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1   **CoSTR Summary**

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3   **2019 International Consensus on Cardiopulmonary Resuscitation and Emergency**

4   **Cardiovascular Care Science With Treatment Recommendations**

5   Summary from the Basic Life Support; Advanced Life Support; Pediatric Life Support; Neonatal

6   Life Support; Education, Implementation, and Teams; and First Aid Task Forces

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[h1]Abstract

The International Liaison Committee on Resuscitation (ILCOR) has initiated a continuous review of new, peer-reviewed, published cardiopulmonary resuscitation (CPR) science. This is the third annual summary of the ILCOR International Consensus on CPR and Emergency Cardiovascular Care Science With Treatment Recommendations. It addresses the most recent published resuscitation evidence reviewed by ILCOR Task Force science experts. This summary addresses the role of cardiac arrest centers and dispatcher-assisted CPR, the role of extracorporeal CPR 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 ILCOR task forces have assessed, discussed, and debated the certainty of the evidence based on 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.

[h1]Introduction

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 summarizes 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 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 by the 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, 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; finally, the task forces have prioritized knowledge gaps requiring future research studies.

The CoSTRs are based on task force analysis of the data, using the GRADE approach to answer specific research questions. Each analysis has been detailed in a systematic review (SR), published by a Knowledge Synthesis Unit (KSU) or systematic reviewer and the ILCOR topic experts.[2-11] The GRADE approach rates the certainty evidence for an intervention and for each outcome as high, moderate, low, or very low. Data from randomized controlled trials (RCTs) is initially rated as high-certainty evidence, and data from observational studies as low-certainty

1   evidence. Five factors may lead to downgrading of the certainty of evidence, and 3 factors may

2   enable an upgrade of the certainty of the evidence (Tables 1 and 2).

3   For each topic, the consensus on science (CoS) generally includes the pertinent outcome data

4   listing (1) relative risk (RR) with 95% confidence interval (CI), and (2) risk difference (RD) with

5   95% CI or absolute risk difference (ARD) with 95% CI and (3) patients with outcome/1000

6   patients with 95% CI. For clarity, much of this data has been presented in tables. The consensus

7   on science is followed by the treatment recommendation (TR), the task force justification for the

8   TR, and the important knowledge gaps identified by the task force.

9   Readers are encouraged to monitor the ILCOR CoSTR website[12] to provide feedback about

10   planned SRs and to provide comments when additional draft reviews are posted.

1   **Table 1. GRADE Terminology for Strength of Recommendation and Criteria for Evidence Certainty Assessment**

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	Large effect
Observational trial	Low or very low	Inconsistency	Dose response
		Indirectness	All plausible confounding would reduce demonstrated effect or
		Imprecision	would suggest a spurious effect when results show no effect
		Publication bias	

2

1   **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 (eg, 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 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 which the guidance is directed.

1   CI, confidence interval; CV indicates compression-ventilation; GRADE, Grading of

2   Recommendations, Assessment, Development, and Evaluation; IHCA, in-hospital cardiac arrest;

3   and OHCA, out-of-hospital cardiac arrest.

4

5   The following topics are addressed in this CoSTR summary:

6   • Basic Life Support

7   − Dispatch Instruction in Adult Cardiopulmonary Resuscitation (CPR)

8   • Advanced Life Support

9   − Advanced Airway Interventions During Adult Cardiac Arrest

10   − Use of Vasopressors in Cardiac Arrest

11   − Extracorporeal Cardiopulmonary Resuscitation (ECPR) for Cardiac Arrest: Adults

12 • Pediatric Life Support

13   − Dispatcher Instruction in CPR: Dispatcher-Assisted CPR (DA-CPR)—Pediatrics

14   − Advanced Airway Interventions in Pediatric Cardiac Arrest

15   − ECPR: Infants and Children

1   −   Targeted Temperature Management (TTM) After Cardiac Arrest

2   •   Neonatal Life Support

3   −   Initial Oxygen Concentration for Term Infants at Birth

4   −   Initial Oxygen Concentration for Preterm Infants at Birth

5   •   Education, Implementation, and Teams (EIT) and Advanced Life Support (ALS)

6   −   Cardiac Arrest Centers (CACs) Versus Non-CACs

7   •   First Aid

8   −   Presyncope

9 Readers are encouraged to monitor the ILCOR website[12] to provide feedback about planned SRs

10 and to provide comments when additional draft reviews are posted.

11 **[h1]Basic Life Support**

12 **[h2]Dispatch Instruction in Adult CPR**

13 The emergency medical dispatcher is an essential link in the chain of survival.[13,14] In addition to

14 dispatching emergency medical services (EMS) resources to medical emergencies, emergency

15 medical dispatchers are increasingly being trained to recognize cardiac arrest, assist bystanders

16 in initiating resuscitation, and support bystanders in optimizing resuscitation efforts. The

17 international community is continuing to explore ways to increase bystander CPR for cardiac

18 arrests. One such strategy involves dispatchers providing CPR instruction to callers/bystanders—

19 DA-CPR. For such a strategy to be successful, it requires (1) the EMS system to be configured to

1 support the dispatcher to offer DA-CPR and (2) the bystander to deliver CPR with support from

2 the dispatcher.

3 ILCOR commissioned an SR to address the effect of DA-CPR on outcomes for patients in out-

4 of-hospital cardiac arrest (OHCA).[2] A draft CoSTR was posted for public comment on the

5 ILCOR website[15]; the draft was viewed 1516 times during the public comment period. The Task

6 Force reviewed the one comment that was posted during this public commenting period.

7 **[h3]Population, Intervention, Comparator, Outcome, Study Design, and Time Frame**

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

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

10 Comparators: Studies with comparators where either systems or specific cardiac arrest cases not

11 offered DA-CPR are included

12 Outcomes: Critical—survival with favorable neurologic function (at hospital discharge, 1 month,

13 or 6 months), survival (to hospital discharge, 1 month, or 1 year), short-term survival (return of

14 spontaneous circulation [ROSC], hospital admission), provision of bystander CPR; Important—

15 initial shockable rhythm, time to CPR

16 Study Designs: RCTs and nonrandomized studies (non-RCTs, interrupted time series, controlled

17 before-and-after studies, cohort studies) eligible for inclusion

18 Time Frame: All years and all languages included with the last search performed July 1, 2018;

19 ongoing or unpublished studies identified through a search of ClinicalTrials.gov online registry[16]

20 PROSPERO registration: CRD42018091427

1 *Note:* The pediatric information is summarized elsewhere in this document (see Pediatric Life

2 Support, Dispatcher Instruction in CPR: DA-CPR—Pediatrics).

3 **[h3]Consensus on Science**

4 Over 5000 citations were reviewed, and 33 were identified as eligible for inclusion. These

5 studies were classified into 2 categories: (1) systems: the comparison of outcomes when DA-

6 CPR was offered versus not offered, and (2) bystander delivery: the comparison of outcomes for

7 patients receiving DA-CPR versus those receiving no bystander CPR or unassisted bystander

8 CPR. No randomized clinical trials were identified. Given that the only available data consisted

9 of observational studies, we separately listed data when it came from an analysis adjusted for

10 known confounders because we felt this provided a better estimate of effect. The reliance on

11 nonrandomized trials in the evidence review also means the reported findings are best regarded

12 as associated with the CPR provided, or not, rather than necessarily caused by the interventions.

13 **[h4]Systems: Studies Comparing Outcomes for Patients When DA-CPR Instruction Was**

14 **Offered With Outcomes for Patients When DA-CPR Was Not Offered**

15 For the comparison of outcomes in systems with DA-CPR programs, we identified 16 studies.

16 These included 5 before-and-after studies,[17-21] and 11 cohort studies[22-32] Only 4 of these studies

17 adjusted in some way for confounding variables.[21,26,28,32] Table 3 provides a summary of the

18 unadjusted and adjusted meta-analysis.

1   **Table 3. Systems: Studies Comparing Outcomes for Adults When Dispatch-Assisted CPR Instruction Was Offered With**

2   **Outcomes for Adults When Dispatch-Assisted CPR Was Not Offered**

	Unadjusted Analysis				Adjusted Analysis			
Outcome	**Studies (n patients)**	**Evidence certainty**	**Odds ratio (95% CI)**	**Absolute difference**	**Studies (n patients)**	**Evidence certainty**	**Odds ratio (95% CI)**	**Absolute difference**
Survival with favorable neurologic outcome at 1 month	3 (44 698)[21,26,32]	Very low	1.10 [1.03, 1.17]	9 more per 1000 (from 3 more to 15 more)	2 (6799)[21,26]	Very low	1.47 [1.03, 2.09]	11 more per 1000 (from 1 more to 25 more)
Survival with favorable neurologic outcome at	2 (5533)[18,22]	Very low	1.70 [1.21, 2.37]	14 more per 1000 (from 4 more to 27 more)	1 (5288)[18]	Very low	1.67 [1.13, 2.47]	14 more per 1000 (from 3 more to 30 more)

	Unadjusted Analysis				Adjusted Analysis			
hospital discharge								
Survival at 1 month	2 (6799)[21,26]	Very low	1.20 [0.99, 1.45]	11 more per 1000 (from 1 fewer to 25 more)	2 (6799)[21,26]	Very low	1.45 [1.09, 1.94]	25 more per 1000 (from 5 more to 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 (from 2 fewer to 73 more)	1 (5288)[18]	Very low	1.33 [1.07, 1.66]	21 more per 1000 (from 5 more to 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 (from 8 fewer to 33 more)	1 (2493)[21]	Very low	0.97 [0.70, 1.34]	4 fewer per 1000 (from 39 fewer to 40 more)
Return of spontaneous circulation	5 (49 229)[18,20,21,28,32]	Very low	1.17 [1.08, 1.27]	27 more per 1000 (from 13 more to 42 more)	1 (2493)[21]	Very low	1.14 [0.88, 1.48]	26 more per 1000 (from 24 fewer to 83 more)

1   CI indicates confidence interval; DA-CPR, dispatcher-assisted cardiopulmonary resuscitation; EMS, emergency medical services.

1

1   **[h5]Survival With Favorable Neurologic Outcomes.**

2   Six studies involving 50 395 patients reported survival with favorable neurologic outcome at

3   time points from hospital discharge to 6 months after cardiac arrest.[18,21,22,26,28,32] The certainty of

4   evidence was assessed as very low (downgraded for serious risk of bias, indirectness, and

5   imprecision).

6   With the exception reported in 1 small series,[28] systems offering DA-CPR were associated with

7   increased favorable neurologic outcome at 1 month after cardiac arrest and at hospital discharge,

8   when compared with systems not offering DA-CPR. These effects persisted after adjustment for

9   confounding variables.

10   **[h5]Survival Including All Neurologic Outcomes.**

11   Nine studies, including 20 938 patients, addressed survival (irrespective of neurologic outcome)

12   at time points including hospital discharge, 1 month, and 1 year after cardiac arrest.[17-21,23,24,26,28]

13   The certainty of evidence for these studies was assessed as very low, downgraded for serious risk

14   of bias and imprecision.

15   With the exception reported in a single small series,[28] systems offering DA-CPR were associated

16   with increased survival at 1 month after cardiac arrest and at hospital discharge (Table 3) when

17   compared with systems not offering DA-CPR. These associations were strengthened after

18   adjustment for confounding variables.

19   **[h5]Short-Term Survival: Return of Spontaneous Circulation, Hospital Admission.**

20   Eight studies, including 45 474 patients, addressed short-term survival including return of

21   spontaneous circulation (ROSC) and survival to hospital admission.[18,20-22,28-30,32] The certainty of

22   evidence was assessed as very low, downgraded for serious risk of bias and imprecision.

1   With a single exception reported in a small series,[21] systems offering DA-CPR were associated

2   with sustained ROSC but not increased survival to hospital admission (Table 4) when compared

3   with systems not offering DA-CPR.

1   **Table 4. Bystander Delivery - Comparison of Outcomes From Adults Receiving DA-CPR Versus Those Receiving No**

2   **Bystander CPR or Unassisted Bystander CPR**

	DA-CPR Versus No CPR (Adjusted Analysis)			DA-CPR Versus Unassisted Bystander CPR (Adjusted Analysis)		
Outcome	**Studies (n patients)**	**Evidence certainty**	**Odds ratio (95% CI)**	**Studies (n patients)**	**Evidence certainty**	**Odds ratio (95% CI)**
Survival with favorable neurologic outcome at 1 month	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 neurologic 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 month	1 (4306)[26]	Very low	1.63 [1.32, 2.01]	2 (78 697)[27,36]	Very low	1.13 [1.06, 1.20]

	DA-CPR Versus No CPR (Adjusted Analysis)			DA-CPR Versus Unassisted Bystander CPR (Adjusted Analysis)		
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]

1   CI indicates confidence interval; CPR, cardiopulmonary resuscitation; DA-CPR, dispatcher-assisted CPR; NA not applicable; ROSC,

2   return of spontaneous circulation.

3

1 **[h4]Bystander Delivery: Comparison of Outcomes From Patients Receiving DA-CPR**

2 **Versus Those Receiving Either No Bystander CPR or Unassisted Bystander CPR**

3 This evidence evaluation compared outcomes of patients who received bystander CPR as the

4 result of DA-CPR with 2 groups of patients: (1) those receiving no bystander CPR or (2) those

5 who received bystander CPR that was performed without dispatch assistance. Twenty

6 observational cohort studies were identified,[21,23,26-28,31-38,40-46] but only 10 of these included

7 adjusted analysis.[26,27,31-38] Because the clinical features of patients who received DA-CPR

8 differed markedly from both the group that received no CPR and the group that received

9 bystander CPR without dispatch assistance, only adjusted outcomes are reported. Summary of

10 the study characteristics and results of the adjusted meta-analysis may be found in Table 4.

11 **[h5]Receipt of DA-CPR Versus No Bystander CPR.**

12 Improvements in survival with favorable neurologic function at hospital discharge[31,33,34] and at 1

13 month[26] were reported among patients with OHCA who received bystander DA-CPR compared

14 with those who received no bystander CPR. In addition, improved survival (regardless of

15 neurologic status) was reported at hospital discharge[31,33,34,37,38] and at 1 month.[26] Recipients of

16 DA-CPR were also more likely to achieve sustained ROSC than those who received no

17 bystander CPR.[34]

18 **[h5]Receipt of Bystander CPR With DA-CPR Versus Bystander CPR Without Dispatch**

19 **Assistance (ie, Unassisted Bystander CPR).**

20 The findings were inconsistent when comparing patients who received bystander CPR with DA-

21 CPR with patients who received bystander CPR that was performed *without* dispatch

22 assistance. Survival with favorable neurologic function did not differ either at hospital

1   discharge[34] or at 1 month[27] between patients who received bystander DA-CPR and those who

2   received bystander CPR without dispatch assistance. Overall survival at hospital discharge did

3   not differ between these groups,[34] although survival at 1 month favored patients who received

4   bystander DA-CPR.[27,36] Recipients of bystander DA-CPR were also more likely to have ROSC

5   upon hospital arrival than when bystander CPR was rendered without dispatch assistance.[27]

6   Although these studies do not prove equivalence or noninferiority, they suggest that DA-CPR

7   could possibly be as effective as spontaneously provided (unassisted) CPR.

8   **[h3]Treatment Recommendations**

9   We recommend that emergency medical dispatch centers have systems in place to enable call

10   handlers to provide CPR instructions for adult patients in cardiac arrest (strong recommendation,

11   very low certainty evidence).

12   We recommend that emergency medical call takers provide CPR instructions (when deemed

13   necessary) for adult patients in cardiac arrest (strong recommendation, very low certainty

14   evidence).

15   **[h3]Justification and Evidence to Decision Framework Highlights**

16   Whereas the strength of these recommendations is greater than the certainty of the supporting

17   evidence, taken together, the preponderance of the evidence evaluated in this review suggests

18   that clinical outcomes after OHCA are more likely to be improved when DA-CPR is available,

19   offered, and provided. The similarity in outcomes when CPR is initiated spontaneously without

20   the need for dispatch assistance (perhaps performed by a more skilled or trained bystander) and

21   when DA-CPR is performed (perhaps with a less skilled or untrained bystander) exemplifies the

22   potential positive impact of such point-of-care instruction. At a minimum, DA-CPR increases the

1 likelihood that bystander CPR will be performed [2], itself an important predictor of favorable

2 outcome from OHCA.[47] The systematic review also found that DA-CPR favored not only

3 bystander CPR, but time to CPR, ROSC and initial shockable rhythm.[2] These considerations,

4 along with the recognition that randomized clinical trials addressing this question are unlikely to

5 be forthcoming, led to the task force's consensus that DA-CPR should be strongly

6 recommended.

7 **[h3]Knowledge Gaps**

8 This evidence evaluation did not address training, logistical, operational, or economic issues

9 pertaining to DA-CPR. The task force identified several knowledge gaps requiring further

10 investigation, including

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

12   CPR

13 • The essential elements of a quality improvement program focused on DA-CPR

14 • The preferred CPR instruction sequence for DA-CPR

15 • The potential impact of dispatcher or call-taker's background or prior experience

16   (nonhealthcare professional versus paramedic or nurse) on DA-CPR performance

17 • The role of automated external defibrillators (AEDs) during the course of DA-CPR

18 • The integration of adjunct technologies (such as artificial intelligence or video) for

19   clinical decision support

20 **[h1]Advanced Life Support**

21 **[h2]Advanced Airway Interventions During Adult Cardiac Arrest**

1   It is important to identify those airway interventions most likely to improve outcomes for both

2   OHCA and IHCA. Chest compressions alone do not provide adequate ventilation during

3   prolonged cardiac arrest. Airway management is therefore required to facilitate ventilation and

4   reduce the risk of gastric regurgitation and aspiration. The best airway strategy for improving

5   patient outcomes is uncertain. Based on the evidence available at the time, the 2015 CoSTR

6   suggested using either an advanced airway or a bag-mask device for airway management during

7   CPR (weak recommendation, very-low-certainty evidence) for cardiac arrest in any setting.[48]

8   Advanced airway management is common during cardiac arrest. The American Heart

9   Association (AHA) Get With the Guidelines–Resuscitation registry of in-hospital cardiac arrest

10   (IHCA) reports that 60% to 70% of patients underwent tracheal intubation within the first 15

11   minutes of cardiac arrest.[49] The US Cardiac Arrest Registry to Enhance Survival (CARES)

12   registry of OHCA[50] showed that 52% of patients underwent tracheal intubation, 29% received a

13   supraglottic airway, and in 18% no advanced airway was inserted. In the recent AIRWAYS-2

14   RCT (Effect of a Strategy of a Supraglottic Airway Device Versus Tracheal Intubation During

15   Out-of-Hospital Cardiac Arrest on Functional Outcome),[51] which compared i-gel (from

16   Intersurgical Limited, Berkshire, United Kingdom) with tracheal intubation for OHCA, 17.3% of

17   patients did not receive an advanced airway.

18   Since 2015, 3 new RCTs investigating airway management during cardiac arrest have been

19   published.[51-53] This topic was given a high priority for review by the ILCOR ALS Task Force,

20   and ILCOR commissioned an SR to identify and analyze all published evidence on advanced

21   airway interventions during OHCA and IHCA.[3] The ALS Task Force analyzed and discussed the

22   SR as well as all of the studies identified by the SR. A draft ALS CoSTR for advanced airway

23   interventions during cardiac arrest was posted online on March 20, 2019 and included the data

1 reviewed and draft treatment recommendations with comments accepted through April 4, 2019.

2 There were 6798 visits and 16 posted comments during the 2-week comment period. The ALS

3 Task Force reviewed all comments and, in the light of these, reevaluated and finalized the draft

4 CoSTR.

5 **[h3]Population, Intervention, Comparator, Outcome, Study Design, and Time Frame**

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

7 etiology

8 Intervention: A specific advanced airway management method (eg, tracheal intubation or a

9 supraglottic airway device) during cardiac arrest

10 Comparators: A different advanced airway management method or no advanced airway

11 management method (eg, bag-mask ventilation [BMV]) during cardiac arrest

12 Outcomes: Survival to hospital discharge/28 days with favorable neurological outcome and

13 survival to hospital discharge/28 days ranked as critical outcomes; ROSC ranked as an important

14 outcome

15 Study Designs: RCTs and nonrandomized studies (non-RCTs, interrupted time series, controlled

16 before-and-after studies, cohort studies) that compared at least 2 airway strategies eligible for

17 inclusion; studies with 10 or fewer patients in either group excluded

18 Time Frame: All years and all languages included; unpublished studies (eg, conference abstracts,

19 trial protocols) excluded; literature search updated to October 30, 2018

20 PROSPERO registration: CRD42018115556

21 **[h3]Consensus on Science**

1   Seventy-one observational studies with 121 combinations of different airway management

2   strategies were included in the SR.[3] Of the 71 comparative studies, 61 included OHCA, 9

3   included IHCA, and 1 combined both. Because of the risk of bias, heterogeneity between studies,

4   and the availability of RCTs, no meta-analyses were performed for observational studies.

5   The SR identified 11 controlled trials of airway management in patients with OHCA.[51-61] Of

6   these, 8 were phase 2/feasibility trials with small sample sizes, generally with a high risk of bias,

7   including some that were published more than 15 years ago.[54-61] Therefore, only 3 trials, all

8   published in 2018, were used for the SR as they were larger and powered for more relevant

9   outcomes.[51-53] Because of different comparisons and heterogeneity, no meta-analyses of these

10   RCTs were undertaken (Table 5).

1 **Table 5. Summary of the Evidence From the 3 RCTs Studying Adult Advanced Airway Management During Cardiac Arrest**

Study (First Author, Year)	Intervention	Comparator	Setting	Outcome	Risk Difference (95% CI)	Certainty in Evidence
Wang, 2018[53]	Laryngeal tube	Tracheal intubation	OHCA	Survival to hospital discharge	27 more per 1000 (from 6 more to 48 more)	• Low in low tracheal intubation success setting (OHCA) • Very low in high tracheal intubation success setting (OHCA) • Very low (IHCA)
Wang, 2018[53]	Laryngeal tube	Tracheal intubation	OHCA	Survival to hospital discharge with a favorable neurological outcome	21 more per 1000 (from 3 more to 38 more)	• Low in low tracheal intubation success setting (OHCA) • Very low in high tracheal intubation success setting (OHCA) • Very low (IHCA)
Benger, 2018[51]	i-gel	Tracheal intubation	OHCA	Survival to hospital discharge	4 fewer per 1000	• Low in low tracheal intubation success setting (OHCA)

Study (First Author, Year)	Intervention	Comparator	Setting	Outcome	Risk Difference (95% CI)	Certainty in Evidence
					(from 14 fewer to 8 more)	• Very low in high tracheal intubation success setting (OHCA) • Very low (IHCA)
Benger, 2018[51]	i-gel	Tracheal intubation	OHCA	Survival to hospital discharge with a favorable neurological outcome	6 more per 1000 (from 16 fewer to 4 more)	• Low in low tracheal intubation success setting (OHCA) • Very low in high tracheal intubation success setting (OHCA) • Very low (IHCA)
Jabre, 2018[52]	Bag-mask ventilation	Tracheal intubation	OHCA	28-day survival	1 more per 1000 (from 18 fewer to 21 more	• Low in low tracheal intubation success setting (OHCA) • Moderate in high tracheal intubation success setting (OHCA)

Study (First Author, Year)	Intervention	Comparator	Setting	Outcome	Risk Difference (95% CI)	Certainty in Evidence
						• Low (IHCA)
Jabre, 2018[52]	Bag-mask ventilation	Tracheal intubation	OHCA	28-day survival with a favorable neurological outcome	1 more per 1000 (from 13 fewer to 23 more)	• Low in low tracheal intubation success setting (OHCA) • Moderate in high tracheal intubation success setting (OHCA) • Low (IHCA)

1 CI indicates confidence interval; IHCA, in-hospital cardiac arrest; OHCA, out-of-hospital cardiac arrest; RCT, randomized controlled

2 trial.

3 i-gel made by Intersurgical Limited, Berkshire, United Kingdom; Laryngeal Tube made by VBM Medizintechnik GmbH, Sulz am

4 Neckar, Germany

5

1   Jabre[52] compared BMV with tracheal intubation in a physician-based system whereas Benger

2   and Wang[51,53] compared supraglottic airway devices with tracheal intubation in non–physician-

3   based systems. The tracheal intubation success rates were 98% in the Jabre trial,[52] 70% in the

4   Benger trial,[51] and 52% in the Wang trial.[53] Success rates were not defined identically in the 3

5   studies; this led to concerns about generalizability of the findings. As a result, the task force

6   considered 2 different settings when evaluating the overall certainty of evidence (ie, the GRADE

7   approach): a setting with a low tracheal intubation success rate (similar to the systems in the

8   Benger[51] and Wang[53] studies) and a setting with a high tracheal intubation success rate (similar

9   to the Jabre system[52]).

10   Overall there is no high-certainty evidence to recommend an advanced airway strategy over

11   BMV and no high-certainty evidence to recommend a specific advanced airway device over

12   another (Table 5).

13   **[h3]Treatment Recommendations**

14   We suggest using bag-mask ventilation or an advanced airway strategy during CPR for adult

15   cardiac arrest in any setting (weak recommendation, low- to moderate-certainty evidence).

16   If an advanced airway is used, we suggest a supraglottic airway for adults with OHCA in settings

17   with a low tracheal intubation success rate (weak recommendation, low certainty of evidence).

18   If an advanced airway is used, we suggest a supraglottic airway or tracheal intubation for adults

19   with OHCA in settings with a high tracheal intubation success rate (weak recommendation, very

20   low certainty of evidence).

21   If an advanced airway is used, we suggest a supraglottic airway or tracheal intubation for adults

22   with IHCA (weak recommendation, very low certainty of evidence).

[h3]Justification and Evidence to Decision Framework Highlights

This topic was given high priority by the ILCOR ALS Task Force. This followed the publication of 3 new RCTs[51-53] since the previous CoSTR in 2015.[48,62]

The 3 new RCTs have enabled the ALS Task Force to provide more specific treatment recommendations. The 2015 treatment recommendation was based on evidence only from observational studies with critical or serious risk of bias primarily caused by confounding and selection bias. [48,62]

There is currently no supporting evidence that an advanced airway (ie, supraglottic airway or tracheal intubation) during CPR improves survival or survival with a favorable neurologic/functional outcome after adult cardiac arrest in any setting when 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 postresuscitation care will eventually require tracheal intubation.

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 based 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, a supraglottic airway 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 definition. Studies have used different definitions of tracheal intubation success. We

1   considered the Wang and Benger RCTs[51,53] as having a low tracheal intubation success rate

2   (51.6% and 69.8%, respectively) and the Jabre RCT[52] as having a high success rate (97.9%).

3   We assumed that tracheal intubation success rates are high in the in-hospital setting, but there is

4   limited evidence to support this, and success is likely to be site-dependent. The recommendations

5   for IHCA are primarily based on indirect evidence from the OHCA studies. There are no airway

6   RCTs for IHCA, and the task force did consider the findings of 1 large (n=71 615) observational

7   study of IHCA that tracheal intubation within any given minute during the first 15 minutes of

8   resuscitation, compared with no intubation during that minute, was associated with decreased

9   survival to hospital discharge.[49] This study used a time-dependent propensity score but did not

10   eliminate confounding by indication and provided only very-low-certainty evidence.

11   We have not expressed a preference for a particular supraglottic airway device of those currently

12   available (the i-gel [from Intersurgical Limited, Berkshire, United Kingdom] was used in the

13   Benger RCT[51] and the Laryngeal Tube [from VBM Medizintechnik GmbH, Sulz am Neckar,

14   Germany] in the Wang RCT[53]). The performance of individual supraglottic airway devices

15   varies, and therefore, we did not pool data from these 2 studies.

16   BMV can be difficult to perform, and effectiveness varies according to provider skills. We have

17   not evaluated the optimal bag-mask technique (eg, 1-person or 2-person) and the use of adjuncts

18   such as oropharyngeal or nasopharyngeal airways.

19   The task force considered that the preferred airway option is likely to depend on the skills of the

20   provider and the specific patient circumstances. In addition, patients may require different airway

21   interventions at different stages of resuscitation.

22   **[h3]ALS Task Force Knowledge Gaps**

1   The task force identified several knowledge gaps requiring further investigation, including

2   • A prospective comparison of BMV with supraglottic airway use

3   • The optimal airway management strategy for IHCA

4   • The impact on outcome of using an advanced airway (supraglottic airway or tracheal

5   intubation) without prior BMV

6   • The optimal supraglottic airway for use during cardiac arrest

7   • The optimal time point during CPR to change to different airway techniques

8   • The impact of different airway strategies on CPR quality (no-flow time), and oxygenation

9   and ventilation during CPR

10   • The training and clinical experience required to maintain proficiency in an airway

11   technique

12   **[h2]Use of Vasopressors in Cardiac Arrest**

13   Vasopressors have been used in CPR since animal experiments in the 1960s, despite lack of RCT

14   evidence in humans at the time.[63,64] In the last 20 years, several human RCTs have provided

15   evidence about vasopressor use for cardiac arrest. ILCOR has reviewed the use of vasopressors

16   regularly, with the most recent update in 2015.[48,62] The ILCOR ALS Task Force targeted the

17   current update after the 2018 publication of a new large RCT on the use of epinephrine in

18   OHCA.[65] This updated CoSTR summary is derived from an ILCOR-commissioned SR and

19   meta-analysis completed in 2019.[4] The ALS Task Force analyzed and discussed the SR as well

20   as all of the studies identified by the SR. A draft CoSTR for vasopressors in cardiac arrest was

21   posted online on March 20, 2019, and included the data reviewed and draft treatment

22   recommendations with comments accepted through April 4, 2019. This site was viewed 3861

1   times during the comment period and 6 comments were posted. The ALS Task Force reviewed

2   the comments and, in the light of these, reevaluated and finalized the draft CoSTR.

3   ### Population, Intervention, Comparator, Outcome, Study Design, and Time Frame

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

5   Intervention: Vasopressor or a combination of vasopressors provided intravenously or

6   intraosseously during cardiopulmonary resuscitation

7   Comparators: No vasopressor, or a different vasopressor, or a combination of vasopressors

8   provided intravenously or intraosseously during CPR

9   Outcomes: Short-term survival (ROSC and survival to hospital admission), midterm survival

10 (survival to hospital discharge, 28 days, 30 days, or 1 month), midterm favorable neurologic

11 outcomes (Cerebral Performance Category score of 1–2 or modified Rankin Scale 0–3 at hospital

12 discharge, 28 days, 30 days, or 1 month), and long-term unfavorable and poor (modified Rankin

13 Score 4–5) neurological outcomes (after 1 month)

14 Study Designs: Randomized trials, nonrandomized trials, and observational studies (cohort and

15 case-control studies) with a comparison group included

16 Time Frame: From inception of databases to November 23, 2018

17 PROSPERO registration: CRD42018116989

18 ### Consensus on Science

19 #### Epinephrine Compared With Placebo

20 For the comparison of epinephrine with placebo, there are 2 RCTs with a total of more than 8500

21 OHCA patients that provide evidence on our critical and important outcomes[65,66] but no RCTs of

1   IHCA. The PARAMEDIC2 trial (A Randomized Trial of Epinephrine in Out-of-Hospital

2   Cardiac Arrest) is a recent RCT that randomized approximately 8000 OHCA patients managed

3   by paramedics in the United Kingdom,[65] and the PACA trial (Placebo-Controlled Trial of

4   Adrenaline in Cardiac Arrest) randomized approximately 500 OHCA patients managed by

5   paramedics in Western Australia.[66] Meta-analysis of these studies was conducted to update the

6   CoSTR for epinephrine use during CPR.[4]

7   The findings of the SR and meta-analysis for all initial rhythms are summarized in Table 6. Only

8   the most recent study reported on 3-month survival.[65] That study found a statistically significant

9   increase in survival at 3 months in the epinephrine group but no statistical differences in survival

10   with favorable or unfavorable neurologic outcome at 3 months. The meta-analysis of the 2

11   studies found no benefit in favorable neurologic outcome at discharge but showed higher rates of

12   survival to discharge, survival to admission, and ROSC in the epinephrine group.[65,66]

1 **Table 6. Relative Risk and Absolute Risk Difference for Each Outcome With Epinephrine Compared With Placebo**

Study (First Author, Year)	Outcome	Relative Risk (95% CI)	Risk Difference (95% CI)	Certainty in Evidence
Perkins, 2018[65]	Favorable neurologic outcome at 3 months	1.30 (0.94–1.80)	5 more per 1000 (from 1 fewer to 13 more)	Low
Perkins, 2018[65]	Survival at 3 months	1.40 (1.07, 1.84)	9 more per 1000 (from 2 more to 18 more)	Moderate
Jacobs, 2011 Perkins, 2018 [65,66]	Favorable neurologic outcome at hospital discharge	1.21 (0.90–1.62)	4 more per 1000 (from 2 fewer to 12 more)	Moderate
Jacobs, 2011 Perkins, 2018[65,66]	Survival to hospital discharge	1.44 (1.11–1.86)	10 more per 1000 (from 2 more to 19 more)	Moderate

Study (First Author, Year)	Outcome	Relative Risk (95% CI)	Risk Difference (95% CI)	Certainty in Evidence
Jacobs, 2011 Perkins, 2018[65,66]	Return of spontaneous circulation	3.09 (2.82–3.39)	243 more per 1000 (from 211 more to 277 more)	High

1   CI indicates confidence interval.

2

1   In the subgroup of patients with nonshockable rhythms, combined evidence from the 2 RCTs

2   showed benefit of epinephrine for survival to discharge (moderate certainty; RR, 2.56; 95% CI,

3   1.37–4.80; ARD, 0.6%; 95% CI, 0.1–1.5) and ROSC (high certainty; RR, 4.45; 95% CI, 3.91–

4   5.08; ARD, 25.4%; 95% CI, 21–30). There was no difference in survival to discharge with

5   favorable neurologic outcome (low certainty).[65,66] In data pending publication from the larger,

6   more recent trial, the subgroup with nonshockable rhythms showed no difference in survival to 3

7   months with favorable or unfavorable neurologic outcome, although this result approached

8   significance (very low certainty; RR, 3.03; 95% CI, 0.98–9.38; ARD, 0.3%; 95% CI, 0–1.1).[65,67]

9   In the subgroup of patients with shockable rhythms, combined evidence from the 2 RCTs

10   showed benefit of epinephrine for ROSC (moderate certainty; RR, 1.68; 95% CI, 1.48–1.92;

11   ARD, 18.5%; 95% CI, 13.0–25.0) but no difference for survival to discharge.[65,66] In data pending

12   publication from the larger, more recent trial, the subgroup with shockable rhythms showed no

13   difference in survival to 3 months with favorable neurologic outcome.[67]

14   [h4]**Vasopressin Compared With Epinephrine**

15   Three RCTs with more than 1500 OHCA patients compared vasopressin with epinephrine; all

16   were published more than 10 years ago.[68-70] The combined results of these studies showed no

17   benefit of vasopressin compared with epinephrine across all outcomes and initial rhythms.

18   One RCT included 200 patients with IHCA randomized to vasopressin or epinephrine with any

19   initial rhythm and showed no benefit from the use of vasopressin compared with epinephrine.[71]

20   [h4]**Initial Epinephrine Plus Vasopressin Compared With Epinephrine Only**

21   Three RCTs with more than 3000 OHCA patients compared epinephrine plus vasopressin with

22   epinephrine only; all were published more than 8 years ago.[72-74] The combined results of these

1 studies showed no benefit across all outcomes and initial rhythms. There were no in-hospital

2 studies of this comparison.

3 **[h3]Treatment Recommendations**

4 We recommend administration of epinephrine during CPR (strong recommendation, low to

5 moderate certainty of evidence).

6 For nonshockable rhythms (pulseless electrical activity [PEA]/asystole), we recommend

7 administration of epinephrine as soon as feasible during CPR (strong recommendation, very-low

8 certainty of evidence).

9 For shockable rhythms (ventricular fibrillation [VF]/ventricular tachycardia [VT]), we suggest

10 administration of epinephrine after initial defibrillation attempts are unsuccessful during CPR

11 (weak recommendation, very-low certainty of evidence).

12 We suggest against the administration of vasopressin in place of epinephrine during CPR (weak

13 recommendation, very-low certainty of evidence).

14 We suggest against the addition of vasopressin to epinephrine during CPR (weak

15 recommendation, low certainty of evidence).

16 **[h3]Justification and Evidence to Decision Framework Highlights**

17 The ILCOR ALS Task Force prioritized this PICOST (population, intervention, comparator,

18 outcome, study design, time frame) after the recent publication of a large RCT comparing

19 administration of epinephrine with placebo in over 8000 OHCA patients.[65] The collective

20 evidence from the recent trial and a small earlier RCT showed that epinephrine for OHCA

21 increases ROSC, survival to discharge, and survival at 3 months but has not been shown

22 definitively to increase survival to discharge with favorable neurologic outcome.[4,65,66] The more

1   recent trial, which was also the only one reporting outcomes at 3 months, found no difference in

2   survival with favorable or unfavorable neurologic outcome at the 3-month time point.[65] The lack

3   of statistical difference in survival with favorable and unfavorable outcome at 3 months may

4   reflect the low event rates for these outcomes and consequent failure to achieve the optimal

5   sample size for these outcomes, resulting in low power to detect a difference. The increase in

6   survival with favorable neurologic outcome at 3 months approaches statistical significance for

7   nonshockable initial rhythms, with the lower limit of the confidence interval being very close to

8   1. Whether the difference in neurologic outcome would be larger in a patient population with

9   higher overall survival than that seen in the PARAMEDIC2 trial is unknown. A very high value

10   is placed on the apparent life-preserving benefit of epinephrine, even if the absolute effect size is

11   likely to be small. Although the PARAMEDIC2 study raised concerns by some about increasing

12   the number of survivors with unfavorable neurologic outcome, the opinion of the ALS task force

13   is that the data at 3 months do not support this assertion. Overall, the impact of epinephrine

14   administration on neurologic outcome for patients with OHCA remains uncertain, but the

15   available data is more suggestive of benefit than harm. Whether the administration of

16   epinephrine earlier than in the available OHCA trials would have a larger beneficial effect also

17   remains uncertain but is suggested by observational data. That stated, the ALS Task Force

18   acknowledged the importance of considering the cost burden incurred with a potential increase in

19   short-term survival with unfavorable neurologic outcome. Conversely, an increase in ROSC may

20   allow for the development of other treatments to prevent or mitigate neurologic injury. The

21   opportunity for families to see patients before death and the possibility for organ donation were

22   additional potential benefits of the increase in short-term survival that were considered. The task

23   force recognized that different healthcare systems and different cultures may weigh these costs

1 and benefits differently. A formal cost-effectiveness analysis was not performed, and this

2 remains a knowledge gap.

3 The use of vasopressin alone or in combination with epinephrine was not shown to be beneficial

4 when compared with epinephrine alone, and thus epinephrine alone is recommended because it

5 reduces complexity.

6 There is a statistically significant benefit of standard dose epinephrine compared with placebo on

7 survival to hospital discharge in OHCA patients with nonshockable initial rhythms but not in

8 those with shockable initial rhythms (although epinephrine improved ROSC in all rhythms). As

9 these are subgroup comparisons, however, and were not separately randomized, the results

10 should be interpreted with some caution. For example, the lack of a statistically significant

11 difference in shockable rhythms may result from inadequate power, as there were far fewer

12 patients in this subgroup than in the nonshockable rhythms groups.

13 In most cases of nonshockable rhythms, there are limited alternative interventions, and survival

14 is very poor unless a reversible cause is identified and treated. Therefore, we recommend

15 provision of epinephrine as soon as feasible in cardiac arrest with nonshockable rhythms.

16 Exceptions may exist where a clear reversible cause can be addressed rapidly.

17 The optimal timing for epinephrine in patients with shockable rhythms is unknown. The studies

18 evaluating administration of epinephrine used protocols for epinephrine administration after the

19 third shock. The task force agrees that it seems prudent to wait to administer epinephrine until

20 initial defibrillation attempts have been unsuccessful. However, the optimal timing or number of

21 shocks after which epinephrine should be administered remains unclear.

1　　There is also very limited data to guide the specific dosing of epinephrine during

2　　cardiopulmonary resuscitation. The 2 OHCA RCTs comparing epinephrine with placebo used

3　　standard dose epinephrine (1 mg intravenous or intraosseous every 3–5 minutes). Although this

4　　CoSTR did not separately evaluate high-dose epinephrine because no new evidence was found, a

5　　previous ILCOR review did not find evidence of a survival benefit for high-dose epinephrine,

6　　and thus the evidence to date supports the dosing used in the 2 RCTs included in meta-analysis

7　　in the current review.

8　　There is limited RCT evidence on the use of epinephrine for IHCA. There are no studies on the

9　　use of standard-dose epinephrine compared with placebo in the in-hospital setting and only 1 on

10　　the use of vasopressin compared with epinephrine.[75] There was no statistical benefit or harm

11　　from the administration of vasopressin compared with epinephrine for in-hospital CPR.

12　　Therefore, the ILCOR ALS Task Force decided to make the same recommendations for

13　　epinephrine administration for in-hospital and OHCA, based upon the evidence for OHCA.

14　　**[h3]ALS Task Force Knowledge Gaps**

15　　With the recent publication of a large RCT comparing epinephrine with placebo in OHCA, we

16　　have greater confidence in the benefit of epinephrine for survival to discharge and ROSC.

17　　However, the effect of epinephrine on neurologic outcomes is still uncertain and remains an

18　　important knowledge gap. The task force identified several other knowledge gaps requiring

19　　further investigation, including

20　　　• The long-term neurologic benefit of epinephrine in cardiac arrest

21　　　• The optimal dose of epinephrine and dosing interval

22　　　• Use of and optimal timing of epinephrine administration in patients with shockable

23　　　　rhythms

- 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 neurologic injury associated with cardiac arrest

[h2]ECPR for Cardiac Arrest: Adults

ECPR is used to support circulation in patients with cardiac arrest refractory to conventional CPR.[76] 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, 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.[5] A draft CoSTR posted for public comment was viewed 1169 times in the 2-week comment period. The Task Force reviewed the 4 posted comments and considered the suggestions when finalizing the "Justification and Evidence to Decision Highlights" section.

[h3]Population, Intervention, Comparator, Outcome, Study Design, and Time Frame

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

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

Comparator: Manual CPR and/or mechanical CPR

1   Outcomes: Clinical outcomes, including short-term survival and neurological outcomes (eg,

2   hospital discharge, 28 days, 30 days, and 1 month), and long-term survival and neurological

3   outcomes (eg, 3 months, 6 months, and 1 year)

4   Study Design: Randomized trials, non-RCTs, and observational studies (cohort studies and case-

5   control studies) with a control group included; animal studies, ecological studies, case series,

6   case reports, reviews, abstracts, editorials, comments, and letters to the editor not included

7   Time Frame: All years and all languages included

8   PROSPERO registration: CRD42018085404

9   *Note:* The pediatric information is summarized in a later section of this document (see Pediatric

10 Life Support, ECPR: Infants and Children)

11 **[h3]Consensus on Science**

12 No randomized clinical trials were identified. Selected summary data are included in Table 7.

13 Fifteen of the included studies were in adult OHCA.[77-91] Three studies included both OHCA and

14 IHCA patients.[78,82,89] Most studies defined the exposure as ECPR use, 1 study[85] defined the

15 exposure as ECPR availability, and 2 studies[90,91] defined exposure as an ECPR strategy. Twelve

16 studies reported survival to hospital discharge,[77-85,87-89] 6 studies reported long-term

17 survival,[78,81,83,85,87,88] 8 studies reported favorable neurologic outcome at hospital discharge,[79-81,84,85,87,90,91]

18 and 6 studies reported long-term favorable neurologic outcomes.[81,83,85-88]

19

1 **Table 7. Summary of Adult ECPR Studies**

Study (First Author, Year)	Country	Years of Patient Inclusion	IHCA Versus OHCA	Inclusion Criteria	Patients Analyzed (Number)	Covariates Included in Adjusted Analysis	Hospital Discharge/1 month		Adjusted Results (OR or RR [95% CI])
							Proportions Number (%)		
							Exposed	Unexposed	
Agostinucci, 2011[77]	France	2005–2010	OHCA	Use of load-distributing band	285	NA	0/27 (0)	3/258 (1)	NR
Blumenstein, 2015[92]	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, 2018[78]	Italy	2011–2015	Combined	Age 18–75 years, witnessed,	148	NA	13/63 (21)	49/85 (58)	NR

Study (First Author, Year)	Country	Years of Patient Inclusion	IHCA Versus OHCA	Inclusion Criteria	Patients Analyzed (Number)	Covariates Included in Adjusted Analysis	Hospital Discharge/1 month		Adjusted Results (OR or RR [95% CI])
							Proportions Number (%)		
							Exposed	Unexposed	
				proven ischemic etiology, absence of severe comorbidities that would have precluded ICU admission and conditioning in the short-term prognosis					
Chen, 2008[93]	Taiwan	2004–2006	IHCA	Age 18–75 years, CPR for >10 min, cardiac origin, witnessed	92	Age, sex, initial cardiac rhythm, time point of CPR, CPR	15/46 (33)	8/46 (17)	2.30 (0.86, 6.13) [Calculated]

Study (First Author, Year)	Country	Years of Patient Inclusion	IHCA Versus OHCA	Inclusion Criteria	Patients Analyzed (Number)	Covariates Included in Adjusted Analysis	Hospital Discharge/1 month		Adjusted Results (OR or RR [95% CI])
							Proportions Number (%)		
							Exposed	Unexposed	
						duration, comorbidities			
Cho, 2014[94]	Korea	2001–2013	IHCA	Pulmonary embolism	20	Hypertension, CPR duration	NR	NR	NR
Choi, 2016[79]	Korea	2011–2015	OHCA	Nontraumatic, age ≤75 years, witnessed cardiac arrest, bystander administration of CPR or no-flow time ≤5 min, prehospital low-flow time ≤30	60	NA	3/10 (30)	4/50 (8)	NR

Study (First Author, Year)	Country	Years of Patient Inclusion	IHCA Versus OHCA	Inclusion Criteria	Patients Analyzed (Number)	Covariates Included in Adjusted Analysis	Hospital Discharge/1 month		Adjusted Results (OR or RR [95% CI])
							Proportions Number (%)		
							Exposed	Unexposed	
				min and refractory arrest >10 min of conventional CPR at the ED, known absence of severe comorbidities that preclude admission to the intensive care unit					
Chou, 2014	Taiwan	2006–2010	IHCA	Age >18 years, acute myocardial	66	NA	NR	NR	1.93 (0.60, 6.23) [Unadjusted]

Study (First Author, Year)	Country	Years of Patient Inclusion	IHCA Versus OHCA	Inclusion Criteria	Patients Analyzed (Number)	Covariates Included in Adjusted Analysis	Hospital Discharge/1 month		
							Proportions Number (%)		Adjusted Results (OR or RR [95% CI])
							Exposed	Unexposed	
				infarction in the ED, CPR for >10 min					
Hase, 2005[80]	Japan	1999–2003	OHCA	Presumed cardiac etiology	100	NA	13/38 (34)	27/62 (44)	NR
Kim, 2014[81]	Korea	2006–2013	OHCA	Age >18 years, not traumatic	104	Age, sex, comorbidity score, bystander CPR, witnessed cardiac arrest, first documented arrest rhythm, presumed etiology of arrest, interval from arrest to CPR started by EMS	9/52 (17)	11/52 (21)	0.78 (0.29, 2.08) [Calculated]

Study (First Author, Year)	Country	Years of Patient Inclusion	IHCA Versus OHCA	Inclusion Criteria	Patients Analyzed (Number)	Covariates Included in Adjusted Analysis	Hospital Discharge/1 month		
							Proportions Number (%)		Adjusted Results (OR or RR [95% CI])
							Exposed	Unexposed	
						provider, CPR duration, and therapeutic hypothermia			
Lee, 2015[82]	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, 2010[95]	Taiwan	2004–2006	IHCA	Age 18–75 years, cardiac	54	Age, sex, initial rhythm, CPR	8/27 (30)	5/27 (19)	1.85 (0.52, 6.63) [Calculated]

Study (First Author, Year)	Country	Years of Patient Inclusion	IHCA Versus OHCA	Inclusion Criteria	Patients Analyzed (Number)	Covariates Included in Adjusted Analysis	Hospital Discharge/1 month		
							Proportions Number (%)		Adjusted Results (OR or RR [95% CI])
							Exposed	Unexposed	
				origin, CPR duration >10 min, ROSC		duration, timing and location, comorbidities (diabetes, hypertension, dyslipidemia, malignancy, COPD, cardiovascular or cerebrovascular, abnormal liver function, dialysis)			
Maekawa, 2013[83]	Japan	2000–2004	OHCA	Presumed cardiac etiology, age >16 years,	48	Not clear, but probably: Age, sex, activities of daily	9/24 (38)	3/24 (13)	4.20 (0.97, 18.2) [Calculated]

Study (First Author, Year)	Country	Years of Patient Inclusion	IHCA Versus OHCA	Inclusion Criteria	Patients Analyzed (Number)	Covariates Included in Adjusted Analysis	Hospital Discharge/1 month		Adjusted Results (OR or RR [95% CI])
							Proportions Number (%)		
							Exposed	Unexposed	
				witnessed, CPR duration >20 min		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 advanced life support			

Study (First Author, Year)	Country	Years of Patient Inclusion	IHCA Versus OHCA	Inclusion Criteria	Patients Analyzed (Number)	Covariates Included in Adjusted Analysis	Hospital Discharge/1 month		Adjusted Results (OR or RR [95% CI])
							Proportions Number (%)		
							Exposed	Unexposed	
Poppe, 2015[84]	Austria	2013–2014	OHCA	Age >18 years, ongoing CPR	96	NA	2/12 (17)	8/84 (10)	NR
Sakamoto, 2014[85]	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	454	NA	69/260 (27)	12/193 (6)	NR

Study (First Author, Year)	Country	Years of Patient Inclusion	IHCA Versus OHCA	Inclusion Criteria	Patients Analyzed (Number)	Covariates Included in Adjusted Analysis	Hospital Discharge/1 month		Adjusted Results (OR or RR [95% CI])
							Proportions Number (%)		
							Exposed	Unexposed	
				the 15 min after hospital arrival					
Schober, 2017[86]	Austria	2002–2012	OHCA	Cardiac origin, CPR duration >30 min	239	NA	NR	NR	NR
Shin, 2011[96], Shin, 2013[98]	Korea	2003–2009	IHCA	Age 18–80 years, CPR duration >10 min, witnessed	120	Age, sex, comorbidities, clinical situation, cause of the arrest, location, year, time during day and week, initial rhythm, CPR duration, prearrest SOFA score, Deyo-	19/60 (32)	6/60 (10)	4.17 (1.53, 11.4) [Calculated]

Study (First Author, Year)	Country	Years of Patient Inclusion	IHCA Versus OHCA	Inclusion Criteria	Patients Analyzed (Number)	Covariates Included in Adjusted Analysis	Hospital Discharge/1 month		Adjusted Results (OR or RR [95% CI])
							Proportions Number (%)		
							Exposed	Unexposed	
						Charlson score, post-CPR variables			
Siao, 2015[87]	Taiwan	2011–2013	OHCA	Age 18–75 years, ventricular fibrillation, no-flow <5 min, refractory cardiac arrest	60	Age, CPR duration, defibrillation, female gender, use of therapeutic hypothermia	10/20 (50)	11/60 (28)	4.10 (0.79, 21.3)
Tanno, 2008[88]	Japan	2000–2004	OHCA	Age >16 years, cardiac origin	398	NA	14/66 (21)	25/332 (8)	NR
Venturini, 2017[89]	United States	2011–2016	Combined	CPR in cardiac catheterization laboratory,	31	NA	1/14 (7)	3/17 (18)	NR

Study (First Author, Year)	Country	Years of Patient Inclusion	IHCA Versus OHCA	Inclusion Criteria	Patients Analyzed (Number)	Covariates Included in Adjusted Analysis	Hospital Discharge/1 month		Adjusted Results (OR or RR [95% CI])
							Proportions Number (%)		
							Exposed	Unexposed	
				mechanical chest compression					
Yannapoulos, 2016[90]	United States	2015–2016	OHCA	Age 18–75 years, cardiac etiology, initial shockable rhythm, minimum 3 direct-current shocks without ROSC, received amiodarone 300 mg, eligible for mechanical CPR,	188	NA	10/18 (53)	NR	NR

Study (First Author, Year)	Country	Years of Patient Inclusion	IHCA Versus OHCA	Inclusion Criteria	Patients Analyzed (Number)	Covariates Included in Adjusted Analysis	Hospital Discharge/1 month		Adjusted Results (OR or RR [95% CI])
							Proportions Number (%)		
							Exposed	Unexposed	
				transfer time from scene to catheterization laboratory <30 min					
Yannapoulos, 2017[91]	United States	2015–2016	OHCA	Age 18–75 years, cardiac etiology, initial shockable rhythm, minimum 3 direct-current shocks without ROSC, received	232	NA	28/62 (45)	NR	NR

Study (First Author, Year)	Country	Years of Patient Inclusion	IHCA Versus OHCA	Inclusion Criteria	Patients Analyzed (Number)	Covariates Included in Adjusted Analysis	Hospital Discharge/1 month		Adjusted Results (OR or RR [95% CI])
							Proportions Number (%)		
							Exposed	Unexposed	
				amiodarone 300 mg, eligible for mechanical CPR, transfer time from scene to catheterization laboratory <30 min					

1 APACHE II indicates Acute Physiology, Age, Chronic Health Evaluation II; CI, confidence interval; COPD, chronic obstructive

2 pulmonary disorder; CPR, cardiopulmonary resuscitation; ED, emergency department; eGFR, estimated glomerular filtration rate;

3 IABP, intra-aortal balloon pump; ICU, intensive care unit; IHCA, in-hospital cardiac arrest; NA, not applicable; OHCA, out-of-

4 hospital cardiac arrest; OR, odds ratio; PCI, percutaneous intubation; ROSC, return of spontaneous circulation; RR, relative risk;

5 SOFA, sequential organ failure assessment; TTM, targeted temperature management.

1   Seven of the included studies were in adult IHCA.[92-98] Most of these studies defined the exposure

2   as ECPR use, although 2 studies[96,98] defined the exposure as ECPR attempt. Six studies reported

3   survival to hospital discharge,[92,93,95-98] 6 studies reported long-term survival, [92,93,95-98] 5 studies

4   reported favorable neurologic outcome at hospital discharge,[92,93,95,96,98] and 5 studies reported

5   long-term favorable neurologic outcome.[92,93,95,96,98] Four studies reported survival analyses with

6   length of follow-up ranging from 1 to 3 years. [92-95]

7   For studies in both OHCA and IHCA, the overall certainty of evidence was rated as very low for

8   all outcomes. Individual studies were all at a very serious risk of bias, mainly because of

9   confounding. Because of this confounding and a high degree of heterogeneity, no meta-analyses

10   could be performed, and individual studies are difficult to interpret.

11   **[h3]Treatment Recommendations**

12   We suggest ECPR may be considered as a rescue therapy for selected patients with cardiac arrest

13   when conventional cardiopulmonary resuscitation is failing in settings where this can be

14   implemented (weak recommendation, very-low certainty of evidence).

15   **[h3]Justification and Evidence to Decision Highlights**

16   In making this weak recommendation, we have considered the extremely high mortality rate of

17   patients with cardiac arrest, particularly when the arrest is refractory to standard ACLS

18   interventions (ie, cardiac arrest where conventional CPR is failing). Therefore, the potential for

19   benefit and value of this intervention remains despite the overall low certainty of supporting

20   evidence and lack of randomized trials.

The published studies used select patients for ECPR and 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 where usual CPR techniques have failed. ECPR can sustain perfusion while another intervention such as coronary angiography and percutaneous coronary intervention can be performed.

[h3]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, including

- The optimal post-cardiac arrest care strategy for patients resuscitated using ECPR
- The patient groups that are most likely to benefit from ECPR
- The optimal ECPR techniques
- The optimal timing to initiate ECPR during resuscitation (ie, 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 versus survivors of conventional CPR
- The cost-effectiveness of ECPR

[h1]Pediatric Life Support

1   The Pediatric Life Support Task Force reviewed 4 topics for this 2019 CoSTR: dispatch

2   instruction in CPR (DA-CPR), advanced airway interventions in pediatric cardiac arrest,

3   extracorporeal membrane oxygenation CPR (ECPR), and TTM during post–cardiac arrest care.

4   An SR was published for each of these topics.[2,5-7] The Pediatric Life Support Task Force then

5   reviewed the SR as well as the studies identified by the SR and generated a CoSTR that was

6   posted on the ILCOR website for public comments for each topic. This document contains a

7   summary of the 4 CoSTRs, including information about task force deliberations and insights.

8   **[h2]Dispatcher Instruction in CPR: DA-CPR—Pediatrics**

9   ILCOR commissioned an SR to identify and analyze all published evidence reporting outcomes

10   of offering DA-CPR for OHCA in infants and children.[2] The Pediatric Life Support Task Force

11   analyzed and discussed the SR as well as all of the studies identified by the SR, developed a draft

12   CoSTR, and posted it online for public comment.[15] The draft CoSTR was visited 1736 times

13   during the 2-week comment period. The task force reviewed the 2 posted comments; both

14   endorsed the summary of science and treatment recommendation.

15   The emergency medical dispatcher is an essential link in the chain of survival. In addition to

16   dispatching EMS resources to medical emergencies, the EMS dispatchers are increasingly being

17   trained to recognize cardiac arrest, assist bystanders in initiating resuscitation, and support

18   bystanders in optimizing resuscitation efforts. The international community is continuing to

19   explore ways to increase bystander CPR for cardiac arrests. One such strategy involves

20   dispatchers providing CPR instruction to callers/bystanders: DA-CPR. For such a strategy to be

21   successful, it requires (1) the EMS system to be configured to support the dispatcher to offer

22   DA-CPR and (2) the bystander to deliver CPR with support from the dispatcher.

1   This COSTR explores the impact of DA-CPR on survival and neurologic outcomes after OHCA

2   in infants and children.

3   **[h3]Population, Intervention, Comparator, Outcome, Study Design, and Time Frame**

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

5   Intervention: Patients/cases or EMS systems where dispatch assisted CPR is offered

6   Comparators: Studies with comparators where either systems or specific cardiac arrest cases are

7   not offered dispatch-assisted CPR

8   Outcomes (critical outcomes included): Survival with favorable neurologic function (at hospital

9   discharge, 1 month, or 6 months), survival (hospital discharge, 1 month, or 1 year), short-term

10 survival (ROSC, hospital admission), provision of bystander CPR; important outcomes were

11 initial shockable rhythm, time to CPR

12 Study Designs: RCTs and non-randomized studies (non-RCTs, interrupted time series, controlled

13 before-and-after studies, cohort studies) eligible for inclusion.

14 Time Frame: All years and all languages included with the last search performed July 1, 2018;

15 ongoing or unpublished studies identified through a search of ClinicalTrials.gov online registry[16]

16 PROSPERO registration: CRD42018091427

17 **[h3]Consensus on Science**

18 Four studies were included in the SR comparing the outcomes for children with OHCA when

19 bystanders were offered DA-CPR.[25,26,39,99] All the studies were cohort studies of registry data: 2

20 from the same registry in Japan and 2 from the same registry in Korea. When the overlapping

21 populations from the same source (registry) were reported for the same outcome, the larger of the

1   2 studies was used in the analysis.[26,39] The studies by Goto and colleagues[26] and Chang and

2   colleagues[39] included adjusted analyses.

3   There were 2 major groups for outcome comparisons:

4   • Those patients from **systems** that included DA-CPR compared with those from systems

5   that offered no dispatcher CPR assistance; in one of the studies, 25% of bystanders who

6   were offered dispatcher CPR assistance did not actually provide CPR.[26]

7   • Those patients who **actually received** D-CPR compared with those who did not receive

8   DA-CPR; the group that did not receive DA-CPR was subdivided into those who

9   received unassisted CPR and those who received no CPR.

10   Because all studies that the task force evaluated were nonrandomized, any reported findings must

11   be considered as occurring in association with the CPR (the intervention) provided, rather than as

12   caused by it.

13   **[h4]Cardiac Arrest Outcomes in EMS Systems With and Without DA-CPR**

14   One study from the All-Japan Utstein Registry[26] reported neurologic outcome at 1 month in a

15   cohort of 4306 infants and children with OHCA. There was no association in either adjusted or

16   unadjusted analysis between favorable neurologic outcome at 1 month and systems offering DA-

17   CPR when compared with such outcomes in systems not offering DACPR. The same study from

18   Japan did not document any association between improved survival at 1 month and DA-CPR in

19   the unadjusted analysis, but such an association was suggested in the adjusted analysis. In a

20   separate analysis, there was no association between the incidence of shockable pediatric arrest

21   rhythms and systems offering DA-CPR.[26]

1   Three studies examined the delivery of bystander CPR in systems that offered DA-CPR

2   compared with those that did not. In addition to the Goto All-Japan study,[26] 2 studies[25,31]

3   included unadjusted analysis of 3309 children with OHCA. These studies reported a significantly

4   higher rate of CPR in the cohorts offered DA-CPR in both unadjusted and adjusted analyses. In

5   addition, the Goto All-Japan study reported earlier time to CPR initiation associated with

6   systems that offered DA-CPR when compared with those that did not.[26] For additional

7   information, see Table 8.

1   **Table 8. Comparison of Outcomes** of Infants and Children with Out-of-Hospital Cardiac Arrest **in EMS Systems With and Without**

2   **DA-CPR Programs (ie, DA-CPR Offered Versus Not Offered)**

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

1   CPR indicates cardiopulmonary resuscitation; DA-CPR, dispatcher-assisted CPR; GRADE, Grading of Recommendations,

2   Assessment, Development, and Evaluation.; EMS, emergency medical services; IQR, interquartile range; OR, odds ratio; RD, risk

3   difference; RR, relative risk.

4   *Relative risks are presented for unadjusted analyses and odds ratios are presented for adjusted analyses.

1 **[h4]Cardiac Arrest Outcomes in Infants and Children with Out-of-Hospital Cardiac Arrest**

2 **Who Received Bystander DA-CPR Compared With Those Who Received No CPR**

3 Goto and colleagues[26] and Chang and colleagues[39] both reported the association of significantly

4 improved neurologic outcomes and DA-CPR, when compared with no CPR. In both unadjusted

5 and adjusted data from the Goto series,[26] there were significantly higher rates of favorable

6 neurologic outcome (Cerebral Performance Category [CPC] 1 and 2) at 1 month associated with

7 those who received DA-CPR compared with those who received no CPR. There were also

8 significantly higher rates of survival to 1 month in the DA-CPR cohort in both unadjusted and

9 adjusted analyses.[26] In both adjusted and unadjusted analyses, Chang's observational study of

10 1661 children with OHCA reported an association between significantly improved likelihood of

11 favorable neurologic outcome at hospital discharge as well as survival to hospital discharge and

12 DA-CPR when compared with no CPR.[39] For further information, see Table 9.

1   **Table 9. Comparison of Outcomes of Infants and Children with Out-of-Hospital Cardiac Arrest Who Received Bystander**

2   **DA-CPR Compared With Those Who Received No CPR**

Outcomes (Importance)	Participants (Studies), n	Certainty of Evidence (GRADE)	OR or RR (95% CI)[*]	RD With DA-CPR and No CPR
Survival with favorable neurologic outcome at 1 month (critical)	4306 (1 cohort study)[26]	Very low	RR: 1.47(1.05–2.07)	12 more per 1000 (1 more to 26 more)
			OR_{adj}:1.81 (1.23–2.67); *P*=0.003	
Survival with favorable neurologic outcome at hospital discharge (critical)	1661 (1 cohort study)[39]	Low	RR: 3.43(2.10–5.59)	54 more per 1000 (25 more to 99 more)
			OR_{adj}: 2.22 (1.27–3.88); *P*=0.005	
Survival at 1 month (critical)	4306 (1 cohort study)[26]	Very low	RR: 1.38(1.15–1.65)	31 more per 1000 (12 more to 53 more)
			OR_{adj}: 1.63 [1.32–2.01]; *P*<0.0001	
Survival to hospital discharge (critical)	1661 (1 cohort study)[39]	Moderate	RR: 2.87(2.02–4.06)	84 more per 1000 (47 more to 132 more)
		Low	OR_{adj}: 2.23 (1.47–3.38); *P*=0.002	
Sustained ROSC (critical)	1661 (1 cohort study)[39]	Very low	RR: 2.68(1.94–3.70)	89 more per 1000 (51 more to 137 more)

Outcomes (Importance)	Participants (Studies), n	Certainty of Evidence (GRADE)	OR or RR (95% CI)*	RD With DA-CPR and No CPR
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 to 89 more)
Arrest to CPR initiation (important)	4306 (1 cohort study)[26]	Very low	Shorter time with DA-CPR: median 1 min [IQR 0–5 min] versus 11 min [IQR 7–15]	
	1265 (1 cohort study)[31]		Shorter time with DA-CPR: median 4 min [IQR 0–13 min] versus 10 min [IQR 6–18] P=0.01	

1   CPR indicates cardiopulmonary resuscitation; DA-CPR, dispatcher-assisted CPR; GRADE, Grading of Recommendations,

2   Assessment, Development, and Evaluation.; EMS, emergency medical services; IQR, interquartile range; OR, odds ratio; RD, risk

3   difference; RR, relative risk.

4   *Relative risks are presented for unadjusted analyses and odds ratios are presented for adjusted analyses.

1   In comparisons of infants and children receiving DA-CPR with those receiving unassisted

2   bystander CPR, Goto reported lower rates of favorable neurologic outcome and survival at 1

3   month in the DA-CPR group.[26] Chang, however, found no difference in either survival or

4   favorable outcome at discharge between those receiving DA-CPR and those receiving unassisted

5   bystander CPR.[39] Chang did report an increase in rates of sustained ROSC associated with DA-

6   CPR when compared with no CPR, but documented no such increase when comparing those who

7   received DA-CPR with those who received unassisted bystander CPR.[39]

8   The Goto and Chang studies both examined presence of a shockable rhythm as an outcome. The

9   pooled data did not document an association between an increased presence of shockable rhythm

10   and receipt of DA-CPR, compared with those who received no CPR, and there was a negative

11   association when those receiving DA-CPR were compared with those receiving unassisted

12   CPR.[26,39]

13   Not surprisingly, Goto and Chang reported an association between DA-CPR and shorter times to

14   CPR initiation, when compared with the no bystander CPR group. These 2 studies, however,

15   reported that time to CPR initiation was longer in the DA-CPR than in the unassisted bystander

16   CPR cohort.[26,39] See Table 10 for further information.

1   **Table 10. Outcomes of Infants and Children with Out-of-Hospital Cardiac Arrest Who Received Bystandaer DA-CPR**

2   **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 neurologic outcome at 1 month (critical)	2722 (1 cohort study)[26]	Very low	RR: 0.59 (0.41–0.84)	26 fewer per 1000 (9 fewer to 37 fewer)
Survival with favorable neurologic outcome at hospital discharge (critical)	970 (1 cohort study)[39]	Very low	RR: 0.97 (0.61–1.56)	2 fewer per 1000 (32 fewer to 43 more)
Survival at 1 month (critical)	2722 (1 cohort study)[26]	Very low	RR:0.77 (0.62–0.95)	34 fewer per 1000 (6 fewer to 57 fewer)
Survival at hospital discharge (critical)	1661 (1 cohort study)[39]	Very low	RR: 0.99 (0.69–1.41)	2 fewer per 1000 (42 fewer to 51 more)
Sustained ROSC (critical)	1661 (1 cohort study)[39]	Very low	RR: 0.84 (0.62–1.16)	26 fewer per 1000 (26 more to 66 fewer)

Outcomes (Importance)	Participants (Studies), n	Certainty of Evidence (GRADE)	RR (95% CI)[*]	RD With DA-CPR and Unassisted CPR
Shockable initial rhythm	3692 (2 cohort studies)[26,39]	Very low	RR: 0.54 (0.35–0.82)	61 fewer per 1000 (31 fewer to 83 fewer)
Arrest to CPR initiation	2722 (1 cohort study)[26]	Very low	Longer time with DA-CPR: median 4 min [IQR 0–13 min] versus 1 min [IQR 0–5]	
	766 (1 cohort study)[31]	Very low	Longer time with DA-CPR: median 4 min [IQR 0–13 min] versus 2 min [IQR 0–10]	

1 CPR indicates cardiopulmonary resuscitation; DA-CPR, dispatcher-assisted CPR; GRADE, Grading of Recommendations,

2 Assessment, Development, and Evaluation.; EMS, emergency medical services; IQR, interquartile range; RD, risk difference; ROSC,

3 return of spontaneous circulation; RR, relative risk.

4 [*]Relative risks are presented for unadjusted analyses and odds ratios are presented for adjusted analyses.

5

[h3]Treatment Recommendations

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

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

[h3]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.[100] In considering the importance of this topic, the Pediatric Life Support Task Force noted that bystander CPR significantly improves the likelihood of survival from OHCA, but bystander CPR rates remain very low.[101]

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 as well as the large positive effect of increased bystander CPR and reduced time to initiation of CPR when DA-CPR was offered.

1   Implementation of DA-CPR appears to be acceptable and feasible, as many EMS systems have

2   demonstrated. However, its cost effectiveness and impact on health equity have not been

3   evaluated and, until documented, may present barriers to implementation in under-resourced

4   regions. Also, successful implementation of any program of DA-CPR requires a process of

5   continuous quality improvement to ensure that dispatchers can quickly identify a likely cardiac

6   arrest and assist the bystander in starting CPR in a very short time.[102]

7   In making a strong recommendation despite low-certainty evidence, the task force valued the

8   consistency of results indicating benefit for all critical and important outcomes, with the

9   exception of shockable rhythm (no benefit). This failure to demonstrate contribution of DA-CPR

10   to improvement in likelihood of shockable initial rhythm aligns with the adult meta-analysis.[2]

11   In abstaining from recommending for or against DA-CPR when bystander CPR is already in

12   progress, the task force noted the very-low-certainty evidence available, the consistency of

13   inferior and neutral results for all of the critical outcomes, and the lack of any adjusted analyses

14   for this group. The negative results associated with DA-CPR compared with unassisted

15   bystander CPR may have several potential explanations: 1) bystander CPR was initiated earlier

16   than DA-CPR because the bystander did not experience the delay required in calling a dispatcher

17   and receiving instruction, or 2) the bystanders who performed CPR and refused dispatch

18   assistance were likely trained in CPR and may have provided a higher quality of CPR than that

19   provided by the untrained bystander who required remote dispatch assistance. This particular

20   finding suggests the potential benefits of widespread community-based CPR training.

21   Consideration of types of DA-CPR systems or interventions to improve the quality of DA-CPR

22   was beyond the scope of this review. A limitation of the evidence that forms the basis of these

23   treatment recommendations is that data are derived from only 2 countries—Japan and Korea.

1   The EMS systems involved may differ in their response to OHCA compared with EMS systems

2   and responses in other regions. Thus, caution is required when attempting to extrapolate these

3   results to different EMS systems of care.

4   Although this review did not address the content of CPR instructions, we elected to specify that

5   CPR instructions should include rescue breaths for pediatric cardiac arrest patients to be

6   consistent with previous CoSTRs[103] and draw attention to this important distinction from adult

7   CPR instructions.

8   **[h3]Knowledge Gaps**

9   The Pediatric Life Support Task Force identified several knowledge gaps requiring further

10   investigation. The overall challenge is the need to determine if dispatchers can effectively guide

11   untrained bystanders to provide effective conventional CPR for a child in cardiac arrest. To

12   ensure that consistent analysis is included in all future studies of DA-CPR in children, we

13   recommend research include/address the following:

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

15   CPR for children

16   • Identification of the specific scripted language used by dispatchers and its effects on the

17   initiation of bystander CPR

18   • Indication of how CPR instructions are provided (by the phrasing and enunciation of

19   words, video adjuncts via cellphone, etc)

20   • Report of the certainty of bystander CPR (including the time required for identification of

21   cardiac arrest, time to initiation of CPR, and whether conventional CPR or chest

22   compression–only CPR was given)

- Inclusion of subsequent in-hospital (postarrest) factors

- Indication of specific dispatcher guidance provided (eg, to pace the compression rate) when bystander CPR is already initiated

- EMS response times

- Analysis of 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

- Adjusting for variables such as bystander CPR characteristics, patient, age, sex, and previous bystander CPR training

[h2]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 a supraglottic airway (SGA) or tracheal intubation (TI), may allow more effective resuscitation than the alternative of BMV. However, uncertainties remain about the relative risk and benefit of each method of managing the airway during CPR. Persistent challenges surround issues of provision of effective (but not excessive) ventilation; delivery of continuous chest compressions; and risk of failed intubation attempts, unrecognized esophageal intubation, prolonged interruptions in chest compressions, and inadvertent excessive ventilation; these issues can all 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.[6] The Pediatric Task Force analyzed and discussed the SR as well as all of the studies identified by the SR, developed a draft CoSTR, and posted it online for public comment.[104] 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 4 or more 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 (eg, conference abstracts, trial protocols) excluded; the last search was performed on September 24, 2018

PROSPERO registration: CRD42018102430

1 **[h3]Consensus on Science**

2 The task force reviewed the evidence of outcomes with the following comparisons: TI with

3 BMV, SGA with BMV, and TI with SGA during pediatric cardiac arrest. Detailed information

4 from all studies reviewed is summarized in Table 11. Summative results from 8 of the studies are

5 included in Table 12, which excluded cohort studies with results too heterogeneous to enable

6 meta-analysis.

1   **Table 11. Pediatric Studies Comparing Use of Bag-Mask Ventilation With Advanced Airways During Cardiac Arrest**

Study	Years Conducted	Setting	Location	Number of Patients/Total Treated (Percent) With:					
				Survival With Good Neurologic Function			Survival to Hospital Discharge		
				TI	BMV	SGA	TI	BMV	SGA
Clinical Trials									
Gausche 2000[105]	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 2016[106]	2000–2014	IHCA	United States	185/987 (18.7%)	211/983 (21.4%)	--	411/1135 (36.2%)	460/1135 (40.7%)	--
Hansen 2017[107]	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 2017[108]	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									

Study	Years Conducted	Setting	Location	Number of Patients/Total Treated (Percent) With:					
				Survival With Good Neurologic Function			Survival to Hospital Discharge		
				TI	BMV	SGA	TI	BMV	SGA
Abe 2012[109]	2005–2008	OHCA	Japan	--	--	--	12/185 (6.5%)	243/2734 (8.9%)	9/270 (3.3%)
Aijian 1989[110]	1984–1987	OCHA	United States	--	--	--	1/28 (3.6%)	1/14 (7.1%)	--
Deasy 2010[111]	1999–2007	OHCA	Australia	--	--	--	13/154 (7.8%)	2/26 (7.7%)	--
Del Castillo 2015[112]	2007–2009	IHCA	Argentina, Brazil, Columbia, Chile, Ecuador Honduras, Italy, Paraguay, Portugal, Spain	44/71 (71.0%)	43/53 (81.1%)	--	--	--	--
Guay 2004[113]	1983–1987	IHCA	Canada	--	--	--	20/90 (22.2%)	30/55 (54.5%)	--

Study	Years Conducted	Setting	Location	Number of Patients/Total Treated (Percent) With:					
				Survival With Good Neurologic Function			Survival to Hospital Discharge		
				TI	BMV	SGA	TI	BMV	SGA
Pitetti 2002[114]	1995–1999	OHCA	United States	--	--	--	5/150 (3.3%)	0/39 (0.0%)	--
Sirbaugh 1999[115]	1992–1995	OHCA	United States	5/229 (2.2%)	0/26 (0.0%)	--	6/229 (2.6%)	0/26 (0.0%)	--
Tham 2018[116]	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 2016[117]	2007–2012	OHCA	United States	--	--	--	aOR 0.64 (CI: 0.37–1.13) favoring BMV over AAW*	--	

Study	Years Conducted	Setting	Location	Number of Patients/Total Treated (Percent) With:					
				Survival With Good Neurologic Function			Survival to Hospital Discharge		
				TI	BMV	SGA	TI	BMV	SGA
Tijssen 2015[118]	2005–2012	OHCA	Canada, USA	--	--	--	aOR 0.69 (CI: 0.43–1.10) favoring BMV over AAW[†]	--	

1   AAW indicates advanced airway; aOR, adjusted odds ratio; BMV, bag-mask ventilation; CI, confidence interval; IHCA, in-hospital

2   cardiac arrest; OHCA, out-of-hospital cardiac arrest; SGA, supraglottic airway; TI, tracheal intubation.

3   [*]Fink 2016[117]: 92% of advanced airway attempts were tracheal intubation attempts.

4   [†]Tijssen 2015[118]: 93% of advanced airway attempts were tracheal intubation attempts.

5

1 **Table 12. Summative Results of Studies Used in the Pediatric Airway Systematic Review, for Each Comparison and Grouped**

2 **by Outcome**

Outcomes (Importance)	Participants (Studies), n	Certainty of Evidence (GRADE)	RR (95% CI)	Absolute Risk With Comparator (C)	Absolute Risk Difference With Intervention (I)
Tracheal Intubation (I) Versus Bag-Mask Ventilation (C)*					
Survival, favorable neurologic outcome (critical)	591 (1 RCT)[105]	Low	0.69 (0.32–1.52)	50/1000	15 fewer per 1000 (from 48 fewer to 17 more)
	3855 (3 propensity-matched observational)[106-108]	Very low	‡	150/1000	49 fewer per 1000 (from 77 fewer to 21 fewer)
Survival to hospital discharge (critical)	591 (1 RCT)[105]	Low	1.04 (0.6–1.79)	80/1000	3 more per 1000 (from 41 fewer to 47 more)
	4155 (3 propensity-matched observational)[106-108]	Very low	†	268/1000	53 fewer per 1000 (from 20 fewer to 87 fewer)
	3992 (2 observational studies)[117,118]	Very low	†	Fink 2016: aOR 0.64 (0.37–1.13)[117] Tijssen 2015: aOR 0.69 (0.43–1.1)[118]	

Outcomes (Importance)	Participants (Studies), n	Certainty of Evidence (GRADE)	RR (95% CI)	Absolute Risk With Comparator (C)	Absolute Risk Difference With Intervention (I)
Survival to hospital admission (important)	1508 (1 propensity-matched observational)[107]	Very low	0.99 (0.83–1.17)	257/1000	3 fewer per 1000 (from 47 fewer to 41 more)
ROSC (important)	4155 (3 propensity-matched observational)[106-108]	Very low	†	417/1000	12 more per 1000 (from 15 fewer to 39 more)
Supraglottic Airway (I) versus Bag-Mask Ventilation (C)*					
Survival, favorable neurologic outcome (critical)	1657 (2 propensity-matched observational)[107,108]	Very low	‡	93/1000	29 fewer per 1000 (from 75 fewer to 17 more)
	900 (1 non-adjusted observational study)[116]	Very low	0.75 (0.23–2.42)	37/1000	9 fewer per 1000 (from 43 fewer to 24 more)
Survival to hospital discharge (critical)	3904 (2 observational studies)[109,116]	Very low	‡	88/1000	35 fewer per 1000 (from 88 fewer to 18 more)

Outcomes (Importance)	Participants (Studies), n	Certainty of Evidence (GRADE)	RR (95% CI)	Absolute Risk With Comparator (C)	Absolute Risk Difference With Intervention (I)
Survival to hospital admission (important)	996 (1 propensity-matched observational)[107]	Very low	1.25 (0.99–1.57)	257/1000	64 more per 1000 (from 6 fewer to 133 more)
	900 (1 observational study)[116]	Very low	0.85 (0.44–1.87)	97/1000	15 fewer per 1000 (from 70 fewer to 41 more)
ROSC (important)	900 (1 observational study)[116]	Very low	1.26 (0.82–1.92)	171/1000	40 more per 1000 (from 41 fewer to 121 more)
Tracheal Intubation (I) versus Supraglottic Airway (C)[*]					
Survival, favorable neurologic outcome (critical)	1288 (2 propensity-matched observational)[107,108]	Very low	[‡]	47/1000	22 fewer per 1000 (from 51 fewer to 6 more)
	127 (1 nonadjusted observational study)[116]	Very low	6.06 (1.32–27.7)	28/1000	139 more per 1000 (from 36 fewer to 314 more)

Outcomes (Importance)	Participants (Studies), n	Certainty of Evidence (GRADE)	RR (95% CI)	Absolute Risk With Comparator (C)	Absolute Risk Difference With Intervention (I)
Survival to hospital discharge (critical)	1288 (2 propensity-matched observational)[107,108]	Very low	‡	130/1000	31 fewer per 1000 (from 73 fewer to 11 more)
	582 (2 observational studies)[109,116]	Very low	‡	47/1000	34 more per 1000 (from 6 fewer to 75 more)
Survival to hospital admission (important)	942 (1 propensity-matched observational)[107]	Very low	0.79 (0.63–1.0)	321/1000	67 fewer per 1000 (from 136 fewer to 4 more)
	127 (1 observational study)[116]	Very low	4.33 (2.28–8.2)	128/1000	472 more per 1000 (from 198 more to 665 more)
ROSC (important)	1288 (2 propensity-matched observational)[107,108]	Very low	‡	162/1000	26 fewer per 1000 (from 129 fewer to 78 more)
	127 (1 observational study)[116]	Very low	3.42 (2.16–5.44)	211/1000	511 more per 1000 (from 291 more to 732 more)

1   aOR indicates adjusted odds ratio; C, comparator; CI, confidence interval; GRADE, Grading of Recommendations, Assessment,

2   Development, and Evaluation; I, intervention; RCT, randomized controlled trial; ROSC, return of spontaneous circulation; RR,

3   relative risk.

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

5   *Cohort studies, amenable to meta-analysis, were not reported in this table if they produced too heterogeneous results (I^2 index >75%).

6   Studies included in this table were therefore 1 clinical trial,[105] 3 propensity-matched observational studies,[106-108] and 4 nonadjusted

7   observational studies.[109,116-118]

8   †The first 2 studies[117,118] provided retrospective cohort data in adjusted form only (aOR), not amenable to meta-analysis.

9   ‡To minimize ambiguity, RR calculations were only reported for single studies and not for meta-analysis. RR calculations were

10   considered less informative and sometimes produced divergent results, likely a consequence of zero-numerator cells.[119]

11

[h4]Studies Comparing Tracheal Intubation With Bag-Mask Ventilation Alone

Fourteen studies were included in the SR comparing TI with BMV, including 1 clinical trial[105] and 13 observational studies.[106-118]

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 neurologic function or survival to hospital discharge.[105]

The 13 identified observational studies provided evidence of very-low or low certainty. Three of these observational studies[106-108] 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 neurologic function or survival to hospital discharge associated with TI.[106-108] The other 10 observational studies found no statistically significant association between TI and these outcomes.[109-116,118,120]

[h4]Studies Comparing SupraGlottic Airway With Bag-Mask Ventilation 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.[107,108] Two other observational

studies reported only nonadjusted data.[109,116] None of these studies found a significant

association between SGA use and survival with favorable neurologic function or survival to

hospital discharge.

[h4]Studies Comparing Tracheal Intubation with SupraGlottic Airway

The evidence comparing TI with SGA during pediatric resuscitation comes from 4 observational

studies of OHCA;[107-109,116] 2 of these employed propensity matching.[107,108] When combined,

neither the propensity-matched studies[107,108] nor the nonadjusted cohort studies[109,116] found a

significant association between the choice of advanced airway and survival with favorable

neurologic function or survival to hospital discharge.

[h3]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 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.

[h3]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 (ie, before ROSC) improves

resuscitation outcomes. The best available data shows no benefit from advanced airway

interventions, and some suggested association with harm for the critical outcomes of survival

with favorable neurologic outcome and survival to hospital discharge. The effects of placement

1 of an advanced airway are uncertain for the short-term resuscitation outcomes of survival to

2 hospital admission and ROSC. Although these short-term outcomes do not ultimately benefit the

3 patient, they may benefit the family.

4 Effective BMV, TI, and insertion of an SGA are all difficult skills that require good initial

5 training, retraining, and quality control to be performed consistently, safely, and effectively. To

6 be effective, pediatric advanced airway programs require a moderate investment in equipment

7 and a significant investment in training, skills maintenance, and quality control programs.

8 The benefit or harm associated with advanced airway-based resuscitation may differ across

9 settings. Importantly, the available data do not inform the questions of whether better outcomes

10 might be achieved by advanced airway-based strategies by highly trained and experienced

11 airway operators, during long distance transport, or in prolonged resuscitation situations. The

12 analyzed data are only relevant to advanced airway interventions during CPR and do not pertain

13 to airway management after ROSC or in other critical situations.

14 **[h3]Knowledge Gaps**

15 This evidence evaluation did not identify any clinical trials addressing airway management

16 during cardiac arrest in the in-hospital setting, and future studies are needed to address this

17 knowledge gap. In addition, the only randomized clinical trial undertaken in the out-of-hospital

18 setting[105] was performed before major changes in resuscitation guidelines; future studies are

19 needed in the out-of-hospital setting. The task force identified several additional knowledge gaps

20 requiring further investigation, including

- 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 etiology 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; these are subgroups about which we have no knowledge and that 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.[121]

ILCOR commissioned an SR to identify and analyze all published evidence reporting outcomes of ECPR in infants, children, and adults after OHCA and IHCA.[5] The Pediatric Life Support Task Force analyzed and discussed the SR as well as all of the pediatric studies identified by the SR, developed a draft CoSTR, and posted it online for public comment.[122] 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 (≥18 years) and children (<18 years) with cardiac arrest in any setting (out-of-hospital or in-hospital)

1   Intervention: ECPR, including extracorporeal membrane oxygenation or cardiopulmonary

2   bypass, during cardiac arrest

3   Comparator: Manual CPR and/or mechanical CPR

4   Outcomes**:** Clinical outcomes, including short-term survival and neurologic outcomes (eg,

5   hospital discharge, 28 days, 30 days, and 1 month), and long-term survival and neurologic

6   outcomes (eg, 3 months, 6 months, and 1 year)

7   Study Design: Randomized trials, non-RCTs, and observational studies (cohort studies and case-

8   control studies) with a control group were included; animal studies, ecological studies, case

9   series, case reports, reviews, abstracts, editorials, comments, and letters to the editor were not

10 included.

11 Time Frame: All years and all languages were included (as long as there was an English

12 abstract); unpublished studies and published abstracts (eg, conference abstracts) and trial

13 protocols were excluded; literature search conducted on December 19, 2017 and updated to May

14 22, 2018

15 PROSPERO registration: CRD42018085404

16 Note: Information about outcomes of ECPR use in adults is addressed elsewhere in this article

17 (see "Advanced Life Support, ECPR for Cardiac Arrest: Adults").

18 **[h3]Consensus on Science**

19 **[h4]In-Hospital Cardiac Arrest**

20 For the critical outcomes of favorable longer-term neurologic outcome or of longer-term

21 survival, no pediatric studies were identified.

1 For the critical outcome of favorable neurologic outcome at hospital discharge, we identified

2 very-low-certainty evidence (downgraded for very serious risk of bias) from 1 observational

3 study; this study associated improved outcomes with ECPR when compared with conventional

4 CPR (conditional logistic analysis adjusted odds ratio [aOR], 2.64; 95% CI, 1.91–3.67;

5 propensity analysis aOR, 1.78; 95% CI, 1.31–2.41).[123]

6 For the critical outcome of survival to hospital discharge, we identified very-low-certainty

7 evidence (downgraded for very serious risk of bias and inconsistency) from 3 studies with

8 pediatric populations. Two studies associated improved survival with ECPR when compared

9 with conventional CPR (aOR, 2.76; 95% CI, 2.08–3.66[123]; aOR, 3.80; 95% CI, 1.40–10.32 in

10 medical cardiac; and aOR, 2.50; 95% CI, 1.3–4.81 in surgical cardiac patients).[124]

11 **[h4]Out-of-Hospital Cardiac Arrest**

12 No studies were identified that addressed this question.

13 **[h3]Treatment Recommendations**

14 We suggest ECPR may be considered as an intervention for selected infants and children (eg,

15 cardiac populations) with IHCA refractory to conventional CPR in settings where resuscitation

16 systems allow ECPR to be well performed and implemented (weak recommendation, very low

17 certainty of evidence).

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

19 ECPR.

20 **[h3]Justification and Evidence to Decision Framework Highlights**

21 In making a weak recommendation about the use of ECPR for pediatric IHCA, we recognize that

22 despite lack of comparative prospective studies identified in infants and children, patients with

1   IHCA refractory to conventional CPR have a high probability of death unless therapies such as

2   ECPR are used.

3   Providers should carefully consider the fact that the pediatric ECPR studies from which these

4   recommendations are drawn consist predominantly of children with cardiac disease. This

5   population may not adequately represent the local population where guidelines may be

6   implemented, so regional resuscitation councils must consider how generalizable the evidence

7   can be to their regional systems of care.

8   The results of ECPR studies conducted in adults cannot be extrapolated to pediatric OHCA,

9   given the difference in causes of cardiac arrest between children and adults, the techniques and

10   equipment applied for ECPR, and the post–cardiac arrest care interventions.

11   As noted, ECPR has been studied in very selected populations (eg, cardiac surgical or cardiac

12   medical) and more rarely for pediatric cardiac arrest in general (ie, across all diseases and in all

13   hospital settings).[123] In addition, it has been used in organizations with strong institutional-based

14   commitment to sustaining a resuscitation system that includes ECPR with appropriate quality

15   improvement systems.[125,126] Such improvement systems include ongoing internal audits and

16   iterative evaluation of performance and outcomes.[125-129] As a result, these findings may not be

17   broadly generalizable to other organizations.

18   ECPR is a complex resuscitation intervention that requires long-term commitment to sustain the

19   expertise, resources, training, and systems to provide support for patients and their families.

20   Delivering this complex intervention involves added up-front investment and costs.[130,131]

21   The healthcare resources necessary to provide high-quality pediatric ECPR are likely to limit its

22   broad adoption.

[h3]Knowledge Gaps

There are no published randomized trials comparing outcomes of ECPR versus conventional CPR in infants and children. As 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 neurologic 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-cardiopulmonary resuscitation outcomes. The Pediatric Life Support Task Force identified the following unresolved issues:

- Optimal timing for ECPR cannulation during conventional CPR
- Conditions (eg, conditions with pulmonary blood flow obstruction) for which ECPR rather than conventional CPR should be considered earlier in the resuscitation
- Type and anatomic approach for cannulation for ECPR that allows best cerebral-cardiopulmonary resuscitation
- Identification of other technical aspects of ECPR that enable optimal cerebral-cardiopulmonary resuscitation, 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

1   decarboxylation to be delivered during ECPR, and the inotrope or vasoactive medications

2   delivered during ECPR that will optimize neurologic and cardiopulmonary outcomes

3   The post–cardiac arrest care strategies after cannulation for ECPR remain to be studied,

4   including how post–cardiac arrest care therapies should be adapted in the context of ongoing

5   ECPR.

6   There is an important gap in comparative studies of resuscitation for OHCA in special

7   circumstances such as submersion or drowning, deep hypothermia or cold environment,

8   respiratory arrest, or in the context of trauma. The Pediatric Life Support Task Force identified

9   the following challenges for studies of ECPR for pediatric OHCA in special circumstances:

10   •   Identification of ideal select populations and circumstances to be considered for initial

11   studies of ECPR for OHCA: Should these include children with cold-water drowning or

12   avalanche victims or cold exposure victims?

13   •   Optimal timing for initiation of ECPR: Should it be initiated at the scene of the arrest (ie,

14   cannulation in the field) or immediately upon arrival at the hospital?

15   There are no published comparative studies on longer term functional outcomes or QoL

16   outcomes in pediatric patients and in their families and/or caregivers after ECPR. The Pediatric

17   Life Support Task Force identified the following issues to be addressed:

18   •   How longer-term functional and QoL outcomes compare between ECPR and

19   conventional CPR for the pediatric population and their families and caregivers

20   •   How bereavement outcomes compare between families and caregivers of nonsurvivors of

21   cardiac arrest with ECPR compared with outcomes of families and caregivers of

22   nonsurvivors of conventional CPR

1 Whereas the cost-effectiveness of ECMO has been addressed in pediatric and adult publications,

2 the cost-effectiveness of ECPR versus conventional CPR in pediatric cardiac arrest populations

3 is not known and should be studied.

4 ## Targeted Temperature Management (TTM) After Cardiac Arrest

5 The last ILCOR Pediatric Life Support CoSTR review of pediatric TTM was published in

6 2015.[121] Since that review, additional studies of pediatric TTM have been published, particularly

7 in the in-hospital target population. ILCOR commissioned an SR to identify and analyze all

8 published evidence reporting outcomes of TTM in children who achieved ROSC after OHCA

9 and IHCA.[7] The Pediatric Life Support Task Force analyzed and discussed the SR as well as all

10 of the studies identified by that review, developed a draft CoSTR, and posted it online for public

11 comment.[132] In response to the 2 posted comments, the task force included additional

12 information in the section "Justification and Evidence to Decision Framework Highlights."

13 ### Population, Intervention, Comparator, Outcome, Study Design, and Time Frame

14 Population: Pediatric patients (>24 hours to 18 years of age) who achieved ROSC after OHCA or

15 IHCA

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

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

18 Outcomes:

19 • Critical: favorable neurologic outcome (good behavioral survival) at 1 year such as

20   Pediatric Cerebral Performance Category 1 or 2, and Vineland Adaptive Behavior Scales

21   II

1   • Important: favorable neurologic outcome (at other time intervals), overall survival, and

2   health-related QoL (HRQoL) at 3 time intervals: long-term (1–3 years), intermediate-term

3   (3–6 months), and short-term (28–30 days or hospital discharge)

4   – HRQoL was defined using pediatric-specific QoL tools (eg, the Pediatric QoL

5   Inventory,[133] the Infant Toddler QoL Questionnaire,[134] or equivalent). Potential in-

6   hospital adverse outcomes were also captured, including infection (culture proven),

7   recurrent cardiac arrest, serious bleeding (red blood cell transfusion), and any

8   arrhythmias (not leading to cardiac arrest).

9   Study Designs: RCTs, quasi-randomized controlled trials (qRCTs), and nonrandomized cohort

10   studies eligible to be included; excluded: animal studies, unpublished studies and published

11   abstracts (eg, conference abstracts), case series

12   Time Frame: All years to December 13, 2018

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

14   A priori Subgroups to Be Examined: Location of cardiac arrest (in-hospital and out-of-hospital),

15   age groups, presumed etiology of cardiac arrest (cardiac, asphyxial, other), and use of

16   extracorporeal membrane oxygenation (ECMO)

17   PROSPERO registration: CRD42018108441

18   **[h3]Consensus on Science**

19   The review identified 2 RCTs[135,136] with moderate clinical heterogeneity (different settings), low

20   methodological heterogeneity (same methods and in-hospital management), and low or moderate

21   statistical heterogeneity, allowing pooling of the results in the meta-analyses and separate

22   subgroup analyses. The 2 RCTs were downgraded to low certainty of effect as the result of

1   inconsistency and imprecision. Because there were only 2 relatively small RCTs available,

2   observational comparative data were considered, but we did not combine the RCT and non-RCT

3   data. The observational studies that reported adequately adjusted results were pooled, whereas

4   nonadjusted results are shown, where relevant, without pooling (Table 13).

1 **Table 13. Pediatric Targeted Temperature Management in Children With Out-of-Hospital Cardiac Arrest Who Are Comatose**

2 **After Return of Spontaneous Circulation: Summary of Studies and Findings**

Authors (Year)	Study Type; Years Enrolled	N	Enrollment Criteria	GCS/ Neuro	Target Temperature Intervention	Temperature Comparison Control	TTM Duration	Outcomes	Comments
Chang (2016)[137]	Retrospective review of national OHCA database Nonrandomized 1/1/2008–12/31/2014	663 total TTM 81 Stratified by shockable versus 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 temp or duration Actual temperature measures not included	No standard care protocol Temperature measures not included	Minimum 12 h	No difference in either 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	Very low certainty resulting from lack of temperature data and nonrandomized treatment allocation

Authors (Year)	Study Type; Years Enrolled	N	Enrollment Criteria	GCS/ Neuro	Target Temperature Intervention	Temperature Comparison Control	TTM Duration	Outcomes	Comments
					No standard care protocol			(22.2%) and control (18.7%) No difference in effect of TTM between shockable and nonshockable presenting rhythm groups	
Cheng (2018)[138]	Retrospective Historic and concurrent Controls 2013–2015; Included	81 events in 75 pts; IHCA	CHD* + CPR >5 min or ECPR* (excluded intracranial hemorrhage)	Not specified	Mean=33.6°C (0.2) 0 had fever 4/30 had T<32°C;	Mean=34.7°C (0.8) 2/51 had fever; 12/51 had T<32°C; TTM	<1=72 h ≥1=48 h 14/30 TTM pts rewarmed early	Survival Control 59.1% TTM 61.5% No significant difference in survival or LOS,	Control group included more patients with single ventricles and had low mean

Authors (Year)	Study Type; Years Enrolled	N	Enrollment Criteria	GCS/ Neuro	Target Temperature Intervention	Temperature Comparison Control	TTM Duration	Outcomes	Comments
	neonates (23–33%)				TTM reached in 1.4 h	reached in 1.4 h		Follow up to 26.5 months; fewer TTM patients had seizures (sig)	temperature with nearly half T<32°C
Fink (2010)[120]	Retrospective cohort TTM patients 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	Consistent with AHA "comatose"; specific neurological criteria not reported	33.5°C–34.8°C, mean 34.1°C ±0.8°C Reached in 2.7 ±4.5 h (mean 0–4); 18% had fever, 15% had T<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 days	24 h (range 16–48 h); 60% of TTM patients presented at or below target temperature, so some	55% survival with no difference between TTM and control; <36°C or >38°C on admission had significantly higher mortality than T36°C–38°C; T<32°C in 15% and associated w/higher mortality;	

Authors (Year)	Study Type; Years Enrolled	N	Enrollment Criteria	GCS/ Neuro	Target Temperature Intervention	Temperature Comparison Control	TTM Duration	Outcomes	Comments
			death prior to arrest)				were warmed to target temperature)	No difference in hospital mortality, LOS	
Lin (2013)[139]	Retrospective chart review 1/1/2010– 6/30/2012	43 total 15 TTM Both OHCA and IHCA	At least 3 min compression; only those surviving 12 h included; CHD excluded	TTM GCS mean 4.67 ±1.94; Control GCS 5 ±2.35	33.5°C ±0.5°C	39% needed active rewarming to normothermia	24–72 h	57% overall survival; higher (78.6%) in TTM group versus 46.4% in control group (sig)	Some internal inconsistencies in numbers throughout manuscript

Authors (Year)	Study Type; Years Enrolled	N	Enrollment Criteria	GCS/ Neuro	Target Temperature Intervention	Temperature Comparison Control	TTM Duration	Outcomes	Comments
Lin (2018)[140]	Retrospective cohort 2010–2017	64 total 25 TTM, all asphyxial 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 neuro disease and 8 with TBI	GCS ≤8 TTM GCS 3.4 ± 1.04 Control GCS 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 T>37.5°C	72 h	Overall 1-month survival 42.2% 1-month survival sig higher in TTM (60%) versus control (30.8%); TTM had significantly better neuro outcomes; TTM group had longer LOS	
Moler (2016)[136]	International, multi-institutional	74 with OHCA drowning ≥2	48 h to <18 years of age; excluded if GCS motor	GCS motor 3 or 4,	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	CPR duration longer in TTM 36°C–37.5°C

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Authors (Year)	Study Type; Years Enrolled	N	Enrollment Criteria	GCS/ Neuro	Target Temperature Intervention	Temperature Comparison Control	TTM Duration	Outcomes	Comments
	prospective RCT (9/1/2009– 12/31/2012)	mins CC[*], remained comatose (GCS motor 3 or 4) and ventilator-dependent after ROSC 46 randomized to TTM group	score 5 or 6, major trauma, inability to randomize within 6 h, decision to withhold aggressive treatment	comatose and vent depended after ROSC				favorable neuro outcome or other secondary outcomes; culture-proven bacterial infection more common in TTM group; the 25 12-mo survivors who received >30 min CC had poor functional outcomes (PCPC≥4)	group and fewer had bystander CPR; blinding of caregivers impossible
Moler (2015)[136]	International, multi-	295 randomized;	48 h to <18 years of age; excluded	GCS motor 3	33°C (32°C– 34°C)	36.8°C (36°C– 37.5°C)	120 h	No difference in 28-d mortality (57% in	Witnessed arrest 39%,

Authors (Year)	Study Type; Years Enrolled	N	Enrollment Criteria	GCS/ Neuro	Target Temperature Intervention	Temperature Comparison Control	TTM Duration	Outcomes	Comments
	institutional prospective RCT (9/1/2009 to 12/31/2012)	260 subjects with data— all OHCA who required ≥2 mins CC, remained comatose and ventilator- dependent 155 assigned to TTM	if GCS motor score 5 or 6, major trauma, inability to randomize within 6 h, decision to withhold aggressive treatment	or 4, comatose and ventilator dependen t after ROSC				TTM, 67% in control group, P=0.08), 12-mo survival (38% in TTM versus 29% in Control) or in 12-mo survival with favorable neuro outcome or other secondary outcomes; no difference in complications (eg, bleeding, arrhythmias, infections), although hypokalemia and	and 66% of these received bystander CPR 72% of patients had respiratory cause of arrest; blinding of caregivers was impossible

Authors (Year)	Study Type; Years Enrolled	N	Enrollment Criteria	GCS/ Neuro	Target Temperature Intervention	Temperature Comparison Control	TTM Duration	Outcomes	Comments
								thrombocytopenia occurred more frequently in TTM group and renal replacement treatment used more often in control group; there was a significant difference in survival time with TTM group although this was secondary outcome	
Moler (2017)[135]	International, multi-	329 patients randomized;	48 h to <18 years of age; excluded	GCS motor 3	33°C (32°C–34°C)	36.8°C (36°C–37.5°C)	120 h	Survival at 28 d and survival with ≥70 at 1	65% had either cardiac

Authors (Year)	Study Type; Years Enrolled	N	Enrollment Criteria	GCS/ Neuro	Target Temperature Intervention	Temperature Comparison Control	TTM Duration	Outcomes	Comments
	institutional prospective RCT (9/1/2009–2/27/2015; stopped for futility)	166 to control (IHCA)	if GCS motor score 5 or 6, major trauma, inability to randomize within 6 h, decision to withhold aggressive treatment	or 4, comatose and ventilator dependent after ROSC				y 36% TTM versus 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	cause of arrest or CHD; blinding of caregivers was impossible

Authors (Year)	Study Type; Years Enrolled	N	Enrollment Criteria	GCS/ Neuro	Target Temperature Intervention	Temperature Comparison Control	TTM Duration	Outcomes	Comments
Scholefield (2015)[141]	Retrospective cohort enrolled January 2004 to December 2010 following OHCA	73 patients; 38 randomized to TTM	1 day; 16 years, admitted after OHCA with ROSC	Not stated although cited the ILCOR guidance for TTM for patients who remain comatose after ROSC from	32°C–34°C; 4 patients (11%) experienced "overshoot" cooling to <32°C and all 11 died; only 3% (1 patient) developed temperature >38°C	Called "standard temperature management or STM)" 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%) versus control (23%); the 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% versus 47%) had bystander CPR; TTM used more often in patients with unknown cause of arrest and higher predicted mortality and

Authors (Year)	Study Type; Years Enrolled	N	Enrollment Criteria	GCS/ Neuro	Target Temperature Intervention	Temperature Comparison Control	TTM Duration	Outcomes	Comments
				cardiac arrest					used less in those with traumatic arrest (including TBI), so control group had more patients with traumatic arrest; study enrollment bridged a period of major change

Authors (Year)	Study Type; Years Enrolled	N	Enrollment Criteria	GCS/ Neuro	Target Temperature Intervention	Temperature Comparison Control	TTM Duration	Outcomes	Comments
									in basic life support guidelines
Torres-Andres (2018)[142]	Retrospective observational study of all witnessed OHCA and IHCA between May 2007 and July 2015 treated with ECPR	58 consecutive patients receiving ECPR; 28 also treated with TTM	Witnessed IHCA (only 3 of 58 patients) or OHCA; receipt of advanced CPR, no ROSC within 15 min of CPR; no contraindication to mechanical circulatory support;	Not stated	34°C–35°C	Controlled normothermia avoiding body temperature >37°C		Overall survival to hospital discharge: 65.5%, and 3-y survival is 62.1%; survival to hospital discharge significantly higher among those treated with TTM (75%) versus control (55%) with good quality of life inventory and	Nonsurvivors more likely to have >1 ECPR event

Authors (Year)	Study Type; Years Enrolled	N	Enrollment Criteria	GCS/ Neuro	Target Temperature Intervention	Temperature Comparison Control	TTM Duration	Outcomes	Comments
			hypothermia was at discretion of care team					family functioning; 50% of survivors had evidence of intracranial injuries (versus 58.3% of nonsurvivors)	

1   CC indicates chest compressions; CHD, congenital heart disease; CPC, Cerebral Performance Category; CPR, cardiopulmonary

2   resuscitation; ECPR, extracorporeal CPR; ED, emergency department; GCS, Glasgow Coma Scale; ICU, intensive care unit; IHCA,

3   in-hospital cardiac arrest; ILCOR, International Liaison Committee on Resuscitation; LOS, length of stay; OHCA, out-of-hospital

4   cardiac arrest; PCPC, Pediatric Cerebral Performance Category ; RCT, randomized controlled trial; ROSC, return of spontaneous

5   circulation; STM, standard temperature management; TBI, traumatic brain injury; TTM, targeted temperature management; VABS-II,

6   Vineland Adaptive Behavior Scales II.

7

1 #### [h4]Favorable Neurobehavioral Survival

2 For the primary outcome of long-term favorable neurologic outcome (1 year), a pooled analysis

3 of the 2 RCTs (low certainty of evidence) found no statistically significant benefit of TTM at

4 32°C to 34°C compared with TTM at 36°C to 37.5°C.[135,136] Two adjusted cohort studies reported

5 no statistically significant benefit in either intermediate-term[143] or short-term favorable

6 neurologic outcome associated with use of TTM 32°C to 34°C compared with TTM at 36°C to

7 37.5°C.[137]

8 #### [h4]Survival

9 For the secondary outcome of overall survival, a pooled analysis of the 2 RCTs (very-low

10 certainty of effect, downgraded for inconsistency and imprecision) found no statistically

11 significant benefit in either long-term or short-term survival of TTM at 32°C to 34°C compared

12 with TTM at 36°C to 37.5°C.[135,136] One retrospective cohort study found no benefit in adjusted

13 intermediate-term survival associated with TTM at 32°C to 34°C versus TTM at 36°C to

14 37.5°C.[143] Three cohort studies also reported no associated increase in adjusted short-term

15 survival associated with use of TTM 32°C to 34°C compared with TTM at 36°C to

16 37.5°C.[120,137,143]

17 #### [h4]Adverse Outcomes: Infection

18 A pooled analysis of the 2 RCTs found no statistical difference in culture-proven infection from

19 TTM at 32°C to 34°C compared with TTM at 36°C to 37.5°C.[135,136] Four cohort studies reported

20 on infection; unadjusted outcomes were not pooled, but none of the studies showed a statistically

21 significant difference in infection with use of TTM 32°C to 34°C compared with TTM at 36°C to

22 37.5°C.[120,138,140,143]

1 **[h4]Adverse Outcomes: Recurrent Cardiac Arrest**

2 Pooled analysis of the 2 RCTs found no difference in rate of recurrent cardiac arrest from TTM

3 at 32°C to 34°C compared with TTM at 36°C to 37.5°C.[135,136] Two cohort studies reported

4 unadjusted recurrent cardiac arrest rates that could not be pooled; none of the individual studies

5 showed statistically significant association of increased recurrent arrest with use of TTM 32°C to

6 34°C compared with TTM at 36°C to 37.5°C.[120,143]

7 **[h4]Adverse Outcomes: Serious Bleeding**

8 Pooled analysis of the 2 RCTs found significant increase in serious bleeding from TTM at 32°C

9 to 34°C compared with TTM at 36°C to 37.5°C.[135,136] Two observational cohort studies reported

10 unadjusted ORs for serious bleeding; none of the individual studies showed association of

11 statistically significant increase in bleeding with use of TTM 32°C to 34°C compared with TTM

12 at 36°C to 37.5°C .[120,143]

13 **[h4]Adverse Outcomes: Arrhythmias**

14 Pooled analysis of the 2 RCTs found no statistical increase in arrhythmias from TTM at 32°C to

15 34°C compared with TTM at 36°C to 37.5°C.[135,136] Five observational studies reported

16 unadjusted outcomes for arrhythmias; 1 reported an association of statistically significant

17 increase in arrhythmias; the other 3 studies reported no statistically significant increase or

18 decrease in arrhythmias associated with use of TTM 32°C to 34°C compared with TTM at 36°C

19 to 37.5°C.[120,138,140,141,143]

20 **[h4]Subgroup Analysis: Location of Cardiac Arrest**

1   For the predetermined subgroup analysis by location of arrest (OHCA or IHCA), no meta-

2   analyses could be completed because there is only 1 RCT for each subgroup and the

3   observational studies had methodologic heterogeneity.

4   For OHCA, the single RCT did not find statistically significant benefit of TTM 32°C to 34°C

5   compared with TTM at 36°C to 37.5°C.[136] One of the 3 cohort studies found (in unadjusted

6   results) association of increased survival and good behavioral survival with 72 hours of TTM at

7   32°C to 34°C compared with TTM at 36°C to 37.5°C.[140] The other 2 cohort studies did not

8   report statistically significant benefit or harm.[137,141] An exploratory analysis was conducted to

9   determine if the addition of a hypothetical OHCA RCT that yielded similar results as the

10   Therapeutic Hypothermia After Pediatric Cardiac Arrest (THAPCA) OHCA study would change

11   the pooled analysis confidence interval to favor TTM at 32°C to 34°C.[136] Enrollment of 200

12   patients in such a hypothetical RCT would be required to demonstrate a statistically significant

13   benefit for favorable neurologic outcome at 1 year.

14   The IHCA RCT did not find statistical benefit or harm of TTM at 32°C to 34°C compared with

15   TTM at 36°C to 37.5°C.[135] The point estimates for outcomes of 3 different observational cohort

16   studies are on both sides of null effect.[138,142,143] An exploratory analysis indicated that an

17   additional hypothetical RCT of 6000 patients with similar outcome to the IHCA THAPCA

18   RCT[135] would be required to demonstrate a statistically significant harm of TTM at 32°C to 34°C

19   in favorable neurologic outcome at 1 year compared with TTM at 36°C to 37.5°C.

20   **[h4]Subgroup Analysis: Etiology of Arrest**

21   Two retrospective observational cohort studies of cardiac arrest with presumed cardiac etiology

22   could not be pooled but separately reported no significant benefit or harm in short-term survival

23   associated with TTM at 32°C to 36°C compared with TTM at 36°C to 37.5°C (or no TTM).[138,142]

1   Two observational cohort studies (and a pilot publication of one of those studies) reported on the

2   favorable neurologic outcome and survival outcomes for patients with predominantly (>80%)

3   presumed asphyxial etiology.[120,139,140] High risk of bias and lack of adjusted outcomes precluded

4   pooling of data. One OHCA study found a statistically significant benefit for both favorable

5   neurologic outcome and survival associated with TTM at 32°C to 36°C for 72 hours.[140] All of the

6   point estimates for outcomes favored TTM at 32°C to 36°C.

7   The OHCA THAPCA study published a nonrandomized subgroup analysis of drowning as an

8   etiology.[144] There was no statistically significant benefit of the intervention for survival or

9   favorable neurologic outcome.

10   **[h4]Subgroup Analysis: ECMO**

11   Although some patients in several of the studies underwent ECMO, outcome data were available

12   from only 2 studies. The THAPCA IHCA RCT (nonrandomized co-intervention, of low-

13   certainty evidence) found no statistically significant difference in long-term favorable neurologic

14   outcome (at 1 year) for TTM at 32°C to 34°C compared with TTM at 36°C to 37.5°C.[135] In 1

15   observational cohort study, all patients received ECMO; they reported no statistical increase in

16   short-term survival.[142]

17   **[h3]Treatment Recommendations**

18   We suggest that for infants and children with OHCA, TTM be used in the post–cardiac arrest

19   period to maintain a central temperature <37.5°C (weak recommendation, moderate-certainty

20   evidence). Based on 2 randomized trials and 8 retrospective observational cohort studies that

21   provided comparative data on favorable neurologic outcome, survival, and in-hospital adverse

22   events, there is inconclusive evidence to support or refute the use of TTM to 32°C to 34°C

1   compared with TTM at 36°C to 37.5°C (or an alternative temperature) for children who achieve

2   ROSC after cardiac arrest.

3   ### [h3]Justification and Evidence to Decision Framework Highlights

4   The evidence in this review is dominated by the 2 THAPCA RCTs.[135,136] These studies included

5   only children aged 2 days to 18 years who had received at least 2 minutes of CPR and who

6   remained comatose and ventilator-dependent after ROSC. There were many patient exclusions,

7   including use of ECMO, severe trauma, previous cardiac arrest, pre-existing life-limiting

8   conditions, severe bleeding, and continuous epinephrine infusion. The findings of this review

9   should be considered in context of this limitation.

10   In making this recommendation, the task force preferred the use of TTM of 32°C to 34°C as

11   opposed to TTM at 36°C to 37.5°C because although the THAPCA OHCA study[136] did not

12   demonstrate success for the primary outcome (favorable neurologic status at 1 year), it was

13   underpowered to show a significant difference for survival, for which the lower 95% CI

14   approached 1. The point estimates for survival in the 3 cohort studies of OHCA or presumed

15   asphyxial arrest[120,139,140] favored TTM 32°C to 34°C. There were insufficient data on IHCA

16   patients, who represent a population with different pre-existing conditions and etiology of arrest.

17   The task force noted that hyperthermia occurs frequently in the postarrest period; fever is

18   potentially harmful and should be avoided. Finally, the provision of TTM can be resource

19   intensive. These resources, the associated expertise necessary to deliver and maintain TTM, and

20   the presence of appropriate systems of critical care are required to provide optimal post-ROSC

21   care. The task force noted that the application of TTM may require sedation, analgesia, and

22   neuromuscular blocking drugs that will modify neurologic 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 several knowledge gaps requiring further investigation, including

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

Neonatal Life Support 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 newly born lungs, eyes, brains, and other organs.[145,146] 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.[147] The evidence review for this question did not use GRADE methodology[148] to analyze the published studies. This topic was not addressed for term infants in the 2015 CoSTR update.[149] 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[148] on the topic of lower oxygen versus higher concentrations of oxygen for initiation of resuscitation of newborn infants at 35 weeks' gestation or greater.[8]

Population, Intervention, Comparator, Outcome, Study Design, and Time Frame

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

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

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

4   Outcomes:

5   • Primary: All-cause short-term mortality (in-hospital or 30 days)

6   • Secondary: All-cause long-term mortality (13 years); long-term neurodevelopmental

7   impairment (NDI) (13 years); hypoxic-ischemic encephalopathy (Sarnat Stage 2–3)[150]

8   Study Designs: RCTs, qRCTs, and nonrandomized cohort studies included; animal studies,

9   unpublished studies and published abstracts (eg, conference abstracts) excluded

10   Time Frame: 1980 to August 10, 2018

11   A priori Subgroups to Be Examined: Gestational age (≥35 weeks, ≥37 weeks); grouped lower

12   and higher oxygen concentrations; explicit oxygen saturation targeting versus no oxygen

13   saturation targeting

14   PROSPERO registration: CRD42018084902

15   **[h3]Consensus on Science**

16   The SR identified 10 trials and 2 follow-up studies involving 2164 newborns, but 3 of the trials

17   had critical risk of bias and were included in only the sensitivity analyses.[8] Data from 1469 term

18   and late preterm infants (≥35 weeks) in 7 randomized and qRCTs were included. All identified

19   studies compared 21% (or air) with 100% oxygen concentration; no other initial oxygen

20   concentrations were reported. No data specific to 37 weeks' gestation or greater was found, and

21   none of the studies used targeted oxygen saturation (SpO_2) monitoring.

1   A draft CoSTR document based on the SR was posted for a 2-week public commenting period

2   on January 15, 2019.[151] During the comment period, the draft CoSTR was viewed 3564 times.

3   The NLS Task Force received 47 comments that were subsequently sorted into 4 main

4   categories: 1) agreement with the CoSTR as written; 2) responses that demonstrated a need for

5   more explicit emphasis that the intent of the PICOST was to address initial oxygen concentration

6   (not a static delivery concentration); 3) questions about special situations, such as oxygen use

7   during cardiac compressions or in the unique circumstance of newborns with anomalies such as

8   pulmonary hypoplasia or congenital diaphragmatic hernia; and 4) desire for stronger emphasis

9   about the need for more evidence using current methods of oxygen monitoring and titration, and

10   additional interval oxygen concentrations for infants at 35 weeks' gestation or greater. In

11   response to the public comments, the NLS Task Force included additional information to address

12   questions and comments about the 3 main categories of concerns.

13   **[h4]Short-Term Mortality (In-Hospital or 30 Days)**

14   For this critical outcome, evidence of low certainty (downgraded for risk of bias and

15   imprecision) from 7 RCTs (and qRCTs) involving 1469 newborn infants at 35 weeks' gestation

16   or greater receiving respiratory support at birth showed benefit of starting with 21% oxygen

17   compared with 100% oxygen (RR, 0.73; 95% CI, 0.57–0.94; I^2=0%); 46/1000 fewer babies died

18   when respiratory support at birth was started with 21% compared with 100% oxygen (95% CI,

19   73/1000 fewer to 10/1000 fewer).[152-158]

20   **[h4]Long-Term Mortality (1–3 Years)**

21   For this critical outcome, no evidence was identified.

22   **[h4]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 ($\geq$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%); 36/1000 more babies with NDI when respiratory support at birth was started with 21% compared with100% oxygen (95% CI, 20/1000 fewer to 142/1000 more).[156,159]

Hypoxic-Ischemic Encephalopathy (Sarnat Stage 2–3)[150]

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 ($\geq$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%); 20/1000 fewer babies with hypoxic-ischemic encephalopathy when respiratory support at birth was started with 21% compared with 100% oxygen (95% CI, 57/1000 fewer to 27/1000 more).[152,153,155,156,158]

Subgroup Infants 37 Weeks' Gestation or Greater

No data for the planned subgroup analysis for infants 37 weeks' gestation or greater was 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

1   For newborn infants at 35 weeks' gestation or greater receiving respiratory support at birth, we

2   suggest starting with 21% oxygen (air) (weak recommendation, low-certainty evidence).

3   We recommend against starting with 100% oxygen (strong recommendation, low-certainty

4   evidence).

5   **[h3]Justification and Evidence to Decision Framework Highlights**

6   Parents and clinicians rate mortality as a critical outcome. Despite the low certainty of the

7   evidence, the large reduction in the primary outcome of short-term mortality (number needed to

8   treat=22) with no demonstrated adverse effects favors use of 21% oxygen as the initial gas for

9   resuscitation for newborns at 35 weeks' gestation or greater. Although there are no published

10   cost data, it is likely that initiating resuscitation with 21% oxygen does not add cost and might

11   result in cost savings compared with use of initial 100% oxygen in some settings. Babies born in

12   low-resource settings demonstrate increased mortality and morbidity. Therefore, it is plausible

13   that using 21% oxygen compared with 100% oxygen has greater impact in low-resource settings.

14   Use of 21% oxygen for initial resuscitation is universally feasible.

15   To be clear, we emphasize that the recommendation for 21% oxygen refers to the *initial*

16   concentration of oxygen at the initiation of respiratory support. It does not address the question

17   of how to titrate the oxygen concentration as resuscitation progresses; no evidence was found to

18   guide this aspect of oxygen delivery. Once such evidence is published, the Neonatal Task Force

19   will initiate a systematic review to assess the effect and optimal methods of titration of oxygen

20   concentrations during resuscitation. We found no studies that evaluated the initial oxygen

21   concentration for specific special circumstances such as congenital diaphragmatic hernia or

22   pulmonary hypoplasia.

23   **[h3]Knowledge Gaps**

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

2   including

3   • Studies in late preterm (35–36 weeks' gestation) infants: few of these infants were

4   included in the published studies, leading to lower certainty in the evidence for this

5   gestational age group

6   • Research to assess the impact of titration of oxygen to oxyhemoglobin saturation (SpO_2)

7   targets as the resuscitation progresses: monitoring SpO_2 and titration of oxygen

8   concentration was not routinely used in the studies included in the SR for this CoSTR

9   • Comparison of initial oxygen concentrations intermediate between 21% and 100%: in the

10   SR for this CoSTR, no studies were found that compared any oxygen concentrations

11   other than 21% versus 100%

12   • Determining if delayed cord clamping affects the impact of initial inspired oxygen

13   concentration

14   • The effect of initial oxygen concentrations on long-term NDI; studies published to this

15   date have been of very-low certainty of evidence

16   • The optimal initial oxygen concentrations needed in special circumstances such as

17   newborns with pulmonary hypoplasia, congenital diaphragmatic hernia, and other

18   anomalies

19   **[h2]Initial Oxygen Concentration for Preterm Infants at Birth**

20   Preterm newborn infants are particularly vulnerable to oxidative stress resulting from reduced

21   antioxidant defenses and frequent exposure to oxygen during stabilization in the delivery

22   room.[160] Many common complications of prematurity are associated with oxygen toxicity,

23   including bronchopulmonary dysplasia, retinopathy of prematurity, and intraventricular

1 hemorrhage. Medical practitioners who stabilize preterm infants at birth must try to prevent

2 hypoxia while limiting excess oxygen to prevent toxic effects. In 2015, the ILCOR NLS Task

3 Force CoSTR Update recommended starting with 21% to 30% oxygen for preterm newborns

4 needing respiratory support in the delivery room.[149] This was based on meta-analysis findings of

5 no benefit for any important or critical outcomes when high oxygen concentrations were used.

6 Additional studies are now available, so the ILCOR NLS Task Force undertook an SR with

7 meta-analysis using GRADE methodology[148] of the relevant available evidence about the effects

8 of lower versus higher oxygen concentrations for initiation of resuscitation of preterm newborn

9 infants.[9]

10 **[h3]Population, Intervention, Comparator, Outcome, Study Design, and Time Frame**

11 Population: Preterm newborn infants (<35 weeks' estimated gestational age) who receive

12 respiratory support at birth

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

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

15 Outcomes:

16 • Primary: All-cause short-term mortality (in-hospital or 30 days)

17 • Secondary: All-cause long-term mortality (1–3 years); long-term NDI (1–3 years);

18   retinopathy of prematurity (stages III–V);[161] necrotizing enterocolitis stage II

19   (pneumotosis) or III (surgical)[162]; bronchopulmonary dysplasia (moderate to severe)[163];

20   major intraventricular hemorrhage (grade III/IV)[164]; time to heart rate greater than

21   100/min

1   Study Designs: RCTs, qRCTs, and nonrandomized cohort studies included; animal studies, case

2   series, and unpublished studies and published abstracts (eg, conference abstracts) excluded

3   Time Frame: 1980 to August 10, 2018

4   A priori Subgroups to Be Examined: Gestational age (≤32 weeks, ≤28 weeks); grouped lower

5   and higher initial oxygen concentrations (21% O_2 compared with 100% O_2, 21%–30% compared

6   with 80%–100% only, 30% compared with 90%–100%, 50% compared with 100%, 30%

7   compared with 60%–65%); explicit SpO_2 targeting versus no SpO_2 targeting

8   PROSPERO registration: CRD42018084902

9   **[h3]Consensus on Science**

10   The SR found 16 eligible studies that included 5697 preterm newborns.[9] This constituted 10

11   RCTs, 2 follow-up studies, and 4 observational cohort studies. The majority (9/10) of the RCTs

12   used 21% to 30% as the initial low oxygen concentration[165-173] with only 1 small RCT

13   employing 50% for the initial low oxygen group.[174] All observational studies used 21% oxygen

14   as the initial low oxygen concentration.[175-178] Six of 10 RCTs used 100% oxygen,[166,168-170,173,174]

15   1 RCT used 90%,[167] 1 RCT used 80%,[165] and 2 RCTs used greater than 60%[171,172] as the high

16   initial oxygen concentration. All observational studies used 100% as the high initial oxygen

17   concentration. A majority of RCTs (8/10),[166-173] as well as all of the observational cohort

18   studies[175-178] used SpO_2 targeting as a co-intervention. All results are presented as RR with 95%

19   CI and absolute difference with 95% CI.

20   A draft CoSTR document based on the SR was posted for a 2-week public commenting period

21   on January 15, 2019.[179] During the comment period, the draft CoSTR was viewed 7387 times,

22   suggesting intense interest within the global neonatal community. The NLS Task Force received

1   52 comments that were subsequently grouped into 3 categories: 1) those that agreed with the

2   draft CoSTR as written; 2) those that wanted clarification on what the phrase "no benefit or

3   harm" truly meant; and 3) those that expressed disappointment that the science does not yet

4   provide a clearer answer. As a result of the public comments, the NLS Task Force included

5   additional information to address these concerns.

6   **[h4]All Preterm Gestational Ages Combined (<35 Weeks' Gestation)**

7   Overall, evidence of very-low certainty (downgraded for risk of bias and imprecision) for

8   newborn infants at less than 35 weeks' gestation receiving respiratory support at birth showed no

9   statistically significant benefit or harm of lower initial oxygen concentration (≤50%) compared

10 with higher initial oxygen concentration (>50%) about the following critical outcomes (see Table

11 14 for data): all-cause short-term mortality (in-hospital or 30 days), all-cause long-term

12 mortality (1–3 years), long-term NDI (moderate-severe, 1–3 years), retinopathy of

13 prematurity (Grade III–V),[161] necrotizing enterocolitis (Bell's Grade II–III),[162]

14 bronchopulmonary dysplasia (moderate to severe),[163] or major intraventricular

15 hemorrhage (Grade III–IV).[164] For the important outcome of time to heart rate greater than

16 100/min after delivery, the limitation of the direct evidence for newborn infants at less than 35

17 weeks' gestation precluded meta-analysis.

1 **Table 14. Meta-analysis of RCTs Comparing Initial Low and High Oxygen Concentration for All Preterm Gestational Ages**

2 **Combined (<35 Weeks' Gestation)**

Outcome	Papers With Outcome of Interest	Total N	Certainty of Evidence	Relative Risk ([95% CI]; I^2)	Absolute Difference (95% CI)
Short-term mortality (in hospital or 30 days)	Lundstrom 1995[165][174] Wang 2009[166] Vento 2009[167]Rabi 2011[168] Armanian 2012[169] Kapadia 2013[170] Aguar 2013[171] Rook 2014[172] Oei 2017[173]	968	Very low	0.83 ([95% CI, 0.50–1.37]; I^2=18%)	15/1000 fewer deaths when lower compared with higher initial oxygen concentration was used (44/1000 fewer to 32/1000 more)
Long-term mortality (1–3 years)	Boronat 2016[180] Thamrin 2018[181]	491	Very low	1.05 ([95% CI, 0.32–3.39]; I^2=79%)	5/1000 more deaths when lower compared with higher initial oxygen concentration was used (71/1000 fewer to 248/1000 more)
NDI (moderate-severe at 1–3 years)	Boronat 2016[180] Thamrin 2018[181]	389	Very low	1.14 ([95% CI, 0.78–1.67]; I^2=0)	27/1000 more with NDI when lower compared with higher initial oxygen

					concentration was used (42/1000 fewer to 129/1000 more)
Retinopathy of prematurity (Grade III–V)	Lundrom 1995[165] Harling 2005[174] Vento 2009[167] Kapadia 2013[170] Aguar 2013[171] Rook 2014[172] Oei 2017[173]	806	Very low	0.73 ([95% CI, 0.42–1.27]; I^2=0%)	19/1000 fewer with retinopathy of prematurity (Grade III–V) when lower compared with higher initial oxygen concentration was used (42/1000 fewer to 19/1000 more)
Necrotizing enterocolitis (Bells's Grade II–III)	Lundstrom 1995[165] Harling 2005[174] Wang 2008[166] Vento 2009[167] Kapadia 2013[170] Aguar 2013[171] Rook 2014[172] Oei 2017[173]	847	Very low	1.34 ([95% CI, 0.63–2.84]; I^2=0%)	12/1000 more with necrotizing enterocolitis when lower initial compared with higher initial oxygen concentration was used (13/1000 fewer to 65/1000 more)
Bronchopulmonary dysplasia (moderate to severe)	Harling 2005[174] Wang 2008[166] Vento 2009[167] Rabi 2011[168] Kapadia 2013[170] Aguar 2013[171] Rook 2014[172] Oei 2017[173]	843	Very low	1.00 ([95% CI, 0.71–1.40]; I^2=47%)	0/1000 fewer with bronchopulmonary dysplasia when lower compared with higher initial oxygen concentration was used (77/1000 fewer to 107/1000 more)

| Major intraventricular hemorrhage (Grade III–IV) | Lundstrom 1995[165] Wang 2009[166] Vento 2009[167] Kapadia 2013[170] Aguar 2013[171] Rook 2014[172] Oei 2017[173] | 795 | Very low | 0.96 ([95% CI, 0.61–1.51]; I^2=0%) | 3/1000 fewer with major intraventricular hemorrhage (Grade III–IV) when lower compared with higher initial oxygen concentration was used (32/1000 fewer to 42/1000 more) |

1 CI indicates confidence interval; NDI, neurodevelopmental impairment; RCT, randomized controlled trial.

[h4]Subgroup Newborn Infants 32 Weeks' Gestation or Less

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 or less 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%); 6/1000 fewer with short-term mortality when lower compared with higher initial oxygen concentration was used (95% CI, 39/1000 fewer to 47/1000 more).[166-168,170-174]

[h4]Subgroup Newborn Infants 28 Weeks' Gestation or Less

For the subgroup analysis of newborn infants 28 weeks' gestation or less 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-severe, 1–3 years); retinopathy of prematurity (Grade III–V),[161] necrotizing enterocolitis (Bell's Grade II–III),[162] bronchopulmonary dysplasia (moderate to severe),[163] major intraventricular hemorrhage (Grade III–IV).[164]

1   **Table 15. Meta-analysis of RCTs Comparing Initial Low and High Oxygen Concentration for 28-Week or Less Gestational**

2   **Age Subgroup**

Outcome	Papers With Outcome of Interest	Total N	Certainty of Evidence	Relative Risk ([95% CI]; I^2)	Absolute Difference (95% CI)
Short-term mortality (in hospital or 30 days)	Wang 2009[166] Vento 2009[167] Rabi 2011[168] Kapadia 2013[170] Aguar 2013[171] Rook 2014[172] Oei 2017[173]	467	Very low	0.92 ([95% CI, 0.43–1.94]; I^2=45%)	10/1000 fewer with short-term mortality when lower compared with higher initial oxygen concentration was used (70/1000 fewer to 116/1000 more)
Long-term mortality (1–3 years)	Thamrin 2018[181]	86	Very low	2.11 ([95% CI, 0.86–5.19]; I^2=N/A)	145/1000 more with long-term mortality when lower compared with higher initial oxygen concentration was used (18/1000 fewer to 547/1000 more)
NDI (moderate-severe at 1–3 years)	Thamrin 2018[181]	69	Very low	1.08 ([95% CI, 0.58–2.03]; I^2=N/A)	28/1000 more with long-term NDI when lower compared with higher initial oxygen concentration was used (147/1000 fewer to 360/1000 more)

Retinopathy of prematurity (Grade III–V)	Wang 2008[166] Vento 2009[167] Kapadia 2013[170] Aguar 2013[171] Rook 2014[172] Oei 2017[173]	441	Very low	0.75 ([95% CI, 0.43–1.33]; I^2=0%)	30/1000 fewer with retinopathy of prematurity when lower compared with higher initial oxygen concentration was used (67/1000 fewer to 39/1000 more)
Necrotizing enterocolitis (Bells's Grade II–III)	Wang 2008[166] Vento 2009[167] Kapadia 2013[170] Aguar 2013[171] Rook 2014[172] Oei 2017[173]	441	Very low	1.62 ([95% CI, 0.66–3.99]; I^2=0%)	20/1000 more with necrotizing enterocolitis when lower compared with higher initial oxygen concentration was used (11/1000 fewer to 95/1000 more)
Bronchopulmonary dysplasia (moderate to severe)	Wang 2008[166] Vento 2009[167] Rabi 2011[168] Kapadia 2013[170] Aguar 2013[171] Rook 2014[172] Oei 2017[173]	467	Very low	0.90 ([95% CI, 0.64–1.28]; I^2=31%)	37/1000 fewer with bronchopulmonary dysplasia when lower compared with higher initial oxygen concentration was used (132/1000 fewer to 102/1000 more)
Major intraventricular hemorrhage (Grade III–IV)	Wang 2009[166] Vento 2009[167] Kapadia 2013[170] Aguar 2013[171] Rook 2014[172] Oei 2017[173]	441	Very low	0.84 ([95% CI, 0.50–1.40]; I^2=12%)	23/1000 fewer with major intraventricular hemorrhage (Grade III–IV) when lower compared with higher initial oxygen concentration was used (73/1000 fewer to 58/1000 more)

1   CI indicates confidence interval; NDI, neurodevelopmental impairment; RCT, randomized controlled trial.

[h4]Subgroup Oxygen Concentration 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 less than 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%); 26/1000 more with short-term mortality when lower initial oxygen concentration (21%) compared with higher initial oxygen concentration (100%) was used (95% CI, 14/1000 fewer to 115/1000 more).[166,168,170,173]

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

- For the critical outcome of long-term NDI (moderate-severe, 1–3 years) in preterm newborns (<35 weeks' gestation), the results are the same as for all groups at less than 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 or not SpO_2 targeting as a co-intervention had any impact, found no differences in primary and secondary outcomes.[9] When data from 2 observational cohort studies with 1225 newborns[177,178] 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 or less (RR, 0.77; 95% CI, 0.59–0.99; I^2=6%).[9]

1 ### [h3]Treatment Recommendations

2 For preterm newborn infants (<35 weeks' gestation) who receive respiratory support at birth, we

3 suggest starting with a lower oxygen concentration (21%–30%), rather than higher initial oxygen

4 concentration (60%–100%) (weak recommendation, very-low certainty of evidence). We suggest

5 the range of 21% to 30% oxygen because all trials but 1 used this for the low oxygen

6 concentration group. Subsequent titration of oxygen concentration using pulse oximetry is

7 advised (weak recommendation, very-low certainty of evidence).

8 Until further evidence is available, implementation of the suggested initial oxygen concentration

9 between 21% to 30% should be based on local practice considerations and should be reevaluated

10 with ongoing audit of care.

11 ### [h3]Justification and Evidence to Decision Framework Highlights

12 Balancing the benefits and serious potential harm of low versus high oxygen concentrations in

13 neonatal care is a continuing concern, particularly for preterm infants. Decades of research

14 clearly demonstrate that oxygen exposure is a determinant of critical neonatal outcomes in

15 preterm infants. Concern remains that if the preterm infant requires resuscitation immediately

16 after birth, the initial oxygen concentration to which the infant is exposed may be a critical

17 contributor to outcomes, regardless of subsequent oxygen exposure. Both parents and clinicians

18 rate the outcomes assessed in this SR as either critical or important. For all of the critical

19 outcomes assessed in the meta-analyses of RCTs, the 95% CIs of RRs were wide enough to

20 include both potential harm as well as potential benefit. Thus, it is unclear whether initial low or

21 high oxygen concentrations may have undesirable effects. In suggesting starting with low

22 oxygen concentrations (21%–30%), we place value on avoiding exposure of preterm babies to

23 additional oxygen without proven benefit for critical or important outcomes because we are

1   cognizant of harms in newborn animals and increased neonatal mortality in term infants exposed

2   to high initial oxygen concentration.[145,182] This review addressed only the initial concentration of

3   oxygen and therefore does not include any recommendation for subsequent administration or

4   titration of oxygen. Subsequent titration of supplementary oxygen should be based on published

5   SpO_2 target ranges.

6   The *a priori* comparisons evaluated only an initial oxygen concentration of 21% to 30% versus

7   80% to100%, which therefore influences the recommendation. We recognize that no studies have

8   compared the safety or efficacy of commencing resuscitation with 21% versus intermediate

9   concentrations such as 30% oxygen. We emphasize that the included studies measured only the

10   effect of varying initial inspired oxygen concentrations and were not designed to assess the

11   safety or efficacy of different SpO_2 targets. As outlined above, careful attention should be paid to

12   the initial as well as the cumulative oxygen load under the investigated regimes. Therefore,

13   starting at a lower oxygen concentration (21%–30%) with the option to titrate according to SpO_2

14   aiming for published SpO_2 target ranges provides an option of minimizing oxygen exposure at

15   birth.

16   **[h3]Knowledge Gaps**

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

18   including

19   •   High-quality studies with appropriate power to determine optimal initial oxygen, as the

20   95% CI for the primary outcome in most studies identified in this review includes both

21   harm and benefit

22   •   Further evidence from randomized studies about long-term NDI outcomes

23   •   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 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 infant

Education, Implementation and Teams (EIT) and Advanced Life Support (ALS) Task Forces

Cardiac Arrest Centers Versus Non-Cardiac Arrest Centers

Cardiac Arrest Centers (CACs) are hospitals providing evidence-based resuscitation treatments including emergency interventional cardiology, bundled critical care with TTM, and protocolized cardiorespiratory support and prognostication.[48,62]

This PICOST was prioritized for review by the EIT and ALS Task Forces based on the publication of several large registry studies[183,184] since the 2015 ILCOR CoSTR.[185,186] In the following sections, we present a summary of the evidence identified by the ILCOR SR[10] and the web-posted CoSTR about the effects of CACs.[187] There was one question posted during the comment period regarding the definition of CACs and we've provided that in our introduction, above.

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 (Cerebral Performance Category 1 or 2 or modified Rankin Scale 0–3)
- Secondary outcomes: ROSC after hospital admission for patients with ongoing CPR, survival at 30 days and/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

[H3]Consensus on Science

A total of 21 observational studies[183,184,188-206] and 1 pilot randomized trial[207] were included in the SR.[10] Of these, 17 observational studies were ultimately included in meta-analysis.[183,184,188-194,199-206] All studies were in OHCA cohorts; 1 study[195] 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 (ie, 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

1   potential for referral bias and other confounding variables, only data from studies reporting

2   adjusted measures of association were pooled in the meta-analysis.

3   CACs were associated with favorable neurological outcome and survival when examined at

4   hospital discharge, but this was nonsignificant when examined at 30 days (Table 16).

5   In addition to the pooled data, 3 observational studies looking exclusively at long-term outcomes

6   of patients discharged alive from hospitals reported that care at a CAC was associated with better

7   patient survival.[194,195,197]

1   **Table 16. Summary of Evidence Regarding Outcomes Associated With Care in Cardiac Arrest Centers**

Outcomes (Importance)	Studies, n=number of participants	Certainty of the Evidence (GRADE)	Odds Ratio (95% CI)	Anticipated Absolute Effects, n	
				Care at Other Hospital	Risk Difference for Care at Cardiac Arrest Center
Survival to 30 days with favorable neurological outcome (critical)	2 studies[183,184] n=45,956	Very low	2.92 (95% CI, 0.6812.48)	359/25,617 (1.4%)	26 more per 1000 (from 4 fewer to 137 more)
Survival to hospital discharge with favorable neurologic outcome (critical)	2 studies[189,190] n=3673	Very low	2.22 (95% CI, 1.74–2.84)	47/584 (8.0%)	82 more per 1000 (from 52 more to 119 more)
Survival to 30 days (critical)	2 studies[193,205] n=2693	Very low	2.14 (95% CI, 0.73–6.29)	123/1695 (7.3%)	71 more per 1000 (from 19 fewer to 257 more)
Survival to hospital discharge (critical)	5 studies[189,190,200-202] n=11662	Very low	1.85 (95% CI, 1.46–2.34)	587/4117 (14.3%)	93 more per 1000 (from 53 more to 138 more)

2   CI indicates confidence interval; GRADE, Grading of Recommendations, Assessment, Development, and Evaluation.

1   Preplanned subgroup analyses identified additional information about the effects of primary

2   transport versus secondary transfer of patients to CACs and about outcomes of patients with

3   shockable versus nonshockable rhythms. Four observational studies examined the potential

4   impact of transfer on patient outcomes from OHCA.[184,194,204,206] One study[206] reported higher

5   adjusted patient survival associated with direct transfer to a CAC compared with patient survival

6   among those who underwent secondary interfacility transfer (odds ratio [OR] 1.97; 95% CI,

7   1.13–3.43). Two other studies[184,194] reported no difference in survival between direct transport

8   versus secondary transfer of patients to a CAC. One study[204] reported higher adjusted survival in

9   patients who underwent a secondary transfer to a CAC compared with survival among those who

10 remained at the initial treating non-CACs (OR, 1.59; 95% CI, 1.30–1.93). One additional

11 observational study[189] reported higher adjusted patient survival to hospital discharge associated

12 with bypassing the nearest non-CAC and transporting patients directly to a CAC, compared with

13 transporting patients to non-CACs (OR, 3.02; 95% CI, 2.01–4.53).

14 Eight observational studies reported outcomes stratified by arresting rhythm into shockable or

15 nonshockable cohorts, but the findings were inconsistent, most reported unadjusted data, and the

16 studies were too heterogenous to pool.[184,188,190,194,198,200,201,203]

17 **[h3]Treatment Recommendations From the EIT and ALS Task Forces**

18 We suggest that adult patients with nontraumatic OHCA be cared for in CACs rather than in

19 non-CACs (weak recommendation, very low certainty of evidence).

20 We cannot make a recommendation for or against regional triage by primary EMS transport of

21 patients with OHCA to a CAC (bypass protocols) or secondary interfacility transfer to a CAC.

22 The current evidence is inconclusive, and confidence in the effect estimates is currently too low

23 to support an EIT and ALS Task Force recommendation.

1 For patients with IHCA, we found no evidence to support an EIT and ALS Task Force

2 recommendation.

3 For the subgroup of patients with shockable or nonshockable initial cardiac rhythm, the current

4 evidence is inconclusive, and the confidence in the effect estimates is currently too low to

5 support an EIT and ALS Task Force recommendation.

6 **[h3]Justification and Evidence to Decision Framework Highlights**

7 In making this recommendation, the EIT and ALS Task Forces concluded that the potential

8 benefits in clinical outcomes outweighed the potential risks and logistical issues with

9 implementation.

10 We specifically considered the consistency of improved outcomes in patients treated at CACs

11 across most studies, the desirability of patients receiving evidence-based postresuscitation care,

12 the evidence supporting specialized acute care for other emergency conditions (eg, trauma,

13 stroke, and ST-segment elevation myocardial infarction), the lack of evidence suggesting clinical

14 harm associated with longer transport times,[208] the potential for referral bias (ie, transporting

15 patients most likely to survive), and the implementation challenges of this recommendation.

16 Regionalized systems of care for cardiac arrest may not be feasible in all areas, as the result of

17 resource constraints, cost, and inherent regional differences in healthcare delivery. In making a

18 weak recommendation in support of CACs, the task forces acknowledge the lack of high-level

19 evidence.

20 **[h3]EIT and ALS Task Force Knowledge Gaps**

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

22 • There is no universal definition of a CAC.

- The precise aspects of CACs that improve outcomes have not been identified (eg, are there 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 (eg, cardiac etiology, 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.[209] This review evaluated nonpharmacologic first aid interventions that can be applied at the onset or immediately after onset of presyncope symptoms. ILCOR commissioned an SR,[11] 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.[210] 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 counter-pressure 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 (eg, conference abstracts) and trial protocols excluded

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

PROSPERO registration: CRD42018107726

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 use of PCM compared with no use of PCM. Physical counterpressure maneuvers involved the contraction of the large muscles of the legs, arms or abdomen, and included leg or arm tensing, crossing or squeezing, squatting, hand-grip, and abdominal compression. Studies included 2 RCTs [211,212] and 6 observational studies,[211,213-217] enrolling a total of 246 participants between 15 and 75 years of age with a history of vasovagal or orthostatic-related syncope. Forms of PCM evaluated included handgrip, squatting, leg crossing with tensing, and abdominal/core muscle tensing. Evidence from the Brignole RCT[211] was downgraded to very-low certainty as the result of risk of bias, inconsistency, indirectness,

1 and imprecision, whereas evidence from the Alizadeh RCT[212] was downgraded to low certainty

2 as the result of risk of bias, inconsistency, and indirectness. The observational studies all provide

3 very-low-certainty evidence.[211,213-217] See Table 17 for Summary of Studies.

Table 17. Summary Data From Presyncope StudiesOutcomes	Intervention: Comparison	Participants (Number of Studies)	Relative Risk (95% CI)	Certainty of Evidence (GRADE)	Risk With Control/ no PCM	Risk With Intervention (RD)
Prevention of syncope	Any PCM versus control (no use of PCM or standing only)	92 OH and VVS etiology (4 observational)[213-216]	1.31 (0.98–1.75)	Very low	594 per 1000	184 more per 1000 (from 12 fewer to 445 more) RD=0.19 (0.01–0.37)
		64 VVS etiology (3 observational)[213-215]	2.20 (0.96–5.05)	Very low	277 per 1000	222 more per 1000 (from 11 fewer to 1000 more)
	Lower-body PCM versus control (no use of PCM or standing only)	36 VVS etiology (1 observational)[215]	2.20 (0.96–5.05)	Very low		333 more per 1000 (from 3 more to 586 more)

Table 17. Summary Data From Presyncope StudiesOutcomes	Intervention: Comparison	Participants (Number of Studies)	Relative Risk (95% CI)	Certainty of Evidence (GRADE)	Risk With Control/ no PCM	Risk With Intervention (RD)
	Upper-body PCM versus control (no use of PCM or standing only)	19 VVS etiology (1 RCT)[211]	1.80 (1.16–2.79)	Very low	526 per 1000	421 more per 1000 (from 84 more to 942 more)
		14 VVS etiology (1 observational)[213]	29.00 (1.90–443.25)	Very low		
		37 VVS etiology 2 observational)[211,217]	99.4% of episodes (349/351) (RR not estimable, no comparisons)	Very low		

Table 17. Summary Data From Presyncope StudiesOutcomes	Intervention: Comparison	Participants (Number of Studies)	Relative Risk (95% CI)	Certainty of Evidence (GRADE)	Risk With Control/ no PCM	Risk With Intervention (RD)
	Lower-body PCM versus upper-body PCM	27 VVS etiology (1 observational)[216]	7.00 (1.10–44.61)	Very low		1000 more per 1000 (from 88 more to 1000 more)
Injuries or adverse events	Upper-body PCM versus control (no use of PCM or standing only)	37 VVS etiology (2 observational)[211,217]	0/37 (0%) (RR not estimable, no comparisons)	Very low		0 fewer per 1000 (0 fewer to 0 fewer)
Symptom improvement	Any PCM versus control (no use of PCM or standing only)	21 VVS etiology (1 observational)[214]	20/20 (RR not estimable)	Very low		

Table 17. Summary Data From Presyncope StudiesOutcomes	Intervention: Comparison	Participants (Number of Studies)	Relative Risk (95% CI)	Certainty of Evidence (GRADE)	Risk With Control/ no PCM	Risk With Intervention (RD)
			(one patient lost to follow-up)			
		96 VVS etiology (1 RCT)[212]	1.57 (0.98–2.51)	Very low	440 per 1000	251 more per 1000 (from 26 more to 409 more)
	Lower-body PCM versus control (no use of PCM or standing only)	96 VVS etiology (1 RCT)[212]	1.66 (1.02–2.69)	Very low		290 more per 1000 (from 9 more to 744 more)

Table 17. Summary Data From Presyncope StudiesOutcomes	Intervention: Comparison	Participants (Number of Studies)	Relative Risk (95% CI)	Certainty of Evidence (GRADE)	Risk With Control/ no PCM	Risk With Intervention (RD)
	Upper-body PCM versus control (no use of PCM or standing only)	19 VVS etiology (1 RCT)[211]	6.00 (1.55–23.26)	Low		526 more per 1000 (from 58 more to 1000 more)
		96 VVS etiology, follow-up phase (1 RCT)[212]	1.47 (0.89–2.44)	Very low		207 more per 1000 (from 48 fewer to 634 more
	Lower-body PCM versus upper-body PCM	96 VVS etiology (1 RCT)[212]	0.89 (0.65–1.22)	Very low		80 fewer per 1000 (from 30 fewer to 130 more)
Heart rate	Upper-body versus control (no use of PCM or standing only)	19 VVS etiology (1 RCT)[211]		Very low		MD: 8 per min higher (6.4 to 22.4 higher)

Table 17. Summary Data From Presyncope StudiesOutcomes	Intervention: Comparison	Participants (Number of Studies)	Relative Risk (95% CI)	Certainty of Evidence (GRADE)	Risk With Control/ no PCM	Risk With Intervention (RD)
	Lower-body PCM versus upper-body PCM	27 VVS etiology, handgrip versus squatting (1 observational)[216]		Very low		MD: 0.8 per min lower (5.5 lower to 3.9 higher)
		27 VVS etiology, leg-crossing versus handgrip (1 observational) [216]		Very low		MD 6.3 beats per minute higher (3.0–9.5 beats per minute higher)
Systolic blood pressure	Any PCM versus control (no use of PCM or standing only)	39 VVS etiology (2 observational)[214,215]		Very low		MD 21 mm Hg higher (18.25–23.41)
	Lower-body PCM versus	18 VVS etiology		Very low		MD 19 mm Hg

Table 17. Summary Data From Presyncope StudiesOutcomes	Intervention: Comparison	Participants (Number of Studies)	Relative Risk (95% CI)	Certainty of Evidence (GRADE)	Risk With Control/ no PCM	Risk With Intervention (RD)
	control (no use of PCM or standing only)	(1 observational)[215]				higher (16.31–21.69)
	Upper-body PCM versus control (no use of PCM or standing only)	19 VVS etiology (1 RCT)[211]		Low		MD 32 mm Hg higher (12.48–51.52)
	Lower-body PCM versus upper-body PCM	27 VVS etiology, squatting versus handgrip (1 observational)[216]		Very low		MD 12.5 mm Hg higher (5.69–19.31)

Table 17. Summary Data From Presyncope StudiesOutcomes	Intervention: Comparison	Participants (Number of Studies)	Relative Risk (95% CI)	Certainty of Evidence (GRADE)	Risk With Control/ no PCM	Risk With Intervention (RD)
		27 VVS etiology, leg crossing versus handgrip (1 observational)[216]		Very low		MD 11.6 mm Hg higher (4.3–18.8)
	Lower-body PCM versus abdominal PCM	9 neurogenic OH etiology (1 observational)[218]		Very low		MD 36.5 higher (15.00–57.99)
	Lower-body PCM versus neck PCM	9 neurogenic OH etiology (1 observational)[218]		Very low		MD 28.2 higher (10.79–45.61)
Diastolic blood	Any PCM versus control	39 VVS etiology (2 observational)[214,215]		Very low		MD 11 mm Hg higher (9.39–13.10)

Table 17. Summary Data From Presyncope StudiesOutcomes	Intervention: Comparison	Participants (Number of Studies)	Relative Risk (95% CI)	Certainty of Evidence (GRADE)	Risk With Control/ no PCM	Risk With Intervention (RD)
pressure	(co use of PCM or standing only)					
	Lower-body PCM versus control (no use of PCM or standing only)	18 VVS etiology (1 observational)[215]		Very low		MD 10 mm Hg higher (8.04–11.96)
	Upper-body PCM versus control (no use of PCM or standing only)	19 VVS etiology (1 RCT)[211]		Very low		MD 20 mm Hg higher (5.95–34.05)
	Lower-body PCM versus upper-body PCM	27 VVS etiology (1 observational) [216]		Very low		MD 3.3 mm Hg higher

Table 17. Summary Data From Presyncope StudiesOutcomes	Intervention: Comparison	Participants (Number of Studies)	Relative Risk (95% CI)	Certainty of Evidence (GRADE)	Risk With Control/ no PCM	Risk With Intervention (RD)
						(2.28 mm Hg lower to 8.88)
		27 VVS etiology (1 observational) [216]		Very low		MD 1.3 mm Hg higher (6.88 mm Hg lower to 4.28 mm Hg higher)

1 CI indicates confidence interval; GRADE, Grading of Recommendations, Assessment, Development, and Evaluation; MD, mean

2 difference; mm Hg, millimeters of mercury; OH, orthostatic hypotension; PCM, physical counterpressure maneuvers; RCT,

3 randomized controlled trial; RD, risk difference; RR, relative risk; VVS, vasovagal syncope.

1   **[h5]Termination of Syncope.**

2   Use of handgrip PCM in 19 participants with vasovagal syncope and a positive tilt-table test

3   increased likelihood of terminating syncope in 1 RCT.[211] However, no association was found

4   between the termination of syncope and any form of PCM in 4 observational studies in

5   laboratory settings with tilt-table testing.[213-216] In 2 observational follow-up studies of 37

6   participants in settings of daily life,[211,217] use of handgrip and arm tensing PCM was associated

7   with termination of syncope in 99% of episodes involving subjects with known vasovagal origin

8   presyncope. No adverse events or complications related to the use of handgrip PCM were

9   reported in any of these studies.

10 **[h5]Alleviation of Symptoms of Presyncope.**

11 One RCT with 96 participants evaluated in daily life settings reported that the use of lower-body

12 PCM (squatting) or upper-body PCM (handgrip) resulted in more alleviation of symptoms of

13 presyncope than no PCM.[212] A second smaller RCT[211] in a tilt-table test setting found more

14 symptom improvement with the use of handgrip PCM compared with no PCM. One

15 observational follow-up study[214] found symptom improvement in all 21 participants with

16 vasovagal origin syncope in association with the use of lower-body PCM (squatting and

17 abdominal tension).

18 **[h5]Increase in Heart Rate and Blood Pressure.**

19 An increase in heart rate after the use of handgrip PCM was reported in a single RCT,[211]although

20 4 observational studies[213-216] did not report consistent changes in heart rate. The same single

21 RCT[211] found improved systolic blood pressure with the use of handgrip PCM, and 2 pooled

1 observational studies[214,215] reported increased systolic and diastolic blood pressure associated

2 with the use of lower-body PCM.

3 **[h5]Subgroup Analysis.**

4 A subgroup weighted meta-analysis of 64 adults with vasovagal presyncope only, from 3

5 observational studies, [214-216] failed to find an association between the use of PCM and reduced

6 likelihood of progression from presyncope to syncope but did show an association with greater

7 likelihood of symptom improvement and an increase in heart rate and blood pressure.

8 **[h5]Upper-Body Compared With Lower-Body PCM.**

9 The use of upper-body PCM compared with lower-body PCM was evaluated by 1 observational

10 study[216] which reported a greater likelihood for termination of syncope and increase in heart rate

11 and blood pressure associated with the use of lower-body PCM. Results from 1 RCT[212] did not

12 find greater improvement in symptoms of presyncope with the use of lower-body PCM

13 compared with upper-body PCM.

14 **[H5]Additional Interventions for Presyncope.**

15 No studies were identified evaluating the use of other interventions such as hydration or change

16 of position applied at the onset of symptoms of presyncope.

17 **[h3]Treatment Recommendations**

18 We recommend the use of any type of PCM by individuals with acute symptoms of presyncope

19 from vasovagal or orthostatic causes in the first aid setting (strong recommendation, low- and

20 very-low-certainty evidence).

21 We suggest that lower-body PCMs, such as leg crossing and tensing or squatting, are preferable

22 to upper-body and abdominal PCMs (weak recommendation, very-low-certainty evidence).

[h3]Justification and Evidence to Decision Framework Highlights

Despite the mixed results and low- or very-low-certainty evidence identified in this review, with use of the *Evidence to Decision Framework*[210] and discussion of all evidence, the First Aid Task Force concluded that the use of PCM for acute symptoms of presyncope warranted a strong recommendation because, together, the included studies suggest that the use of PCM results in better outcomes with no reported adverse events. In addition, PCM interventions are simple and inexpensive, and they may prevent progression from presyncope to syncope and risks of subsequent injury. Successful treatment of presyncope may improve the quality of life for those with recurrent vasovagal or orthostatic syncope, and it may ultimately decrease associated healthcare costs. Included studies demonstrated that training of participants in use of PCM 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 PCM, observational studies suggested that the use of lower-body PCM may have an advantage over upper-body PCM for the outcome of terminating presyncope. Despite this, the task force recognizes the practicality in the use of a variety of PCM techniques for first aid, particularly when PCM interventions may be limited by patient location and position.

[h3]Knowledge Gaps

The task force identified several knowledge gaps requiring further investigation, including

- Validity of conventional first aid recommendation to place a person with symptoms of presyncope into a sitting or supine position with or without combination of PCM
- Effectiveness of additional interventions such as hydration

- Clinical outcomes related to the use of PCM and possible variation based on age, gender, and etiology of presyncope

- Ability of first aid providers to recognize vasovagal and orthostatic presyncope and to assess clinical outcomes after instruction in and use of PCM

[H1]Acknowledgments

[h1]Disclosures

[h2]Writing Group Disclosures

[h2]Reviewer Disclosures

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