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| Question |
| **Should a specific blood pressure target (I) vs no blood pressure target or a different blood pressure target be used for infants and children in any setting (in-hospital or out-of-hospital cardiac arrest) after return of spontaneous circulation (ROSC) (P)?** |
| **Population:** | infants and children after return of spontaneous circulation (ROSC) (P),  |
| **Intervention:** | A specific blood pressure target |
| **Comparison:** | No blood pressure target or a different blood pressure target |
| **Main outcomes:** | Survival to hospital discharge; Survival with favourable neurological outcome; |
| **Setting:** | in-hospital or out of hospital cardiac arrest (IHCA, OHCA) |
| **Perspective:** |  |
| **Background:** |  |
| **Conflict of interests:** | A Topjian – Senior author on included studies was recused from Pediatric Task Force recommendations. However, did provide context and background information. |

# Assessment

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| ProblemIs the problem a priority? |
| Judgement | Research evidence | Additional considerations |
| ○ No○ Probably no○ Probably yes● Yes○ Varies○ Don't know | Cardiac arrest In and out of hospital is a major cause of morbidity and mortality in infants and children. Once return of circulation (ROC) is achieved, the next phase is ensuring adequate organ perfusion and reducing the risk of further neurological injury during the post-resuscitation syndrome. Blood pressure control is among the critical factors influencing prognosis and outcome after cardiac arrest. Maintaining an adequate blood pressure may be linked to maintaining adequate tissue perfusion and optimizing patient outcomes.Determining the optimal blood pressure targets in infants and children after ROC poses a significant challenge due to lack of evidence. Clinical practice in this area is largely based upon a few pediatric studies, extrapolation from studies conducted in adult populations or expert consensus recommendations. While studies identified an association between hypotension post-ROC in infants and children, these studies are small and it is also difficult to know if the association is causal or is a surrogate marker of more severe cardiac arrest. Potential benefits include both more survivors to hospital discharge and also more survivors with favourable neurological outcomes. However, use of higher blood pressure targets may have undesirable patient effects, such as longer length of hospital or intensive care stay and complications of requiring central intravenous access to deliver medication.  | This is the first systematic review on this topic for the pediatric task force  |
| Desirable EffectsHow substantial are the desirable anticipated effects? |
| Judgement | Research evidence | Additional considerations |
| ○ Trivial○ Small● Moderate○ Large○ Varies○ Don't know | Six studies were included from the systematic review (Topjian 2014, 1518; Topjian 2018, 143; Topjian 2019a, 88; Topjian 2019b, 24, Laverriere 2020, 143; Gardner 2023, 388). All six were non-randomized observational cohort studies, with five being secondary analyses. The review identified significant variation in BP target definitions (e.g. systolic, mean and diastolic BP; and >5th, >10th and >50th centile for age) and time frames for measurement (<20 minutes, 0 to 6 hours, within 24 hours, and within 0-72 hours).  In our final analysis, we included four studies (Topjian 2014, 1518; Topjian 2018, 143; Topjian 2019a, 88; Laverriere 2020, 143) examining the BP targets of systolic BP >5th centile for age compared with systolic BP ≤5th centile within the first six hours post return of circulation. The pooled sample included 463/930 (49.8%) patients following in-hospital cardiac arrest (IHCA), and 467/930 (50.2%) after out-of-hospital cardiac arrest). We also included one study (Gardiner 2023, 388) which enrolled 693 infants and children after IHCA (excluding patients requiring extra-corporeal life support). This study compared systolic BP >10th centile with systolic BP ≤10th centile within the first six hours post return of circulation. The systolic BP cut off at the 10th centile was generated from receiver operator characteristic curves and spline curves created from the study data.For the critically important outcome of survival, we identified very-low-certainty evidence (downgraded for inconsistency and indirectness) from four observational studies (Topjian 2014, 1518; Topjian 2018, 143; Topjian 2019a, 88; Laverriere 2020, 143) enrolling 931 children after in-hospital or out-of-hospital cardiac arrests, in the first six hours post return of circulation (ROC), that showed benefit from exposure to a systolic BP >5th centile when compared with systolic BP ≤5th centile (pooled adjusted Relative Risk (aRR), 1.34; 95%CI, 1.07 to 1.52); P = 0.01); 143 more patients/1000 survived with the intervention [95% CI, 30 more patients/1000 to 219 more patients/1000 survived with the intervention]).For the critically important outcome of survival with good neurological outcome, we identified very-low-certainty evidence (downgraded for inconsistency and indirectness) from two observational studies (Topjian 2014, 1518; Laverriere 2020, 143) enrolling 584 children after in-hospital or out-of-hospital cardiac arrests, in the first six hours post ROC, that showed benefit from exposure to a systolic BP >5th centile when compared with SBP ≤5th centile (pooled aRR, 1.30; 95%CI, 1.06 to 1.60); P = 0.01); 156 more patients/1000 survived with the intervention [95% CI, 31 more patients/1000 to 312 more patients/1000 survived with the intervention]).

| **Outcomes** | **№ of participants(studies)Follow-up** | **Certainty of the evidence(GRADE)** | **Relative effect(95% CI)** | **Anticipated absolute effects\* (95% CI)** |
| --- | --- | --- | --- | --- |
| **Risk >5th SBP centile systolic blood pressure target within 6 hours compared with** ≤**5th** | **Risk difference with >5th centile systolic blood pressure target within 6 hours compared with** ≤**5th.**  |
| Survival to hospital dischargeassessed with: survival | 931(4 non-randomised studies)1,2,3,4 | ⨁◯◯◯Very lowa,b | **RR 1.41**(1.20 to 1.60) | Study population |
| 422 per 1,000 | **173 more per 1,000**(84 more to 253 more) |
| Survival with favourable neurological outcomeassessed with: PCPC 1-2 and 0-1 change from baseline, or 1-3 and no change from baseline  | 584(2 non-randomised studies)1,4 | ⨁◯◯◯Very lowc,d | **RR 1.30**(1.06 to 1.60) | Study population |
| 520 per 1,000 | **156 more per 1,000**(31 more to 312 more) |

1. Topjian, et al. Early postresuscitation hypotension is associated with increased mortality following pediatric cardiac arrest. Critical care medicine ; 2014.
2. Topjian, et al. Association of Early Postresuscitation Hypotension With Survival to Discharge After Targeted Temperature Management for Pediatric Out-of-Hospital Cardiac Arrest: Secondary Analysis of a Randomized Clinical Trial. JAMA pediatrics ; 2018.
3. Topjian, et al. Therapeutic Hypothermia after Pediatric Cardiac Arrest Trial, Investigators. The association of early post-resuscitation hypotension with discharge survival following targeted temperature management for pediatric in-hospital cardiac arrest.. Resuscitation; 2019.
4. Laverriere, et al.. Association of Duration of Hypotension With Survival After Pediatric Cardiac Arrest. Pediatric. Pediatric critical care medicine; 2020.
5. Combining OHCA and IHCA with different BP monitoring devices.
6. Secondary analysis of RCTs. BP assessment was not primary goal
7. Similar assessment of hypotension and burden of hypotension.
8. Only 2 studies available

For the critically important outcome of survival, we identified very-low-certainty evidence (downgraded for indirectness) from one study (Gardner 2023, 388), showing benefit from exposure to a systolic BP > 10th centile when compared with systolic BP ≤10th centile (aRR, 1.21; 95%CI, 1.00 to 1.33); P <0.01); 138 more patients/1000 survived with the intervention [95% CI, 66 more patients/1000 to 213 more patients/1000 survived with the intervention]).For the critically important outcome of survival with good neurological outcome, we identified very-low-certainty evidence (downgraded for indirectness) from one study (Gardner 2023, 388), that showed benefit from exposure to a systolic BP >10th centile when compared with systolic BP ≤10th centile (aRR, 1.22; 95%CI, 1.10 to 1.35); P <0.01); 134 more patients/1000 survived with the intervention [95% CI, 61 more patients/1000 to 213 more patients/1000 survived with the intervention]).

| **Outcomes** | **№ of participants(studies)Follow-up** | **Certainty of the evidence(GRADE)** | **Relative effect(95% CI)** | **Anticipated absolute effects\* (95% CI)** |
| --- | --- | --- | --- | --- |
| **Risk >10th SBP centile systolic blood pressure target within 6 hours compared with ≤10th** | **Risk difference with >10th centile systolic blood pressure target within 6 hours compared with ≤10th.** |
| Survival | 693(1 non-randomised study)1 | ⨁◯◯◯Very lowa,b | **RR 1.210**(1.100 to 1.333) | Study population |
| 657 per 1,000 | **138 more per 1,000**(66 more to 219 more) |
| Survival with favourable neurological outcomeassessed with: PCPC 1-3 or no change from baseline | 692(1 non-randomised study)1 | ⨁◯◯◯Very lowa,b | **RR 1.22**(1.10 to 1.35) | Study population |
| 610 per 1,000 | **134 more per 1,000**(61 more to 213 more) |

1. Gardner, et al. Identification of post-cardiac arrest blood pressure thresholds associated with outcomes in children: an ICU-Resuscitation study.. Critical Care; 2023.
2. Only contained IHCA.
3. Only one study available.

 | Although the size effect from the combines studies is small, the value of the outcomes is of high value and the potential impact on infants and children globally who get ROSC following a CA is large.The three studies (Gardner 2023, 388; Topjian 2019a, 88; Topjian 2019b, 24) use BP norms adjusted for age, sex and height, Topjian (2018, 1518) uses age, and the other papers used BP norms adjusted for age and sex. The task force felt it was most appropriate to use BP norms adjusted for age, sex and height.Two studies (Topijan 2019b, 24; Topijan 2014, 143) targeted temperature management was applied. The SBP measurements were obtained during the 0-6 hour time frame from when the targeted temperature management was applied and not from the time of sustained ROC. In both studies targeted temperature management was initiated within the first 6 hours of sustained ROC.Two studies were excluded as the definition of hypotension could not be ascertained (Lin 2010, 410; Lin 2013, 439). |
| Undesirable EffectsHow substantial are the undesirable anticipated effects? |
| Judgement | Research evidence | Additional considerations |
| ○ Trivial○ Small● Moderate○ Large○ Varies○ Don't know | The undesirable effects of not surviving to hospital discharge and surviving with unfavourable neurological outcomes are significant. However, we did not look at reasons for non-survival as an *a priori* outcome, and the studies do not report value to families of survival with un-favourable neurological outcomes vs death.  |  |
| Certainty of evidenceWhat is the overall certainty of the evidence of effects? |
| Judgement | Research evidence | Additional considerations |
| ● Very low○ Low○ Moderate○ High○ No included studies | Six studies were included in the systematic review. All studies were non-randomised cohort studies, with five out of the six being secondary analyses of other studies. Two of these (Topjian 2018, 1518; Topjian 2019b,24) were secondary analysis of multicentre RCT's (Therapeutic hypothermia after pediatric cardiac arrest (THAPCA) In Hospital Cardiac Arrest and out of Hospital Cardiac Arrest) (Moler 2015, 372; Moler 2017, 318). Topjian (2019a, 88), was a secondary analysis of a prospective multicentre cohort study, Topjian (2014, 143) was a retrospective cohort study from a multicentre database of cardiac arrest, the Pediatric Emergency Care Applied Research Network (PECARN). The only single centre study, (Laverriere 2020, 143), was a retrospective cohort study of both IHCA and OHCA from a prospectively collected database. The largest study, of 693 infants and children, (Gardiner 2023, 388), was a secondary analysis of prospectively collected data for the ICU-RESUS trial and involved 18 US centres (ICU-RESUS Groups 2022, 327). The blood pressure cut offs of systolic blood pressure greater than 10th centile and diastolic blood pressure of greater than 50th centile were generated from receiver operator characteristic curves and spline curves. | For the question of > 5th centile blood pressure target within 6 hours, the 4 papers included were, Topjian 2019b (p 24), Laverriere 2020 (p 143), Topjian 2014 (p 143) and Topjian 2018 (p 1518) including a total of 933 patients with both IHCA and OHCA. The combined population in the studies included patients with IHCA and OHCA, (463/930 (49.8%) IHCA, and 467/930 (50.2%) OHCA).For the question of > 10th centile blood pressure target within 6 hours there was one paper, Gardner (2023; 388), with 693 patients included over 18 pediatric intensive care units, who all had IHCA. |
| ValuesIs 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 | The ILCOR P-COSCA initiative developed a core outcome set specific for pediatric cardiac arrest studies. The design and methods of the initiative included use of a Delphi process to develop consensus on a core domain set. (Topjian 2020 e246) The P-COSCA outcomes of survival to discharge and survival to discharge with favourable neurological outcomes were chosen as critical outcomes for this review and are highly valued.  |  |
| Balance of effectsDoes 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 | Acknowledging the very low level of certainty the current available data suggest that exposure to a systolic blood pressure (SBP) target of > 5th centile for age and height within the first 6 hours post ROSC is better compared to exposure to ≤5th centile for the critical outcomes of both survival to hospital discharge and also favourable neurological outcomes at discharge. Evidence, with low level of certainty, also suggest that exposure to a systolic blood pressure (SBP) target of >10th centile for age and height within the first 6 hours post ROSC is better compared to exposure to ≤10th centile for the critical outcomes of both survival to hospital discharge and also favourable neurological outcomes at discharge. No studies compared 5th centile with 10th centile targets. The Task Force considered that the 5th centile target was included (overlapped) within the comparison group of the <10th centile target population. The 10th centile cut off was chosen after discussion on 1) the statistical methods to identify the 10th centile target (using receiver operator and cubic spline analysis), 2) evidence that patients exposed to systolic BP between 5th to 10th centile in the study by Gardener (2023; 388) experience worse outcome (lower risk of survival, or survival with favourable neurological outcome).  | It is unclear if 10th centile systolic BP targets are superior to 5th centile BP targets. In addition higher BP targets were not compared. Also, there was no comparison between systolic versus mean arterial BP or diastolic BP.  |
| AcceptabilityIs the intervention acceptable to key stakeholders? |
| Judgement | Research evidence | Additional considerations |
| ○ No○ Probably no○ Probably yes● Yes○ Varies○ Don't know | There are no specific studies looking at this, but in settings where ICU level of care is available, measuring and managing blood pressure is standard of care. In all 4 studies information was provided around inotrope use, but this was not analysed as it was not an *a priori* question or subgroup. There was heterogeneity between the studies as to how they reported inotrope use.  | In places where ICU level of care is not available for infants and children post cardiac arrest this will be more difficult to achieve, but the principle is likely to still be acceptable to stakeholders. It was felt by the task force that in infants and children who have cardiac arrest followed by ROC, blood pressure should be measured as part of their post cardiac arrest care. |
| FeasibilityIs the intervention feasible to implement? |
| Judgement | Research evidence | Additional considerations |
| ○ No○ Probably no● Probably yes○ Yes○ Varies○ Don't know | There is no specific research evidence to support the intervention being feasible to implement, but management of blood pressure ispresently part of standardpost cardiac arrest care. | In places where ICU level of care is not available for infants and children post cardiac arrest this will be more difficult to achieve, but the principle is likely to still be acceptable to stakeholders.  |

# 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** | Trivial | Small | **Moderate** | Large |  | 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 |
| **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 in infants and children post return of circulation, following an in-hospital or out-of-hospital cardiac arrest, that a systolic blood pressure >10th centile for age should be targeted (weak recommendation, very low certainty evidence). |
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| Justification |
| The Pediatric Task Force considered that the measurement and treatment of blood pressure is a standard component of the post-resuscitation bundle of care after cardiac arrest. However, current post-cardiac arrest blood pressure treatment targets and thresholds for treatment have been suggested through expert consensus and evidence extrapolated from individual studies. The Pediatric Task Force therefore undertook an ILCOR led systematic review of the current evidence.  Measurement of blood pressure is a low-cost intervention and available in nearly all resource settings. However, the taskforce did not review the cost-effectiveness of intermittent, non-invasive blood pressure measurement with invasive arterial or continuous BP measurement. There were no randomized controlled studies comparing two treatment approaches, or two BP targets following cardiac arrest. The available evidence consisted of observational data demonstrating the impact of exposure to two different blood pressure thresholds on clinically important outcomes. However, the blood pressure thresholds were chosen either a-priori by investigators as a clinically important threshold (eg ≤5th centile), or the cut off value was derived statistically from the population data, as the most significant inflection point (≤10th centile). The Pediatric Task Force focused on the impact of hypotension on clinical outcome and did not include studies assessing normotension or hypertension on outcomes. This will form part of future assessments. The Pediatric Task Force considered the exposure overlap of the two thresholds ≤5th centile and ≤10th centile. It was not statistically possible to perform meta-regression to compare the two treatment targets. The consensus of the Pediatric Task Force was that higher threshold cut off target (<10th centile) included the population included in the ≤5th centile group and felt that, accepting the low certainty of evidence, the target of >10th centile SBP was the more conservative systolic BP goal to suggest until more evidence is available.The Task Force felt, that although the effect size from the pooled studies is small, the value of the outcome is high and the potential impact on infants and children survivors globally is therefore large. |

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| Implementation considerations |
| Management of blood pressure is a component of standard pediatric care treatment. |

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| Monitoring and evaluation |
| See research priorities below. |

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| Research priorities |
| There are no interventional randomized controlled trials comparing benefit or harm of targeting specific BP targets. Information on impact of pre-hospital BP measurement or treatment for OHCA is missing. It is unclear if specific sub-groups of pediatric patients post return of circulation require different BP targets. Observational data demonstrate an association between exposure to lower BP targets and worse outcome; however, more data are required to demonstrate a causal relationship between treatment interventions to achieve higher BP targets and improved outcomes. In addition, the TF was unable to assess the benefits or harm of exposure to hypertension in the period after cardiac arrest. We encourage consistent reporting of BP monitoring definitions (e.g. site, repeated measurement, component of BP (systolic, diastolic, mean BP) and definitions of exposure to hypotension (e.g. single episode versus percentage of time).Majority of included data report exposure to BP thresholds within six hours; impact of BP interventions outside this timeframe is important. It is unclear which strategy is optimal to achieve a BP above the threshold level (e.g. fluids, vasopressor support, mechanical support), and interventions themselves may be associated with harm. There is limited data if a BP target or another marker of end organ perfusion is the most appropriate target. Optimal BP targets during extracorporeal life support (ECLS) post-cardiac arrest are unknown. Some patients on ECLS may have a lack of heart pulsatilty which also limits use of systolic BP targets in this patient group. There is limited data available on the optimal strategy to use when cerebral autoregulation is impaired.  |

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