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| Question | |
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| **Population:** | Adults in any setting (in-hospital or out-of-hospital) with cardiac arrest. |
| **Intervention:** | Placement of an intraosseous (IO) cannula and drug administration through this IO during cardiac arrest. |
| **Comparison:** | Placement of an intravenous (IV) cannula and drug administration through this IV during cardiac arrest. |
| **Main outcomes:** | Return of spontaneous circulation, survival to hospital discharge, and survival to hospital discharge with a favorable neurological outcome. |

# ASSESsment

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| Problem Is the problem a priority? | | |
| Judgement | Research evidence | Additional considerations |
| ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know | Cardiac arrest, both in the out-of-hospital and in-hospital setting, is relatively common and has a very high mortality. Certain drugs (epinephrine, amiodarone, lidocaine) are suggested/recommended during cardiac arrest in order to improve patient outcome. However, it can often be difficult to obtain intravascular access especially in the prehospital setting. Intraosseous (IO) access as an alternative to intravenous (IV) access is increasingly used during cardiac arrest. However, whether drugs are as effective when administered IO vs. IV is unknown. | A number of observational studies addressing this topic has been published within the last years. |
| Desirable Effects How substantial are the desirable anticipated effects? | | |
| Judgement | Research evidence | Additional considerations |
| ● Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know | Use of IO access might result in faster drug delivery (Reades 2011 509) which could lead to improved outcomes. Furthermore, when IV access is not possible, IO access can facilitate drug administration.  The survival to hospital discharge outcome is considered critical. Given that the effect of drugs during cardiac arrest on this outcome is likely small (Holmberg 2019 111; Ali 2018 63), any difference in critical outcomes between IO and IV drug administration is likely to be small. The findings from observational studies (see table below) do not indicate that there is any desirable effect of IO access.   | **Outcomes** | **№ of participants (studies) Follow up** | **Certainty of the evidence (GRADE)** | **Relative effect (95% CI)** | **Anticipated absolute effects\* (95% CI)** | | | --- | --- | --- | --- | --- | --- | | **Risk with IV** | **Risk difference with IO** | | Return of spontaneous circulation | 34686 (3 observational studies) | ⨁◯◯◯ VERY LOWa,b | **OR 0.74** (0.67 to 0.81) | Study population | | | 311 per 1.000 | **61 fewer per 1.000** (79 fewer to 43 fewer) | | Survival to hospital discharge | 34686 (3 observational studies) | ⨁◯◯◯ VERY LOWa,b | **OR 0.79** (0.66 to 0.93) | Study population | | | 84 per 1.000 | **17 fewer per 1.000** (27 fewer to 5 fewer) |  1. Assessed using the ROBINS-I tool. Table X. Overall rated as serious risk of bias due to confounding and selection bias. 2. Based on variations in effect size and I2 statistics |  |
| Undesirable Effects How substantial are the undesirable anticipated effects? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Large ● Moderate ○ Small ○ Trivial ○ Varies ○ Don't know | Use of IO access might result in decreased drug effectiveness due to a changed pharmacokinetic profile or misplaced IO lines. Complications could include bone injury and infection.  The survival to hospital discharge is considered critical. Given that the effect of drugs during cardiac arrest on this outcome is likely small/moderate (Holmberg 2019 111; Ali 2018 63), any difference in critical outcomes between IO and IV drug administration is likely to be small/moderate. It is therefore unlikely that the relatively strong association seen in observational studies (see GRADE table above) entirely reflects a causal effect. It is therefore likely that any anticipated undesirable effect is small to moderate. |  |
| Certainty of evidence What is the overall certainty of the evidence of effects? | | |
| Judgement | Research evidence | Additional considerations |
| ● Very low ○ Low ○ Moderate ○ High ○ No included studies | The overall certainty in the evidence from the observational studies is very low (see GRADE table). |  |

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| Values Is there important uncertainty about or variability in how much people value the main outcomes? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability | Patients and providers are likely to value the included outcomes (Haywood 2018 e789). | Longer term outcomes and health-related quality of life was not addressed in the available studies |
| Balance of effects Does the balance between desirable and undesirable effects favor the intervention or the comparison? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Favors the comparison ● Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know | The pooled results from the observational studies favor the comparison (IV). However, there is very low certainty in these results as noted above. |  |
| Resources required How large are the resource requirements (costs)? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ● Don't know | We did not identify any studies that specifically compared resources including costs between the two interventions. | The costs will vary according to the setting, type, and availability of devices. Both IV and IO access require specific training and experience. |

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| Certainty of evidence of required resources What is the certainty of the evidence of resource requirements (costs)? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Very low ○ Low ○ Moderate ○ High ● No included studies | We did not identify any studies that specifically compared resources including costs between the two interventions. |  |
| Cost effectiveness Does the cost-effectiveness of the intervention favor the intervention or the comparison? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies | We did not identify any studies that addressed cost-effectiveness. |  |
| Equity What would be the impact on health equity? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ● Don't know | We did not identify any studies that addressed health equity. | IO access is not available in all locations especially in low-resource settings. A recommendation for IO access could therefore increase inequity. |
| Acceptability Is the intervention acceptable to key stakeholders? | | |
| Judgement | Research evidence | Additional considerations |
| ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know | We have not identified any research that assessed acceptability. | Both IO and IV access is likely acceptable to key stakeholders as both are currently being used in clinical practice. |
| Feasibility Is the intervention feasible to implement? | | |
| Judgement | Research evidence | Additional considerations |
| ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know | Feasibility was not a pre-specified outcome in this systematic review. In the only randomized trial on the topic, tibial IO access as compared to humeral IO or peripheral IV had a higher successful first attempt success (Reades 2011 509). Observational studies have had mixed results, but IO access appears to be feasible although there is some concern related to potential unrecognized misplacement. IO access was used in 20-30% of patients in two recent large trials (ALPS, PARAMEDIC2). |  |

# Summary of judgements

|  | **Judgement** | | | | | | |
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| **Problem** | No | Probably no | Probably yes | **Yes** |  | Varies | Don't know |
| **Desirable Effects** | **Trivial** | Small | Moderate | Large |  | Varies | Don't know |
| **Undesirable Effects** | Large | **Moderate** | Small | Trivial |  | Varies | Don't know |
| **Certainty of evidence** | **Very low** | Low | Moderate | High |  |  | No included studies |
| **Values** | Important uncertainty or variability | Possibly important uncertainty or variability | **Probably no important uncertainty or variability** | No important uncertainty or variability |  |  |  |
| **Balance of effects** | Favors the comparison | **Probably favors the comparison** | Does not favor either the intervention or the comparison | Probably favors the intervention | Favors the intervention | Varies | Don't know |
| **Resources required** | Large costs | Moderate costs | Negligible costs and savings | Moderate savings | Large savings | Varies | **Don't know** |
| **Certainty of evidence of required resources** | Very low | Low | Moderate | High |  |  | **No included studies** |
| **Cost effectiveness** | Favors the comparison | Probably favors the comparison | Does not favor either the intervention or the comparison | Probably favors the intervention | Favors the intervention | Varies | **No included studies** |
| **Equity** | Reduced | Probably reduced | Probably no impact | Probably increased | Increased | Varies | **Don't know** |
| **Acceptability** | No | Probably no | **Probably yes** | Yes |  | Varies | Don't know |
| **Feasibility** | No | Probably no | **Probably yes** | Yes |  | Varies | Don't know |

# Type of recommendation

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| Strong recommendation against the intervention | **Conditional recommendation against the intervention** | Conditional recommendation for either the intervention or the comparison | Conditional recommendation for the intervention | Strong recommendation for the intervention |
| ○ | **●** | ○ | ○ | ○ |

# Conclusions

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| Recommendation |
| **We suggest IV access as compared to IO access as the first attempt for drug administration during adult cardiac arrest (weak recommendation, very low-certainty evidence).**  **If attempts at IV access are unsuccessful or IV access is not feasible, we suggest IO access as a route for drug administration during adult cardiac arrest (weak recommendation, very low-certainty evidence).** |
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| Justification |
| Although the overall certainty in the evidence is very low, the current evidence suggests that outcomes might be better when drugs are administered intravenously as compared to intraosseously.  Current guidelines suggest that IO access should only be used if IV access is "difficult or impossible" (Soar 2015 110) or "not readily available" (Link 2015 S459). There is no new evidence to support a change to these guidelines. |

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| Subgroup considerations |
| The included studies did not allow for meaningful analyses of specific subgroups. The IO site was often not documented or primarily tibial. As such, no statements can be made about difference between tibial and humeral (or other) IO access.  All studies were conducted in out-of-hospital cardiac arrest. Although most in-hospital cardiac arrest patients likely have pre-existing IV access, this is not universally the case. Although there might be differences in provider skills and patient characteristics between out-of-hospital and in-hospital cardiac arrest, we consider it unlikely that these would lead to substantial effect modification. As such, the above recommendations apply to both out-of-hospital and in-hospital cardiac arrest. |

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| Implementation considerations |
| Since both IO and IV access are currently used in clinical practice, we see no substantial concerns related to implementation. |

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| Monitoring and evaluation |
| Since both IO and IV access are currently used in clinical practice, we see no substantial concerns related to monitoring and evaluation. |

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| Research priorities |
| The overall certainty in the evidence is very low. As such, there is clinical equipoise for additional trials related to IV vs. IO drug administration during cardiac arrest. These could include trials that directly compare IV to different sites of IO access (e.g. tibial, humeral). |

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