors cite a recent systematic review (Couper et al- reference 19), but make no attempt to explain what this review adds to the literature.

Response: Thank you for pointing this out. We agree that the original manuscript did not sufficiently clarify the unique contribution of our review to the existing literature. We have added contents in the manuscript as follows page 5, line 95-98: "Several meta-analyses have been conducted comparing IO and IV administration using direct study designs.^{2,3} However, subgroup analyses from previous RCTs comparing IO and IV routes have also provided valuable insights into the differences in their effectiveness."

Comment 3: The authors uploaded a review registration to OSF 15 days after the search (10th Feb v 25th Feb).

Response : Thank you for your observation. It is correct that the review registration on OSF was completed 15 days after the initial literature search. We initially attempted to register the meta-analysis in PROSPERO but later realized that the registration was unsuccessful. As a result, we subsequently registered the protocol with OSF after the literature search.

We acknowledge that registration should precede or coincide with the start of the review process to ensure methodological transparency. However, we confirm that the review protocol—including eligibility criteria, outcomes of interest, and planned methods of analysis—was fully developed before the search and remained unchanged throughout the study. The delayed registration was purely administrative and did not influence the conduct or outcomes of the review.

Comment 4: I could not see the full search strategy- lines 115-119 refer to some search terms, but this is obviously too superficial to be the full search strategy.

Response: Thank you for your valuable comment. We apologize for the insufficient detail provided in the original manuscript. As you correctly pointed out, the content in lines 115–119 offered only a brief summary of the search terms and did not reflect the full search strategy. In response, we have now included the complete search strategies for all databases in Table S1 (Page 2 in Supplementary information). These details encompass all search terms, databases and results.

Comment 5: At several points, the authors suggest that IO access is quicker than IV without providing any supporting evidence. This is wrong- the three recent RCTs showed consistently that IO was not faster than IV.

Response: Thank you for pointing out this critical issue. We acknowledge that our previous expression was inaccurate. Accordingly, we have revised the manuscript to remove content suggesting that IO access is quicker and updated the discussion to accurately reflect the current evidence (page 13, lines 244- 247).

This correction helps ensure that our discussion remains evidence-based and balanced. Thank you again for your careful review.

Reviewer: 2

Major Comment 1: In 2020, Granfeldt et al. published a systematic review in Resuscitation covering virtually the same research question: Granfeldt et al., "Intravenous vs. intraosseous administration of drugs during cardiac arrest: A systematic review", Resuscitation 2020, DOI: 10.1016/j.resuscitation. 2020.02.025 [reference 29 of the present manuscript]. Granfeldt et al. included 10 observational studies and RCTs, only one of which has also been identified in the present study (Daya et al., Circulation, 2020) What is the substantial addition provided by the present review? Does it confirm, contradict or otherwise contribute to the findings of Granfeldt et al.? Why aren't all publications, or at least all RCTs identified by Granfeldt et al., also included in the present study?

Response: Thank you for your valuable comment. We appreciate you highlighting the work by Granfeldt et al. (2020), which indeed addressed a similar research question by reviewing both RCTs and observational studies comparing IV and IO administration during cardiac arrest.

In preparing our review, we re-examined the five RCTs cited in Granfeldt et al.'s study. Upon review, we found that only two of those trials conducted subgroup analyses that directly compared IO and IV routes. One of these, Daya et al. (2020), was already included in our original analysis.⁴ However, we initially overlooked the other relevant RCT—Nolan et al. (2020).¹ We have incorporated this study into our review and updated the data and corresponding analyses throughout the manuscript accordingly.

Major Comment 2: The scope of the present seems too wide in two crucial ways: It does not consider types of medications (namely catecholamines vs. antiarrhythmic drugs) when comparing access types. Due to the vastly differing half-life of different drugs, the different plasma times achievable through different access types might be highly relevant or rather negligible, making a pooled analysis questionable. Generally speaking, different drugs used during cardiopulmonary resuscitation show vastly differing pharmacodynamics and pharmacokinetics. Both could be substantially altered by different access routes in some drugs but not in others.

Response: Thank you for your thoughtful and important comment. We agree that pharmacokinetic and pharmacodynamic differences between drug classes, such as catecholamines and antiarrhythmic agents, may influence the relevance of access routes during cardiopulmonary resuscitation. However, the scope of our analysis was limited by the available evidence.

Three of the six randomized controlled trials in our final analysis directly compared IO and IV access without specifying the medications used. The remaining three studies conducted subgroup analyses by access route. Two were summarized in the meta-analysis by Granfeldt et al. (2020),⁵ and the third one, Vallentin et al. (2021),⁶ investigated calcium versus saline administration, which could not be pooled with the others due to its different intervention focus. We could not conduct meaningful subgroup analyses by drug class because of the limited number of studies and the lack of consistent or detailed reporting on specific medications across trials.

We added content in the discussion section as follows (page 14, line 262-267): "Furthermore, although drug classes commonly used during cardiopulmonary resuscitation, such as catecholamines and antiarrhythmic agents, have distinct pharmacokinetic and pharmacodynamic profiles, our analysis was constrained by the available evidence. Three RCTs directly comparing IV and IO administration did not specify the medications used, while the remaining studies either lacked consistent reporting or involved non-standard interventions. Consequently, subgroup analyses based on drug class were not feasible."

Major Comment 3: It does not differentiate between the locations of IO access (humeral, tibial, sternal). Due to differing plasma times and flow capacity of different IO sites, a pooled analysis potentially obscures clinically relevant benefits or risks behind the group average. While the differentiation between humeral and tibial intraosseous access locations might not be of equal importance for all resuscitative drugs, please also address the drugs implicitly underlying the comparisons, not only the access types as such.

Please explain why a meta-analysis pooling both drug type and IO access location from multiple studies seems worthwhile in terms of teasing out subtle differences of OHCA outcome beyond the established findings in the existing literature. Please also discuss the relevance of the specific drugs for the comparison of access types.

Response: We appreciate the reviewer's insightful comment regarding the heterogeneity of IO access locations. We carefully re-examined the studies included in our meta-analysis that directly compared IV and IO administration. Among these, the study by Ko (2024)⁷ involved patients with IO access exclusively at the humeral site. Couper (2025)⁸ reported 3,013 cases with tibial access and 679 with humeral access, but did not provide subgroup analyses to assess differences in efficacy between the two sites. Vallentin (2025)⁶ performed a subgroup analysis comparing humeral and tibial access; however, the data were insufficient for inclusion in a pooled meta-analysis.⁹ The earlier RCT by Reades (2011)¹⁰ also compared humeral and tibial sites, but the results were not reported in a format suitable for quantitative synthesis.¹⁰

While we acknowledge the potential differences in plasma drug levels and flow dynamics between IO sites (humeral, tibial, sternal), the limited and inconsistent reporting across studies precluded a stratified meta-analysis by IO location. We added the contents in the discussion as follows (page 14, line 252-258): "Although IO access sites, such as humeral, tibial, and sternal, differ in flow capacity and drug delivery kinetics, the included studies offered limited or inconsistent data on site-specific outcomes. One study focused exclusively on humeral access,⁷ while others combined multiple IO sites without stratified analysis. Due to this heterogeneity and lack of detailed reporting, subgroup analyses by IO location could not be conducted. Nevertheless, pooling the available data remains valuable for identifying general trends in efficacy between IO and IV access."

Minor comment 1: P4, line 72ff: "...advanced interventions such as supraglottic airways and endotracheal intubation, with recent evidence supporting the efficacy of supraglottic devices." The emphasis on "the efficacy of supraglottic" devices raises the question, of the relative efficacy compared to endotracheal airways. Do the authors want to merely mention an existing yet inferior alternative, do they want to claim non-inferiority or do they want to imply superiority of the supraglottic airway during OHCA? Please clarify the intended meaning.

Response: Thank you for your thoughtful comment. Our intention was to highlight the growing body of evidence supporting the use of supraglottic airway (SGA) devices as a viable alternative to endotracheal intubation (ETI) during out-of-hospital cardiac arrest (OHCA), particularly in terms of ease of use and rapid deployment in prehospital settings. We do not intend to imply the superiority of SGAs over ETI, but rather to reflect findings from recent studies suggesting that SGAs may offer comparable, or in some contexts non-inferior, outcomes to ETI. To clarify this point, we have revised the sentence to read as follows (page4, line72-74): "Airway management strategies range from basic maneuvers to advanced interventions such as supraglottic airways and endotracheal intubation, with recent evidence supporting the efficacy of supraglottic devices."

Minor comment 2: P5, line 90ff: "Another randomized trial reported...[18,19]" Please specify whether the trial cited is reference [18] or [19]. Please note that both 18 and 19 don't seem to fit the quote. [18] did not randomize for vascular access but for continuous vs. interrupted chest compressions. [19] is a meta study, not an RCT.

Response: Thank you for pointing this out. We agree that the originally cited references ([18] and [19]) were not appropriate in this context. Reference [18] did not involve randomization based on vascular access, and reference [19] is a meta-analysis rather than a randomized controlled trial. Accordingly, we have removed these citations.

To improve the clarity and relevance of this section, we have added a new citation in place of reference [18] and included the following paragraph summarizing recent findings (page 5, line 88-91; line 95-98):

"However, significant heterogeneity across studies necessitates cautious interpretation of these findings. Another randomized trial reported that an IO-first vascular access strategy did not lead to higher 30-day survival compared to an IV-first strategy.¹¹"

"Several meta-analyses have been conducted comparing IO and IV administration using direct study designs.^{2,3} However, subgroup analyses from previous RCTs comparing IO and IV routes have also provided valuable insights into the differences in their effectiveness."

Minor comment 3: P5, line 98ff: "These findings may influence emergency medical services (EMS) protocols"

Reviews and pooled analyses are scientifically relevant and can be insightful. Yet one should in principle be very careful with direct practice changing recommendations. The study design is

not equipped to yield such strong levels of evidence that EMS protocols should be amended based on its results.

Response: Thank you for your insightful comment. We agree that caution is warranted when translating findings from reviews and meta-analyses into direct clinical practice recommendations. Our intention was not to suggest immediate changes to EMS protocols but to highlight the potential implications of our findings. To reflect this, we have revised the sentence to adopt a more cautious and appropriately measured tone. We revised the contents in page 6 line 100-102: "These findings may provide insights that could inform future considerations in developing or refining emergency medical services (EMS) protocols, pending further high-quality evidence."

Minor comment 4: P8, line 131: Would it be possible to specify the access location for the IO group, presumably tibial or humeral?

Response: Thank you for your comment. We have clarified this point in the manuscript. As not all studies impose restrictions on the anatomical site of access, we have added the following sentence on page 8, lines 136-137: "There were no restrictions regarding the anatomical site of IO or IV access."

Minor comment 5: P9, line 148: "We also assessed the type of vasopressor used."

Were any vasopressors other than adrenaline used in any of the included RCTs? Are the results of this subgroup analyses reported?

Response: Thank you for your helpful comment. We acknowledge that this was an oversight. There were insufficient data across the included RCTs to conduct a meaningful subgroup analysis based on the type of vasopressor used. Therefore, we have removed the corresponding sentence from the manuscript to avoid any confusion.

Minor comment 6: P12, line 212: "reinforcing IV access as the preferred route due to its potential advantages in drug efficacy and pharmacokinetics" Please elaborate on these IV advantages in terms of efficacy and pharmacokinetics, especially since the final conclusion will again mention pharmacokinetic advantages of IV access as one of the study's central findings in P14, line 256.

Response: Thank you for your valuable comment. We agree clarification is needed. IV access is considered the gold standard in resuscitation due to its direct entry into central circulation, enabling faster and more predictable drug absorption. In contrast, IO access—especially via the tibia—may result in slower circulation times and delayed drug delivery. However, the purpose of this meta-analysis was not aimed to clarify the mechanism of IO and IV, we delete the contents of pharmacokinetics and modified the manuscript as follows "These results align with prior research, reinforcing IV access as the preferred route." (page 13 line 229-230)

Due to the lack of data on pharmacokinetics in this meta-analysis. We have modified the conclusion section as follows (page 16, lines 285-286): "These findings reaffirm IV access as the preferred approach but also highlight the critical role of IO access when IV placement is difficult or delayed, particularly in prehospital settings."

Minor comment 7: P12, line 216: "The consistency of these findings with previous studies underscores the ongoing debate" Wouldn't consistency across multiple studies rather settle a debate instead of invigorating it?

Response: Thank you for your thoughtful observation. We agree that the original wording may have been misleading. Consistency across multiple studies helps clarify clinical questions rather than perpetuate debate. We have revised the sentence to:

"The consistency of these findings with previous studies highlights the importance of selecting an optimal vascular access strategy in emergency settings and offers evidence-based insights to inform clinical decision-making."

Minor comment 8: Table 1: Please specify if "CPR" means "bystander CPR" before arrival of EMS personnel or any chest compressions at all. Is there a reason, the studies are abbreviated by the main author without reference to colleagues? Why e.g. "Couper 2025" instead of "Couper et al. 2025"? This applies to the majority of figures and tables.

Response: Thank you for your helpful comment. We have clarified in Table 1 that "CPR" refers specifically to bystander CPR administered before the arrival of EMS personnel. Regarding the study abbreviations, we appreciate your suggestion and have revised all instances in the tables and figures to use the full citation format (e.g., "Couper et al. 2025") to maintain consistency with standard referencing conventions.

Minor comment 8: Table 2. Please make specify within the table whether the respective odd's ratios, while not significant, would favor the IO or the IV access.

Response: Thank you for your suggestion. We have revised Table 2 to clearly indicate the direction of effect for each odds ratio. Odds ratios below 1.0 favor IO access, while those above 1.0 favor IV access. This clarification has been added to the table and its footnote (page 22).

Minor comment 9: Figures 1-3 and S2-S3: Please clarify which side of the forest plots favors IO and which IV.

Response: Thank you for your helpful comment. We have updated the captions of Figures 1-3 and Supplementary Figures S2-S3 to explicitly state which side of the forest plots favors IO access and which favors IV access, thereby improving clarity for the reader.

Minor comment 10: Figure S1: There seem to be reports, records and studies included and excluded. Eventually there are 5 studies and 5 reports being included, yielding seemingly the inclusion of 10 publications which does not match the text body of the manuscript. Please use uniform language and revise the chart.

Response: Thank you for pointing this out. We agree that the terminology in Figure S1 was inconsistent and may have caused confusion. We have revised the figure and accompanying labels to use uniform terminology, clarifying that six studies were included in the final analysis, as described in the main text and Supplementary Information (page 3).

Minor comment 11: Figures S5-S7: Please add explanatory caption and figure legend for data points.

Response: We have included the results of Egger's test with corresponding p-values to indicate the assessment of publication bias.

We sincerely appreciate the reviewers' thoughtful feedback and the opportunity to revise our manuscript. We believe the changes made have significantly improved the clarity and rigor of our work, and we hope that the revised version meets your expectations.

Thank you for your time and consideration.

Sincerely,

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Reference

1. Nolan JP, Deakin CD, Ji C, et al. Intraosseous versus intravenous administration of adrenaline in patients with out-of-hospital cardiac arrest: a secondary analysis of the PARAMEDIC2 placebo-controlled trial. *Intensive Care Med.* May 2020;46(5):954-962. doi:10.1007/s00134-019-05920-7
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3. Alliou S, Moskowitz A, Rashedi S. Intraosseous versus intravenous vascular access in out-of-hospital cardiac arrest: a systematic review and meta-analysis of randomized controlled trials. *Crit Care.* Mar 19 2025;29(1):124. doi:10.1186/s13054-025-05362-2
4. Daya MR, Leroux BG, Dorian P, et al. Survival After Intravenous Versus Intraosseous Amiodarone, Lidocaine, or Placebo in Out-of-Hospital Shock-Refractory Cardiac Arrest. *Circulation.* Jan 21 2020;141(3):188-198. doi:10.1161/circulationaha.119.042240
5. Granfeldt A, Avis SR, Lind PC, et al. Intravenous vs. intraosseous administration of drugs during cardiac arrest: A systematic review. *Resuscitation.* Apr 2020;149:150-157. doi:10.1016/j.resuscitation.2020.02.025
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8. Couper K, Ji C, Deakin CD, et al. A Randomized Trial of Drug Route in Out-of-Hospital Cardiac Arrest. *N Engl J Med.* Jan 23 2025;392(4):336-348. doi:10.1056/NEJMoa2407780
9. Vallentin MF, Granfeldt A, Klitgaard TL, et al. Intraosseous or Intravenous Vascular Access for Out-of-Hospital Cardiac Arrest. *N Engl J Med.* Jan 23 2025;392(4):349-360. doi:10.1056/NEJMoa2407616
10. Patel H, Mahtani AU, Mehta LS, et al. Outcomes of out of hospital sudden cardiac arrest in India: A review and proposed reforms. *Indian Heart J.* Sep-Oct 2023;75(5):321-326. doi:10.1016/j.ihj.2023.08.005
11. Brebner C, Asamoah-Boaheng M, Zaidel B, et al. The association of intravenous vs. humeral-intraosseous vascular access with patient outcomes in adult out-of-hospital cardiac arrests. *Resuscitation.* 2024;202doi:10.1016/j.resuscitation.2024.110360

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