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ILCOR Summary Statement

2019 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science With Treatment Recommendations☆,☆☆

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☆☆ Summary From the Basic Life Support; Advanced Life Support; Pediatric Life Support; Neonatal Life Support; Education, Implementation, and Teams; and First Aid Task Forces.

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Abstract

The International Liaison Committee on Resuscitation has initiated a continuous review of new, peer-reviewed, published cardiopulmonary resuscitation science. This is the third annual summary of the International Liaison Committee on Resuscitation International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science With Treatment Recommendations. It addresses the most recent published resuscitation evidence reviewed by International Liaison Committee on Resuscitation Task Force science experts. This summary addresses the role of cardiac arrest centers and dispatcher-assisted cardiopulmonary resuscitation, the role of extracorporeal cardiopulmonary resuscitation in adults and children, vasopressors in adults, advanced airway interventions in adults and children, targeted temperature management in children after cardiac arrest, initial oxygen concentration during resuscitation of newborns, and interventions for presyncope by first aid providers. Members from 6 International Liaison Committee on Resuscitation task forces have assessed, discussed, and debated the certainty of the evidence on the basis of the Grading of Recommendations, Assessment, Development, and Evaluation criteria, and their statements include consensus treatment recommendations. Insights into the deliberations of the task forces are provided in the Justification and Evidence to Decision Framework Highlights sections. The task forces also listed priority knowledge gaps for further research.

Keywords: AHA Scientific Statements, Airway management, Cardiopulmonary resuscitation, Child, Epinephrine, Extracorporeal circulation, Heart arrest, Infant

This is the third in a series of annual International Liaison Committee on Resuscitation (ILCOR) International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science With Treatment Recommendations (CoSTR) summary publications that summarize the ILCOR task force analyses of published resuscitation evidence. The review this year addresses 12 topics by 6 task forces. Draft CoSTRs were posted online between November 12, 2018, and March 20, 2019,[1] and included the data reviewed and draft treatment recommendations, with comments accepted through April 4, 2019. The 12 draft CoSTR statements are now available online[1] and have been viewed 23,654 times since the first posting.

This summary statement contains the final wording of the CoSTR statements as approved by the ILCOR task forces and ILCOR member councils. This statement differs in several respects from the website draft CoSTRs: The language used to describe the evidence is not restricted to standard Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) terminology,[2] making it more transparent to a wider audience; the Justification and Evidence to Decision Framework Highlights sections have been expanded to provide more information about the rationale for treatment recommendations; and finally, the task forces have prioritized knowledge gaps requiring future research studies.

The CoSTRs are based on task force analysis of the data, with the GRADE approach used to answer specific research questions. Each analysis has been detailed in a systematic review (SR), published by a Knowledge Synthesis Unit or systematic reviewer and the ILCOR topic experts.[3–12] The GRADE approach rates the certainty of the evidence for an intervention and for each outcome as high, moderate, low, or very low. Data from randomized controlled trials (RCTs) are initially rated as high-certainty evidence; data from observational studies, as low-certainty evidence. Five factors may lead to downgrading of the certainty of evidence, and 3 factors may enable an upgrade of the certainty of the evidence (Tables 1 and 2).

For each topic, the consensus on science generally includes the pertinent outcome data listing relative risk (RR) with 95% CI and risk difference with 95% CI or absolute risk difference (ARD) with 95% CI and patients with outcome per 1000 patients with 95% CI. For clarity, much of this information is presented in tables. The consensus on science is followed by the treatment recommendation, the task force justification for the treatment recommendation, and the important knowledge gaps identified by the task force.

The following topics are addressed in this CoSTR summary:

- Basic life support
- Dispatch instruction in adult cardiopulmonary resuscitation (CPR)

Table 1 – GRADE terminology for strength of recommendation and criteria for evidence certainty asessment.

Strength of recommendation			
Strong recommendation = we recommend		Weak recommendation = we suggest	
Assessment criteria for certainty of effect			
Study design	Certainty of effect begins at this level	Lower if	Higher if
Randomized trial	High or moderate	Risk of bias Inconsistency Indirectness Imprecision Publication bias	Large effect Dose response All plausible confounding would reduce demonstrated effect or would suggest a spurious effect when results show no effect
Observational trial	Low or very low		

GRADE indicates Grading of Recommendations, Assessment, Development, and Evaluation.

Table 2 – GRADE terminology.

Risk of bias	Study limitations in randomized trials include lack of allocation concealment, lack of blinding, incomplete accounting of patients and outcome events, selective outcome reporting bias, and stopping early for benefit. Study limitations in observational studies include failure to apply appropriate eligibility criteria, flawed measurement of exposure and outcome, failure to adequately control confounding, and incomplete follow-up.
Inconsistency	Criteria for inconsistency in results include the following: Point estimates vary widely across studies; CIs show minimal or no overlap; statistical test for heterogeneity shows a low *P* value; and the I^2 is large (a measure of variation in point estimates resulting from among-study differences).
Indirectness	Sources of indirectness include data from studies with differences in population (eg, OHCA instead of IHCA, adults instead of children), differences in the intervention (e.g., different CV ratios), differences in outcome, and indirect comparisons.
Imprecision	Low event rates or small sample sizes will generally result in wide CIs and therefore imprecision.
Publication bias	Several sources of publication bias include tendency not to publish negative studies and the influence of industry-sponsored studies. An asymmetrical funnel plot increases the suspicion of publication bias.
Good practice statements	Guideline panels often consider it necessary to issue guidance on specific topics that do not lend themselves to a formal review of research evidence. The reason might be that research into the topic is unlikely to be located or would be considered unethical or infeasible. Criteria for issuing a nongraded good practice statement include the following: There is overwhelming certainty that the benefits of the recommended guidance will outweigh harms, and a specific rationale is provided; the statements should be clear and actionable to a specific target population; the guidance is deemed necessary and might be overlooked by some providers if not specifically communicated; and the recommendations should be readily implementable by the specific target audience to whom the guidance is directed.

CV indicates compression-ventilation; GRADE, Grading of Recommendations, Assessment, Development, and Evaluation; IHCA, in-hospital cardiac arrest; and OHCA, out-of-hospital cardiac arrest.

- Advanced life support (ALS)
- Advanced airway interventions during adult cardiac arrest
- Use of vasopressors in cardiac arrest
- Extracorporeal CPR (ECPR) for cardiac arrest in adults
- Pediatric life support
- Dispatcher-assisted CPR (DA-CPR) in pediatrics
- Advanced airway interventions in pediatric cardiac arrest
- ECPR in infants and children
- Targeted temperature management (TTM) after cardiac arrest
- Neonatal life support (NLS)
- Initial oxygen concentration for term infants at birth
- Initial oxygen concentration for preterm infants at birth
- Education, Implementation, and Teams (EIT) and ALS
- Cardiac Arrest Centers (CACs) versus non-CACs
- First aid
- Presyncope

Readers are encouraged to monitor the ILCOR website[1] to provide feedback about planned SRs and to provide comments when additional draft reviews are posted.

Basic life support

Dispatcher instruction in CPR: DA-CPR—adults

The emergency medical dispatcher is an essential link in the chain of survival.[13,14] In addition to dispatching emergency medical services (EMS) resources to medical emergencies, emergency medical dispatchers are increasingly being trained to recognize cardiac arrest, to assist bystanders in initiating resuscitation, and to support bystanders in optimizing resuscitation efforts. The international community is continuing to explore ways to increase bystander CPR for cardiac arrests. One such strategy involves dispatchers providing CPR instruction to callers/bystanders: DA-CPR. For such a strategy to be successful, it requires the EMS system to be configured to support the dispatcher to offer DA-CPR and the bystander to deliver CPR with support from the dispatcher.

ILCOR commissioned an SR to address the effect of DA-CPR on outcomes for patients in out-of-hospital cardiac arrest (OHCA).[3] A draft CoSTR was posted for public comment on the ILCOR website[15]; the draft was viewed 1516 times during the public comment period. The task force reviewed the 1 comment posted during this public commenting period.

Population, intervention, comparator, outcome, study design, and time frame

Population: Adults with presumed cardiac arrest in out-of-hospital settings

Intervention: Patients/cases or EMS systems where DA-CPR is offered

Comparators: Studies with comparators where either systems or specific cardiac arrest cases not offered DA-CPR are included

Outcomes: Critical: survival with favorable neurological function (at hospital discharge, 1 month, or 6 months), survival (to hospital discharge, 1 month, or 1 year), short-term survival (return of spontaneous circulation [ROSC], hospital admission), and provision of bystander CPR. Important: initial shockable rhythm and time to CPR

Study designs: RCTs and nonrandomized studies (non-RCTs, interrupted time series, controlled before-and-after studies, cohort studies) eligible for inclusion

Time frame: All years and all languages included with the last search performed July 1, 2018; ongoing or unpublished studies identified through a search of ClinicalTrials.gov online registry16

PROSPERO registration: CRD42018091427

Note: The pediatric information is summarized elsewhere in this document (see the Dispatcher Instruction in CPR: DA-CPR—Pediatrics section).

Table 3 – Systems: studies comparing outcomes for adults when DA-CPR instruction was offered with outcomes for adults when DA-CPR was not offered.

Outcome	Unadjusted analysis				Adjusted analysis			
	Studies (patients), n	Evidence certainty	Odds ratio (95% CI)	Absolute difference	Studies (patients), n	Evidence certainty	Odds ratio (95% CI)	Absolute difference
Survival with favorable neurological outcome at 1 mo	3 (44, 698)[21,26,32]	Very low	1.10 (1.03–1.17)	9 more per 1000 (3–15 more)	2 (6799)[21,26]	Very low	1.47 (1.03–2.09)	11 more per 1000 (1–25 more)
Survival with favorable neurological outcome at hospital discharge	2 (5533)[18,22]	Very low	1.70 (1.21–2.37)	14 more per 1000 (4–27 more)	1 (5288)[18]	Very low	1.67 (1.13–2.47)	14 more per 1000 (3–30 more)
Survival at 1 mo	2 (6799)[21,26]	Very low	1.20 (0.99–1.45)	11 more per 1000 (1 fewer–25 more)	2 (6799)[21,26]	Very low	1.45 (1.09–1.94)	25 more per 1000 (5–51 more)
Survival at hospital discharge	7 (14,139)[17–20,23,24,28]	Very low	1.23 (0.99–1.53)	33 more per 1000 (2 fewer–73 more)	1 (5288)[18]	Very low	1.33 (1.07–1.66)	21 more per 1000 (5–42 more)
Survival at hospital admission	6 (9548)[18,20–22,29,30]	Very low	1.08 (0.95–1.23)	12 more per 1000 (8 fewer–33 more)	1 (2493)[21]	Very low	0.97 (0.70–1.34)	4 fewer per 1000 (39 fewer–40 more)
ROSC	5 (49,229)[18,20,21,28,32]	Very low	1.17 (1.08–1.27)	27 more per 1000 (13–42 more)	1 (2493)[21]	Very low	1.14 (0.88–1.48)	26 more per 1000 (24 fewer–83 more)

DA-CPR indicates dispatcher-assisted cardiopulmonary resuscitation; and ROSC, return of spontaneous circulation.

Consensus on science

More than 5000 citations were reviewed, and 33 were identified as eligible for inclusion. These studies were classified into 2 categories: (1) systems, the comparison of outcomes when DA-CPR was offered versus not offered, and (2) bystander delivery, the comparison of outcomes for patients receiving DA-CPR versus those receiving no bystander CPR or unassisted bystander CPR. No randomized clinical trials were identified. Given that the only available data consisted of observational studies, we separately listed data when they came from an analysis adjusted for known confounders because we felt that this provided a better estimate of effect. The reliance on nonrandomized trials in the evidence review also means that the reported findings are best regarded as associated with the CPR provided, or not, rather than necessarily caused by the interventions.

Systems: studies comparing outcomes for patients when DA-CPR instruction was offered with outcomes for patients when DA-CPR was not offered. For the comparison of outcomes in systems with DA-CPR programs, we identified 16 studies. These included 5 before-and-after studies[17–21] and 11 cohort studies.[22–32] Only 4 of these studies adjusted in some way for confounding variables.[21,26,28,32] Table 3 provides a summary of the unadjusted and adjusted meta-analyses.

Survival with favorable neurological outcomes. Six studies involving 50,395 patients reported survival with favorable neurological outcome at time points from hospital discharge to 6 months after cardiac arrest.[18,21,22,26,28,32] The certainty of evidence was assessed as very low (downgraded for serious risk of bias, indirectness, and imprecision).

With the exception reported in 1 small series,[28] systems offering DA-CPR were associated with increased favorable neurological outcome at 1 month after cardiac arrest and at hospital discharge compared with systems not offering DA-CPR. These effects persisted after adjustment for confounding variables.

Survival including all neurological outcomes. Nine studies including 20,938 patients addressed survival (regardless of neurological outcome) at time points such as hospital discharge and 1 month and 1 year after cardiac arrest.[17–21,23,24,26,28] The certainty of evidence for these studies was assessed as very low, downgraded for serious risk of bias and imprecision.

With the exception reported in a single small series,[28] systems offering DA-CPR were associated with increased survival at 1 month after cardiac arrest and at hospital discharge (Table 3) compared with systems not offering DA-CPR. These associations were strengthened after adjustment for confounding variables.

Short-term survival: ROSC, hospital admission

Eight studies including 45,474 patients addressed short-term survival, including ROSC and survival to hospital admission.[18,20–22,28–30,32] The certainty of evidence was assessed as very low, downgraded for serious risk of bias and imprecision.

With a single exception reported in a small series,[21] systems offering DA-CPR were associated with sustained ROSC but not increased survival to hospital admission (Table 4) compared with systems not offering DA-CPR.

Bystander delivery: comparison of outcomes from patients receiving DA-CPR versus those receiving either no bystander CPR or unassisted bystander CPR. This evidence evaluation compared outcomes of patients who received bystander CPR as a

Table 4 – Bystander delivery: comparison of outcomes from adults receiving DA-CPR and those receiving no bystander CPR or unassisted bystander CPR.

Outcome	DA-CPR vs no CPR (adjusted analysis)			DA-CPR vs unassisted bystander CPR (adjusted analysis)		
	Studies (patients), n	Evidence certainty	Odds ratio (95% CI)	Studies (patients), n	Evidence certainty	Odds ratio (95% CI)
Survival with favorable neurological outcome at 1 mo	1 (4306)[26]	Very low	1.81 (1.23–2.67)	1 (78, 112)[27]	Very low	1.00 (0.91–1.10)
Survival with favorable neurological outcome at hospital discharge	3 (35, 921)[33–35]	Very low	1.54 (1.35–1.76)	1 (17, 209)[34]	Very low	1.12 (0.94–1.34)
Survival at 1 mo	1 (4306)[26]	Very low	1.63 (1.32–2.01)	2 (78, 697)[27,36]	Very low	1.13 (1.06–1.20)
Survival at hospital discharge	5 (43, 550)[33,34,37–39]	Very low	1.40 (1.09–1.78)	1 (17, 209)[34]	Very low	0.95 (0.83–1.09)
ROSC at hospital admission	NA	NA	NA	1 (78, 150)[27]	Very low	1.09 (1.04–1.14)
ROSC	1 (32, 506)[34]	Very low	1.51 (1.32–1.73)	3 (34 811)[32,34,36]	Very low	1.04 (0.94–1.14)

CPR indicates cardiopulmonary resuscitation; DA-CPR, dispatcher-assisted cardiopulmonary resuscitation; NA, not applicable; and ROSC, return of spontaneous circulation.

result of DA-CPR with 2 groups of patients: those receiving no bystander CPR or those who received bystander CPR that was performed without dispatch assistance. Twenty observational cohort studies were identified,[21,23,26–28,31–38,40–46] but only 10 of these studies included adjusted analysis.[26,27,31–38] Because the clinical features of patients who received DA-CPR differed markedly from those of both the group who received no CPR and the group who received bystander CPR without dispatch assistance, only adjusted outcomes are reported. Table 4 summarizes the study characteristics and results of the adjusted meta-analysis.

Receipt of DA-CPR versus no bystander CPR. Improvements in survival with favorable neurological function at hospital discharge[31,33,34] and at 1 month[26] were reported among patients with OHCA who received bystander DA-CPR compared with those who received no bystander CPR. In addition, improved survival (regardless of neurological status) was reported at hospital discharge[31,33,34,37,38] and at 1 month.[26] Recipients of DA-CPR were also more likely to achieve sustained ROSC than those who received no bystander CPR.[34]

Receipt of bystander CPR With DA-CPR versus bystander CPR without dispatch assistance (i.e., unassisted bystander CPR). The findings were inconsistent when we compared patients who received bystander CPR with DA-CPR with patients who received bystander CPR that was performed without dispatch assistance. Survival with favorable neurological function did not differ either at hospital discharge[34] or at 1 month[27] between patients who received bystander DA-CPR and those who received bystander CPR without dispatch assistance. Overall survival at hospital discharge did not differ between these groups,[34] although survival at 1 month favored patients who received bystander DA-CPR.[27,36] Recipients of bystander DA-CPR were also more likely to have ROSC on hospital arrival than when bystander CPR was rendered without dispatch assistance.[27] Although these studies do not prove equivalence or noninferiority, they suggest that DA-CPR could possibly be as effective as spontaneously provided (unassisted) CPR.

Treatment recommendations

We recommend that emergency medical dispatch centers have systems in place to enable call handlers to provide CPR instructions for adult patients in cardiac arrest (strong recommendation, very low certainty of evidence).

We recommend that emergency medical call-takers provide CPR instructions (when deemed necessary) for adult patients in cardiac arrest (strong recommendation, very low certainty of evidence).

Justification and evidence to decision framework highlights

Whereas the strength of these recommendations is greater than the certainty of the supporting evidence, taken together, the preponderance of the evidence evaluated in this review suggests that clinical outcomes after OHCA are more likely to be improved when DA-CPR is available, offered, and provided. The similarity in outcomes when CPR is initiated spontaneously without the need for dispatch assistance (perhaps performed by a more skilled or trained bystander) and when DA-CPR is performed (perhaps with a less skilled or untrained bystander) exemplifies the potential positive impact of such point-of-care instruction. At a minimum, DA-CPR increases the likelihood that bystander CPR will be performed,[3] itself an important predictor of favorable outcome from OHCA.[47] The SR also found that DA-CPR favored not only bystander CPR but also time to CPR, ROSC, and initial shockable rhythm.[3] These considerations, along with the recognition that randomized clinical trials addressing this question are unlikely to be forthcoming, led to the task force's consensus that DA-CPR should be strongly recommended.

Knowledge gaps

This evidence evaluation did not address training, logistical, operational, or economic issues pertaining to DA-CPR. The task force identified several knowledge gaps requiring further investigation, including the following:

- Optimal dispatcher training (and retraining) in recognizing OHCA and in providing DA-CPR

- The essential elements of a quality improvement program focused on DA-CPR
- The preferred CPR instruction sequence for DA-CPR
- The potential impact of dispatcher or call-taker's background or prior experience (nonhealthcare professional versus paramedic or nurse) on DA-CPR performance
- The role of automated external defibrillators during the course of DA-CPR
- The integration of adjunct technologies (eg, artificial intelligence or video) for clinical decision support

Advanced life support

Advanced airway interventions during adult cardiac arrest

It is important to identify those airway interventions most likely to improve outcomes for both OHCA and IHCA. Chest compressions alone do not provide adequate ventilation during prolonged cardiac arrest. Airway management is therefore required to facilitate ventilation and to reduce the risk of gastric regurgitation and aspiration. The best airway strategy for improving patient outcomes is uncertain. On the basis of the evidence available at the time, the 2015 CoSTR suggested using either an advanced airway or a bag-mask device for airway management during CPR (weak recommendation, very low certainty of evidence) for cardiac arrest in any setting.[48]

Advanced airway management is common during cardiac arrest. The American Heart Association Get With The Guidelines –Resuscitation registry of in-hospital cardiac arrest (IHCA) reports that 60% to 70% of patients underwent tracheal intubation (TI) within the first 15 min of cardiac arrest.[49] The US CARES registry (Cardiac Arrest Registry to Enhance Survival) of OHCA[50] showed that 52% of patients underwent TI, 29% received a supraglottic airway (SGA), and in 18% no advanced airway was inserted. In the recent AIRWAYS-2 RCT (Effect of a Strategy of a Supraglottic Airway Device Versus Tracheal Intubation During Out-of-Hospital Cardiac Arrest on Functional Outcome),[51] which compared i-gel (Intersurgical Ltd, Berkshire, UK) with TI for OHCA, 17.3% of patients did not receive an advanced airway.

Since 2015, 3 new RCTs investigating airway management during cardiac arrest have been published.[51–53] This topic was given a high priority for review by the ILCOR ALS Task Force, and ILCOR commissioned an SR to identify and analyze all published evidence on advanced airway interventions during OHCA and IHCA.[4] The ALS Task Force analyzed and discussed the SR and all of the studies identified by the SR. A draft ALS CoSTR for advanced airway interventions during cardiac arrest was posted online on March 20, 2019, and included the data reviewed and draft treatment recommendations with comments accepted through April 4, 2019.[54] There were 6798 visits and 16 posted comments during the 2-week comment period. The ALS Task Force reviewed all comments and, in the light of these, reevaluated and finalized the draft CoSTR.

Population, intervention, comparator, outcome, study design, and time frame

Population: Adults any setting (in-hospital or out-of-hospital) with cardiac arrest from any cause

Intervention: A specific advanced airway management method (e.g., TI or an SGA device) during cardiac arrest

Comparators: A different advanced airway management method or no advanced airway management method (e.g., bag-mask ventilation [BMV]) during cardiac arrest

Outcomes: Survival to hospital discharge/28 days with favorable neurological outcome and survival to hospital discharge/28 days ranked as critical outcomes; ROSC ranked as an important outcome

Study designs: RCTs and nonrandomized studies (non-RCTs, interrupted time series, controlled before-and-after studies, cohort studies) that compared at least 2 airway strategies eligible for inclusion; studies with $\leq$10 patients in either group excluded

Time frame: All years and all languages included; unpublished studies (e.g., conference abstracts, trial protocols) excluded; literature search updated to October 30, 2018

PROSPERO registration: CRD42018115556

Consensus on science

Seventy-one observational studies with 121 combinations of different airway management strategies were included in the SR.[4] Of the 71 comparative studies, 61 included OHCA, 9 included IHCA, and 1 combined both. Because of the risk of bias, heterogeneity between studies, and the availability of RCTs, no meta-analyses were performed for observational studies.

The SR identified 11 controlled trials of airway management in patients with OHCA.[51–53,55–62] Of these, 8 were phase 2/feasibility trials with small sample sizes, generally with a high risk of bias, including some that were published >15 years ago.[55–62] Therefore, only 3 trials, all published in 2018, were used for the SR because they were larger and powered for more relevant outcomes.[51,52,53] Because of different comparisons and heterogeneity, no meta-analyses of these RCTs were undertaken (Table 5).

Jabre et al.[52] compared BMV with TI in a physician-based system, whereas Benger et al.[51] and Wang et al.[53] compared SGA devices with TI in non–physician-based systems. The TI success rates were 98% in the Jabre et al. trial, 70% in the Benger et al. trial, and 52% in the Wang et al. trial. Success rates were not defined identically in the 3 studies; this led to concerns about generalizability of the findings. As a result, the task force considered 2 different settings when evaluating the overall certainty of evidence (i.e., the GRADE approach): a setting with a low TI success rate (similar to the systems in the Benger et al. and Wang et al. studies) and a setting with a high TI success rate (similar to the Jabre et al. system).

Overall, there is no high-certainty evidence to recommend an advanced airway strategy over BMV and no high-certainty evidence to recommend a specific advanced airway device over another (Table 5).

Treatment recommendations

We suggest using BMV or an advanced airway strategy during CPR for adult cardiac arrest in any setting (weak recommendation, low to moderate certainty of evidence).

If an advanced airway is used, we suggest an SGA for adults with OHCA in settings with a low TI success rate (weak recommendation, low certainty of evidence).

If an advanced airway is used, we suggest an SGA or TI for adults with OHCA in settings with a high TI success rate (weak recommendation, very low certainty of evidence).

If an advanced airway is used, we suggest an SGA or TI for adults with IHCA (weak recommendation, very low certainty of evidence).

Table 5 – Summary of the evidence from the 3 RCTs studying adult advanced airway management during cardiac arrest.

Study, year	Intervention	Comparator	Setting	Outcome	Risk difference (95% CI)	Certainty in evidence
Wang et al.[53] 2018	Laryngeal tube	TI	OHCA	Survival to hospital discharge	27 more per 1000 (6–48 more)	Low in low TI success setting (OHCA) Very low in high TI success setting (OHCA) Very low (IHCA)
Wang et al.[53] 2018	Laryngeal tube	TI	OHCA	Survival to hospital discharge with a favorable neurological outcome	21 more per 1000 (3–38 more)	Low in low TI success setting (OHCA) Very low in high TI success setting (OHCA) Very low (IHCA)
Benger et al.[51] 2018	i-gel	TI	OHCA	Survival to hospital discharge	4 fewer per 1000 (14 fewer–8 more)	Low in low TI success setting (OHCA) Very low in high TI success setting (OHCA) Very low (IHCA)
Benger et al.[51] 2018	i-gel	TI	OHCA	Survival to hospital discharge with a favorable neurological outcome	6 more per 1000 (16 fewer–4 more)	Low in low TI success setting (OHCA) Very low in high TI success setting (OHCA) Very low (IHCA)
Jabre et al.[52] 2018	BMV	TI	OHCA	28-d survival	1 more per 1000 (18 fewer–21 more)	Low in low TI success setting (OHCA) Moderate in high TI success setting (OHCA) Low (IHCA)
Jabre et al.[52] 2018	BMV	TI	OHCA	28-d survival with a favorable neurological outcome	1 more per 1000 (13 fewer–23 more)	Low in low TI success setting (OHCA) Moderate in high TI success setting (OHCA) Low (IHCA)

BMV indicates bag-mask ventilation; IHCA in-hospital cardiac arrest; OHCA, out-of-hospital cardiac arrest; RCT, randomized controlled trial; and TI, tracheal intubation.

Justification and evidence to decision framework highlights

This topic was given high priority by the ILCOR ALS Task Force, following the publication of 3 new RCTs[51–53] since the previous CoSTR in 2015.[48,63]

The 3 new RCTs have enabled the ALS Task Force to provide more specific treatment recommendations. The 2015 treatment recommendation was based on evidence from only observational studies with critical or serious risk of bias, primarily confounding and selection bias.[48,63]

There is currently no supporting evidence that an advanced airway (i.e., SGA or TI) during CPR improves survival or survival with a favorable neurological/functional outcome after adult cardiac arrest in any setting compared with BMV.

This ILCOR 2019 CoSTR addresses airway management during CPR in adults; it does not address airway management after ROSC. After ROSC, survivors requiring mechanical ventilation and post-resuscitation care will eventually require TI.

We have used the term *advanced airway strategy* because advanced airway device placement usually starts with a variable period of BMV. The timing and reasons for transitioning to an advanced airway device will vary, depending on the clinical scenario. In the 3 recent RCTs,[51–53] patients treated with advanced airways had a period of BMV while providers prepared for device insertion; in some patients, an SGA was inserted as the first airway intervention without BMV. The term *advanced airway strategy* includes all of these options.

We have not provided a precise value or range of values for low and high intubation success rate or an agreed-on definition. Studies have used different definitions of TI success. We considered the Wang et al.[53] and Benger et al.[51] RCTs as having a low TI success rate (51.6% and 69.8%, respectively) and the Jabre et al.[52] RCT as having a high success rate (97.9%).

We assumed that TI success rates are high in the in-hospital setting, but there is limited evidence to support this, and success is likely to be site dependent. The recommendations for IHCA are based primarily on indirect evidence from the OHCA studies. There are no airway RCTs for IHCA, and the task force did consider the findings of 1 large (n = 71,615) observational study of IHCA that TI within any given minute during the first 15 min of resuscitation, compared with no intubation during that minute, was associated with decreased survival to hospital discharge.[49] This study used a time-dependent propensity score but did not eliminate confounding by indication and provided only very-low-certainty evidence.

We have not expressed a preference for a particular SGA device of those currently available (i-gel was used in the Benger et al.[51] RCT, and the Laryngeal Tube [VBM Medizintechnik GmbH, Sulz am Neckar, Germany] was used in the Wang et al.[53] RCT). The performance of individual SGA devices varies; therefore, we did not pool data from these 2 studies.

BMV can be difficult to perform, and effectiveness varies according to provider skills. We have not evaluated the optimal bag-mask technique (e.g., 1-person or 2-person methods) and the use of adjuncts such as oropharyngeal or nasopharyngeal airways.

The task force considered that the preferred airway option is likely to depend on the skills of the provider and the specific patient circumstances. In addition, patients may require different airway interventions at different stages of resuscitation.

ALS task force knowledge gaps

The task force identified several knowledge gaps requiring further investigation:

- A prospective comparison of BMV with SGA use
- The optimal airway management strategy for IHCA
- The impact on outcome of using an advanced airway (SGA or TI) without prior BMV
- The optimal SGA for use during cardiac arrest
- The optimal time point during CPR to change to different airway techniques
- The impact of different airway strategies on CPR quality (no-flow time), as well as oxygenation and ventilation during CPR
- The training and clinical experience required to maintain proficiency in an airway technique

Use of vasopressors in cardiac arrest

Vasopressors have been used in CPR since animal experiments in the 1960s, despite a lack of RCT evidence in humans at the time.[64,65] In the past 20 years, several human RCTs have provided evidence for vasopressor use for cardiac arrest. ILCOR has reviewed the use of vasopressors regularly, with the most recent update in 2015.[48,63] The ILCOR ALS Task Force targeted the current update after the 2018 publication of a new large RCT on the use of epinephrine in OHCA.[66] This updated CoSTR summary is derived from an ILCOR-commissioned SR and meta-analysis completed in 2019.[5] The ALS Task Force analyzed and discussed the SR and all of the studies identified by the SR. A draft CoSTR for vasopressors in cardiac arrest was posted online on March 20, 2019, and included the data reviewed and draft treatment recommendations with comments accepted through April 4, 2019.[67] This site was viewed 3861 times during the comment period, and 6 comments were posted. The ALS Task Force reviewed the comments and, in light of these comments, reevaluated and finalized the draft CoSTR.

Population, intervention, comparator, outcome, study design, and time frame

Population: Adults (age >18 years) with cardiac arrest in any setting (out of hospital or in hospital)

Intervention: Vasopressor or a combination of vasopressors provided intravenously or intraosseously during CPR

Comparators: No vasopressor, a different vasopressor, or a combination of vasopressors provided intravenously or intraosseously during CPR

Outcomes: Short-term survival (ROSC and survival to hospital admission), midterm survival (survival to hospital discharge, 28 days, 30 days, or 1 month), midterm favorable neurological outcomes (Cerebral Performance Category [CPC] 1–2 or modified Rankin Scale score 0–3 at hospital discharge, 28 days, 30 days, or 1 month), and long-term unfavorable and poor (modified Rankin Scale score 4–5) neurological outcomes (after 1 month)

Study designs: Randomized trials, nonrandomized trials, and observational studies (cohort and case-control studies) with a comparison group included

Time frame: From inception of databases to November 23, 2018

PROSPERO registration: CRD42018116989

Consensus on science

Epinephrine compared with placebo. For the comparison of epinephrine with placebo, there are 2 RCTs with a total of >8500 patients with OHCA that provide evidence on our critical and important outcomes[66,68] but no RCTs of IHCA. The PARAMEDIC2 trial (A Randomized Trial of Epinephrine in Out-of-Hospital Cardiac Arrest) is a recent RCT that randomized ≈8000 patients with OHCA managed by paramedics in the United Kingdom,[66] and the PACA trial (Placebo-Controlled Trial of Adrenaline in Cardiac Arrest) randomized ≈500 patients with OHCA managed by paramedics in Western Australia.[68] A meta-analysis of these studies was conducted to update the CoSTR for epinephrine use during CPR.[5]

The findings of the SR and meta-analysis for all initial rhythms are summarized in Table 6. Only the most recent study reported 3-month survival.[66] That study found a statistically significant increase in survival at 3 months in the epinephrine group but no statistical differences in survival with favorable or unfavorable neurological outcome at 3 months. The meta-analysis of the 2 studies found no benefit in favorable neurological outcome at discharge but showed higher rates of survival to discharge, survival to admission, and ROSC in the epinephrine group.[66,68]

In the subgroup of patients with nonshockable rhythms, combined evidence from the 2 RCTs showed benefit of epinephrine for survival to discharge (moderate certainty; RR, 2.56 [95% CI, 1.37–4.80]; ARD, 0.6% [95% CI, 0.1–1.5]) and ROSC (high certainty; RR, 4.45 [95% CI,

Table 6 – RR and ARD for each outcome with epinephrine compared with placebo.

Study, year	Outcome	RR (95% CI)	ARD (95% CI)	Certainty in evidence
Perkins et al.[66] 2018	Favorable neurological outcome at 3 mo	1.30 (0.94–1.80)	5 more per 1000 (1 fewer–13 more)	Low
Perkins et al.[66] 2018	Survival at 3 mo	1.40 (1.07–1.84)	9 more per 1000 (2–18 more)	Moderate
Jacobs et al.[68] 2011 Perkins et al.[66] 2018	Favorable neurological outcome at hospital discharge	1.21 (0.90–1.62)	4 more per 1000 (2 fewer–12 more)	Moderate
Jacobs et al.[68] 2011 Perkins et al.[66] 2018	Survival to hospital discharge	1.44 (1.11–1.86)	10 more per 1000 (2–19 more)	Moderate
Jacobs et al.[68] 2011 Perkins et al.[66] 2018	ROSC	3.09 (2.82–3.39)	243 more per 1000 (211–277 more)	High

ARD indicates absolute risk difference; ROSC, return of spontaneous circulation; and RR, relative risk.

3.91−5.08]; ARD, 25.4% [95% CI, 21−30]).[66,68] There was no difference in survival to discharge with favorable neurological outcome (low certainty).[66] In data pending publication from the larger, more recent trial, the subgroup with nonshockable rhythms showed no difference in survival to 3 months with favorable neurological outcome, although this result approached significance (very low certainty; RR, 3.03 [95% CI, 0.98−9.38]; ARD, 0.3% [95% CI, 0−1.1]).[66,69]

In the subgroup of patients with shockable rhythms, combined evidence from the 2 RCTs showed benefit of epinephrine for ROSC (moderate certainty; RR, 1.68 [95% CI, 1.48−1.92]; ARD, 18.5% [95% CI, 13.0−25.0]) but no difference for survival to discharge.[66,68] In data pending publication from the larger, more recent trial, the subgroup with shockable rhythms showed no difference in survival to 3 months with favorable neurological outcome.[69]

Vasopressin compared with epinephrine. Three RCTs with >1500 patients with OHCA compared vasopressin with epinephrine; all were published >10 years ago.[70−72] The combined results of these studies showed no benefit of vasopressin compared with epinephrine across all outcomes and initial rhythms.

One RCT included 200 patients with IHCA randomized to vasopressin or epinephrine with any initial rhythm and showed no benefit from the use of vasopressin compared with epinephrine.[73]

Initial epinephrine plus vasopressin compared with epinephrine only. Three RCTs with >3000 patients with OHCA compared epinephrine plus vasopressin with epinephrine only; all were published >8 years ago.[74−76] The combined results of these studies showed no benefit across all outcomes and initial rhythms. There were no in-hospital studies of this comparison.

Treatment recommendations

We recommend administration of epinephrine during CPR (strong recommendation, low to moderate certainty of evidence).

For nonshockable rhythms (pulseless electrical activity/asystole), we recommend administration of epinephrine as soon as feasible during CPR (strong recommendation, very low certainty of evidence).

For shockable rhythms (ventricular fibrillation/pulseless ventricular tachycardia), we suggest administration of epinephrine after initial defibrillation attempts are unsuccessful during CPR (weak recommendation, very low certainty of evidence).

We suggest against the administration of vasopressin in place of epinephrine during CPR (weak recommendation, very low certainty of evidence).

We suggest against the addition of vasopressin to epinephrine during CPR (weak recommendation, low certainty of evidence).

Justification and evidence to decision framework highlights

The ILCOR ALS Task Force prioritized this population, intervention, comparator, outcome, study design, and time frame after the recent publication of a large RCT comparing administration of epinephrine with placebo in >8000 patients with OHCA.[66] The collective evidence from the recent trial and a small earlier RCT showed that epinephrine for OHCA increases ROSC, survival to discharge, and survival at 3 months, but epinephrine has not been shown definitively to increase survival to discharge with favorable neurological outcome.[5,66,68] The more recent trial, which was also the only one reporting outcomes at 3 months, found no difference in survival with favorable or unfavorable neurological outcome at the 3-month time point.[66] The lack of statistical difference in survival with favorable and unfavorable outcome at 3 months may reflect the low event rates for these outcomes and the consequent failure to achieve the optimal sample size for these outcomes, resulting in low power to detect a difference. The increase in survival with favorable neurological outcome at 3 months approaches statistical significance for nonshockable initial rhythms, with the lower limit of the CI being very close to 1. Whether the difference in neurological outcome would be larger in a patient population with higher overall survival than that seen in the PARAMEDIC2 trial is unknown. A very high value is placed on the apparent life-preserving benefit of epinephrine, even if the absolute effect size is likely to be small. Although the PARAMEDIC2 study raised concerns about increasing the number of survivors with unfavorable neurological outcome, the opinion of the ALS task force is that the data at 3 months do not support this assertion. Overall, the impact of epinephrine administration on neurological outcome for patients with OHCA remains uncertain, but the available data are more suggestive of benefit than harm. Whether the administration of epinephrine earlier than in the available OHCA trials would have a larger beneficial effect also remains uncertain but is suggested by observational data. That stated, the ALS Task Force acknowledged the importance of considering the cost burden incurred with a potential increase in short-term survival with unfavorable neurological outcome. Conversely, an increase in ROSC may allow the development of other treatments to prevent or mitigate neurological injury. The opportunity for families to see patients before death and the possibility for organ donation were additional potential benefits of the increase in short-term survival that were considered. The task force recognized that different healthcare systems and different cultures may weigh these costs and benefits differently. A formal cost-effectiveness analysis was not performed, and this remains a knowledge gap.

The use of vasopressin alone or in combination with epinephrine was not shown to be beneficial compared with epinephrine alone; thus, epinephrine alone is recommended because it reduces complexity.

There is a statistically significant benefit of standard-dose epinephrine compared with placebo on survival to hospital discharge in patients with OHCA with nonshockable initial rhythms but not in those with shockable initial rhythms (although epinephrine improved ROSC in all rhythms). Because these are subgroup comparisons, however, and were not separately randomized, the results should be interpreted with some caution. For example, the lack of a statistically significant difference in shockable rhythms may result from inadequate power because there were far fewer patients in this subgroup than in the nonshockable rhythms groups.

In most cases of nonshockable rhythms, there are limited alternative interventions, and survival is very poor unless a reversible cause is identified and treated. Therefore, we recommend provision of epinephrine as soon as feasible in cardiac arrest with nonshockable rhythms. Exceptions may exist when a clear reversible cause can be addressed rapidly.

The optimal timing for epinephrine in patients with shockable rhythms is unknown. The studies evaluating administration of epinephrine used protocols for epinephrine administration after the third shock. The task force agrees that it seems prudent to wait to administer epinephrine until initial defibrillation attempts have been unsuccessful. However, the optimal timing and number of shocks after which epinephrine should be administered remain unclear.

There are also very limited data to guide the specific dosing of epinephrine during CPR. The 2 OHCA RCTs comparing epinephrine with placebo used standard-dose epinephrine (1 mg intravenously or intraosseously every 3–5 min). Although this CoSTR did not separately evaluate high-dose epinephrine because no new evidence was found, a previous ILCOR review did not find evidence of a survival benefit for high-dose epinephrine. Thus, the evidence to date supports the dosing used in the 2 RCTs included in the meta-analysis in the current review.

There is limited RCT evidence on the use of epinephrine for IHCA. No studies have assessed the use of standard-dose epinephrine compared with placebo in the in-hospital setting, and only 1 study examined the use of vasopressin compared with epinephrine.[77] There was no statistical benefit or harm from the administration of vasopressin compared with epinephrine for in-hospital CPR. Therefore, using the evidence for OHCA, the ILCOR ALS Task Force decided to make the same recommendations for epinephrine administration for IHCA and OHCA.

ALS task force knowledge gaps

With the recent publication of a large RCT comparing epinephrine with placebo in OHCA, we have greater confidence in the benefit of epinephrine for survival to discharge and ROSC. However, the effect of epinephrine on neurological outcomes is still uncertain and remains an important knowledge gap. The task force identified several other knowledge gaps requiring further investigation:

- The long-term neurological benefit of epinephrine in cardiac arrest
- The optimal dose of epinephrine and dosing interval
- The use and optimal timing of epinephrine administration in patients with shockable rhythms
- The use of epinephrine for IHCA
- The cost-effectiveness of epinephrine
- The effect of different routes of administration (intravenous versus intraosseous)
- The effect of increased ROSC on organ donation
- Effective therapies to prevent or mitigate against neurological injury associated with cardiac arrest

ECPR for cardiac arrest: adults

ECPR is used to support circulation in patients with cardiac arrest refractory to conventional CPR.[78] ECPR maintains vital organ perfusion while potential reversible causes of the cardiac arrest can be identified and treated. ECPR can be considered in select patients when rapid expert deployment is possible; however, the optimal patient selection and timing of the therapy are not well defined. An SR was undertaken by ILCOR to assess the effectiveness of ECPR, compared with manual or mechanical CPR, for OHCA and IHCA of all causes in adults and children.[6] A draft CoSTR posted for public comment was viewed 1169 times in the 2-week comment period.[79] The task force reviewed the 4 posted comments and considered the suggestions when finalizing the Justification and Evidence to Decision Framework Highlights section.

Population, intervention, comparator, outcome, study design, and time frame

Population: Adults (age ≥18 years) and children (age <18 years) with cardiac arrest in any setting (out of hospital or in hospital)

Intervention: ECPR, including extracorporeal membrane oxygenation (ECMO) or cardiopulmonary bypass, during cardiac arrest

Comparator: Manual CPR and/or mechanical CPR

Outcomes: Clinical outcomes, including short-term survival and neurological outcomes (eg, hospital discharge, 28 days, 30 days, and 1 month) and long-term survival and neurological outcomes (eg, 3 months, 6 months, and 1 year)

Study design: Randomized trials, non-RCTs, and observational studies (cohort studies and case-control studies) with a control group included; animal studies, ecological studies, case series, case reports, reviews, abstracts, editorials, comments, and letters to the editor not included

Time frame: All years and all languages included

PROSPERO registration: CRD42018085404

Note: The pediatric information is summarized in a later section of this document (see the ECPR: Infants and Children section).

Consensus on science

No randomized clinical trials were identified. Selected summary data are included in Table 7. Fifteen of the included studies were in adult OHCA.[80,82,85,87–89,91–94,97–101] Three studies included both patients with OHCA and those with IHCA.[82,89,99] Most studies defined the exposure as ECPR use; 1 study93 defined the exposure as ECPR availability; and 2 studies[100,101] defined the exposure as an ECPR strategy. Twelve studies reported survival to hospital discharge[80,82,85,87–89,91–93,97–99]; 6 studies reported long-term survival[82,88,91,93,97,98]; 8 studies reported favorable neurological outcome at hospital discharge[85,87,88,92,93,97,100,101]; and 6 studies reported long-term favorable neurological outcomes.[88,91,93,94,97,98]

Seven of the included studies were in adult IHCA.[81,83,84,86,90,95,96] Most of these studies defined the exposure as ECPR use, although 2 studies[95,96] defined the exposure as an ECPR attempt. Six studies reported survival to hospital discharge[81,83,86,90,95,96]; 6 studies reported long-term survival[81,83,86,90,95,96]; 5 studies reported favorable neurological outcome at hospital discharge[81,83,90,95,96]; and 5 studies reported long-term favorable neurological outcome.[81,83,90,95,96] Four studies reported survival analyses with length of follow-up ranging from 1 to 3 years.[81,83,84,90]

For studies in both OHCA and IHCA, the overall certainty of evidence was rated as very low for all outcomes. All individual studies were at a very serious risk of bias, mainly because of confounding. As a result of this confounding and a high degree of heterogeneity, no meta-analyses could be performed, and individual studies are difficult to interpret.

Treatment recommendations

We suggest that ECPR may be considered as a rescue therapy for selected patients with cardiac arrest when conventional CPR is failing in settings in which it can be implemented (weak recommendation, very low certainty of evidence).

Justification and evidence to decision framework highlights

In making this weak recommendation, we have considered the extremely high mortality rate of patients with cardiac arrest, particularly when the arrest is refractory to standard advanced cardiac life support interventions (i.e., cardiac arrest when conventional CPR is failing). Therefore, the potential for benefit and the value of this intervention remain despite the overall low certainty of supporting evidence and lack of randomized trials.

Table 7 – Summary of adult ECPR studies.

Study, year	Country	Years of patient inclusion	IHCA vs OHCA	Inclusion criteria	Patients analyzed, n	Covariates included in adjusted analysis	Hospital discharge/1 mo		
							Exposed, n (%)	Unexposed, n (%)	Adjusted results, OR or RR (95% CI)
Agostinucci et al.[80] 2011	France	2005–2010	OHCA	Use of load- distributing band	285	NA	0/27 (0)	3/258 (1)	NR
Blumenstein et al.[81] 2015	Germany	2009–2013	IHCA	Cardiovascular admission, witnessed	353	Age, APACHE II score, CPR duration, obesity, dyslipidemia, coronary artery disease, lactate, creatine kinase, eGFR, creatinine, ICU, OR, dose of norepinephrine	14/52 (27)	9/52 (17)	1.76 (0.68–4.53) (calculated)
Cesana et al.[82] 2018	Italy	2011–2015	Combined	Age 18–75 y, witnessed, proven ischemic origin, absence of severe comorbidities that would have precluded ICU admission and conditioning in the short-term prognosis	148	NA	13/63 (21)	49/85 (58)	NR
Chen et al.[83] 2008	Taiwan	2004–2006	IHCA	Age 18–75 y, CPR for >10 min, cardiac origin, witnessed	92	Age, sex, initial cardiac rhythm, time point of CPR, CPR duration, comorbidities	15/46 (33)	8/46 (17)	2.30 (0.86–6.13) (calculated)
Cho et al.[84] 2014	Korea	2001–2013	IHCA	Pulmonary embolism	20	Hypertension, CPR duration	NR	NR	NR
Choi et al.[85] 2016	Korea	2011–2015	OHCA	Nontraumatic, age ≤75 y, witnessed cardiac arrest, bystander administration of CPR or no-flow time ≤5 min, prehospital low- flow time ≤30 min and refractory arrest >10 min of conventional CPR in the ED, known absence of severe comorbidities that preclude admission to the intensive care unit	60	NA	3/10 (30)	4/50 (8)	NR
Chou et al.[86] 2014	Taiwan	2006–2010	IHCA	Age >18 y, acute myocardial infarction in the ED, CPR for >10 min	66	NA	NR	NR	1.93 (0.60–6.23) (unadjusted)
Hase et al.[87] 2005	Japan	1999–2003	OHCA	Presumed cardiac cause	100	NA	13/38 (34)	27/62 (44)	NR
Kim et al.[88] 2014	Korea	2006–2013	OHCA	Age >18 y, not traumatic	104	Age, sex, comorbidity score, bystander CPR, witnessed cardiac arrest, first documented arrest rhythm, presumed cause of arrest, interval from arrest to CPR started by EMS provider,	9/52 (17)	11/52 (21)	0.78 (0.29–2.08) (calculated)

(continued on next page)

Table 7 *(continued)*

Study, year	Country	Years of patient inclusion	IHCA vs OHCA	Inclusion criteria	Patients analyzed, n	Covariates included in adjusted analysis	Hospital discharge/1 mo		
							Exposed, n (%)	Unexposed, n (%)	Adjusted results, OR or RR (95% CI)
						CPR duration, and therapeutic hypothermia			
Lee et al.[89] 2015	Korea	2009–2014	Combined	NR	955	Age, main diagnosis, location, CPR duration, initial rhythm, hypertension, malignancy, stroke, chronic renal failure, cardiovascular disease	18/81 (22)	120/874 (14)	0.37 (0.13–1.06)
Lin et al.[90] 2010	Taiwan	2004–2006	IHCA	Age 18–75 y, cardiac origin, CPR duration >10 min, ROSC	54	Age, sex, initial rhythm, CPR duration, timing and location, comorbidities (diabetes mellitus, hypertension, dyslipidemia, malignancy, COPD, cardiovascular or cerebrovascular, abnormal liver function, dialysis)	8/27 (30)	5/27 (19)	1.85 (0.52–6.63) (calculated)
Maekawa et al.[91] 2013	Japan	2000–2004	OHCA	Presumed cardiac origin, age >16 y, witnessed, CPR duration >20 min	48	Not clear but probably age, sex, activities of daily living, location of OHCA, bystander CPR, initial rhythm, number of shocks, airway insertion, venous access, physician- staffed ambulance, ROSC during transport, times, TTM, IABP, PCI, CPR duration, time from arrest to ALS	9/24 (38)	3/24 (13)	4.20 (0.97–18.2) (calculated)
Poppe et al.[92] 2015	Austria	2013–2014	OHCA	Age >18 y, ongoing CPR	96	NA	2/12 (17)	8/84 (10)	NR
Sakamoto et al.[93] 2014	Japan	2008–2011	OHCA	Shockable rhythm, cardiac arrest on arrival, within 45 min from reception of the emergency call or the onset of cardiac arrest to the hospital arrival, no ROSC at least during the 15 min after hospital arrival	454	NA	69/260 (27)	12/193 (6)	NR
Schober et al.[94] 2017	Austria	2002–2012	OHCA	Cardiac origin, CPR duration >30 min	239	NA	NR	NR	NR
Shin et al.[95] 2011, Shin et al.[96] 2013	Korea	2003–2009	IHCA	Age 18–80 y, CPR duration >10 min, witnessed	120	Age, sex, comorbidities, clinical situation, cause of the arrest, location, year, time during day and	19/60 (32)	6/60 (10)	4.17 (1.53–11.4) (calculated)

Table 7 *(continued)*

Study, year	Country	Years of patient inclusion	IHCA vs OHCA	Inclusion criteria	Patients analyzed, n	Covariates included in adjusted analysis	Hospital discharge/1 mo		
							Exposed, n (%)	Unexposed, n (%)	Adjusted results, OR or RR (95% CI)
Charlson score, post-						week, initial rhythm, CPR duration, prearrest SOFA score, Deyo-			
CPR variables									
Siao et al.[97] 2015	Taiwan	2011–2013	OHCA	Age 18–75 y, ventricular fibrillation, no-flow <5 min, refractory cardiac arrest	60	Age, CPR duration, defibrillation, female sex, use of therapeutic hypothermia	10/20 (50)	11/40 (28)	4.10 (0.79–21.3)
Tanno et al.[98] 2008	Japan	2000–2004	OHCA	Age >16 y, cardiac origin	398	NA	14/66 (21)	25/332 (8)	NR
Venturini et al.[99] 2017	United States	2011–2016	Combined	CPR in cardiac catheterization laboratory, mechanical chest compression	31	NA	1/14 (7)	3/17 (18)	NR
Yannapoulos et al.[100] 2016	United States	2015–2016	OHCA	Age 18–75 y, cardiac cause, initial shockable rhythm, minimum 3 direct-current shocks without ROSC, received amiodarone 300 mg, eligible for mechanical CPR, transfer time from scene to catheterization laboratory <30 min	188	NA	10/18 (53)	NR	NR
Yannapoulos et al.[101] 2017	United States	2015–2016	OHCA	Age 18–75 y, cardiac cause, initial shockable rhythm, minimum 3 direct-current shocks without ROSC, received amiodarone 300 mg, eligible for mechanical CPR, transfer time from scene to catheterization laboratory <30 min	232	NA	28/62 (45)	NR	NR

ALS indicates advanced life support; APACHE II, Acute Physiology, Age, Chronic Health Evaluation II; COPD, chronic obstructive pulmonary disorder; CPR, cardiopulmonary resuscitation; ECPR, extracorporeal cardiopulmonary resuscitation; ED, emergency department; eGFR, estimated glomerular filtration rate; EMS, emergency medical services; IABP, intra-aortal balloon pump; ICU, intensive care unit; IHCA, in-hospital cardiac arrest; NA, not applicable; NR, not reported; OHCA, out-of-hospital cardiac arrest; OR, odds ratio; PCI, percutaneous coronary intervention; ROSC, return of spontaneous circulation; RR, relative risk; SOFA, sequential organ failure assessment; and TTM, targeted temperature management.

The published studies used select patients for ECPR, not the general population of all cardiac arrest cases. Guidelines for ECPR use in clinical practice should ideally apply to similar populations, although RCTs have not been performed to define the optimal population.

We acknowledge that ECPR is a complex intervention that requires considerable resources and training that are not universally available, but we also acknowledge the value of an intervention that may be successful in individuals in whom usual CPR techniques have failed. ECPR can sustain perfusion while another intervention such as coronary angiography and percutaneous coronary intervention can be performed.

ALS task force knowledge gaps

There are currently no published randomized trials of ECPR, although several are pending. The task force identified several knowledge gaps requiring further investigation:

- The optimal post–cardiac arrest care strategy for patients resuscitated with ECPR
- The patient groups most likely to benefit from ECPR
- The optimal ECPR techniques
- The optimal timing to initiate ECPR during resuscitation (i.e., early, late, when in the sequence)
- The potential role of ECPR during the periarrest period
- The population-specific differences in indications for ECPR for IHCA and OHCA
- The differences in quality of life (QOL) between survivors of ECPR and survivors of conventional CPR
- The cost-effectiveness of ECPR

Pediatric life support

The Pediatric Life Support Task Force reviewed 4 topics for this 2019 CoSTR: DA-CPR, advanced airway interventions in pediatric cardiac arrest, ECMO CPR (ECPR), and TTM during post–cardiac arrest care. An SR was published for each of these topics.[3,6–8] The Pediatric Life Support Task Force then reviewed the SR and the studies identified by the SR and generated a CoSTR that was posted on the ILCOR website for public comments for each topic. This document contains a summary of the 4 CoSTRs, including information about task force deliberations and insights.

Dispatcher instruction in CPR

DA-CPR—pediatrics

ILCOR commissioned an SR to identify and analyze all published evidence reporting outcomes of offering DA-CPR for OHCA in infants and children.[3] The Pediatric Life Support Task Force analyzed and discussed the SR and all of the studies identified by the SR, developed a draft CoSTR, and posted it online for public comment.[102] The draft CoSTR was visited 1736 times during the 2-week comment period. The task force reviewed the 2 posted comments; both endorsed the summary of science and treatment recommendation.

The emergency medical dispatcher is an essential link in the chain of survival. In addition to dispatching EMS resources to medical emergencies, EMS dispatchers are increasingly being trained to recognize cardiac arrest, to assist bystanders in initiating resuscitation, and to support bystanders in optimizing resuscitation efforts. The international community is continuing to explore ways to increase bystander CPR for cardiac arrests. One such strategy involves dispatchers providing CPR instruction to callers/bystanders: DA-CPR. For such a strategy to be successful, it requires the EMS system to be configured to support the dispatcher to offer DA-CPR and the bystander to deliver CPR with support from the dispatcher.

This COSTR explores the impact of DA-CPR on survival and neurological outcomes after OHCA in infants and children.

Population, intervention, comparator, outcome, study design, and time frame

Population: Infants and children with presumed cardiac arrest in out-of-hospital settings

Intervention: Patients/cases or EMS systems where DA-CPR is offered

Comparators: Studies with comparators where either systems or specific cardiac arrest cases are not offered dispatch-assisted CPR

Outcomes (critical outcomes included): Survival with favorable neurological function (at hospital discharge, 1 month, or 6 months), survival (hospital discharge, 1 month, or 1 year), short-term survival (ROSC, hospital admission), and provision of bystander CPR; important outcomes were initial shockable rhythm and time to CPR

Study designs: RCTs and nonrandomized studies (non-RCTs, interrupted time series, controlled before-and-after studies, cohort studies) eligible for inclusion

Time frame: All years and all languages included with the last search performed July 1, 2018; ongoing or unpublished studies identified through a search of ClinicalTrials.gov online registry[16]

PROSPERO registration: CRD42018091427

Consensus on science

Four studies were included in the SR comparing the outcomes for children with OHCA when bystanders were offered DA-CPR.[25,26,39,103] All the studies were cohort studies of registry data: 2 from the same registry in Japan and 2 from the same registry in Korea. When the overlapping populations from the same source (registry) were reported for the same outcome, the larger of the 2 studies was used in the analysis.[26,39] The studies by Goto and colleagues26 and Chang and colleagues[39] included adjusted analyses.

There were 2 major groups for outcome comparisons:

- Those patients from systems that included DA-CPR compared with those from systems that offered no dispatcher CPR assistance; in 1 study, 25% of bystanders who were offered DA-CPR did not actually provide CPR.26
- Those patients who actually received DA-CPR compared with those who did not receive DA-CPR; the group who did not receive DA-CPR was subdivided into those who received unassisted CPR and those who received no CPR.

Because all studies the task force evaluated were nonrandomized, any reported findings must be considered as occurring in association with the CPR (the intervention) provided rather than as caused by it.

Cardiac arrest outcomes in EMS systems with and without DA-CPR. One study from the All-Japan Utstein Registry[26] reported neurological outcome at 1 month in a cohort of 4306 infants and children with OHCA. There was no association in either adjusted or unadjusted analysis between favorable neurological outcome at 1

Table 8 – Comparison of outcomes of infants and children with OHCA in EMS systems with and without DA-CPR programs (i.e., DA-CPR offered versus not offered).

Outcomes (importance)	Pediatric participants (studies), n	Certainty of evidence (GRADE)	OR or RR (95% CI)[a]	RD with DA-CPR and no DA-CPR
Survival with favorable neurological outcome at 1 mo (critical)	4306 (1 cohort study)[26]	Very low	RR, 1.03 (0.73–1.46) AOR, 1.45 (0.98–2.15); $P=0.06$	1 more per 1000 (8 fewer–14 more)
Survival to 1 mo (critical)	4306 (1 cohort study)[26]	Very low	RR, 1.15 (0.95–1.40) AOR, 1.46 (1.05–2.03); $P=0.02$	14 more per 1000 (4 fewer–35 more)
Delivery of bystander CPR (critical)	3309 (2 studies)[25,31] 4306 (1 cohort study)[26]	Low Moderate	RR, 2.25 (2.05–2.47) AOR, 7.51 (6.58–8.57); $P<0.0001$	315 more per 1000 (188–437 more)
Shockable initial rhythm (important)	4306 (1 cohort study)[26]	Very low	RR, 0.82 (0.61–1.10)	8 fewer per 1000 (5–18 fewer)
Arrest to CPR initiation (important)	4306 (1 cohort study)[26]	Very low	Shorter time to CPR: median, 4 (IQR, 1–9) min with DA-CPR vs 11 (IQR 7–16) min; $P<0.000$	

AOR indicates adjusted odds ratio; CPR, cardiopulmonary resuscitation; DA-CPR, dispatcher-assisted cardiopulmonary resuscitation; EMS, emergency medical services; GRADE, Grading of Recommendations, Assessment, Development, and Evaluation; IQR, interquartile range; OHCA, out-of-hospital cardiac arrest; OR, odds ratio; RD, risk difference; and RR, relative risk.

[a] RRs are presented for unadjusted analyses, and ORs are presented for adjusted analyses.

month and systems offering DA-CPR compared with such outcomes in systems not offering DA-CPR. The same study from Japan did not document any association between improved survival at 1 month and DA-CPR in the unadjusted analysis, but such an association was suggested in the adjusted analysis. In a separate analysis, there was no association between the incidence of shockable pediatric arrest rhythms and systems offering DA-CPR.[26]

Three studies examined the delivery of bystander CPR in systems that offered DA-CPR compared with those that did not. In addition to the All-Japan study reported by Goto et al.,[26] 2 studies[25,31] included unadjusted analysis of 3309 children with OHCA. These studies reported a significantly higher rate of CPR in the cohorts offered DA-CPR in both unadjusted and adjusted analyses. In addition, the Goto et al. All-Japan study reported earlier time to CPR initiation associated with systems that offered DA-CPR compared with those that did not.[26] Table 8 provides additional information.

Cardiac arrest outcomes in infants and children with OHCA who received bystander DA-CPR compared with those who received no CPR. Goto et al.[26] and Chang et al.[39] reported the association of significantly improved neurological outcomes and DA-CPR compared with no CPR. In both unadjusted and adjusted data from the Goto et al. series, there were significantly higher rates of favorable neurological outcome (CPC 1 and 2) at 1 month associated with those who received DA-CPR compared with those who received no CPR. There were also significantly higher rates of survival to 1 month in the DA-CPR cohort in both unadjusted and adjusted analyses.[26] In both adjusted and unadjusted analyses, the Chang et al. observational study of 1661 children with OHCA reported an association between significantly improved likelihood of favorable neurological outcome at hospital discharge and survival to hospital discharge and DA-CPR compared with no CPR.[39] Table 9 gives further information.

In comparisons of infants and children receiving DA-CPR with those receiving unassisted bystander CPR, Goto et al.[26] reported lower rates of favorable neurological outcome and survival at 1 month in the DA-CPR group. Chang et al.,[39] however, found no difference in either survival or favorable outcome at discharge between those receiving DA-CPR and those receiving unassisted bystander CPR. Chang et al. reported an increase in rates of sustained ROSC associated with DA-CPR compared with no CPR but documented no such increase when comparing those who received DA-CPR with those who received unassisted bystander CPR.[39]

Both the Goto et al.[26] and Chang et al.[39] studies examined the presence of a shockable rhythm as an outcome. The pooled data did not document an association between an increased presence of shockable rhythm and receipt of DA-CPR compared with those who received no CPR, and there was a negative association when those receiving DA-CPR were compared with those receiving unassisted CPR.

Not surprisingly, Goto et al.[26] and Chang et al.[39] reported an association between DA-CPR and shorter times to CPR initiation compared with the group with no bystander CPR. These 2 studies, however, reported that time to CPR initiation was longer in the DA-CPR than in the unassisted bystander CPR cohort. Table 10 provides further information.

Treatment recommendations

We recommend that EMS dispatch centers offer dispatch CPR instruction (DA-CPR) for presumed pediatric cardiac arrest (strong recommendation, very low certainty of evidence).

We recommend that emergency dispatchers provide CPR instruction for pediatric cardiac arrest when no bystander CPR is in progress (strong recommendation, very low certainty of evidence).

We cannot make a recommendation for or against emergency dispatch provision of CPR instructions for pediatric cardiac arrest when bystander CPR is already in progress (no recommendation, very low certainty of evidence).

Justification and evidence to decision framework highlights

This topic was prioritized by the Pediatric Life Support Task Force after publication of several new studies since the previous pediatric SR was published in 2011. The 2011 review found limited evidence to support DA-CPR.[104] In considering the importance of this topic, the Pediatric Life Support Task Force noted that bystander CPR significantly improves the likelihood of survival after OHCA, but bystander CPR rates remain very low.[105]

Table 9 – Comparison of outcomes of infants and children with OHCA who received bystander DA-CPR compared with those who received no CPR.

Outcomes (importance)	Participants (studies), n	Certainty of evidence (GRADE)	OR or RR (95% CI)[a]	RD with DA-CPR and no CPR
Survival with favorable neurological outcome at 1 mo (critical)	4306 (1 cohort study)[26]	Very low	RR, 1.47 (1.05–2.07) AOR,1.81 (1.23–2.67); $P=0.003$	12 more per 1000 (1–26 more)
Survival with favorable neurological outcome at hospital discharge (critical)	1661 (1 cohort study)[39]	Low	RR, 3.43 (2.10–5.59) AOR, 2.22 (1.27–3.88); $P=0.005$	54 more per 1000 (25–99 more)
Survival at 1 mo (critical)	4306 (1 cohort study)[26]	Very low	RR, 1.38 (1.15–1.65) AOR, 1.63 (1.32–2.01); $P<0.0001$	31 more per 1000 (12–53 more)
Survival to hospital discharge (critical)	1661 (1 cohort study)[39]	Moderate Low	RR, 2.87 (2.02–4.06) AOR, 2.23 (1.47–3.38); $P=0.002$	84 more per 1000 (47–132 more)
Sustained ROSC (critical)	1661 (1 cohort study)[39]	Very low	RR, 2.68 (1.94–3.70)	89 more per 1000 (51–137 more)
Shockable initial rhythm (important)	5967 (2 cohort studies)[26,39]	Very low	RR, 1.52 (0.81–2.86)	26 more per 1000 (10 fewer–89 more)
Arrest to CPR initiation (important)	4306 (1 cohort study)[26] 1265 (1 cohort study)[31]	Very low	Shorter time with DA-CPR: median, 1 (IQR, 0–5) vs 11 (IQR, 7–15) min Shorter time with DA-CPR: median, 4 (IQR, 0–13) vs 10 (IQR, 6–18) min; $P=0.01$	

Table 10 – Outcomes of infants and children with OHCA who received bystander DA-CPR compared with those who received unassisted bystander CPR.

Outcomes (importance)	Participants (studies), n	Certainty of evidence (GRADE)	RR (95% CI)*	RD with DA-CPR and unassisted CPR
Survival with favorable neurological outcome at 1 mo (critical)	2722 (1 cohort study)[26]	Very low	0.59 (0.41–0.84)	26 fewer per 1000 (9–37 fewer)
Survival with favorable neurological outcome at hospital discharge (critical)	970 (1 cohort study)[39]	Very low	0.97 (0.61–1.56)	2 fewer per 1000 (32 fewer–43 more)
Survival at 1 mo (critical)	2722 (1 cohort study)[26]	Very low	0.77 (0.62–0.95)	34 fewer per 1000 (6–57 fewer)
Survival at hospital discharge (critical)	1661 (1 cohort study)[39]	Very low	0.99 (0.69–1.41)	2 fewer per 1000 (42 fewer–51 more)
Sustained ROSC (critical)	1661 (1 cohort study)[39]	Very low	0.84 (0.62–1.16)	26 fewer per 1000 (26 more–66 fewer)
Shockable initial rhythm	3692 (2 cohort studies)[26,39]	Very low	0.54 (0.35–0.82)	61 fewer per 1000 (31–83 fewer)
Arrest to CPR initiation	2722 (1 cohort study)[26] 766 (1 cohort study)[31]	Very low Very low	Longer time with DA-CPR: median, 4 (IQR, 0–13) vs 1 (IQR, 0–5) min Longer time with DA-CPR: median, 4 (IQR, 0–13) vs 2 (IQR, 0–10) min	

In developing the CoSTR, the Pediatric Life Support Task Force agreed that consideration of both unadjusted and adjusted analyses was essential to adequately evaluate the published evidence. We recognize that unadjusted analysis might be confounded by temporal changes and systematic and patient care differences between and within EMS systems.

In making a strong recommendation for dispatch centers to offer DA-CPR despite very-low-certainty evidence, the Pediatric Life Support Task Force considered the benefit for the critical outcome of survival in the adjusted analyses and the large positive effect of increased bystander CPR and reduced time to initiation of CPR when DA-CPR was offered. Implementation of DA-CPR appears to be

acceptable and feasible, as many EMS systems have demonstrated. However, its cost-effectiveness and impact on health equity have not been evaluated and, until documented, may present barriers to implementation in underresourced regions. In addition, successful implementation of any program of DA-CPR requires a process of continuous quality improvement to ensure that dispatchers can quickly identify a likely cardiac arrest and assist the bystander in starting CPR in a very short time.[106]

In making a strong recommendation despite low-certainty evidence, the task force valued the consistency of results indicating benefit for all critical and important outcomes, with the exception of shockable rhythm (no benefit). This failure to demonstrate contributions of DA-CPR to improvement in likelihood of shockable initial rhythm aligns with the adult meta-analysis.[3]

In abstaining from recommending for or against DA-CPR when bystander CPR is already in progress, the task force noted the very-low-certainty evidence available, the consistency of inferior and neutral results for all of the critical outcomes, and the lack of any adjusted analyses for this group. The negative results associated with DA-CPR compared with unassisted bystander CPR may have several potential explanations: Bystander CPR was initiated earlier than DA-CPR because the bystander did not experience the delay resulting from calling a dispatcher and receiving instruction, or the bystanders who performed CPR and refused dispatch assistance were likely trained in CPR and may have provided a higher quality of CPR than that provided by the untrained bystander who required remote dispatch assistance. This particular finding suggests the potential benefits of widespread community-based CPR training.

Consideration of types of DA-CPR systems or interventions to improve the quality of DA-CPR was beyond the scope of this review. A limitation of the evidence that forms the basis of these treatment recommendations is that data are derived from only 2 countries: Japan and Korea. The EMS systems involved may differ in their response to OHCA compared with EMS systems and responses in other regions. Thus, caution is required in attempts to extrapolate these results to different EMS systems of care.

Although this review did not address the content of CPR instructions, we elected to specify that CPR instructions should include rescue breaths for pediatric patients with cardiac arrest to be consistent with previous CoSTRs[107] and to draw attention to this important distinction from adult CPR instructions.

Knowledge gaps

The Pediatric Life Support Task Force identified several knowledge gaps requiring further investigation. The overall challenge is the need to determine whether dispatchers can effectively guide untrained bystanders to provide effective conventional CPR for a child in cardiac arrest. To ensure that consistent analysis is included in all future studies of DA-CPR in children, we recommend the research include/address the following:

- Optimal dispatcher training (and retraining) in recognizing OHCA and in providing DA-CPR for children
- Identification of the specific scripted language used by dispatchers and its effects on the initiation of bystander CPR
- Indication of how CPR instructions are provided (by the phrasing and enunciation of words, video adjuncts via cellphone, etc.)
- Report of the certainty of bystander CPR (including the time required for identification of cardiac arrest, time to initiation of CPR, and whether conventional CPR or chest compression–only CPR was given)
- Inclusion of subsequent in-hospital (postarrest) factors
- Indication of specific dispatcher guidance provided (e.g., to pace the compression rate) when bystander CPR is already initiated
- EMS response times
- Analysis of the cost-effectiveness of DA-CPR
- Content of CPR/DA-CPR instructions, specifically addressing the role of ventilation in infant and child CPR
- Report of long-term outcomes, including QOL outcomes
- Adjustment for variables such as bystander CPR characteristics, patient, age, sex, and previous bystander CPR training

Advanced airway interventions in pediatric cardiac arrest

The management of the airway is central in pediatric resuscitation, particularly because respiratory conditions are a frequent cause of pediatric cardiac arrest. Placement of an advanced airway device such as an SGA or TI may allow more effective resuscitation than the alternative of BMV. However, uncertainties remain about the risk and benefit of each method of managing the airway during CPR. Persistent challenges surround issues of the provision of effective (but not excessive) ventilation; delivery of continuous chest compressions; and risks of failed intubation attempts, unrecognized esophageal intubation, prolonged interruptions in chest compressions, and inadvertent excessive ventilation. These issues can affect the quality of resuscitation.

ILCOR commissioned an SR to identify and analyze all published evidence reporting outcomes of advanced airway placement during CPR in infants and children during OHCA and IHCA.[7] The Pediatric Task Force analyzed and discussed the SR and all of the studies identified by the SR, developed a draft CoSTR, and posted it online for public comment.[108] The draft CoSTR was viewed 341 times during the 2-week comment period. The 4 posted comments endorsed the CoSTR, and all acknowledged the complexity of the issues surrounding use of an advanced airway during pediatric resuscitation and the need for adequate training in all techniques.

Population, intervention, comparator, outcome, study design, and time frame

Population: Infants and children in any setting (in hospital or out of hospital) who have received chest compressions or a defibrillation dose on whom CPR is being performed

Intervention: Placement of an advanced airway device

Comparators: Primary—BMV alone or with non–advanced airway interventions; secondary—another advanced airway device

Outcomes: Any clinical outcome

Study designs: RCTs and nonrandomized studies (non-RCTs, interrupted time series, controlled before-and-after studies, cohort studies) of pediatric patients eligible for inclusion; if insufficient studies available from which to draw a conclusion, case series of $\geq$4 may be included; case reports, unpublished studies, and nonhuman studies excluded

Time frame: All years and all languages included (as long as there is an English abstract); unpublished studies (e.g., conference abstracts, trial protocols) excluded; the last search was performed on September 24, 2018

PROSPERO registration: CRD42018102430

Table 11 – Pediatric studies comparing use of BMV with advanced airways during cardiac arrest.

Study	Years conducted	Setting	Location	Patients/total treated, n (%)					
				Survival with good neurological function			Survival to hospital discharge		
				TI	BMV	SGA	TI	BMV	SGA
Clinical trials									
Gausche et al.[109] 2000	1994–1997	OHCA	United States	10/290 (3.4)	15/301 (5.0)	–	24/290 (8.3)	24/301 (8.0)	–
Observational studies with propensity matching									
Andersen et al.[110] 2016	2000–2014	IHCA	United States	185/987 (18.7)	211/983 (21.4)	–	411/1135 (36.2)	460/1135 (40.7)	–
Hansen et al.[111] 2017	2013–2015	OHCA	United States	34/727 (4.7)	89/781 (11.4)	13/215 (6.0)	51/727 (7.0)	110/781 (14.1)	22/215 (10.2)
Ohashi- Fukuda et al.[112] 2017	2011–2012	OHCA	Japan	0/31 (0.0)	16/346 (4.6)	12/315 (3.8)	4/31 (12.9)	37/346 (11.0)	47/315 (14.9)
Simple observational studies									
Abe et al.[113] 2012	2005–2008	OHCA	Japan	–	–	–	12/185 (6.5)	243/2734 (8.9)	9/270 (3.3)
Aijian et al.[114] 1989	1984–1987	OHCA	United States	–	–	–	1/28 (3.6)	1/14 (7.1)	–
Deasy et al.[115] 2010	1999–2007	OHCA	Australia	–	–	–	13/154 (7.8)	2/26 (7.7)	–
Del Castillo et al.[116] 2015	2007–2009	IHCA	Argentina, Brazil, Columbia, Chile, Ecuador Honduras, Italy, Paraguay, Portugal, Spain	44/71 (71.0)	43/53 (81.1)	–	–	–	–
Guay and Lorti[117] 2004	1983–1987	IHCA	Canada	–	–	–	20/90 (22.2)	30/55 (54.5)	–
Pitetti et al.[118] 2002	1995–1999	OHCA	United States	–	–	–	5/150 (3.3)	0/39 (0.0)	–
Sirbaugh et al.[119] 1999	1992–1995	OHCA	United States	5/229 (2.2)	0/26 (0.0)	–	6/229 (2.6)	0/26 (0.0)	–
Tham et al.[120] 2018	2009–2012	OHCA	Japan, Korea, Malaysia, Singapore, Taiwan, Thailand, United Arab Emirates	3/18 (16.7)	29/791 (3.7)	3/109 (2.8)	3/18 (16.7)	68/791 (8.6)	9/109 (8.3)
Simple observational studies without raw data (analyzed separately from meta-analysis)									
Fink et al.[121] 2016	2007–2012	OHCA	United States	–	–	–	AOR, 0.64 (95% CI, 0.37–1.13) favoring BMV over AAW[a]		–
Tijssen et al.[122] 2015	2005–2012	OHCA	Canada, United States	–	–	–	AOR, 0.69 (95% CI, 0.43–1.10) favoring BMV over AAW[b]		–

AAW indicates advanced airway; AOR, adjusted odds ratio; BMV, bag-mask ventilation; IHCA, in-hospital cardiac arrest; OHCA, out-of-hospital cardiac arrest; SGA, supraglottic airway; and TI, tracheal intubation.

[a] In the study by Fink et al.[121] 92% of AAW attempts were TI attempts.

[b] In the study by Tijssen et al.[122] 93% of AAW attempts were TI attempts.

Consensus on science

The task force reviewed the evidence of outcomes with the following comparisons: TI with BMV, SGA with BMV, and TI with SGA during pediatric cardiac arrest. Detailed information from all studies reviewed is summarized in Table 11. Summative results from 8 of the studies are included in Table 12, which excluded cohort studies with results too heterogeneous to enable meta-analysis.

Studies comparing TI With BMV alone. Fourteen studies were included in the SR comparing TI with BMV, including 1 clinical trial[109] and 13 observational studies.[110–122]

Although the clinical trial was excellent in design and execution, it was downgraded to low certainty as a result of indirectness. The study was conducted in 1994 to 1996, before more recent revisions in resuscitation guidelines that emphasize minimally interrupted chest compressions as part of high-quality CPR. This study assigned 591 children with OHCA to TI or BMV on an odd- and even-day basis. The use of TI resulted in no difference in likelihood of survival with the critical outcome of favorable neurological function or survival to hospital discharge.[109]

The 13 identified observational studies provided evidence of very low or low certainty. Three of these observational studies[110–112] used propensity matching to attempt to control for factors driving the decision to intubate. However, a limitation of all 3 studies was the failure to distinguish patients with unsuccessful attempts at advanced airway placement from those who were managed with BMV alone. When combined, these studies found a reduced likelihood of survival with favorable neurological function or survival to hospital discharge associated with TI. [110–112] The other 10 observational studies found no statistically significant association between TI and these outcomes.[113–120,122,124]

Studies comparing SGA with BMV alone. The 4 observational studies comparing SGA with BMV provided very-low-certainty evidence. Two studies used propensity matching to reduce bias, but both had the limitation of failure to distinguish between patients who had unsuccessful attempts at SGA insertion and those who were managed with BMV without attempted SGA insertion.[111,112] Two other observational studies reported only unadjusted data.[113,120] None of these studies found a significant association between SGA use and survival with favorable neurological function or survival to hospital discharge.

Studies comparing TI with SGA. The evidence comparing TI with SGA during pediatric resuscitation comes from 4 observational studies of OHCA[111–113,120]; 2 of these studies used propensity matching.[111,112] When combined, neither the propensity-matched studies[111,112] nor the unadjusted cohort studies[113,120] found a significant association between the choice of advanced airway and survival with favorable neurological function or survival to hospital discharge.

Treatment recommendations

We suggest the use of BMV rather than TI or SGA in the management of children during cardiac arrest in the out-of-hospital setting (weak recommendation, very low certainty of evidence).

There is insufficient evidence to support any recommendation about the use of TI or SGA in the management of children with cardiac arrest in the in-hospital setting.

Justification and evidence to decision framework highlights

Advanced airway interventions have been long-established components of the advanced life support bundle of care in adults and children. As a result of inherent limitations in their design and data sources, the available studies provide only very-low-certainty evidence about whether attempting advanced airway placement during resuscitation (i.e., before ROSC) improves resuscitation outcomes. The best available data show no benefit from advanced airway interventions, and some suggested association with harm for the critical outcomes of survival with favorable neurological outcome and survival to hospital discharge. The effects of placement of an advanced airway are uncertain for the short-term resuscitation outcomes of survival to hospital admission and ROSC. Although these short-term outcomes do not ultimately benefit the patient, they may benefit the family.

Effective BMV, TI, and insertion of an SGA are all difficult skills that require good initial training, retraining, and quality control to be performed consistently, safely, and effectively. To be effective, pediatric advanced airway programs require a moderate investment in equipment and a significant investment in training, skills maintenance, and quality control programs.

The benefit or harm associated with advanced airway–based resuscitation may differ across settings. The available data do not inform the questions of whether better outcomes might be achieved by advanced airway–based strategies by highly trained and experienced airway operators, during long distance transport, or in prolonged resuscitation situations. The analyzed data are relevant only to advanced airway interventions during CPR and do not pertain to airway management after ROSC or in other critical situations.

Knowledge gaps

This evidence evaluation did not identify any clinical trials addressing airway management during cardiac arrest in the in-hospital setting, and future studies are needed to address this knowledge gap. In addition, the only randomized clinical trial undertaken in the out-of-hospital setting[109] was performed before major changes in resuscitation guidelines; future studies are needed in the out-of-hospital setting. The task force identified several additional knowledge gaps requiring further investigation:

- Prehospital, emergency department–based, and in-hospital studies of similar design comparing TI, SGA, and BMV with planned subgroup analyses based on patient age and cause of arrest
- Studies of advanced airway use in specific contexts such as long-distance transport and prolonged resuscitation situations in the hands of highly trained and experienced airway operators; we have no knowledge about these subgroups, which are likely to be important

ECPR: infants and children

ECPR has been used with increasing frequency as rescue therapy for refractory cardiac arrest. In pediatrics, ECPR is used most frequently after postoperative IHCA associated with congenital heart disease and progression of low cardiac output or arrhythmias, although there are recent reports of applications for cardiac arrest from other causes. This topic was last reviewed by the Pediatric Life Support Task Force in 2015.[125]

ILCOR commissioned an SR to identify and analyze all published evidence reporting outcomes of ECPR in infants, children, and adults after OHCA and IHCA.[6] The Pediatric Life Support Task Force analyzed and discussed the SR and all of the pediatric studies identified by the SR, developed a draft CoSTR, and posted it online for

Table 12 – Summative results of studies used in the pediatric airway systematic review for each comparison and grouped by outcome.

Outcomes (Importance)	Participants (studies), n	Certainty of evidence (GRADE)	RR (95% CI)	Absolute risk with comparator	ARD with intervention
TI (I) vs BMV (C)[a]					
Survival, favorable neurological outcome (critical)	591 (1 RCT)[109]	Low	0.69 (0.32–1.52)	50/1000	15 fewer per 1000 (48 fewer–17 more)
	3855 (3 propensity-matched observational)[110–112]	Very low	[b]	150/1000	49 fewer per 1000 (77–21 fewer)
Survival to hospital discharge (critical)	591 (1 RCT)[109]	Low	1.04 (0.6–1.79)	80/1000	3 more per 1000 (41 fewer–47 more)
	4155 (3 propensity-matched observational)[110–112]	Very low	[c]	268/1000	53 fewer per 1000 (20–87 fewer)
	3992 (2 observational studies)[121,122]	Very low	[c]	Fink et al.[121]: AOR, 0.64 (0.37–1.13)	
Tijssen et al.[122]: AOR, 0.69 (0.43–1.1)					
Survival to hospital admission (important)	1508 (1 propensity-matched observational)[111]	Very low	0.99 (0.83–1.17)	257/1000	3 fewer per 1000 (47 fewer–41 more)
ROSC (important)	4155 (3 propensity-matched observational)[110–112]	Very low	[c]	417/1000	12 more per 1000 (15 fewer–39 more)
SGA (I) vs BMV (C)[a]					
Survival, favorable neurological outcome (critical)	1657 (2 propensity-matched observational)[111,112]	Very low	[b]	93/1000	29 fewer per 1000 (75–fewer to 17 more)
	900 (1 nonadjusted observational study)[120]	Very low	0.75 (0.23–2.42)	37/1000	9 fewer per 1000 (43 fewer–24 more)
Survival to hospital discharge (critical)	3904 (2 observational studies)[113,120]	Very low	[b]	88/1000	35 fewer per 1000 (88 fewer–18 more)
Survival to hospital admission (important)	996 (1 propensity-matched observational)[111]	Very low	1.25 (0.99–1.57)	257/1000	64 more per 1000 (6 fewer–133 more)
	900 (1 observational study)[120]	Very low	0.85 (0.44–1.87)	97/1000	15 fewer per 1000 (70 fewer–41 more)
ROSC (important)	900 (1 observational study)[120]	Very low	1.26 (0.82–1.92)	171/1000	40 more per 1000 (41 fewer–121 more)
TI (I) vs SGA (C)[a]					
Survival, favorable neurological outcome (critical)	1288 (2 propensity-matched observational)[111,112]	Very low	[b]	47/1000	22 fewer per 1000 (51 fewer–6 more)
	127 (1 nonadjusted observational study)[120]	Very low	6.06 (1.32–27.7)	28/1000	139 more per 1000 (36 fewer–314 more)
Survival to hospital discharge (critical)	1288 (2 propensity-matched observational)[111,112]	Very low	[b]	130/1000	31 fewer per 1000 (73 fewer–11 more)
	582 (2 observational studies)[113,120]	Very low	[b]	47/1000	34 more per 1000 (6 fewer–75 more)
Survival to hospital admission (important)	942 (1 propensity-matched observational)[111]	Very low	0.79 (0.63–1.0)	321/1000	67 fewer per 1000 (136 fewer–4 more)
	127 (1 observational study)[120]	Very low	4.33 (2.28–8.2)	128/1000	472 more per 1000 (198–665 more)
ROSC (important)	1288 (2 propensity-matched observational)[111,112]	Very low	[b]	162/1000	26 fewer per 1000 (129 fewer–78 more)
	127 (1 observational study)[120]	Very low	3.42 (2.16–5.44)	211/1000	511 more per 1000 (291–732 more)

AOR indicates adjusted odds ratio; ARD, absolute risk difference; BMV, bag-mask ventilation; C, comparator; GRADE, Grading of Recommendations, Assessment, Development, and Evaluation; I, intervention; RCT, randomized controlled trial; ROSC, return of spontaneous circulation; RR, relative risk; SGA, supraglottic airway; and TI, tracheal intubation.

Summative results of studies used in the systematic review are shown for each comparison and grouped by outcome.

[a] Cohort studies, amenable to meta-analysis, were not reported in this table if they produced results that were too heterogeneous (I^2 index >75%). Studies included in this table were therefore 1 clinical trial,[109] 3 propensity-matched observational studies,[110–112] and 4 nonadjusted observational studies [113,120–122].

[b] To minimize ambiguity, RR calculations were reported only for single studies, not for meta-analyses. RR calculations were considered less informative and sometimes produced divergent results, likely a consequence of zero-numerator cells [123].

public comment.[126] The draft document was viewed 264 times during the 2-week comment period. The task force reviewed the single posted comment, which endorsed the CoSTR.

Population, intervention, comparator, outcome, study design, and time frame

Population: Adults (age ≥18 years) and children (age <18 years) with cardiac arrest in any setting (out of hospital or in hospital)

Intervention: ECPR, including ECMO or cardiopulmonary bypass, during cardiac arrest

Comparator: Manual and/or mechanical CPR

Outcomes: Clinical outcomes, including short-term survival and neurological outcomes (e.g., hospital discharge, 28 days, 30 days, and 1 month) and long-term survival and neurological outcomes (e.g., 3 months, 6 months, and 1 year)

Study design: Randomized trials, non-RCTs, and observational studies (cohort studies and case-control studies) with a control group included; animal studies, ecological studies, case series, case reports, reviews, abstracts, editorials, comments, and letters to the editor not included

Time frame: All years and all languages included (as long as there was an English abstract); unpublished studies, published abstracts (e.g., conference abstracts), and trial protocols excluded; literature search conducted on December 19, 2017, and updated May 22, 2018

PROSPERO registration: CRD42018085404

Note: Information about outcomes of ECPR use in adults is addressed elsewhere in this article (see ECPR for Cardiac Arrest: Adults).

Consensus on science

In-hospital cardiac arrest. For the critical outcomes of favorable longer-term neurological outcome or of longer-term survival, no pediatric studies were identified.

For the critical outcome of favorable neurological outcome at hospital discharge, we identified very-low-certainty evidence (downgraded for very serious risk of bias) from 1 observational study; this study associated improved outcomes with ECPR compared with conventional CPR (conditional logistic analysis adjusted odds ratio [AOR], 2.64 [95% CI, 1.91–3.67]; propensity analysis AOR, 1.78 [95% CI, 1.31–2.41]).[127]

For the critical outcome of survival to hospital discharge, we identified very-low-certainty evidence (downgraded for very serious risk of bias and inconsistency) from 3 studies with pediatric populations. Two studies associated improved survival with ECPR compared with conventional CPR (AOR, 2.76 [95% CI, 2.08–3.66][127]; AOR, 3.80 [95% CI, 1.40–10.32] in medical cardiac patients; and AOR, 2.50 [95% CI, 1.3–4.81] in surgical cardiac patients).[128]

Out-of-hospital cardiac arrest. No studies were identified that addressed this question.

Treatment recommendations

We suggest that ECPR may be considered as an intervention for selected infants and children (e.g., cardiac populations) with IHCA refractory to conventional CPR in settings where resuscitation systems allow ECPR to be well performed and implemented (weak recommendation, very low certainty of evidence).

There is insufficient evidence in pediatric OHCA to formulate a recommendation for the use of ECPR.

Justification and evidence to decision framework highlights

In making a weak recommendation about the use of ECPR for pediatric IHCA, we recognize that despite a lack of comparative prospective studies identified in infants and children, patients with IHCA refractory to conventional CPR have a high probability of death unless therapies such as ECPR are used.

Providers should carefully consider the fact that the pediatric ECPR studies from which these recommendations are drawn consist predominantly of children with cardiac disease. This population may not adequately represent the local population for which guidelines may be implemented, so regional resuscitation councils must consider how generalizable the evidence can be to their regional systems of care.

The results of ECPR studies conducted in adults cannot be extrapolated to pediatric OHCA given the difference in causes of cardiac arrest between children and adults, the techniques and equipment applied for ECPR, and the post–cardiac arrest care interventions.

As noted, ECPR has been studied in very selected populations (e.g., cardiac surgical or cardiac medical) and more rarely for pediatric cardiac arrest in general (i.e., across all diseases and in all hospital settings).[127] In addition, it has been used in organizations with a strong institution-based commitment to sustaining a resuscitation system that includes ECPR with appropriate quality improvement systems.[129,130] Such improvement systems include ongoing internal audits and iterative evaluation of performance and outcomes.[129–133] As a result, these findings may not be broadly generalizable to other organizations.

ECPR is a complex resuscitation intervention that requires long-term commitment to sustain the expertise, resources, training, and systems to provide support for patients and their families. Delivering this complex intervention involves added up-front investment and costs.[134,135]

The healthcare resources necessary to provide high-quality pediatric ECPR are likely to limit its broad adoption.

Knowledge gaps

No published randomized trials have compared the outcomes of ECPR and conventional CPR in infants and children. Because some high-volume organizations have adopted ECPR for selected pediatric populations, this comparison may not be perceived as having sufficient equipoise to allow randomization. As a result, alternative comparative study designs may be necessary to conduct clinical trials to study the following:

- Comparison of the probability of survival between ECPR and conventional CPR in IHCA
- Comparison of the likelihood of favorable neurological and functional outcome between ECPR and conventional CPR in IHCA

The timing and type of cannulation strategy for optimal transition from conventional CPR to ECPR remain to be studied to optimize neuro-CPR outcomes. The Pediatric Life Support Task Force identified the following unresolved issues:

- Optimal timing for ECPR cannulation during conventional CPR
- Conditions (e.g., pulmonary blood flow obstruction) for which ECPR, rather than conventional CPR, should be considered earlier in the resuscitation attempt

- Type and anatomic approach for cannulation for ECPR that allows best cerebral-CPR
- Identification of other technical aspects of ECPR that enable optimal cerebral-CPR, including ideal temperature management strategy, best circuit prime solution (reconstituted whole blood versus crystalloid), optimal fraction of device oxygenation to be delivered by the membrane lung, target oxygenation and decarboxylation to be delivered during ECPR, and the inotrope or vasoactive medications delivered during ECPR that will optimize neurological and cardiopulmonary outcomes

The post–cardiac arrest care strategies after cannulation for ECPR remain to be studied, including how post–cardiac arrest care therapies should be adapted in the context of ongoing ECPR.

There is an important gap in comparative studies of resuscitation for OHCA in special circumstances such as submersion or drowning, deep hypothermia or cold environment, respiratory arrest, or in the context of trauma. The Pediatric Life Support Task Force identified the following challenges for studies of ECPR for pediatric OHCA in special circumstances:

- Identification of ideal select populations and circumstances to be considered for initial studies of ECPR for OHCA: Should these include children with cold-water drowning, people in an avalanche, or individuals with cold exposure?
- Optimal timing for initiation of ECPR: Should it be initiated at the scene of the arrest (i.e., cannulation in the field) or immediately on arrival at the hospital?

There are no published comparative studies on longer-term functional outcomes or QOL outcomes in pediatric patients and in their families and caregivers after ECPR. The Pediatric Life Support Task Force identified the following issues to be addressed:

- How longer-term functional and QOL outcomes compare between ECPR and conventional CPR for the pediatric population and their families and caregivers
- How bereavement outcomes compare between families and caregivers of nonsurvivors of cardiac arrest with ECPR compared with outcomes of families and caregivers of nonsurvivors of conventional CPR

Whereas the cost-effectiveness of ECMO has been addressed in pediatric and adult publications, the cost-effectiveness of ECPR versus conventional CPR in pediatric cardiac arrest populations is not known and should be studied.

TTM after cardiac arrest

The last ILCOR Pediatric Life Support CoSTR review of pediatric TTM was published in 2015.[125] Since that review, additional studies of pediatric TTM have been published, particularly in the in-hospital target population. ILCOR commissioned an SR to identify and analyze all published evidence reporting outcomes of TTM in children who achieved ROSC after OHCA and IHCA.[8] The Pediatric Life Support Task Force analyzed and discussed the SR and all of the studies identified by that review, developed a draft CoSTR, and posted it online for public comment.[136] In response to the 2 posted comments, the task force included additional information in the Justification and Evidence to Decision Framework Highlights section.

Population, intervention, comparator, outcome, study design, and time frame

Population: Pediatric patients (age >24 h–18 years) who achieved ROSC after OHCA or IHCA

Intervention: TTM with a target temperature of 32 °C–36 °C

Comparators: No TTM or TTM at an alternative target temperature range

Outcomes:

- Critical: favorable neurological outcome (good behavioral survival) at 1 year such as Pediatric CPC 1 or 2[137] and Vineland Adaptive Behavior Scales (Vineland-II) ≥70.[138]
- Important: favorable neurological outcome (at other time intervals), overall survival, and health-related QOL at 3 time intervals: long term (1–3 years), intermediate term (3–6 months), and short term (28–30 days or hospital discharge)
- Health-related QOL was defined with the use of pediatric-specific QOL tools (e.g., the Pediatric QOL Inventory,[139] the Infant Toddler QOL Questionnaire,[140] or equivalent). Potential in-hospital adverse outcomes were also captured, including infection (culture proven), recurrent cardiac arrest, serious bleeding (red blood cell transfusion), and any arrhythmias (not leading to cardiac arrest).

Study designs: RCTs, quasi-RCTs (qRCTs), and nonrandomized cohort studies eligible to be included; animal studies, unpublished studies, published abstracts (e.g., conference abstracts), and case series excluded

Time frame: All years to December 13, 2018

Languages: All languages included (if English abstract was available)

A priori subgroups to be examined: Location of cardiac arrest (in hospital and out of hospital), age groups, presumed type of cardiac arrest (cardiac, asphyxial, other), and use of ECMO

PROSPERO registration: CRD42018108441

Consensus on science

The review identified 2 RCTs[141,142] with moderate clinical heterogeneity (different settings), low methodological heterogeneity (same methods and in-hospital management), and low or moderate statistical heterogeneity, allowing pooling of the results in the meta-analyses and separate subgroup analyses. The 2 RCTs were downgraded to low certainty of effect as a result of inconsistency and imprecision. Because only 2 relatively small RCTs were available, observational comparative data were considered, but we did not combine the RCT and non-RCT data. The observational studies that reported adequately adjusted results were pooled, whereas unadjusted results are shown, when relevant, without pooling (Table 13).

Favorable neurobehavioral survival. For the primary outcome of long-term favorable neurological outcome (1 year), a pooled analysis of the 2 RCTs (low certainty of evidence) found no statistically significant benefit of TTM 32 °C–34 °C compared with TTM 36 °C –37.5 °C.[141,142] Two adjusted cohort studies reported no statistically significant benefit in either intermediate-term[149] or short-term favorable neurological outcome associated with use of TTM 32 °C –34 °C compared with TTM 36 °C–37.5 °C.[143]

Survival. For the secondary outcome of overall survival, a pooled analysis of the 2 RCTs (very low certainty of effect, downgraded for inconsistency and imprecision) found no statistically significant

Table 13 – Pediatric TTM in children with OHCA who are comatose after ROSC: summary of studies and findings.

Study, year	Study type; years enrolled	n	Enrollment criteria	GCS/ neurological	Target temperature intervention	Temperature comparison control	TTM duration	Outcomes	Comments
Chang et al.[143] 2016	Retrospective review of national OHCA database; nonrandomized; January 1, 2008 −December 31, 2014	663 Total, 81 TTM; stratified by shockable vs nonshockable presenting rhythm	OHCA surviving to hospital admission (excluding deaths in ED, alert status after ED resuscitation, or unknown neurological status at discharge)	Not specified	32 °C−34 °C based on intention to treat regardless of achieved temperature or duration; actual temperature measures not included; no standard care protocol	No standard care protocol; temperature measures not included	Minimum 12 h	No difference in survival to hospital discharge between TTM (48.1%) and control (40.2%); no difference in good neurological recovery (CPC 1 or 2 at discharge) between TTM (22.2%) and control (18.7%); no difference in effect of TTM between shockable and nonshockable presenting rhythm groups	Very low certainty resulting from lack of temperature data and nonrandomized treatment allocation
Cheng et al.[144] 2018	Retrospective; historic and concurrent; controls 2013 −2015; included neonates (23% −33%)	81 Events in 75 patients; IHCA	CHD + CPR >5 min or ECPR (excluded intracranial hemorrhage)	Not specified	Mean, 33.6 ± 0.2 °C; 0 had fever; 4/30 had temperature <32 °C; TTM reached in 1.4 h (median)	Mean, 34.7 ± 0.8 °C; 2/51 had fever; 12/51 had temperature <32 °C; TTM reached in 1.4 h (median)	<1 y = 72 h (actual median: 63.1 h), ≥1 y = 48 h (actual median: 45.9 h); 14/30 TTM patients rewarmed early	Survival: Control, 59.1%; TTM, 61.5%; no significant difference in survival or LOS; follow-up to 26.5 mo; fewer patients with TTM had seizures (significant)	Control group included more patients with single ventricles and had low mean temperature with nearly half with temperature <32 °C
Fink et al.[124] 2010	Retrospective cohort; patients with TTM after 2002	181 Total, 40 TTM; OHCA and IHCA	Admission to ICU with ROSC after cardiac arrest (even brief) who remained comatose after ROSC (excluded CHD, respiratory arrest no ROSC, brain death before arrest)	Consistent with AHA comatose; specific neurological criteria not reported	33.5 °C–34.8 °C; mean, 34.1 ± 0.8 °C; reached in 2.7 ± 4.5 h (mean, 0 −4 h); 18% had fever, 15% had temperature <32 °C (associated with higher mortality)	Standard 33.6 °C −36.3 °C; mean, 31.6 ± 19.5 h; 38% had fever in first 4 d	24 h (range 16 −48 h); 60% of patients with TTM presented at or below target temperature, so some were warmed to target temperature)	55% Survival with no difference between TTM and control; those with <36 °C or >38 °C on admission had significantly higher mortality than those with temperature 36 °C −38 °C; temperature <32 °C in 15% and associated with higher mortality; no difference in hospital mortality, LOS	
Lin et al.[145] 2013	Retrospective chart review; January 1, 2010−June 30, 2012	43 Total, 15 TTM; both OHCA and IHCA	At least 3 min of compression; only those surviving 12 h	TTM GCS mean score 4.67 ± 1.94; control GCS score 5 ± 2.35	33.5 ± 0.5 °C	39% Needed active rewarming to normothermia	24−72 h	57% Overall survival; higher (78.6%) in TTM group vs 46.4% in control group (significant)	Some internal inconsistencies in numbers throughout article

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Table 13 *(continued)*

Study, year	Study type; years enrolled	n	Enrollment criteria	GCS/ neurological	Target temperature intervention	Temperature comparison control	TTM duration	Outcomes	Comments
			included; CHD excluded						
Lin et al.[146] 2018	Retrospective cohort 2010–2017	64 Total; 25 TTM, all asphyxia OHCA	CPR at least 3 min and survival at least 12 h; excluded 45 children, including 10 who died within 12 h, 10 not in coma after ROSC, 8 with preexisting neurological disease, and 8 with TBI	GCS score ≤8; TTM GCS score 3.4 ± 1.04; control GCS score 3.2 ± 0.76	33 °C within 6 h of arrest	35.5 °C–37.5 °C; 56.4% needed active warming; 12.8% needed treatment for temperature >37.5 °C	72 h	Overall 1-mo survival, 42.2%; 1-mo survival significantly higher in TTM (60%) vs control (30.8%) group; TTM group had significantly better neurological outcomes; TTM group had longer LOS	
Moler et al.[142] 2015	International, multi-institutional prospective RCT (September 1, 2009–December 31, 2012)	74 With OHCA drowning ≥2 min of CC, remained comatose (GCS motor score 3 or 4) and ventilator dependent after ROSC; 46 randomized to TTM group	48 h to <18 y of age; excluded if GCS motor score 5 or 6, major trauma, inability to randomize within 6 h, decision to withhold aggressive treatment	GCS motor score 3 or 4, comatose and ventilator dependent after ROSC	33 °C (32 °C –34 °C)	36.8 °C (36 °C –37.5 °C)	120 h	No difference in 28-d mortality or 12-mo survival with favorable neurological outcome or other secondary outcomes; culture-proven bacterial infection more common in TTM group; the 25 survivors at 12 mo who received >30 min of CC had poor functional outcomes (PCPC ≥4)	CPR duration longer in TTM 36 °C –37.5 °C group and fewer had bystander CPR; blinding of caregivers impossible
Moler et al.[142] 2015	International, multi-institutional prospective RCT (September 1, 2009–December 31, 2012)	295 Randomized; 260 subjects with data, all OHCA who required ≥2 min of CC, remained comatose and ventilator dependent; 155 assigned to TTM	48 h to <18 y of age; excluded if GCS motor score 5 or 6, major trauma, inability to randomize within 6 h, decision to withhold aggressive treatment	GCS motor score 3 or 4, comatose and ventilator dependent after ROSC	33 °C (32 °C– 34 °C)	36.8 °C (36 °C– 37.5 °C)	120 h	No difference in 28-d mortality (57% in TTM, 67% in control group, $P = 0.08$), 12-mo survival (38% in TTM vs 29% in control) or in 12-mo survival with favorable neurological outcome or other secondary outcomes; no difference in complications (e.g., bleeding, arrhythmias, infections), although	Witnessed arrest, 39%, and 66% of these received bystander CPR; 72% of patients had respiratory cause of arrest; blinding of caregivers was impossible

Table 13 *(continued)*

Study, year	Study type; years enrolled	n	Enrollment criteria	GCS/ neurological	Target temperature intervention	Temperature comparison control	TTM duration	Outcomes	Comments
								hypokalemia and thrombocytopenia occurred more frequently in TTM group and renal replacement treatment used more often in control group; significant difference in survival time with TTM group, although this was a secondary outcome	
Moler et al.[141] 2017	International, multi-institutional prospective RCT (September 1, 2009–February 27, 2015; stopped for futility)	329 Patients randomized; 166 to control (IHCA)	48 h to <18 y of age; excluded if GCS motor score 5 or 6, major trauma, inability to randomize within 6 h, decision to withhold aggressive treatment	GCS motor score 3 or 4; comatose and ventilator dependent after ROSC	33 °C (32 °C–34 °C)	36.8 °C (36 °C–37.5 °C)	120 h	Survival at 28 d and survival with VABS-II ≥70 at 1 y: 36% TTM vs 39% control (no difference); no difference in secondary outcomes, including alive at 1 y or change in VABS-II score from baseline; no difference in infection, blood product use, serious arrhythmias within 7 d	65% had either cardiac cause of arrest or CHD; blinding of caregivers was impossible
Scholefield et al.[147] 2015	Retrospective cohort enrolled January 2004–December 2010 after OHCA	73 Patients; 38 randomized to TTM	1 d to 16 y of age, admitted after OHCA with ROSC	Not stated although cited the ILCOR guidance for TTM for patients who remain comatose after ROSC from cardiac arrest	32 °C – 34 °C; 4 patients (11%) experienced "overshoot" cooling to <32 °C and all died; only 3% (1 patient) developed temperature >38 °C	Called standard temperature management with rescue temperature-controlling measures to keep temperature ≤38 °C; 38% had fever >38 °C	22.5 h	Overall survival was 29% and was not significantly different between TTM (34%) and control (23%) groups; study was underpowered to detect significant difference in hospital survival; TTM group had more bradycardia and hypotension and had longer LOS	Significantly more patients in TTM group (81% vs 47%) had bystander CPR; TTM used more often in patients with unknown cause of arrest and higher predicted mortality and used less in those with traumatic arrest

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Table 13 *(continued)*

Study, year	Study type; years enrolled	n	Enrollment criteria	GCS/ neurological	Target temperature intervention	Temperature comparison control	TTM duration	Outcomes	Comments
									(including TBI), so control group had more patients with traumatic arrest; study enrollment bridged a period of major change in basic life support guidelines
Torres-Andres et al.[148] 2018	Retrospective observational study of all witnessed OHCAs and IHCAs between May 2007 and July 2015 treated with ECPR	58 Consecutive patients receiving ECPR; 28 also treated with TTM	Witnessed IHCA (only 3/58 patients) or OHCA; receipt of advanced CPR, no ROSC within 15 min of CPR; no contraindication to mechanical circulatory support; hypothermia was at discretion of care team	Not stated	34 °C – 35 °C	Controlled normothermia avoiding body temperature >37 °C		Overall survival to hospital discharge, 65.5%; 3-y survival, 62.1%; survival to hospital discharge significantly higher among those treated with TTM (75%) vs control subjects (55%) with good QOL inventory and family functioning; 50% of survivors had evidence of intracranial injuries (vs 58.3% of nonsurvivors)	Nonsurvivors more likely to have >1 ECPR event

AHA indicates American Heart Association; CC, chest compressions; CHD, congenital heart disease; CPC, Cerebral Performance Category; CPR, cardiopulmonary resuscitation; ECPR, extracorporeal cardiopulmonary resuscitation; ED, emergency department; GCS, Glasgow Coma Scale; ICU, intensive care unit; IHCA, in-hospital cardiac arrest; ILCOR, International Liaison Committee on Resuscitation; LOS, length of stay; OHCA, out-of-hospital cardiac arrest; PCPC, Pediatric Cerebral Performance Category; QOL, quality of life; RCT, randomized controlled trial; ROSC, return of spontaneous circulation; TBI, traumatic brain injury; TTM, targeted temperature management; and VABS-II, Vineland Adaptive Behavior Scales II.[138]

benefit in either long-term or short-term survival of TTM 32 °C–34 °C compared with TTM 36 °C–37.5 °C.[141,142] One retrospective cohort study found no benefit in adjusted intermediate-term survival associated with TTM 32 °C–34 °C versus TTM 36 °C–37.5 °C.[149] Three cohort studies also reported no associated increase in adjusted short-term survival associated with the use of TTM 32 °C–34 °C compared with TTM 36 °C–37.5 °C.[124,143,149]

Adverse outcomes: infection. A pooled analysis of the 2 RCTs found no statistical difference in culture-proven infection from TTM 32 °C –34 °C compared with TTM 36 °C–37.5 °C.[141,142] Four cohort studies reported infection; unadjusted outcomes were not pooled, but none of the studies showed a statistically significant difference in infection with use of TTM 32 °C–34 °C compared with TTM 36 °C –37.5 °C.[124,144,146,149]

Adverse outcomes: recurrent cardiac arrest. Pooled analysis of the 2 RCTs found no difference in the rate of recurrent cardiac arrest from TTM 32 °C–34 °C compared with TTM 36 °C–37.5 °C.[141,142] Two cohort studies reported unadjusted recurrent cardiac arrest rates that could not be pooled; none of the individual studies showed statistically significant association of increased recurrent arrest with the use of TTM 32 °C–34 °C compared with TTM 36 °C–37.5 °C.[124,149]

Adverse outcomes: serious bleeding. Pooled analysis of the 2 RCTs found a significant increase in serious bleeding from TTM 32 °C –34 °C compared with TTM 36 °C–37.5 °C.[141,142] Two observational cohort studies reported unadjusted odds ratios for serious bleeding; none of the individual studies showed association of statistically significant increase in bleeding with the use of TTM 32 °C–34 °C compared with TTM 36 °C–37.5 °C.[124,149]

Adverse outcomes: arrhythmias. Pooled analysis of the 2 RCTs found no statistical increase in arrhythmias from TTM 32 °C–34 °C compared with TTM 36 °C–37.5 °C.[141,142] Five observational studies reported unadjusted outcomes for arrhythmias; 1 reported an association of a statistically significant increase in arrhythmias; the other 3 studies reported no statistically significant increase or decrease in arrhythmias associated with the use of TTM 32 °C –34 °C compared with TTM 36 °C–37.5 °C.[124,144,146,147,149]

Subgroup analysis: location of cardiac arrest. For the predetermined subgroup analysis by location of arrest (OHCA or IHCA), no meta-analyses could be completed because there is only 1 RCT for each subgroup and the observational studies had methodological heterogeneity.

For OHCA, the single RCT did not find statistically significant benefit of TTM 32 °C–34 °C compared with TTM 36 °C–37.5 °C.142 One of the 3 cohort studies found (in unadjusted results) association of increased survival and good behavioral survival with 72 h of TTM 32 °C–34 °C compared with TTM 36 °C–37.5 °C.[146] The other 2 cohort studies did not report statistically significant benefit or harm.[143,147] An exploratory analysis was conducted to determine whether the addition of a hypothetical OHCA RCT that yielded results similar to the THAPCA OHCA study (Therapeutic Hypothermia After Pediatric Cardiac Arrest) would change the pooled analysis CI to favor TTM 32 °C–34 °C.[142] Enrollment of 200 patients in such a hypothetical RCT would be required to demonstrate a statistically significant benefit for favorable neurological outcome at 1 year.

The IHCA RCT did not find statistical benefit or harm of TTM 32 °C–34 °C compared with TTM 36 °C–37.5 °C.[141] The point estimates for outcomes of 3 different observational cohort studies are on both sides of the null effect.[144,148,149] An exploratory analysis indicated that an additional hypothetical RCT of 6000 patients with an outcome similar to the THAPCA IHCA RCT141 would be required to demonstrate a statistically significant harm of TTM 32 °C –34 °C in favorable neurological outcome at 1 year compared with TTM 36 °C–37.5 °C.

Subgroup analysis: cause of arrest. Two retrospective observational cohort studies of cardiac arrest with presumed cardiac cause could not be pooled but separately reported no significant benefit or harm in short-term survival associated with TTM 32 °C–36 °C compared with TTM 36 °C–37.5 °C (or no TTM).[144,148]

Two observational cohort studies (and a pilot publication of one of those studies) reported favorable neurological outcome and survival outcomes for patients with predominantly (>80%) presumed asphyxial origin.[124,145,146] A high risk of bias and lack of adjusted outcomes precluded the pooling of data. One OHCA study found a statistically significant benefit for both favorable neurological outcome and survival associated with TTM 32 °C–36 °C for 72 h.[146] All of the point estimates for outcomes favored TTM 32 °C–36 °C.

The THAPCA OHCA study published a nonrandomized subgroup analysis of drowning as a cause.[150] There was no statistically significant benefit of the intervention for survival or favorable neurological outcome.

Subgroup analysis: ECMO. Although some patients in several of the studies underwent ECMO, outcome data were available from only 2 studies. The THAPCA IHCA RCT (nonrandomized cointervention, of low-certainty evidence) found no statistically significant difference in long-term favorable neurological outcome (at 1 year) for TTM 32 °C –34 °C compared with TTM 36 °C–37.5 °C.[141] In 1 observational cohort study, all patients received ECMO; that study reported no statistical increase in short-term survival.[148]

Treatment recommendations

We suggest that for infants and children with OHCA, TTM be used in the post–cardiac arrest period to maintain a central temperature ≤37.5 °C (weak recommendation, moderate certainty of evidence). On the basis of 2 randomized trials and 8 retrospective observational cohort studies that provided comparative data on favorable neurological outcome, survival, and in-hospital adverse events, there is inconclusive evidence to support or refute the use of TTM 32 °C –34 °C compared with TTM 36 °C–37.5 °C (or an alternative temperature) for children who achieve ROSC after cardiac arrest.

Justification and evidence to decision framework highlights

The evidence in this review is dominated by the 2 THAPCA RCTs.[141,142] These studies included only children 2 days to 18 years of age who had received at least 2 min of CPR and who remained comatose and ventilator dependent after ROSC. There were many patient exclusions, including the use of ECMO, severe trauma, previous cardiac arrest, preexisting life-limiting conditions, severe bleeding, and continuous epinephrine infusion. The findings of this review should be considered in the context of this limitation.

In making this recommendation, the task force preferred the use of TTM 32 °C–34 °C as opposed to TTM 36 °C–37.5 °C because, although the THAPCA OHCA study[142] did not demonstrate success

for the primary outcome (favorable neurological status at 1 year), it was underpowered to show a significant difference for survival, for which the lower 95% CI approached 1. The point estimates for survival in the 3 cohort studies of OHCA or presumed asphyxial arrest[124,145,146] favored TTM 32 °C–34 °C. There were insufficient data on patients with IHCA, who represent a population with different preexisting conditions and cause of arrest.

The task force noted that hyperthermia occurs frequently in the postarrest period; fever is potentially harmful and should be avoided. Finally, the provision of TTM can be resource intensive. These resources, the associated expertise necessary to deliver and maintain TTM, and the presence of appropriate systems of critical care are required to provide optimal post-ROSC care. The task force noted that the application of TTM may require sedation, analgesia, and neuromuscular blocking drugs that will modify neurological assessment.

Knowledge gaps

This evidence evaluation did not address training, logistical, operational, or economic issues pertaining to TTM. It also did not compare other temperature ranges and did not address the duration of TTM. In addition, the task force identified knowledge gaps requiring further investigation:

- The use of TTM 32 °C–34 °C for children after OHCA
- Asphyxial arrest and the use of TTM 36 °C–37.5 °C in patients with IHCA

NLS task force

Initial oxygen concentration for term infants at birth

Administration of high oxygen concentrations leads to free radical formation and may be toxic to lungs, eyes, brains, and other organs of the newborn.[151,152] In 2010, the ILCOR NLS Task Force CoSTR update noted that it was best to start with 21% oxygen when term newborns received positive-pressure ventilation in the delivery room. The recommendation was based on a meta-analysis that found lower mortality when room air instead of 100% oxygen was used.[153] The evidence review for this question did not use GRADE methodology[2] to analyze the published studies. This topic was not addressed for term infants in the 2015 CoSTR update.[154] Questions remain about the risks of hypoxemia versus hyperoxemia for late preterm and term newborns who receive respiratory support in the delivery room. As a consequence, the ILCOR NLS Task Force undertook an SR with meta-analysis of the relevant available evidence using GRADE methodology[2] on the topic of lower versus higher concentrations of oxygen for the initiation of resuscitation of newborn infants at ≥35 weeks' gestation.[9]

Population, intervention, comparator, outcome, study design, and time frame

Population: Newborn infants (≥35 weeks' gestation) who receive respiratory support at birth

Intervention: Lower initial oxygen concentration (≤50% O_2)

Comparison: Higher initial oxygen concentration (>50% O_2)

Outcomes:

- Primary: All-cause short-term mortality (in hospital or 30 days)
- Secondary: All-cause long-term mortality (13 years); long-term neurodevelopmental impairment (NDI; 13 years); hypoxic-ischemic encephalopathy (Sarnat stage 2–3)[155]

Study designs: RCTs, qRCTs, and nonrandomized cohort studies included; animal studies, unpublished studies, and published abstracts (eg, conference abstracts) excluded

Time frame: 1980 to August 10, 2018

A priori subgroups to be examined: Gestational age (≥35, ≥37 weeks); grouped lower and higher oxygen concentrations; explicit oxygen saturation targeting versus no oxygen saturation targeting

PROSPERO registration: CRD42018084902

Consensus on science

The SR identified 10 trials and 2 follow-up studies involving 2164 newborns, but 3 of the trials had critical risk of bias and were included in only the sensitivity analyses.[9] Data from 1469 term and late preterm infants (≥35 weeks' gestation) in 7 randomized and qRCTs were included. All identified studies compared 21% (or air) with 100% oxygen concentration; no other initial oxygen concentrations were reported. No data specific to ≥37 weeks' gestation were found, and none of the studies used targeted oxygen saturation (Spo_2) monitoring.

A draft CoSTR document based on the SR was posted for a 2-week public commenting period on January 15, 2019.[156] During the comment period, the draft CoSTR was viewed 3564 times. The NLS Task Force received 47 comments that were subsequently sorted into 4 main categories: (1) agreement with the CoSTR as written; (2) responses that demonstrated a need for more explicit emphasis that the intent of the population, intervention, comparator, outcome, study design, and time frame was to address initial oxygen concentration (not a static delivery concentration); (3) questions about special situations such as oxygen use during cardiac compressions or in the unique circumstance of newborns with anomalies such as pulmonary hypoplasia or congenital diaphragmatic hernia; and (4) a desire for stronger emphasis on the need for more evidence using current methods of oxygen monitoring and titration and additional interval oxygen concentrations for infants at ≥35 weeks' gestation. In response to the public comments, the NLS Task Force included additional information to address questions and comments about the 3 main categories of concerns.

Short-term mortality (In hospital or 30 days). For this critical outcome, evidence of low certainty (downgraded for risk of bias and imprecision) from 7 RCTs (and qRCTs) involving 1469 newborn infants at ≥35 weeks' gestation receiving respiratory support at birth showed benefit of starting with 21% oxygen compared with 100% oxygen (RR, 0.73 [95% CI, 0.57–0.94]; $I^2 = 0\%$); 46 of 1000 fewer (95% CI, 73–10 fewer) babies died when respiratory support at birth was started with 21% compared with 100% oxygen.[157–163]

Long-term mortality (1–3 years). For this critical outcome, no evidence was identified.

NDI (13 years). Among survivors who were assessed for this critical outcome, evidence of very low certainty (downgraded for risk of bias and imprecision) from 2 RCTs (and qRCTs) involving 360 term and late preterm newborns (≥35 weeks) who received respiratory support at birth showed no statistically significant benefit or harm of starting with 21% compared with 100% oxygen (RR, 1.41 [95% CI, 0.77

−2.60]; I^2 = 0%): 36 of 1000 more (95% CI, 20 fewer−142 more) babies with NDI when respiratory support at birth was started with 21% compared with 100% oxygen.[161,164]

Hypoxic-ischemic encephalopathy (Sarnat stage 2–3)[155]. For this critical outcome, evidence of low certainty (downgraded for risk of bias and imprecision) from 5 RCTs (and qRCTs) involving 1359 term and late preterm newborns (≥35 weeks' gestation) receiving respiratory support at delivery showed no statistically significant benefit or harm of 21% compared with 100% oxygen (RR, 0.90 [95% CI, 0.71−1.14]; I^2 = 8%): 20 per 1000 fewer (95% CI, 57 fewer−27 more) babies with hypoxic-ischemic encephalopathy when respiratory support at birth was started with 21% compared with 100% oxygen.[157,158,160,161,163]

Subgroup infants ≥37 weeks' gestation. No data for the planned subgroup analysis for infants of ≥37 weeks' gestation were found.

Intermediate initial oxygen concentrations. No studies were identified that compared any intermediate initial oxygen concentrations.

Oxygen saturation targeting versus no oxygen saturation targeting. No studies were identified that used Spo_2 targeting.

Treatment recommendations

For newborn infants at ≥35 weeks' gestation receiving respiratory support at birth, we suggest starting with 21% oxygen (air; weak recommendation, low certainty of evidence). We recommend against starting with 100% oxygen (strong recommendation, low certainty of evidence).

Justification and evidence to decision framework highlights

Parents and clinicians rate mortality as a critical outcome. Despite the low certainty of the evidence, the large reduction in the primary outcome of short-term mortality (number needed to treat, 22) with no demonstrated adverse effects favors the use of 21% oxygen as the initial gas for resuscitation for newborns at ≥35 weeks' gestation. Although there are no published cost data, it is likely that initiating resuscitation with 21% oxygen does not add cost and might result in cost savings compared with the use of initial 100% oxygen in some settings. Babies born in low-resource settings demonstrate increased mortality and morbidity. Therefore, it is plausible that using 21% oxygen compared with 100% oxygen has greater impact in low-resource settings. Use of 21% oxygen for initial resuscitation is universally feasible.

To be clear, we emphasize that the recommendation for 21% oxygen refers to the initial concentration of oxygen at the initiation of respiratory support. It does not address the question of how to titrate the oxygen concentration as resuscitation progresses; no evidence was found to guide this aspect of oxygen delivery. Once such evidence is published, the NLS Task Force will initiate an SR to assess the effect and optimal methods of titration of oxygen concentrations during resuscitation. We found no studies that evaluated the initial oxygen concentration for specific special circumstances such as congenital diaphragmatic hernia or pulmonary hypoplasia.

Knowledge gaps

The NLS Task Force identified the following knowledge gaps requiring further investigation:

- Studies in late preterm (35–36 weeks' gestation) infants: few of these infants were included in the published studies, leading to lower certainty in the evidence for this gestational age group
- Research to assess the impact of titration of oxygen to oxyhemoglobin saturation (Spo_2) targets as the resuscitation progresses: monitoring Spo_2 and titration of oxygen concentration were not routinely used in the studies included in the SR for this CoSTR
- Comparison of initial oxygen concentrations intermediate between 21% and 100%: in the SR for this CoSTR, no studies were found that compared any oxygen concentrations other than 21% versus 100%
- Determination of whether delayed cord clamping affects the impact of initial inspired oxygen concentration
- The effect of initial oxygen concentrations on long-term NDI; studies published to date have been of very low certainty of evidence
- The optimal initial oxygen concentrations needed in special circumstances such as newborns with pulmonary hypoplasia, congenital diaphragmatic hernia, and other anomalies

Initial oxygen concentration for preterm infants at birth

Preterm newborn infants are particularly vulnerable to oxidative stress resulting from reduced antioxidant defenses and frequent exposure to oxygen during stabilization in the delivery room.[165] Many common complications of prematurity are associated with oxygen toxicity, including bronchopulmonary dysplasia, retinopathy of prematurity, and intraventricular hemorrhage. Medical practitioners who stabilize preterm infants at birth must try to prevent hypoxia while limiting excess oxygen to prevent toxic effects. In 2015, the ILCOR NLS Task Force CoSTR update recommended starting with 21% to 30% oxygen for preterm newborns needing respiratory support in the delivery room.[154] This was based on meta-analysis findings of no benefit for any important or critical outcomes when high oxygen concentrations were used. Additional studies are now available, so the ILCOR NLS Task Force undertook an SR with meta-analysis using GRADE methodology[2] of the relevant available evidence on the effects of lower versus higher oxygen concentrations for initiation of resuscitation of preterm newborn infants.[10]

Population, intervention, comparator, outcome, study design, and time frame

Population: Preterm newborn infants (<35 weeks' estimated gestational age) who receive respiratory support at birth

Intervention: Lower initial oxygen concentration (≤50% O_2)

Comparison: Higher initial oxygen concentration (>50% O_2)

Outcomes:

- Primary: All-cause short-term mortality (in hospital or 30 days)
- Secondary: All-cause long-term mortality (1–3 years); long-term NDI (1–3 years); retinopathy of prematurity (stages III–V)[166]; necrotizing enterocolitis stage II (pneumatosis) or III (surgical)[167]; bronchopulmonary dysplasia (moderate to severe)[168]; major intraventricular hemorrhage (grade III–IV)[169]; and time to heart rate >100 bpm

Study designs: RCTs, qRCTs, and nonrandomized cohort studies included; animal studies, case series, unpublished studies, and published abstracts (e.g., conference abstracts) excluded

Time frame: 1980 to August 10, 2018

A priori subgroups to be examined: Gestational age (≤32, ≤28 weeks); grouped lower and higher initial oxygen concentrations (21% O_2 compared with 100% O_2, 21%–30% compared with 80%–100% only, 30% compared with 90%–100%, 50% compared with 100%, 30% compared with 60%–65%); and explicit Spo_2 targeting versus no Spo_2 targeting

PROSPERO registration: CRD42018084902

Consensus on science

The SR found 16 eligible studies that included 5697 preterm newborns.[10] This constituted 10 RCTs, 2 follow-up studies, and 4 observational cohort studies. The majority (9 of 10) of the RCTs used 21% to 30% as the initial low oxygen concentration,[170–178] with only 1 small RCT using 50% for the initial low oxygen group.[179] All observational studies used 21% oxygen as the initial low oxygen concentration.[180–183] Six of 10 RCTs used 100% oxygen,[171,173–175,178,179] 1 RCT used 90%,[172] 1 RCT used 80%,[170] and 2 RCTs used >60%[176,177] as the high initial oxygen concentration. All observational studies used 100% as the high initial oxygen concentration. A majority of RCTs (8 of 10)[171–178] and all of the observational cohort studies[180–183] used Spo_2 targeting as a cointervention. All results are presented as RR with 95% CI and absolute difference with 95% CI.

A draft CoSTR document based on the SR was posted for a 2-week public commenting period on January 15, 2019.[184] During the comment period, the draft CoSTR was viewed 7387 times, suggesting intense interest within the global neonatal community. The NLS Task Force received 52 comments that were subsequently grouped into 3 categories: those that agreed with the draft CoSTR as written, those that wanted clarification on what "no benefit or harm" truly meant, and those that expressed disappointment that the science does not yet provide a clearer answer. As a result of the public comments, the NLS Task Force included additional information to address these concerns.

All preterm gestational ages combined (<35 weeks' gestation). Overall, evidence of very low certainty (downgraded for risk of bias and imprecision) for newborn infants at <35 weeks' gestation receiving respiratory support at birth showed no statistically significant benefit or harm of lower initial oxygen concentration (≤50%) compared with higher initial oxygen concentration (>50%) for the following critical outcomes (see Table 14 for data): all-cause short-term mortality (in hospital or 30 days), all-cause long-term mortality (1–3 years), long-term NDI (moderate to severe, 1–3 years), retinopathy of prematurity (grade III–V),[166] necrotizing enterocolitis (Bell grade II–III),[167] bronchopulmonary dysplasia (moderate to severe),[168] or major intraventricular hemorrhage (grade III–IV).[169] For the important outcome of time to heart rate >100 bpm after delivery, the limitation of the direct evidence for newborn infants at <35 weeks' gestation precluded meta-analysis.

Subgroup newborn infants at ≤32 weeks' gestation. For the critical outcome of all-cause short-term mortality (in hospital or 30 days), the evidence of very low certainty (downgraded for risk of bias and imprecision) from 8 RCTs with 837 newborn infants at ≤32 weeks' gestation receiving respiratory support at birth showed no statistically significant benefit or harm of lower initial oxygen concentration compared with higher initial oxygen concentration (RR, 0.93 [95% CI, 0.55–1.55]; I^2 = 15%): 6 of 1000 fewer (95% CI, 39 fewer–47 more) with short-term mortality when lower compared with higher initial oxygen concentration was used.[171–173,175–179]

Subgroup newborn infants at ≤28 weeks' gestation. For the subgroup analysis of newborn infants at ≤28 weeks' gestation receiving respiratory support at birth, evidence of very low certainty (downgraded for risk of bias and imprecision) showed no statistically significant benefit or harm of lower initial oxygen concentration (≤50%) compared with higher initial oxygen concentration (>50%) for the following critical outcomes (see Table 15 for data): short-term mortality (in hospital or 30 days), long-term mortality (1–3 years), long-term NDI (moderate to severe, 1–3 years), retinopathy of prematurity (grade III–V),[166] necrotizing enterocolitis (Bell grade II–III),[167] bronchopulmonary dysplasia (moderate to severe),[168] or major intraventricular hemorrhage (grade III–IV).[169]

Subgroup of 21% compared with 100% oxygen concentration (<35 weeks' gestation). For the critical outcome of all-cause short-term mortality (in hospital or 30 days), evidence of very low certainty (downgraded for risk of bias and imprecision) from 4 RCTs with 484 newborn infants at <35 weeks' gestation receiving respiratory support at birth showed no statistically significant benefit or harm of initial room air (21% O_2) compared with initial 100% oxygen concentration (RR, 1.58 [95% CI, 0.70–3.55]; I^2 = 4%): 26 per 1000 more (95% CI, 14 fewer–115 more) with short-term mortality when lower initial oxygen concentration (21%) compared with higher initial oxygen concentration (100%) was used.[171,173,175,178]

- For the critical outcome of all-cause long-term mortality (1–3 years), in newborns at <35 weeks' gestation, the results are the same as for all groups at <35 weeks' gestation.
- For the critical outcome of long-term NDI (moderate to severe, 1–3 years) in preterm newborns (<35 weeks' gestation), the results are the same as for all groups at <35 weeks' gestation.

Additional subgroup analyses that evaluated the effect of varying the definition of low and high oxygen concentration (21%–30% compared with 80%–100% only; 30% compared with 90%–100%; 50% compared with 100%; 30% compared with 60%–65%) and whether Spo_2 targeting as a cointervention had any impact found no differences in primary and secondary outcomes.[10] When data from 2 observational cohort studies with 1225 newborns[182,183] were pooled, initiating resuscitation with lower oxygen was associated with a statistically significant benefit in long-term mortality for all preterm newborns and the subgroup of ≤28 weeks' gestation (RR, 0.77 [95% CI, 0.59–0.99]; I^2 = 6%).[10]

Treatment recommendations

For preterm newborn infants (<35 weeks' gestation) who receive respiratory support at birth, we suggest starting with a lower oxygen concentration (21%–30%) rather than higher initial oxygen concentration (60%–100%; weak recommendation, very low certainty of evidence). We suggest the range of 21%–30% oxygen because all trials but one used this for the low oxygen concentration group. Subsequent titration of oxygen concentration using pulse oximetry is advised (weak recommendation, very low certainty of evidence).

Until further evidence is available, implementation of the suggested initial oxygen concentration between 21% and 30% should be based on local practice considerations and should be reevaluated with ongoing audit of care.

Table 14 – Meta-analysis of RCTs comparing initial low and high oxygen concentration for all preterm gestational ages combined (<35 weeks' gestation).

Outcome	Article with outcome of interest	Total, n	Certainty of evidence	RR (95% CI); I^2	Absolute difference (95% CI)
Short-term mortality (in hospital or 30 d)	Lundstrøm et al.[170] 1995 Harling et al.[179] 2005 Wang et al.[171] 2008 Vento et al.[172] 2009 Rabi et al.[173] 2011 Armanian and Badiee[174] 2012 Kapadia et al[175] 2013 Aguar et al.[176] 2013 Rook et al.[177] 2014 Oei et al.[178] 2017	968	Very low	0.83 (0.50–1.37); 18%	15/1000 fewer deaths when lower vs higher initial oxygen concentration was used (44 fewer–32 more)
Long-term mortality (1–3 y)	Boronat et al.[185] 2016 Thamrin et al.[186] 2018	491	Very low	1.05 (0.32–3.39); 79%	5/1000 more deaths when lower vs higher initial oxygen concentration was used (71 fewer–248 more)
NDI (moderate to severe at 1–3 y)	Boronat et al.[185] 2016 Thamrin et al.[186] 2018	389	Very low	1.14 (0.78–1.67); 0%	27/1000 more with NDI when lower vs higher initial oxygen concentration was used (42 fewer–129 more)
Retinopathy of prematurity (grade III–V)	Lundstrøm et al.[170] 1995 Harling et al.[179] 2005 Vento et al.[172] 2009 Kapadia et al.[175] 2013 Aguar et al.[176] 2013 Rook et al.[177] 2014 Oei et al.[178] 2017	806	Very low	0.73 (0.42–1.27); 0%	19/1000 fewer with retinopathy of prematurity (grade III–V) when lower vs higher initial oxygen concentration was used (42 fewer–19 more)
Necrotizing enterocolitis (Bell grade II–III)	Lundstrøm et al.[170] 1995 Harling et al.[179] 2005 Wang et al.[171] 2008 Vento et al.[172] 2009 Kapadia et al.[175] 2013 Aguar et al.[176] 2013 Rook et al.[177] 2014 Oei et al.[178] 2017	847	Very low	1.34 (0.63–2.84); 0%	12/1000 more with necrotizing enterocolitis when lower initial vs higher initial oxygen concentration was used (13 fewer–65 more)
Bronchopulmonary dysplasia (moderate to severe)	Harling et al.[179] 2005 Wang et al.[171] 2008 Vento et al.[172] 2009 Rabi et al.[173] 2011 Kapadia et al.[175] 2013 Aguar et al.[176] 2013 Rook et al.[177] 2014 Oei et al.[178] 2017	843	Very low	1.00 (0.71–1.400); 47%	0/1000 fewer with bronchopulmonary dysplasia when lower vs higher initial oxygen concentration was used (77 fewer–107 more)
Major intraventricular hemorrhage (grade III–IV)	Lundstrøm et al.[170] 1995 Wang et al.[171] 2008 Vento et al.[172] 2009 Kapadia et al.[175] 2013 Aguar et al.[176] 2013 Rook et al.[177] 2014 Oei et al.[178] 2017	795	Very low	0.96 (0.61–1.51); 0%	3/1000 fewer with major intraventricular hemorrhage (grade III–IV) when lower vs higher initial oxygen concentration was used (32 fewer –42 more)

NDI indicates neurodevelopmental impairment; RCT, randomized controlled trial; and RR, relative risk.

Justification and evidence to decision framework highlights

Balancing the benefits and serious potential harm of low versus high oxygen concentrations in neonatal care is a continuing concern, particularly for preterm infants. Decades of research clearly demonstrate that oxygen exposure is a determinant of critical neonatal outcomes in preterm infants. Concern remains that if the preterm infant requires resuscitation immediately after birth, the initial oxygen concentration to which the infant is exposed may be a critical contributor to outcomes, regardless of subsequent oxygen exposure.

Both parents and clinicians rate the outcomes assessed in this SR as either critical or important. For all of the critical outcomes assessed in the meta-analyses of RCTs, the 95% CIs of RRs were wide enough to include both potential harm and potential benefit. Thus, it is unclear whether initial low or high oxygen concentrations may have undesirable effects. In suggesting starting with low oxygen concentrations (21%–30%), we place value on avoiding exposure of preterm babies to additional oxygen without proven benefit for critical or important outcomes because we are cognizant of harms in newborn

Table 15 – Meta-analysis of RCTs comparing initial low and high oxygen concentration for ≤28-week gestational age subgroup.

Outcome	Article with outcome of interest	Total, n	Certainty of evidence	RR (95% CI); I^2	Absolute difference (95% CI)
Short-term mortality (in hospital or 30 d)	Wang et al.[171] 2008 Vento et al.[172] 2009 Rabi et al.[173] 2011 Kapadia et al.[175] 2013 Aguar et al.[176] 2013 Rook et al.[177] 2014 Oei et al.[178] 2017	467	Very low	0.92 (0.43–1.94); 45%	10/1000 fewer with short-term mortality when lower vs higher initial oxygen concentration was used (70 fewer–116 more per 1000)
Long-term mortality (1–3 y)	Thamrin et al.[186] 2018	86	Very low	2.11 (0.86–5.19); NA	145/1000 more with long-term mortality when lower vs higher initial oxygen concentration was used (18 fewer–547 more per 1000)
NDI (moderate to severe at 1–3 y)	Thamrin et al.[186] 2018	69	Very low	1.08 (0.58–2.03); NA	28/1000 more with long-term NDI when lower vs higher initial oxygen concentration was used (147 fewer–360 more per 1000)
Retinopathy of prematurity (grade III–V)	Wang et al.[171] 2008 Vento et al.[172] 2009 Kapadia et al.[175] 2013 Aguar et al.[176] 2013 Rook et al.[177] 2014 Oei et al.[178] 2017	441	Very low	0.75 (0.43–1.33); 0%	30/1000 fewer with retinopathy of prematurity when lower vs higher initial oxygen concentration was used (67 fewer–39 more per 1000)
Necrotizing enterocolitis (Bell grade II–III)	Wang et al.[171] 2008 Vento et al.[172] 2009 Kapadia et al.[175] 2013 Aguar et al.[176] 2013 Rook et al.[177] 2014 Oei et al.[178] 2017	441	Very low	1.62 (0.66–3.99); 0%	20/1000 more with necrotizing enterocolitis when lower vs higher initial oxygen concentration was used (11 fewer–95 more per 1000)
Bronchopulmonary dysplasia (moderate to severe)	Wang et al.[171] 2008 Vento et al.[172] 2009 Rabi et al.[173] 2011 Kapadia et al.[175] 2013 Aguar et al.[176] 2013 Rook et al.[177] 2014 Oei et al.[178] 2017	467	Very low	0.90 (0.64–1.28); 31%	37/1000 fewer with bronchopulmonary dysplasia when lower vs higher initial oxygen concentration was used (132 fewer–102 more per 1000)
Major intraventricular hemorrhage (grade III–IV)	Wang et al.[171] 2008 Vento et al.[172] 2009 Kapadia et al.[175] 2013 Aguar et al.[176] 2013 Rook et al.[177] 2014 Oei et al.[178] 2017	441	Very low	0.84 (0.50–1.40); 12%	23/1000 fewer with major intraventricular hemorrhage (grade III–IV) when lower vs higher initial oxygen concentration was used (73 fewer–58 more per 1000)

NDI indicates neurodevelopmental impairment; RCT, randomized controlled trial; and RR, relative risk.

animals and increased neonatal mortality in term infants exposed to high initial oxygen concentration.[151,187] This review addressed only the initial concentration of oxygen and therefore does not include any recommendation for subsequent administration or titration of oxygen. Subsequent titration of supplementary oxygen should be based on published Spo_2 target ranges.

The a priori comparisons evaluated only an initial oxygen concentration of 21%–30% versus 80%–100%, which therefore influences the recommendation. We recognize that no studies have compared the safety or efficacy of beginning resuscitation with 21% oxygen and intermediate concentrations such as 30% oxygen. We emphasize that the included studies measured only the effect of varying initial inspired oxygen concentrations and were not designed to assess the safety or efficacy of different Spo_2 targets. As outlined above, careful attention should be paid to the initial and cumulative oxygen loads under the investigated regimens. Therefore, starting at a lower oxygen concentration (21%–30%) with the option to titrate according to Spo_2 aiming for published Spo_2 target ranges provides an option of minimizing oxygen exposure at birth.

Knowledge gaps

The NLS Task Force identified the following knowledge gaps requiring further investigation:

- High-quality studies with appropriate power to determine optimal initial oxygen because the 95% CI for the primary outcome in most studies identified in this review includes both harm and benefit
- Further evidence from randomized studies on long-term NDI outcomes
- Studies to address the actual oxygen requirements for specific gestational age groups
- Further evidence to identify the optimal Spo_2 targets for preterm infants
- Evidence to identify the optimal methods of titrating oxygen for preterm infants in the delivery room
- Potential effects of delayed cord clamping on the impact of initial inspired oxygen concentration for preterm infants

EIT and ALS task forces

CACs versus non-CACs

CACs are hospitals providing evidence-based resuscitation treatments, including emergency interventional cardiology, bundled critical care with TTM, and protocolized cardiorespiratory support and prognostication.[48,63]

This population, intervention, comparator, outcome, study design, and time frame was prioritized for review by the EIT and ALS Task Forces on the basis of the publication of several large registry studies[188,189] since the 2015 ILCOR ALS[48,63] and EIT CoSTRs.[190,191] In the following sections, we present a summary of the evidence identified by the ILCOR SR11 and the web-posted CoSTR about the effects of CACs.[192] One question was posted during the comment period on the definition of CACs, and we have provided that in this introduction.

Population, intervention, comparator, outcome, study design, and time frame

Population: Adults with attempted resuscitation after nontraumatic IHCA or OHCA

Intervention: Specialized CAC care

Comparators: Care at non-CAC

Outcomes:

- Primary outcome: survival at 30 days or hospital discharge with favorable neurological outcome (CPC 1 or 2 or modified Rankin Scale score 0–3)
- Secondary outcomes: ROSC after hospital admission for patients with ongoing CPR and survival at 30 days or hospital discharge

Study designs: Published RCTs and nonrandomized studies (non-RCTs, interrupted time series, controlled before-and-after studies, cohort studies) reporting data from adult patients

Time frame: All years and all languages included (provided there was an English abstract); literature search updated on August 1, 2018

PROSPERO registration: CRD42018091427

Consensus on science

A total of 21 observational studies[188,189,193–211] and 1 pilot randomized trial[212] were included in the SR.[11] Of these, 17 observational studies were ultimately included in the meta-analysis.[188,189,193–199,204–211] All studies were in OHCA cohorts; 1 study[200] also included patients with IHCA, but outcomes were not reported separately.

The observational studies provided very low certainty of evidence for all outcomes. The included studies all reported outcomes from patients with OHCA who were cared for at a CAC compared with those cared for at a non-CAC. The manner of arrival at a CAC or non-CAC varied greatly across studies (i.e., prehospital triage of all patients to the closest hospital, prehospital triage of select patients to a CAC, prehospital triage of all patients to a CAC, secondary interhospital transfer from a non-CAC to a CAC, or not described). Given the potential for referral bias and other confounding variables, only data from studies reporting adjusted measures of association were pooled in the meta-analysis.

CACs were associated with favorable neurological outcome and survival when examined at hospital discharge, but this was nonsignificant when examined at 30 days (Table 16).

In addition to the pooled data, 3 observational studies looking exclusively at long-term outcomes of patients discharged alive from hospitals reported that care at a CAC was associated with better patient survival.[199,200,202]

Table 16 – Summary of evidence on outcomes associated with care in CACs.

Outcomes (importance)	Studies (participants), n	Certainty of the evidence (GRADE)	Odds ratio (95% CI)	Anticipated absolute effects, n	
				Care at other hospital, n (%)	Risk difference for care at CAC
Survival to 30 d with favorable neurological outcome (critical)	2 studies[188,189] (45,956)	Very low	2.92 (0.68–12.48)	359/25 617 (1.4)	26 more per 1000 (4 fewer–137 more)
Survival to hospital discharge with favorable neurological outcome (critical)	2 studies[194,195] (3673)	Very low	2.22 (1.74–2.84)	47/584 (8.0)	82 more per 1000 (52–119 more)
Survival to 30 d (critical)	2 studies[198,210] (2693)	Very low	2.14 (0.73–6.29)	123/1695 (7.3)	71 more per 1000 (19 fewer–257 more)
Survival to hospital discharge (critical)	5 studies[194,195,205–207] (11,662)	Very low	1.85 (1.46–2.34)	587/4117 (14.3)	93 more per 1000 (53–138 more)

CAC indicates cardiac arrest centers; and GRADE, Grading of Recommendations, Assessment, Development, and Evaluation.

Preplanned subgroup analyses identified additional information about the effects of primary transport versus secondary transfer of patients to CACs and about the outcomes of patients with shockable versus nonshockable rhythms. Four observational studies examined the potential impact of transfer on patient outcomes after OHCA.[189,199,209,211] One study[211] reported higher adjusted patient survival associated with direct transfer to a CAC compared with patient survival among those who underwent secondary interfacility transfer (odds ratio, 1.97 [95% CI, 1.13–3.43]). Two other studies[189,199] reported no difference in survival between direct transport and secondary transfer of patients to a CAC. One study[209] reported higher adjusted survival in patients who underwent a secondary transfer to a CAC compared with those who remained at the initial treating non-CACs (odds ratio, 1.59 [95% CI, 1.30–1.93]). One additional observational study[194] reported higher adjusted patient survival to hospital discharge associated with bypassing the nearest non-CAC and transporting patients directly to a CAC compared with transporting patients to non-CACs (odds ratio, 3.02 [95% CI, 2.01–4.53]).

Eight observational studies reported outcomes stratified by arresting rhythm into shockable or nonshockable cohorts, but the findings were inconsistent, most reported unadjusted data, and the studies were too heterogeneous to pool.[189,193,195,199,203,205,206,208]

Treatment recommendations from the EIT and ALS task forces

We suggest that adult patients with nontraumatic OHCA be cared for in CACs rather than in non-CACs (weak recommendation, very low certainty of evidence).

We cannot make a recommendation for or against regional triage by primary EMS transport of patients with OHCA to a CAC (bypass protocols) or secondary interfacility transfer to a CAC. The current evidence is inconclusive, and confidence in the effect estimates is currently too low to support an EIT and ALS Task Forces recommendation.

For patients with IHCA, we found no evidence to support an EIT and ALS Task Forces recommendation.

For the subgroup of patients with shockable or nonshockable initial cardiac rhythm, the current evidence is inconclusive, and the confidence in the effect estimates is currently too low to support an EIT and ALS Task Forces recommendation.

Justification and evidence to decision framework highlights

In making this recommendation, the EIT and ALS Task Forces concluded that the potential benefits in clinical outcomes outweighed the potential risks and logistical issues with implementation.

We specifically considered the consistency of improved outcomes in patients treated at CACs across most studies, the desirability of patients receiving evidence-based postresuscitation care, the evidence supporting specialized care for other emergency conditions (e.g., trauma, stroke, and ST-segment–elevation myocardial infarction), the lack of evidence suggesting clinical harm associated with longer transport times,[213] the potential for referral bias (i.e., transporting patients most likely to survive), and the implementation challenges of this recommendation.

Regionalized systems of care for cardiac arrest may not be feasible in all areas as a result of resource constraints, cost, and inherent regional differences in healthcare delivery. In making a weak recommendation in support of CACs, the task forces acknowledge the lack of high-level evidence.

EIT and ALS task forces knowledge gaps

Numerous knowledge gaps were identified in this SR. Key gaps include the following:

- There is no universal definition of a CAC.
- The precise aspects of CACs that improve outcomes have not been identified (e.g., if there are specific bundles of care that CACs offer that improve outcomes).
- The effect of delayed secondary interfacility transfer to a CAC is unknown.
- The potential benefit of CACs for IHCA and other subgroups (e.g., cardiac pathogenesis, shockable rhythm) has not been reported.

First aid task force

Presyncope

Presyncope, or near-syncope, is the prodrome of syncope and is characterized by light-headedness, nausea, diaphoresis, and a feeling of impending loss of consciousness. A progression to syncope results in global cerebral hypoperfusion and transient loss of consciousness; loss of postural tone can result in physical injury in up to 30% of patients.[214] This review evaluated nonpharmacological first aid interventions that can be applied at the onset or immediately after the onset of presyncope symptoms. ILCOR commissioned an SR,[12] and the task force studied all evidence cited in the SR and developed a draft CoSTR. The draft CoSTR was posted for public comment on the ILCOR website; the draft was viewed 285 times during the comment period, and no comments were posted.[215] This document summarizes the final CoSTR for first aid treatment of presyncope.

Population, intervention, comparator, outcome, study design, and time frame

Population: Adults and children with signs and symptoms of faintness or presyncope of suspected vasovagal or orthostatic origin

Intervention: Physical counterpressure maneuvers (PCMs), body positioning, hydration, or other

Comparison: Compared with no intervention or 1 intervention compared with another

Outcomes:

- Abortion of syncope (termination of progression from presyncope to syncope; critical)
- Injuries or adverse events (critical)
- Symptom improvement (important)
- Change in heart rate (important)
- Change in systolic blood pressure (important)
- Change in diastolic blood pressure (important)

Study designs: RCTs and nonrandomized studies (non-RCTs, interrupted time series, controlled before-and-after studies, cohort studies) eligible for inclusion; case series and unpublished studies, published abstracts (e.g., conference abstracts), and trial protocols excluded

Time frame: All years and all languages included (provided an English abstract was available)

PROSPERO registration: CRD42018107726

Table 17 – Summary data from presyncope studies.

Outcomes	Intervention: comparison	Participants (studies), n	RR (95% CI)	Certainty of evidence (GRADE)	Risk with control/no PCM	Risk with intervention (risk difference)
Prevention of syncope	Any PCM vs control (no use of PCM or standing only)	92 OH and VVS pathogenesis (4 observational)[218–221]	1.31 (0.98– 1.75)	Very low	594 per 1000	184 more per 1000 (12 fewer–445 more) Risk difference, 0.19 (0.01–0.37)
		64 VVS pathogenesis (3 observational)[218–220]	2.20 (0.96–5.05)	Very low	277 per 1000	222 more per 1000 (11 fewer–1000 more)
	Lower-body PCM vs control (no use of PCM or standing only)	36 VVS pathogenesis (1 observational)[220]	2.20 (0.96–5.05)	Very low		333 more per 1000 (3–586 more)
	Upper-body PCM vs control (no use of PCM or standing only)	19 VVS pathogenesis (1 RCT)[216]	1.80 (1.16–2.79)	Very low	526 per 1000	421 more per 1000 (84 –942 more)
		14 VVS pathogenesis (1 observational)[218]	29.00 (1.90–443.25)	Very low		
		37 VVS pathogenesis (2 observational)[216,222]	99.4% of episodes (349/351) (RR not estimable, no comparisons)	Very low		
	Lower-body PCM vs upper-body PCM	27 VVS pathogenesis (1 observational)[221]	7.00 (1.10–44.61)	Very low		1000 more per 1000 (88–1000)
Injuries or adverse events	Upper-body PCM vs control (no use of PCM or standing only)	37 VVS pathogenesis (2 observational)216,222	0/37 (0%) (RR not estimable, no comparisons)	Very low		0 fewer per 1000 (0–0 fewer)
Symptom improvement	Any PCM vs control (no use of PCM or standing only)	21 VVS pathogenesis (1 observational)[219]	20/20 (RR not estimable; 1 patient lost to follow-up)	Very low		
		96 VVS pathogenesis (1 RCT)[217]	1.57 (0.98–2.51)	Very low	440 per 1000	251 more per 1000 (26–409 more)
	Lower-body PCM vs control (no use of PCM or standing only)	96 VVS pathogenesis (1 RCT)[217]	1.66 (1.02–2.69)	Very low		290 more per 1000 (9–744 more)
	Upper-body PCM vs control (no use of PCM or standing only)	19 VVS pathogenesis (1 RCT)[216]	6.00 (1.55–23.26)	Low		526 more per 1000 (58–1000 more)
		96 VVS pathogenesis, follow-up phase (1 RCT)[217]	1.47 (0.89–2.44)	Very low		207 more per 1000 (48 fewer–634 more)
	Lower-body PCM vs upper-body PCM	96 VVS pathogenesis (1 RCT)[217]	0.89 (0.65–1.22)	Very low		80 fewer per 1000 (30 fewer–130 more)
Heart rate	Upper-body vs control (no use of PCM or standing only)	19 VVS pathogenesis (1 RCT)[216]		Very low		MD, 8 bpm higher (6.4–22.4 higher)
	Lower-body PCM vs upper-body PCM	27 VVS pathogenesis, handgrip vs squatting (1 observational)[221]		Very low		MD, 0.8 bpm lower (5.5 lower–3.9 higher)
		27 VVS pathogenesis, leg crossing vs handgrip (1 observational)[221]		Very low		MD, 6.3 bpm higher (3.0–9.5 higher)
Systolic blood pressure	Any PCM vs control (no use of PCM or standing only)	39 VVS pathogenesis (2 observational)[219,220]		Very low		MD, 21 mm Hg higher (18.25–23.41 higher)
	Lower-body PCM vs control (no use of PCM or standing only)	18 VVS pathogenesis (1 observational)[220]		Very low		MD, 19 mm Hg higher (16.31–21.69 higher)

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Table 17 *(continued)*

Outcomes	Intervention: comparison	Participants (studies), n	RR (95% CI)	Certainty of evidence (GRADE)	Risk with control/no PCM	Risk with intervention (risk difference)
	Upper-body PCM vs control (no use of PCM or standing only)	19 VVS pathogenesis (1 RCT)[216]		Low		MD, 32 mm Hg higher (12.48−51.52 higher)
Systolic blood pressure Continued	Lower-body PCM vs upper-body PCM	27 VVS pathogenesis, squatting vs handgrip (1 observational)[221]		Very low		MD, 12.5 mm Hg higher (5.69−19.31 higher)
		27 VVS pathogenesis, leg crossing vs handgrip (1 observational)[221]		Very low		MD, 11.6 mm Hg higher (4.3−18.8 higher)
	Lower-body PCM vs abdominal PCM	9 neurogenic OH pathogenesis (1 observational)[223]		Very low		MD, 36.5 higher (15.00−57.99 higher)
	Lower-body PCM vs neck PCM	9 neurogenic OH pathogenesis (1 observational)[223]		Very low		MD, 28.2 higher (10.79−45.61 higher)
Diastolic blood pressure	Any PCM vs control (no use of PCM or standing only)	39 VVS pathogenesis (2 observational)[219,220]		Very low		MD, 11 mm Hg higher (9.39−13.10 higher)
	Lower-body PCM vs control (no use of PCM or standing only)	18 VVS pathogenesis (1 observational)[220]		Very low		MD, 10 mm Hg higher (8.04−11.96 higher)
	Upper-body PCM vs control (no use of PCM or standing only)	19 VVS pathogenesis (1 RCT)[221]		Very low		MD, 20 mm Hg higher (5.95−34.05 higher)
	Lower-body PCM vs upper-body PCM	27 VVS pathogenesis (1 observational)[221]		Very low		MD, 3.3 mm Hg higher (2.28 lower−8.88 higher)
		27 VVS pathogenesis (1 observational)[221]		Very low		MD, 1.3 mm Hg higher (6.88 lower−4.28 mm Hg higher)

GRADE indicates Grading of Recommendations, Assessment, Development, and Evaluation; MD, mean difference; OH, orthostatic hypotension; PCM, physical counterpressure maneuvers; RCT, randomized controlled trial; RR, relative risk; and VVS, vasovagal syncope.

Consensus on science

Studies comparing use of PCMs with a control or no use of PCMs. Eight studies were included in the SR, all evaluating the use of PCMs compared with no use of PCMs. PCMs involved the contraction of the large muscles of the legs, arms, or abdomen and included leg or arm tensing, crossing, or squeezing; squatting; handgrip; and abdominal compression. Studies included 2 RCTs[216,217] and 6 observational studies,[216,218–222] enrolling a total of 246 participants between 15 and 75 years of age with a history of vasovagal or orthostatic-related syncope. Forms of PCMs evaluated included handgrip, squatting, leg crossing with tensing, and abdominal/core muscle tensing. Evidence from the Brignole et al.[216] RCT was downgraded to very low certainty as a result of risk of bias, inconsistency, indirectness, and imprecision, whereas evidence from the Alizadeh et al.[217] RCT was downgraded to low certainty as a result of risk of bias, inconsistency, and indirectness. The observational studies all provide very-low-certainty evidence.[216,218–222] Table 17 gives a summary of studies.

Termination of syncope. Use of handgrip PCMs in 19 participants with vasovagal syncope and a positive tilt-table test increased the likelihood of terminating syncope in 1 RCT.[216] However, no association was found between the termination of syncope and any form of PCM in 4 observational studies in laboratory settings with tilt-table testing.[218–221] In 2 observational follow-up studies of 37 participants in settings of daily life,[216,222] use of handgrip and arm-tensing PCMs was associated with termination of syncope in 99% of episodes involving subjects with known vasovagal origin presyncope. No adverse events or complications related to the use of handgrip PCMs were reported in any of these studies.

Alleviation of Symptoms of Presyncope. One RCT with 96 participants evaluated in daily life settings reported that the use of lower-body PCMs (squatting) or upper-body PCMs (handgrip) resulted in more alleviation of symptoms of presyncope than no PCMs.[217] A second smaller RCT[216] in a tilt-table test setting found more symptom improvement with the use of handgrip PCMs compared with no PCMs. One observational follow-up study[219] found symptom improvement in all 21 participants with syncope of vasovagal origin in association with the use of lower-body PCMs (squatting and abdominal tension).

Increase in heart rate and blood pressure. An increase in heart rate after the use of handgrip PCMs was reported in a single RCT,[216] although 4 observational studies[218–221] did not report consistent changes in heart rate. The same single RCT[216] found improved systolic blood pressure with the use of handgrip PCMs, and 2 pooled observational studies[219,220] reported increased systolic and diastolic blood pressures associated with the use of lower-body PCMs.

Subgroup analysis. A subgroup weighted meta-analysis of 64 adults with vasovagal presyncope only from 3 observational studies[219–221] failed to find an association between the use of PCMs and reduced likelihood of progression from presyncope to syncope but did show an association with a greater likelihood of symptom improvement and an increase in heart rate and blood pressure.

Upper-body compared with lower-body PCMs. The use of upper-body PCMs compared with lower-body PCMs was evaluated by 1 observational study[221] that reported a greater likelihood for termination of syncope and increase in heart rate and blood pressure associated with the use of lower-body PCMs. Results from 1 RCT[217] did not find greater improvement in symptoms of presyncope with the use of lower-body PCMs compared with upper-body PCMs.

Additional interventions for presyncope. No studies were identified that evaluated the use of other interventions such as hydration or change of position applied at the onset of symptoms of presyncope.

Treatment recommendations

We recommend the use of any type of PCM by individuals with acute symptoms of presyncope from vasovagal or orthostatic causes in the first aid setting (strong recommendation, low and very low certainty of evidence).

We suggest that lower-body PCMs such as leg crossing and tensing or squatting are preferable to upper-body and abdominal PCMs (weak recommendation, very low certainty of evidence).

Justification and evidence to decision framework highlights

Despite the mixed results and low- or very-low-certainty evidence identified in this review, using the Evidence to Decision Framework[215] and discussing all evidence, the First Aid Task Force concluded that the use of PCMs for acute symptoms of presyncope warranted a strong recommendation because, together, the included studies suggest that the use of PCMs results in better outcomes with no reported adverse events. In addition, PCM interventions are simple and inexpensive, and they may prevent the progression from presyncope to syncope and risks of subsequent injury. Successful treatment of presyncope may improve the QOL for those with recurrent vasovagal or orthostatic syncope, and it may ultimately decrease associated healthcare costs. Included studies demonstrated that training of participants in the use of PCMs at symptom onset was feasible and similar to a first aid situation, making it likely that first aid providers can also be trained in their use.

Although there is little evidence comparing different methods of PCMs, observational studies suggested that the use of lower-body PCMs may have an advantage over upper-body PCMs for the outcome of terminating presyncope. Despite this, the task force recognizes the practicality of the use of a variety of PCM techniques for first aid, particularly when PCM interventions may be limited by patient location and position.

Knowledge gaps

The task force identified several knowledge gaps requiring further investigation:

- Validity of conventional first aid recommendation to place a person with symptoms of presyncope into a sitting or supine position with or without a combination of PCMs
- Effectiveness of additional interventions such as hydration
- Clinical outcomes related to the use of PCMs and possible variation based on age, sex, and cause of presyncope
- Ability of first aid providers to recognize vasovagal and orthostatic presyncope and to assess clinical outcomes after instruction in and use of PCMs

Disclosures

Writing group disclosures

Writing group member	Employment	Research grant	Other research support	Speakers' Bureau/Honoraria	Expert witness	Ownership interest	Consultant/advisory board	Other
Jasmeet Soar	Southmead Hospital North Bristol NHS Trust (United Kingdom)	None	None	None	None	None	None	None
Richard Aickin	Starship Children's Hospital (New Zealand)	None	None	None	None	None	None	None
Lars W. Andersen	Aarhus University (Denmark)	Amomed Pharma GmbH (PI on a clinical trial involving vasopressin and methylprednisolone. The trial is funded by government. Vasopressin is provided free of charge by Amomed Pharma GmbH, which provides no funding and has no role in the trial.)*	None	None	None	None	None	None
Dianne L. Atkins	University of Iowa	None	None	None	None	None	None	None
Khalid Aziz	University of Alberta (Canada)	Canadian Institutes of Health Research (Parent-EPIQ quality improvement research†; family-integrated care 18- mo follow-up)†; Alberta Children's Hospital Research Institute (family-integrated care 6-mo follow-up)†	None	None	CMPA*	None	None	University of Alberta (professor)†
Jason Bendall	University of Newcastle School of Medicine & Public Health (Australia)	None	None	None	None	None	None	None
Katherine M. Berg	Beth Israel Deaconess Medical Center	NIH*	None	None	None	None	None	None
David C. Berry	Saginaw Valley State University	None	None	None	None	None	None	None
Farhan Bhanji	McGill University (Canada)	None	None	None	None	None	None	None
Blair L. Bigham	McMaster University (Canada)	None	None	None	None	None	None	None
Robert Bingham	Great Ormond Street Hospital NHS	None	None	None	None	None	None	None

Table *(continued)*

Writing group member	Employment	Research grant	Other research support	Speakers' Bureau/Honoraria	Expert witness	Ownership interest	Consultant/advisory board	Other
Vere Borra	Foundation Trust (United Kingdom) Belgian Red Cross Centre for Evidence-Based Practice (Belgium)	None	None	None	None	None	None	Belgian Red Cross (researcher; unpaid)*
Bernd W. Böttiger	University of Cologne (Germany)	None	None	Bayer Vital GmbH*; Baxalta Deutschland GmbH*; Boehringer Ingelheim Pharma GmbH & Co KG*; ZOLL Medical Deutschland GmbH*; Forum für medizinische Fortbildung (FomF)*; C.R. Bard GmbH*; GS Elekrtomedizinische Geräte G. Stemple GmbH*; Novartis Pharma GmbH*; Phillips GmbH Market DACH*	None	None	None	None
Janet E. Bray	Monash University (Australia)	None	None	None	None	None	None	None
Jan Breckwoldt	University Hospital of Zurich Institute for Anesthesiology (Switzerland)	None	None	None	None	None	None	None
Steven C. Brooks	Queen's University (Canada)	Canadian Institutes of Health Research (peer- reviewed grant to study the PulsePoint mobile device application in a randomized trial)†	None	None	Borden Ladner Gervais†	None	None	None
Jason Buick	University of Toronto Institute of Health Policy, Management and Evaluation (Canada)	None	None	None	None	None	None	None
Clifton W. Callaway	University of Pittsburgh	NIH (grants to university)†	None	None	None	None	None	None
Jestin N. Carlson	Allegheny Health Network	American Heart Association (funds for intubation research)†	None	None	None	None	AHA†	None
Pascal Cassan	Emergency physician (private	None	None	None	None	None	None	None

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Writing group member	Employment	Research grant	Other research support	Speakers' Bureau/Honoraria	Expert witness	Ownership interest	Consultant/advisory board	Other
	practice); International Federation of Red Cross and Red Crescent National Societies							
Maaret Castrén	Helsinki University Hospital (Finland)	None	None	None	None	None	None	None
Wei-Tien Chang	National Taiwan University Hospital and College of Medicine (Taiwan)	None	None	None	None	None	None	None
Nathan P. Charlton	University of Virginia	None	None	None	None	None	None	None
Adam Cheng	Alberta Children's Hospital (Canada)	None	None	None	None	None	None	University of Calgary (professor)†
Sung Phil Chung	Yonsei University College of Medicine (Republic of Korea)	None	None	None	None	None	None	None
Julie Considine	Deakin University School of Nursing & Midwifery (Australia)	None	None	None	None	None	Helsinki University Hospitals†	Deakin University-Eastern Health (professor of nursing)†; College of Emergency Nursing Australasia (senior editor)*
Keith Couper	University of Warwick, Warwick Medical School (United Kingdom)	None	None	None	None	None	None	None
Thomaz Bittencourt Couto	Hospital Israelita Albert Einstein and Universidade de São Paulo (Brazil)	None	None	None	None	None	None	None
Katie N. Dainty	North York General Hospital	Canadian Institutes of Health Research (resuscitation grants from CIHR)*	None	None	None	None	None	None
Jennifer Anne Dawson	The Royal Women's Hospital Newborn	None	None	None	None	None	None	None

Table *(continued)*

Writing group member	Employment	Research grant	Other research support	Speakers' Bureau/Honoraria	Expert witness	Ownership interest	Consultant/advisory board	Other
	ResearchCentre (Australia)							
Maria Fernanda de Almeida	Universidade Federal de Sao Paulo (Brazil)	None	None	None	None	None	None	None
Allan R. de Caen	University of Alberta (Canada)	None	None	None	None	None	None	None
Charles D. Deakin	NIHR, University Hospital Southampton (United Kingdom)	None	None	None	None	None	None	None
Michael W. Donnino	Beth Israel Deaconess Medical Center	Kaneka (investigator- initiated study with CoQ10)*; GE (investigator-initiated study with VO2)*	None	None	None	None	None	None
Ian R. Drennan	St. Michael's Hospital Rescu, Li Ka Shing Knowledge Institute (Canada)	None	None	None	None	None	None	None
Jonathan P. Duff	University of Alberta and Stollery Children's Hospital	None	None	None	None	None	None	None
Jonathan L. Epstein	American Red Cross	None	None	None	None	None	None	None
Raffo Escalante	Inter-American Heart Foundation (Peru)	None	None	None	None	None	None	None
Raúl J. Gazmuri	Rosalind Franklin University of Medicine and Science Resuscitation Institute	DoD (sustained V1A receptor activation for prolonged hemodynamic support and neurological protection after noncompressible hemorrhage and traumatic brain injury)†; VA Merit Review (cyclophilin D: a regulator of mitochondrial oxidative phosphorylation)†; Zoll Foundation (myocardial effects of shock burden during defibrillation attempts)†	None	None	None	None	None	None
			None	None	None	None	None	None

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Writing group member	Employment	Research grant	Other research support	Speakers' Bureau/Honoraria	Expert witness	Ownership interest	Consultant/advisory board	Other
Elaine Gilfoyle	Alberta Children's Hospital (Canada)	Zoll Corp (in-kind donation of equipment (defibrillator with CPR feedback) for research project)*						
Asger Granfeldt	Aarhus University Hospital (Denmark)	None	None	None	None	None	None	None
Robert Greif	Bern University Hospital, and University of Bern (Switzerland)	Department of Anesthesia, Bern University Hospital (departmental research grant)*; Storz Co*	European Resuscitation Council (board director of education and training)*; ILCOR (task force chair Education, Implementation, Team)*	None	None	None	None	Bern University Hospital (professor of anesthesiology)†; University of Bern (vice chair of Cantonal Ethic Committee Bern)*
Anne-Marie Guerguerian	The Hospital for Sick Children (Canada)	None	None	None	None	None	None	None
Ruth Guinsburg	Federal University of Sao Paulo (Brazil)	None	None	None	None	None	None	None
Tetsuo Hatanaka	Emergency Life Saving Technique Academy (Japan)	None	None	None	None	None	None	None
Mary Fran Hazinski	Vanderbilt University School of Nursing	None	None	None	None	None	AHA Emergency Cardiovascular Care Programs†	None
Mathias J. Holmberg	Aarhus University (Denmark)	None	None	None	None	None	None	None
Natalie Hood	Monash Medical Centre (Australia)	None	None	None	None	None	None	None
Shigeharu Hosono	Jichi Medical University, Saitama Medical Center (Japan)	None	None	None	None	None	None	None
Ming-Ju Hsieh	National Taiwan University Hospital (Taiwan)	None	None	None	None	None	None	None
Tetsuya Isayama	National Center for Child Health and Development (Japan)	Nihon-Kohden Corp (member of research project led by researcher at Nihon-Kohden. The topic of the research is an application of a respiratory monitoring device in neonatal	None	None	None	None	None	None

Table *(continued)*

Writing group member	Employment	Research grant	Other research support	Speakers' Bureau/Honoraria	Expert witness	Ownership interest	Consultant/advisory board	Other
		resuscitation that has been developed by Nihon−Kohden.)*						
Taku Iwami	Kyoto University Health Service (Japan)	Grants-in-aid for scientific research, KAKENHI Scientific Research (Japanese national research grant)†; Zoll Medical Corp (donation to enhance studies for out-of-hospital cardiac arrests)†; Hamamatsu Photonics (joint research grant)†	None	None	None	None	None	None
Jan L. Jensen	Emergency Health Services, Dalhousie University (Canada)	None	None	None	None	None	None	None
Vishal Kapadia	UT Southwestern	None	None	None	None	None	None	None
Han-Suk Kim	Seoul National University College of Medicine (Republic of Korea)	None	None	None	None	None	None	None
Monica E. Kleinman	Boston Children's Hospital	None	None	None	2018 −2019 defense, pediatric critical care*	None	Up-to-Date*	Boston Children's Hospital (medical director ICU)†
Peter J. Kudenchuk	University of Washington Medical Center	NIH/NINDS (PI at the University of Washington for the NIH/ NINDS −supported SIREN Network)†	None	None	None	None	None	None
Eddy Lang	University of Calgary (Canada)	None	None	None	None	None	None	None
Eric Lavonas	Denver Health	None	None	None	None	None	None	None
Swee Han Lim	Singapore General Hospital (Singapore)	None	None	None	None	None	None	None
Andrew Lockey	European Resuscitation Council (United Kingdom)	None	None	None	None	None	None	None
Bo Lofgren		None	None	None	None	None	None	None

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Writing group member	Employment	Research grant	Other research support	Speakers' Bureau/Honoraria	Expert witness	Ownership interest	Consultant/advisory board	Other
	Aarhus University Hospital Institute of Clinical Medicine (Denmark)							
Matthew Huei-Ming Ma	National Taiwan University Hospital (Taiwan)	None	None	None	None	None	None	None
Ian Maconochie	Imperial College Healthcare Trust (United Kingdom)	None	None	None	None	None	None	None
Mary E. Mancini	University of Texas at Arlington College of Nursing and Health Innovation	None	None	Stryker*	None	None	None	None
David Markenson	Sky Ridge Medical Center	None	American Red Cross (chair, SAC and CMO Training Services)†	None	None	None	American Red Cross†	None
Peter A. Meaney	Stanford University School of Medicine	None	None	None	None	None	None	None
Daniel Meyran	French Red Cross (France)	None	None	None	None	None	None	None
Lindsay Mildenhall	Middlemore Hospital (New Zealand)	None	None	None	None	None	None	None
Koenraad G. Monsieurs	Antwerp University Hospital (Belgium)	None	None	None	None	None	None	None
William Montgomery	Straub Clinic and Hospital	None	None	None	None	None	None	None
Peter T. Morley	University of Melbourne Clinical School, Royal Melbourne Hospital (Australia)	None	None	None	None	None	None	None
Laurie J. Morrison	Rescu Li Ka Shing Knowledge Institute (Canada)	The Canadian Institutes of Health Research (CIHR)†	None	None	None	None	None	None
Vinay M. Nadkarni	Children's Hospital Philadelphia	NIH (research grant: cardiac arrest)*; Zoll Medical (unrestricted research grant: quality of CPR)*; American Heart	None	None	None	None	None	None

Table *(continued)*

Writing group member	Employment	Research grant	Other research support	Speakers' Bureau/Honoraria	Expert witness	Ownership interest	Consultant/advisory board	Other
		Association (research grant: quality of CPR)*; Nihon-Kohden (research grant to his institution)*						
Kevin Nation	New Zealand Resuscitation Council (New Zealand)	None	None	None	None	None	None	None
Robert W. Neumar	University of Michigan	NIH (R34 HL130738†, R44 HL091606*, R01 HL133129†, K12 HL133304*); PhysioControl (equipment support for laboratory and clinical research)*	None	None	None	None	None	None
Kee-Chong Ng	KK Hospital (Singapore)	None	None	None	None	None	None	None
Tonia Nicholson	Waikato Hospital (New Zealand)	None	None	None	None	None	None	None
Nikolaos Nikolaou	Konstantopouleio General Hospital (Greece)	None	None	None	None	None	None	None
Chika Nishiyama	Kyoto University (Japan)	None	None	None	None	None	None	None
Jerry P. Nolan	Warwick Medical School, University of Warwick, Anaesthesia Royal United Hospital (United Kingdom)	NIHR grants for PARAMEDIC-2 and AIRWAYS-2 trials*	None	None	None	None	None	None
Gabrielle Nuthall	Starship Children's Hospital (New Zealand)	None	None	None	None	None	None	None
Shinichiro Ohshimo	The JAPAN Foundation for Aging and Health (no significant conflict of interest with the manuscript)*	None	None	None	None	None	None	None
Deems Okamoto	Self-employed	None	None	None	None	None	None	None
			None	None	None	None	None	None

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Writing group member	Employment	Research grant	Other research support	Speakers' Bureau/Honoraria	Expert witness	Ownership interest	Consultant/advisory board	Other
Theresa M. Olasveengen	Oslo University Hospital (Norway)	Zoll Foundation*; Laerdal Foundation* (unrestricted grants for research project)						
Brian O'Neil	Wayne State University	Zoll Circulation (study PI)*; SIREN Network (hub PI)*	None	Zoll Circulation*; Bard Corp*	None	None	None	None
Gene Yong-Kwang Ong	KK Women's and Children's Hospital (Singapore)	None	None	None	None	None	None	None
Edison F. Paiva	Hospital das Clinicas (Brazil)	None	None	None	None	None	None	None
Michael Parr	Liverpool Hospital (Australia)	None	None	None	None	None	None	None
Jeffrey L. Pellegrino	Aultman College of Nursing & Health Sciences	American Red Cross (research in first aid educational development)*	American Red Cross (volunteer member of Science Advisory Council)*	None	None	None	International Red Cross (unpaid)*	None
Gavin D. Perkins	Warwick Medical School and Heart of England NHS Foundation Trust (United Kingdom)	None	National Institute for Health Research (grant to evaluate effectiveness of adrenaline for out-of-hospital cardiac arrest)†	None	None	None	None	None
Jeffrey Perlman	Weill Cornell Medical College	None	None	None	None	None	None	None
Yacov Rabi	University of Calgary, Foothills Medical Center (Canada)	None	None	None	None	Masimo Corp*	None	None
Amelia Reis	Inter-American Heart Foundation (Brazil)	None	None	None	None	None	None	None
Joshua C. Reynolds	Michigan State University College of Human Medicine	None	None	None	None	None	None	None
Giuseppe Ristagno	Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan,	None	None	None	None	None	None	None

Table *(continued)*

Writing group member	Employment	Research grant	Other research support	Speakers' Bureau/Honoraria	Expert witness	Ownership interest	Consultant/advisory board	Other
	University of Milan (Italy)							
Charles C. Roehr	University of Oxford, John Radcliffe Hospital, Oxford University Hospitals (United Kingdom)	NIHR/HTA Project 15/188/106, Neo-CLEAR; Health Technology Assessment Grant by NIHR (UK): competitive, peer- reviewed governmental grant scheme (as chief investigator of a UK national RCT study on the efficacy and safety of a novel way to perform neonatal lumbar punctures [nonpharmaceutical or other] trial, received a fraction of his salary through this national, peer-reviewed grant)*	None	Received small honoraria for speaking at university and industry-initiated symposia by Chiesi Farmaceutici (Italy) and Abbvie (UK)*	None	None	Chair of Data Monitoring Board for a pharmaceutical study investigating nebulized surfactant (after stabilization, not as a medication/route used for resuscitation of preterm infants)*	NIHR/HTA project 15/188/106, Neo-CLEAR; Health Technology Assessment Grant by NIHR (UK): competitive, peer-reviewed governmental grant scheme (as chief investigator of a UK national RCT study on the efficacy and safety of a novel way to perform neonatal lumbar punctures [nonpharmaceutical or other] trial; received a fraction of his salary through this national, peer- reviewed grant)*
Tetsuya Sakamoto	Teikyo University School of Medicine (Japan)	Japan MHLW*	None	None	None	None	None	None
Claudio Sandroni	Università Cattolica del Sacro Cuore, Policlinico Gemelli (Italy)	None	None	None	None	None	None	None
Stephen M. Schexnayder	University of Arkansas/Arkansas Children's Hospital	None	None	None	None	None	None	None
Barnaby R. Scholefield	University of Birmingham Institute of Inflammation and Ageing (United Kingdom)	NIHR grant funding (awarded academic NIHR Clinician Scientist Fellowship by the National Institute of Health Research [NHS, UK])†	None	None	None	None	None	NIHR Clinician Scientist Fellowship (clinician scientist [academic, non-commercial])†

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Writing group member	Employment	Research grant	Other research support	Speakers' Bureau/Honoraria	Expert witness	Ownership interest	Consultant/advisory board	Other
Naoki Shimizu	St. Marianne University School of Medicine (Japan)	None	None	None	None	None	None	None
Eunice M. Singletary	University of Virginia	None	None	None	None	None	None	None
Markus B. Skrifvars	Helsinki University Hospital and University of Helsinki (Finland)	Several unrestricted research grants in the field of postarrest care†; GE Healthcare (research grant for project performed 2015–2017)*	None	BARD*; Covidien (INVOS)*	None	None	None	None
Michael A. Smyth	University of Warwick (United Kingdom)	None	None	None	None	None	None	None
David Stanton	Resuscitation Council of Southern Africa (South Africa)	None	None	None	None	None	None	None
Janel Swain	Emergency Health Services Nova Scotia (Canada)	None	None	None	None	None	None	None
Edgardo Szyld	University of Oklahoma	None	None	None	None	None	None	None
Janice Tijssen	London Health Sciences Center (Canada)	MedEvac Foundation (for transport research)*	None	None	None	None	None	None
Andrew Travers	Emergency Health Services, Nova Scotia (Canada)	None	None	None	None	None	None	None
Daniele Trevisanuto	University of Padova (Italy)	None	None	None	None	None	None	None
Christian Vaillancourt	University of Ottawa, Ottawa Hospital Research Institute (Canada)	Heart and Stroke Foundation of Canada (grant funding for dispatch-assisted CPR interventions)†	University of Ottawa (chair of Emergency Cardiac Resuscitation [salary support])†	None	None	None	None	None
Patrick van de Voorde	NA	None	None	None	None	None	None	None
Sithembiso Velaphi	Resuscitation Council of Southern Africa (South Africa)	None	None	None	None	None	None	None
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Mohamud Daya	Oregon Health & Science University	None	None	None	None	None	None	None
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This table represents the relationships of reviewers that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all reviewers are required to complete and submit. A relationship is considered to be "significant" if (a) the person receives $10 000 or more during any 12-month period, or 5% or more of the person's gross income; or (b) the person owns 5% or more of the voting stock or share of the entity, or owns $10 000 or more of the fair market value of the entity. A relationship is considered to be "modest" if it is less than "significant" under the preceding definition.

* Modest.

† Significant.

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