

Manuscript version: Author's Accepted Manuscript

The version presented in WRAP is the author's accepted manuscript and may differ from the published version or Version of Record.

Persistent WRAP URL:

<http://wrap.warwick.ac.uk/130626>

How to cite:

Please refer to published version for the most recent bibliographic citation information. If a published version is known of, the repository item page linked to above, will contain details on accessing it.

Copyright and reuse:

The Warwick Research Archive Portal (WRAP) makes this work by researchers of the University of Warwick available open access under the following conditions.

Copyright © and all moral rights to the version of the paper presented here belong to the individual author(s) and/or other copyright owners. To the extent reasonable and practicable the material made available in WRAP has been checked for eligibility before being made available.

Copies of full items can be used for personal research or study, educational, or not-for-profit purposes without prior permission or charge. Provided that the authors, title and full bibliographic details are credited, a hyperlink and/or URL is given for the original metadata page and the content is not changed in any way.

Publisher's statement:

Please refer to the repository item page, publisher's statement section, for further information.

For more information, please contact the WRAP Team at: wrap@warwick.ac.uk.

1 **CoSTR Summary**

2
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

7
8 Jasmeet Soar, MA, MB, BChir, FRCA, FFICM, FRCP; Ian Maconochie, FRCPCH, FRCM,
9 FRCPI, PhD; Myra Wyckoff, MD; Theresa Olasveengen, MD, PhD; Eunice Singletary, MD;

10 Robert Greif, MD, MME;

11 Richard Aickin, BMedSc, MBChB; Farhan Bhanji, MD, MSc, FAHA; Michael Donnino, MD;
12 Mary Beth Mancini, RN, PhD, FAHA; Jonathan Wyllie, MBChB, BSC, FERC; David Zideman,

13 LVO, MBBS;

14 Lars Andersen, MD, MPH, PhD, DMSc; Dianne Atkins, MD, FAHA; Khalid Aziz, MA, MEd;
15 Jason Bendall, MBBS, MM, PhD; Kate Berg, MD; David Berry, PhD, MHA, AT, ATC; Blair
16 Bigham, MD, MSc; Robert Bingham, MD, BS, FRCA; Thomaz Bittencourt Couto, MD, PhD;
17 Bernd Böttiger, MD, ML, DEAA, FESC, FERC, FAHA; Vere Borra, PhD; Janet Bray, RN, PhD,

18 FAHA; Jan Breckwoltdt, MD, MME; Steven Brooks, MD, MHSc, FRCPC; Jason Buick, MSc,
19 ACPF; Clifton Callaway, MD, PhD, FAHA; Jestin Carlson, MD, MS; Pascal Cassan, MD;

20 Maaret Castrén, MD, PhD, FERC; Wei-Tien Chang, MD, PhD; Nathan Charlton, MD; Adam
21 Cheng, MD; Sung Phil Chung, MD, PhD; Julie Considine, RN, PhD; Keith Couper, RN, PhD;

22 Katie Dainty, PhD; Jennifer Anne Dawson, RN, PhD; Maria Fernanda de Almeida, MD; Allan

1 de Caen, MD; Charles Deakin, MD, FRCA, FERC; Ian R. Drennan, ACP, BScHK, PhD;
2 Jonathan Duff, MD, FRCPR, MEd; Jonathan Epstein, MEMS, NRP; Raffo Escalante, MD; Raul
3 Gazmuri, MD, PhD, FCCM; Elaine Gilfoyle, MD, MMed, FRCPC; Asger Granfeldt, MD, PhD,
4 DMSc; Anne-Marie Guerguerian, MD, PhD, FAHA, FRCP(C); Ruth Guinsburg; MD, PhD;
5 Tetsuo Hatanaka, MD, PhD; Mathias J. Holmberg, MD, MPH; Natalie Hood, MD, MBBS,
6 FACEM; Shigeharu Hosono, MD, PhD; Ming-Ju Hsieh, MD, MSc, PhD; Tetsuya Isayama, MD,
7 MSc, PhD; Taku Iwami, MD, PhD; Jan Jensen, ACP, MAHSR; Vishal Kapadia, MD, MSCS;
8 Han-Suk Kim, MD, PhD; Monica Kleinman, MD; Peter Kudenchuk, MD, FAHA; Eddy Lang,
9 MD; Eric Lavonas, MD, MS; Helen Liley, MBChB; Swee Han Lim, MBBS, FRCSEd, FRCPEd;
10 Andrew Lockey, MB, ChB, MMedED; Bo Lofgren, MD, PhD, FAHA; Matthew Ma, MD, PhD;
11 David Markenson, MD, MBA, FCCM, FAAP, FACEP, FACHE; Peter Meaney, MD, MPH;
12 Daniel Meyran, MD; Lindsay Mildenhall, MBChB; Koen Monsieurs, MD, PhD, FAHA; William
13 Montgomery, MD, FAHA; Peter Morley, MBBS, FAHA; Laurie Morrison, MD, MSC, FRCPC,
14 Vinay Nadkarni, MD, FAHA; Kevin Nation, NZRN; Robert Neumar, MD, PhD, FAHA; Kee-
15 Chong Ng; MD, MBBS, MMed, FRCPCH; Tonia Nicholson, MBBS, BScPsych, FRCP, FACE
16 M; Nikolaos Nikolaou, MD; Chika Nishiyama, RN, DrPH; Gabrielle Nuthall, MBChB, FRACP,
17 FCICM; Shinichiro Ohshimo, MD, PhD; Deems Okamoto, MD; Brian O'Neil, MD, FACEP,
18 FAHA; Yong-Kwang Gene Ong, MBBS, MRCPCH; Edison Paiva, MD, PhD; Michael Parr,
19 MB, BS, FRCP, FRCA, FANZCA, FDICM; Jeffrey Pellegrino, PhD, MPH; Gavin Perkins, MD,
20 FERC, FRCP, FFICM; Jeff Perlman, MB ChB; Jack Rabi, MD, FRCPC; Amelia Reis, MD,
21 PhD; Joshua Reynolds, MD, MS; Charles Roehr, MD, PhD; Tetsuya Sakamoto, MD, PhD;
22 Claudio Sandroni, MD; Steve Schexnayder, MD; Barney Scholefield, MBBS, MRCPCH, PhD;
23 Naoki Shimizu, MD, PhD; Markus Skrifvars, MD, PhD; Michael Smyth, MSc, PhD; David

1 Stanton, CCA; Janel Swain, BSc, BEd, ACP; Edgardo Szyld, MD, MSc; Janice Tijssen, MD,
2 MSC, FRCPC; Andrew Travers, MD, MSC, FRCPC; Daniele Trevisanuto, MD; Christian
3 Vaillancourt, MD, MSc; Patrick Van de Voorde, MD, PhD; Sithembiso Velaphi, MBChB, FC
4 Paed, PhD; Tzong-Luen Wang, MD, PhD, JM, FESC, FACC, FCAPSC; Gary Weiner, MD;
5 Michelle Welsford, MD; Jeff Woodin, NRP, FAHA; Myra Wyckoff, MD; Jonathan Wyllie,
6 MBChB, BSc, FERC; Joyce Yeung, MBChB, PhD; Jerry P. Nolan, FRCA, FRCP, FFICM,
7 FRCEM; Mary Fran Hazinski, RN, MSN, FAHA

8
9 **Key Words:** AHA Scientific Statements, cardiac arrest, cardiopulmonary resuscitation, cardiac
10 arrest centers, dispatcher-assisted CPR, extracorporeal CPR, epinephrine, vasopressors, airway
11 management, advanced airway management, newborn resuscitation

12
13 **Correspondence:**

14 Jasmeet Soar, MA, MB, Chir

15 Southmead Hospital

16 North Bristol NHS Trust

17 United Kingdom

18 Phone: 00441174145114

19 Email: Jasmeet.Soar@nbt.nhs.uk

1 [h1]Abstract

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

17

1 [h1]Introduction

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

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

18 The CoSTRs are based on task force analysis of the data, using the GRADE approach to answer
19 specific research questions. Each analysis has been detailed in a systematic review (SR),
20 published by a Knowledge Synthesis Unit (KSU) or systematic reviewer and the ILCOR topic
21 experts.²⁻¹¹ The GRADE approach rates the certainty evidence for an intervention and for each
22 outcome as high, moderate, low, or very low. Data from randomized controlled trials (RCTs) is
23 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 website¹² 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 Indirectness Imprecision Publication bias	Dose response All plausible confounding would reduce demonstrated effect or would suggest a spurious effect when results show no effect

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

	<p>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.</p>
--	--

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 website¹² 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 website¹⁵; 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](https://www.clinicaltrials.gov) online registry¹⁶

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 studies²²⁻³² 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**

Outcome	Unadjusted Analysis				Adjusted Analysis			
	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 **[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**

Outcome	DA-CPR Versus No CPR (Adjusted Analysis)			DA-CPR Versus Unassisted Bystander CPR (Adjusted Analysis)		
	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 month²⁶ 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 discharge³⁴ or at 1 month²⁷ 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 performed², 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 OHCA⁵⁰ 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)	<ul style="list-style-type: none"> • 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)	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • 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)	<ul style="list-style-type: none"> • 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)	<ul style="list-style-type: none"> • 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)	<ul style="list-style-type: none"> • 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
						<ul style="list-style-type: none"> • 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)	<ul style="list-style-type: none"> • 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 Jabre⁵² compared BMV with tracheal intubation in a physician-based system whereas Bengier
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 Bengier 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 Bengier⁵¹ and Wang⁵³ studies) and a setting with a high tracheal intubation success rate (similar
9 to the Jabre system⁵²).

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).

1 [h3]Justification and Evidence to Decision Framework Highlights

2 This topic was given high priority by the ILCOR ALS Task Force. This followed the publication
3 of 3 new RCTs⁵¹⁻⁵³ since the previous CoSTR in 2015.^{48,62}

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

8 There is currently no supporting evidence that an advanced airway (ie, supraglottic airway or
9 tracheal intubation) during CPR improves survival or survival with a favorable
10 neurologic/functional outcome after adult cardiac arrest in any setting when compared with
11 BMV.

12 This ILCOR 2019 CoSTR addresses airway management during CPR in adults; it does not
13 address airway management after ROSC. After ROSC, survivors requiring mechanical
14 ventilation and postresuscitation care will eventually require tracheal intubation.

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

21 We have not provided a precise value or range of values for low and high intubation success rate
22 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 RCT⁵² 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 RCT⁵¹ and the Laryngeal Tube [from VBM Medizintechnik GmbH, Sulz am Neckar,
14 Germany] in the Wang RCT⁵³). 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 **[h3]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 **[h3]Consensus on Science**

19 **[h4]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

- 1 • Use of epinephrine for IHCA
- 2 • The cost-effectiveness of epinephrine
- 3 • The effect of different routes of administration (intravenous versus intraosseous)
- 4 • The effect of increased ROSC on organ donation
- 5 • Effective therapies to prevent or mitigate against neurologic injury associated with
- 6 cardiac arrest

7 **[h2]ECPR for Cardiac Arrest: Adults**

8 ECPR is used to support circulation in patients with cardiac arrest refractory to conventional
9 CPR.⁷⁶ ECPR maintains vital organ perfusion while potential reversible causes of the cardiac
10 arrest can be identified and treated. ECPR can be considered in select patients, when rapid expert
11 deployment is possible; however, optimal patient selection and timing of the therapy are not well
12 defined. An SR was undertaken by ILCOR to assess the effectiveness of ECPR, compared with
13 manual or mechanical CPR, for OHCA and IHCA of all causes in adults and children.⁵ A draft
14 CoSTR posted for public comment was viewed 1169 times in the 2-week comment period. The
15 Task Force reviewed the 4 posted comments and considered the suggestions when finalizing the
16 “Justification and Evidence to Decision Highlights” section.

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

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

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

22 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 study⁸⁵ 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,<sup>79-
18 81,84,85,87,90,91</sup> 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		
							Proportions Number (%)		Adjusted Results (OR or RR [95% CI])
							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		
							Proportions Number (%)		Adjusted Results (OR or RR [95% CI])
							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		
							Proportions Number (%)		Adjusted Results (OR or RR [95% CI])
							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		
							Proportions Number (%)		Adjusted Results (OR or RR [95% CI])
							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		
							Proportions Number (%)		Adjusted Results (OR or RR [95% CI])
							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		
							Proportions Number (%)		Adjusted Results (OR or RR [95% CI])
							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		
							Proportions Number (%)		Adjusted Results (OR or RR [95% CI])
							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		
							Proportions Number (%)		Adjusted Results (OR or RR [95% CI])
							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		
							Proportions Number (%)		Adjusted Results (OR or RR [95% CI])
							Exposed	Unexposed	
				mechanical chest compression					
Yannopoulos, 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		
							Proportions Number (%)		Adjusted Results (OR or RR [95% CI])
							Exposed	Unexposed	
				transfer time from scene to catheterization laboratory <30 min					
Yannopoulos , 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		
							Proportions Number (%)		Adjusted Results (OR or RR [95% CI])
							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.

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

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

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

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

- 12 • The optimal post-cardiac arrest care strategy for patients resuscitated using ECPR
- 13 • The patient groups that are most likely to benefit from ECPR
- 14 • The optimal ECPR techniques
- 15 • The optimal timing to initiate ECPR during resuscitation (ie, early, late, when in the
16 sequence)
- 17 • The potential role of ECPR during the periarrest period
- 18 • The population-specific differences in indications for ECPR for IHCA and OHCA
- 19 • The differences in quality of life (QoL) between survivors of ECPR versus survivors of
20 conventional CPR
- 21 • The cost-effectiveness of ECPR

22 **[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 registry¹⁶

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 colleagues²⁶ and Chang and
2 colleagues³⁹ 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 Registry²⁶ 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), <i>P</i> =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), <i>P</i> =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), <i>P</i> <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); <i>P</i> <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 colleagues²⁶ and Chang and colleagues³⁹ 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); <i>P</i> =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); <i>P</i> =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]; <i>P</i> <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); <i>P</i> =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] <i>P</i> =0.01	

- 1 CPR indicates cardiopulmonary resuscitation; DA-CPR, dispatcher-assisted CPR; GRADE, Grading of Recommendations, Assessment, Development, and Evaluation.; EMS, emergency medical services; IQR, interquartile range; OR, odds ratio; RD, risk difference; RR, relative risk.
- 2
- 3
- 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 Bystander 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

1 [h3]Treatment Recommendations

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

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

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

9 [h3]Justification and Evidence to Decision Framework Highlights

10 This topic was prioritized by the Pediatric Life Support Task Force after publication of several
11 new studies since the previous pediatric SR was published in 2011. The 2011 review found
12 limited evidence to support DA-CPR.¹⁰⁰ In considering the importance of this topic, the Pediatric
13 Life Support Task Force noted that bystander CPR significantly improves the likelihood of
14 survival from OHCA, but bystander CPR rates remain very low.¹⁰¹

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

19 In making a strong recommendation for dispatch centers to offer DA-CPR despite very-low-
20 certainty evidence, the Pediatric Life Support Task Force considered the benefit for the critical
21 outcome of survival in the adjusted analyses as well as the large positive effect of increased
22 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 CoSTRs¹⁰³ 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)

- 1 • Inclusion of subsequent in-hospital (postarrest) factors
- 2 • Indication of specific dispatcher guidance provided (eg, to pace the compression rate)
- 3 when bystander CPR is already initiated
- 4 • EMS response times
- 5 • Analysis of cost-effectiveness of DA-CPR
- 6 • Content of CPR/DA-CPR instructions, specifically addressing the role of ventilation in
- 7 infant and child CPR
- 8 • Report of long-term outcomes, including QoL outcomes
- 9 • Adjusting for variables such as bystander CPR characteristics, patient, age, sex, and
- 10 previous bystander CPR training

11 [h2]Advanced Airway Interventions in Pediatric Cardiac Arrest

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

1 ILCOR commissioned an SR to identify and analyze all published evidence reporting outcomes
2 of advanced airway placement during CPR in infants and children during OHCA and IHCA.⁶
3 The Pediatric Task Force analyzed and discussed the SR as well as all of the studies identified by
4 the SR, developed a draft CoSTR, and posted it online for public comment.¹⁰⁴ The draft CoSTR
5 was viewed 341 times during the 2-week comment period. The 4 posted comments endorsed the
6 CoSTR, and all acknowledged the complexity of the issues surrounding use of an advanced
7 airway during pediatric resuscitation and the need for adequate training in all techniques.

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

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

11 Intervention: Placement of an advanced airway device

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

14 Outcomes: Any clinical outcome

15 Study Designs: RCTs and nonrandomized studies (non-RCTs, interrupted time series, controlled
16 before-and-after studies, cohort studies) of pediatric patients eligible for inclusion; if insufficient
17 studies available from which to draw a conclusion, case series of 4 or more may be included;
18 case reports, unpublished studies, and nonhuman studies excluded

19 Time Frame: All years and all languages included (as long as there is an English abstract);
20 unpublished studies (eg, conference abstracts, trial protocols) excluded; the last search was
21 performed on September 24, 2018

22 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 2016¹¹⁷: 92% of advanced airway attempts were tracheal intubation attempts.

4 †Tijssen 2015¹¹⁸: 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

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

2 Fourteen studies were included in the SR comparing TI with BMV, including 1 clinical trial¹⁰⁵
3 and 13 observational studies.¹⁰⁶⁻¹¹⁸

4 Although the clinical trial was excellent in design and execution, it was downgraded to low
5 certainty as a result of indirectness; the study was conducted in 1994 to 1996, before more recent
6 revisions in resuscitation guidelines that emphasize minimally interrupted chest compressions as
7 part of high-quality CPR. This study assigned 591 children with OHCA to TI or BMV on an
8 odd- and even-day basis. The use of TI resulted in no difference in likelihood of survival with the
9 critical outcome of favorable neurologic function or survival to hospital discharge.¹⁰⁵

10 The 13 identified observational studies provided evidence of very-low or low certainty. Three of
11 these observational studies¹⁰⁶⁻¹⁰⁸ used propensity matching to attempt to control for factors
12 driving the decision to intubate. However, a limitation of all 3 studies was the failure to
13 distinguish patients with unsuccessful attempts at advanced airway placement from those who
14 were managed with BMV alone. When combined, these studies found a reduced likelihood of
15 survival with favorable neurologic function or survival to hospital discharge associated with
16 TI.¹⁰⁶⁻¹⁰⁸ The other 10 observational studies found no statistically significant association between
17 TI and these outcomes.^{109-116,118,120}

18 [h4]Studies Comparing SupraGlottic Airway With Bag-Mask Ventilation Alone

19 The 4 observational studies comparing SGA with BMV provided very-low certainty evidence.
20 Two studies used propensity matching to reduce bias, but both had the limitation of failure to
21 distinguish between patients who had unsuccessful attempts at SGA insertion and those who
22 were managed with BMV without attempted SGA insertion.^{107,108} Two other observational

1 studies reported only nonadjusted data.^{109,116} None of these studies found a significant
2 association between SGA use and survival with favorable neurologic function or survival to
3 hospital discharge.

4 **[h4]Studies Comparing Tracheal Intubation with SupraGlottic Airway**

5 The evidence comparing TI with SGA during pediatric resuscitation comes from 4 observational
6 studies of OHCA;^{107-109,116} 2 of these employed propensity matching.^{107,108} When combined,
7 neither the propensity-matched studies^{107,108} nor the nonadjusted cohort studies^{109,116} found a
8 significant association between the choice of advanced airway and survival with favorable
9 neurologic function or survival to hospital discharge.

10 **[h3]Treatment Recommendations**

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

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

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

16 Advanced airway interventions have been long-established components of the advanced life
17 support bundle of care in adults and children. As a result of inherent limitations in their design
18 and data sources, the available studies provide only very-low-certainty evidence about whether
19 attempting advanced airway placement during resuscitation (ie, before ROSC) improves
20 resuscitation outcomes. The best available data shows no benefit from advanced airway
21 interventions, and some suggested association with harm for the critical outcomes of survival
22 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 setting¹⁰⁵ 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

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

8 **[h2]ECPR: Infants and Children**

9 ECPR has been used with increasing frequency as rescue therapy for refractory cardiac arrest. In
10 pediatrics, ECPR is used most frequently after postoperative IHCA associated with congenital
11 heart disease and progression of low cardiac output or arrhythmias, although there are recent
12 reports of applications for cardiac arrest from other causes. This topic was last reviewed by the
13 Pediatric Life Support Task Force in 2015.¹²¹

14 ILCOR commissioned an SR to identify and analyze all published evidence reporting outcomes
15 of ECPR in infants, children, and adults after OHCA and IHCA.⁵ The Pediatric Life Support
16 Task Force analyzed and discussed the SR as well as all of the pediatric studies identified by the
17 SR, developed a draft CoSTR, and posted it online for public comment.¹²² The draft document
18 was viewed 264 times during the 2-week comment period. The task force reviewed the single
19 posted comment, which endorsed the CoSTR.

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

21 Population: Adults (≥ 18 years) and children (< 18 years) with cardiac arrest in any setting (out-
22 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, 2.08–3.66¹²³; 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.

1 [h3]Knowledge Gaps

2 There are no published randomized trials comparing outcomes of ECPR versus conventional
3 CPR in infants and children. As some high-volume organizations have adopted ECPR for
4 selected pediatric populations, this comparison may not be perceived as having sufficient
5 equipoise to allow randomization. As a result, alternative comparative study designs may be
6 necessary to conduct clinical trials to study the following:

- 7 • Comparison of the probability of survival between ECPR and conventional CPR in IHCA
- 8 • Comparison of the likelihood of favorable neurologic and functional outcome between
9 ECPR and conventional CPR in IHCA

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

- 13 • Optimal timing for ECPR cannulation during conventional CPR
- 14 • Conditions (eg, conditions with pulmonary blood flow obstruction) for which ECPR
15 rather than conventional CPR should be considered earlier in the resuscitation
- 16 • Type and anatomic approach for cannulation for ECPR that allows best cerebral-
17 cardiopulmonary resuscitation
- 18 • Identification of other technical aspects of ECPR that enable optimal cerebral-
19 cardiopulmonary resuscitation, including ideal temperature management strategy, best
20 circuit prime solution (reconstituted whole blood versus crystalloid), optimal fraction of
21 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 **[h2]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 **[h3]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 Nonrandomize d 1/1/2008- 12/31/2014	663 total TTM 81 Stratified by shockable versus nonshockabl e 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 nonrandomize d 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) e)	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 inconsistencie s 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

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 dependent 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 \geq 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 dependen t 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-term¹⁴³ 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 RCT¹³⁵ 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 study¹³⁶ 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.

1 [h3]Knowledge Gaps

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

- 6 • The use of TTM 32°C to 34°C for children after OHCA
- 7 • Asphyxial arrest and the use of TTM at 36°C to 37.5°C in IHCA patients

8 [h1]Neonatal Life Support Task Force

9 [h2]Initial Oxygen Concentration for Term Infants at Birth

10 Administration of high oxygen concentrations leads to free radical formation and may be toxic to
11 newly born lungs, eyes, brains, and other organs.^{145,146} In 2010, the ILCOR NLS Task Force
12 CoSTR Update noted that it was best to start with 21% oxygen when term newborns received
13 positive-pressure ventilation in the delivery room. The recommendation was based on a meta-
14 analysis that found lower mortality when room air instead of 100% oxygen was used.¹⁴⁷ The
15 evidence review for this question did not use GRADE methodology¹⁴⁸ to analyze the published
16 studies. This topic was not addressed for term infants in the 2015 CoSTR update.¹⁴⁹ Questions
17 remain about the risks of hypoxemia versus hyperoxemia for late preterm and term newborns
18 who receive respiratory support in the delivery room. As a consequence, the ILCOR NLS Task
19 Force undertook an SR with meta-analysis of the relevant available evidence using GRADE
20 methodology¹⁴⁸ on the topic of lower oxygen versus higher concentrations of oxygen for
21 initiation of resuscitation of newborn infants at 35 weeks' gestation or greater.⁸

22 [h3]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 ($\leq 50\%$ O₂)

3 Comparison: Higher initial oxygen concentration ($> 50\%$ O₂)

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 (SpO₂) 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)**

1 Among survivors who were assessed for this critical outcome, evidence of very-low certainty
2 (downgraded for risk of bias and imprecision) from 2 RCTs (and qRCTs) involving 360 term and
3 late preterm newborns (≥ 35 weeks) who received respiratory support at birth showed no
4 statistically significant benefit or harm of starting with 21% compared with 100% oxygen (RR,
5 1.41; 95% CI, 0.77–2.60; $I^2=0\%$); 36/1000 more babies with NDI when respiratory support at
6 birth was started with 21% compared with 100% oxygen (95% CI, 20/1000 fewer to 142/1000
7 more).^{156,159}

8 **[h4] Hypoxic-Ischemic Encephalopathy (Sarnat Stage 2–3)¹⁵⁰**

9 For this critical outcome, evidence of low certainty (downgraded for risk of bias and
10 imprecision) from 5 RCTs (and qRCTs) involving 1359 term and late preterm newborns (≥ 35
11 weeks' gestation) receiving respiratory support at delivery showed no statistically significant
12 benefit or harm of 21% compared with 100% oxygen (RR, 0.90; 95% CI, 0.71–1.14; $I^2=8\%$);
13 20/1000 fewer babies with hypoxic-ischemic encephalopathy when respiratory support at birth
14 was started with 21% compared with 100% oxygen (95% CI, 57/1000 fewer to 27/1000
15 more).^{152,153,155,156,158}

16 **[h4] Subgroup Infants 37 Weeks' Gestation or Greater**

17 No data for the planned subgroup analysis for infants 37 weeks' gestation or greater was found.

18 **[h4] Intermediate Initial Oxygen Concentrations**

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

20 **[h4] Oxygen Saturation Targeting Versus No Oxygen Saturation Targeting**

21 No studies were identified that used SpO₂ targeting.

22 **[h3] 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 (SpO₂)
7 targets as the resuscitation progresses: monitoring SpO₂ 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 methodology¹⁴⁸ 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 ($\leq 50\%$ O₂)

14 Comparison: Higher initial oxygen concentration ($> 50\%$ O₂)

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% O₂ compared with 100% O₂, 21%–30% compared
6 with 80%–100% only, 30% compared with 90%–100%, 50% compared with 100%, 30%
7 compared with 60%–65%); explicit SpO₂ targeting versus no SpO₂ 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 concentration¹⁶⁵⁻¹⁷³ 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 studies¹⁷⁵⁻¹⁷⁸ used SpO₂ 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 ($\leq 50\%$) 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]; I²)	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.

1 [h4]Subgroup Newborn Infants 32 Weeks' Gestation or Less

2 For the critical outcome of all-cause short-term mortality (in-hospital or 30 days), the evidence
3 of very-low certainty (downgraded for risk of bias and imprecision) from 8 RCTs with 837
4 newborn infants at 32 weeks' gestation or less receiving respiratory support at birth showed no
5 statistically significant benefit or harm of lower initial oxygen concentration compared with
6 higher initial oxygen concentration (RR, 0.93; 95% CI, 0.55–1.55; $I^2=15%$); 6/1000 fewer with
7 short-term mortality when lower compared with higher initial oxygen concentration was used
8 (95% CI, 39/1000 fewer to 47/1000 more).^{166-168,170-174}

9 [h4]Subgroup Newborn Infants 28 Weeks' Gestation or Less

10 For the subgroup analysis of newborn infants 28 weeks' gestation or less receiving respiratory
11 support at birth, evidence of very-low certainty (downgraded for risk of bias and imprecision)
12 showed no statistically significant benefit or harm of lower initial oxygen concentration ($\leq 50%$)
13 compared with higher initial oxygen concentration ($>50%$), for the following critical outcomes
14 (see Table 15 for data): short-term mortality (in-hospital or 30 days), long-term mortality (1–3
15 years), long-term NDI (moderate-severe, 1–3 years); retinopathy of prematurity (Grade III–V),¹⁶¹
16 necrotizing enterocolitis (Bell's Grade II–III),¹⁶² bronchopulmonary dysplasia (moderate to
17 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]; I²)	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.

1 **[h4]Subgroup Oxygen Concentration 21% Compared With 100% Oxygen Concentration**
2 **(<35 Weeks' Gestation)**

3 For the critical outcome of all-cause short-term mortality (in-hospital or 30 days), evidence
4 of very-low certainty (downgraded for risk of bias and imprecision) from 4 RCTs with 484
5 newborn infants at less than 35 weeks' gestation receiving respiratory support at birth showed no
6 statistically significant benefit or harm of initial room air (21% O₂) compared with initial 100%
7 oxygen concentration (RR, 1.58; 95% CI, 0.70–3.55; I²=4%); 26/1000 more with short-term
8 mortality when lower initial oxygen concentration (21%) compared with higher initial oxygen
9 concentration (100%) was used (95% CI, 14/1000 fewer to 115/1000 more).^{166,168,170,173}

- 10 • For the critical outcome of all-cause long-term mortality (1–3 years), in newborns at less
11 than 35 weeks' gestation, the results are the same as for all groups at less than 35 weeks'
12 gestation.
- 13 • For the critical outcome of long-term NDI (moderate-severe, 1–3 years) in preterm
14 newborns (<35 weeks' gestation), the results are the same as for all groups at less than 35
15 weeks' gestation.

16 Additional subgroup analyses that evaluated the effect of varying the definition of low and high
17 oxygen concentration (21%–30% compared with 80%–100% only; 30% compared with 90%–
18 100%; 50% compared with 100%; 30% compared with 60%–65%) and whether or not SpO₂
19 targeting as a co-intervention had any impact, found no differences in primary and secondary
20 outcomes.⁹ When data from 2 observational cohort studies with 1225 newborns^{177,178} were
21 pooled, initiating resuscitation with lower oxygen was associated with a statistically significant
22 benefit in long-term mortality for all preterm newborns and the subgroup of 28 weeks' gestation
23 or less (RR, 0.77; 95% CI, 0.59–0.99; I²=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 SpO₂ target ranges.

6 The *a priori* comparisons evaluated only an initial oxygen concentration of 21% to 30% versus
7 80% to 100%, 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 SpO₂ 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 SpO₂
14 aiming for published SpO₂ 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

- 1 • Further evidence to identify the optimal SpO₂ targets for preterm infants
- 2 • Evidence to identify optimal methods of titrating oxygen for preterm infants in the
- 3 delivery room
- 4 • Potential effects of delayed cord clamping on the impact of initial inspired oxygen
- 5 concentration for preterm infant

6 **[h1]Education, Implementation and Teams (EIT) and Advanced Life Support (ALS) Task**

7 **Forces**

8 **[h2]Cardiac Arrest Centers Versus Non-Cardiac Arrest Centers**

9 Cardiac Arrest Centers (CACs) are hospitals providing evidence-based resuscitation treatments
10 including emergency interventional cardiology, bundled critical care with TTM, and protocolized
11 cardiorespiratory support and prognostication.^{48,62}

12 This PICOST was prioritized for review by the EIT and ALS Task Forces based on the
13 publication of several large registry studies^{183,184} since the 2015 ILCOR CoSTR.^{185,186} In the
14 following sections, we present a summary of the evidence identified by the ILCOR SR¹⁰ and the
15 web-posted CoSTR about the effects of CACs.¹⁸⁷ There was one question posted during the
16 comment period regarding the definition of CACs and we've provided that in our introduction,
17 above.

18 **[H3]Population, Intervention, Comparator, Outcome, Study Design, and Time Frame**

19 Population: Adults with attempted resuscitation after nontraumatic IHCA or OHCA

20 Intervention: Specialized CAC care

21 Comparators: Care at non-CAC

1 Outcomes:

- 2 • Primary outcome: survival at 30 days or hospital discharge with favorable neurological
3 outcome (Cerebral Performance Category 1 or 2 or modified Rankin Scale 0–3)
- 4 • Secondary outcomes: ROSC after hospital admission for patients with ongoing CPR,
5 survival at 30 days and/or hospital discharge

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

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

10 PROSPERO registration: CRD42018091427

11 **[H3]Consensus on Science**

12 A total of 21 observational studies^{183,184,188-206} and 1 pilot randomized trial²⁰⁷ were included in
13 the SR.¹⁰ Of these, 17 observational studies were ultimately included in meta-analysis.<sup>183,184,188-
14 194,199-206</sup> All studies were in OHCA cohorts; 1 study¹⁹⁵ also included patients with IHCA, but
15 outcomes were not reported separately.

16 The observational studies provided very-low certainty of evidence for all outcomes. The
17 included studies all reported outcomes from patients with OHCA who were cared for at a CAC
18 compared with those cared for at a non-CAC. The manner of arrival at a CAC or non-CAC
19 varied greatly across studies (ie, prehospital triage of all patients to the closest hospital,
20 prehospital triage of select patients to a CAC, prehospital triage of all patients to a CAC,
21 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, 0.68-2.48)	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 study²⁰⁶ 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 study²⁰⁴ 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 study¹⁸⁹ 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.

- 1 • The precise aspects of CACs that improve outcomes have not been identified (eg, are
2 there specific bundles of care that CACs offer that improve outcomes?).
- 3 • The effect of delayed secondary interfacility transfer to a CAC is unknown.
- 4 • The potential benefit of CACs for IHCA and other subgroups (eg, cardiac etiology,
5 shockable rhythm) has not been reported.

6 **[h1]First Aid Task Force**

7 **[h2]Presyncope**

8 Presyncope, or near-syncope, is the prodrome of syncope, and is characterized by light
9 headedness, nausea, diaphoresis and a feeling of impending loss of consciousness. A progression
10 to syncope results in global cerebral hypoperfusion and transient loss of consciousness; loss of
11 postural tone can result in physical injury in up to 30% of patients.²⁰⁹ This review evaluated
12 nonpharmacologic first aid interventions that can be applied at the onset or immediately after
13 onset of presyncope symptoms. ILCOR commissioned an SR,¹¹ and the task force studied all
14 evidence cited in the SR and developed a draft CoSTR. The draft CoSTR was posted for public
15 comment on the ILCOR website; the draft was viewed 285 times during the comment period
16 and no comments were posted.²¹⁰ This document summarizes the final CoSTR for first aid
17 treatment of presyncope.

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

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

21 Intervention: Physical counter-pressure maneuvers (PCMs), body positioning, hydration, or other

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

1 Outcomes:

- 2 • Abortion of syncope (termination of progression from presyncope to syncope) (critical)
- 3 • Injuries or adverse events (critical)
- 4 • Symptom improvement (important)
- 5 • Change in heart rate (important)
- 6 • Change in systolic blood pressure (important)
- 7 • Change in diastolic blood pressure (important)

8 Study Designs: RCTs and nonrandomized studies (non-RCTs, interrupted time series, controlled
9 before-and-after studies, cohort studies) eligible for inclusion; case series and unpublished
10 studies, published abstracts (eg, conference abstracts) and trial protocols excluded

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

12 PROSPERO registration: CRD42018107726

13 **[h3]Consensus on Science**

14 **[h4]Studies Comparing Use of PCMs With a Control or No Use of PCMs**

15 Eight studies were included in the SR, all evaluating use of PCM compared with no use of PCM.

16 Physical counterpressure maneuvers involved the contraction of the large muscles of the legs,
17 arms or abdomen, and included leg or arm tensing, crossing or squeezing, squatting, hand-grip,
18 and abdominal compression. Studies included 2 RCTs^{211,212} and 6 observational studies,^{211,213-217}
19 enrolling a total of 246 participants between 15 and 75 years of age with a history of vasovagal
20 or orthostatic-related syncope. Forms of PCM evaluated included handgrip, squatting, leg
21 crossing with tensing, and abdominal/core muscle tensing. Evidence from the Brignole RCT²¹¹
22 was downgraded to very-low certainty as the result of risk of bias, inconsistency, indirectness,

1 and imprecision, whereas evidence from the Alizadeh RCT²¹² 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 StudiesOutc omes	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 StudiesOutc omes	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 StudiesOutc omes	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 improveme nt	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 StudiesOutc omes	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 StudiesOutc omes	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 StudiesOutc omes	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 StudiesOutc omes	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 StudiesOutc omes	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 StudiesOutc omes	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 StudiesOutc omes	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 RCT²¹¹ 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 study²¹⁴ 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 studies²¹³⁻²¹⁶ did not report consistent changes in heart rate. The same single
21 RCT²¹¹ 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 study²¹⁶ 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 RCT²¹² 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).

1 [h3]Justification and Evidence to Decision Framework Highlights

2 Despite the mixed results and low- or very-low-certainty evidence identified in this review, with
3 use of the *Evidence to Decision Framework*²¹⁰ and discussion of all evidence, the First Aid Task
4 Force concluded that the use of PCM for acute symptoms of presyncope warranted a strong
5 recommendation because, together, the included studies suggest that the use of PCM results in
6 better outcomes with no reported adverse events. In addition, PCM interventions are simple and
7 inexpensive, and they may prevent progression from presyncope to syncope and risks of
8 subsequent injury. Successful treatment of presyncope may improve the quality of life for those
9 with recurrent vasovagal or orthostatic syncope, and it may ultimately decrease associated
10 healthcare costs. Included studies demonstrated that training of participants in use of PCM at
11 symptom onset was feasible and similar to a first aid situation, making it likely that first aid
12 providers can also be trained in their use.

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

18 [h3]Knowledge Gaps

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

- 20 • Validity of conventional first aid recommendation to place a person with symptoms of
21 presyncope into a sitting or supine position with or without combination of PCM
- 22 • Effectiveness of additional interventions such as hydration

- 1 • Clinical outcomes related to the use of PCM and possible variation based on age, gender,
2 and etiology of presyncope
- 3 • Ability of first aid providers to recognize vasovagal and orthostatic presyncope and to
4 assess clinical outcomes after instruction in and use of PCM

5 **[H1]Acknowledgments**

6 **[h1]Disclosures**

7 **[h2]Writing Group Disclosures**

8 **[h2]Reviewer Disclosures**

9 **[H1]References**

- 10 1. International Liaison Committee on Resuscitation. Consensus on Science with Treatment
11 Recommendations (CoSTR) website.
- 12 2. Nikolaou N, Dainty KN, Couper K, Morley P, Tijssen J, Vaillancourt C; on behalf of the
13 International Liaison Committee on Resuscitation's (ILCOR) Basic Life Support and Pediatric
14 Task Forces. A systematic review and meta-analysis of the effect of dispatcher-assisted CPR on
15 outcomes from sudden cardiac arrest in adults and children. *Resuscitation*. 2019. doi:
16 10.1016/j.resuscitation.2019.02.035
- 17 3. Granfeldt A, Avis SR, Nicholson TC, Holmberg MJ, Moskowitz A, Coker A, Berg KM,
18 Parr MJ, Donnino MW, Soar J, Nation K, Andersen LW; on behalf of the Advanced Life
19 Support Task Force of the International Liaison Committee of Resuscitation. Advanced airway
20 management during adult cardiac arrest: a systematic review. *Resuscitation*. In press;
- 21 4. Holmberg MJ, Issa MS, Moskowitz A, Morley P, Welsford M, Neumar R, Paiva E,
22 Coker A, Hansen CK, Andersen LW, Donnino MW, Berg KM; on behalf of the Advanced Life

- 1 Support Task Force of the International Liaison Committee of Resuscitation. Vasopressors
2 during adult cardiac arrest: a systematic review and meta-analysis. *Resuscitation*. In press;
- 3 5. Holmberg MJ, Geri G, Wiberg S, Guerguerian AM, Donnino MW, Nolan JP, Deakin CD,
4 Andersen LW; on behalf of the International Liaison Committee on Resuscitation's (ILCOR)
5 Advanced Life Support and Pediatric Task Forces. Extracorporeal cardiopulmonary resuscitation
6 for cardiac arrest: a systematic review. *Resuscitation*. 2018;131:91–100. doi:
7 10.1016/j.resuscitation.2018.07.029
- 8 6. Lavonas EJ, Ohshimo S, Nation K, Van de Voorde P, Nuthall G, Maconochie I, Torabi
9 N, Morrison LJ; on behalf of International Liaison Committee on Resuscitation (ILCOR)
10 Pediatric Life Support Task Force. Advanced airway interventions for paediatric cardiac arrest: a
11 systematic review and meta-analysis. *Resuscitation*. 2019;138:114–128. doi:
12 10.1016/j.resuscitation.2019.02.040
- 13 7. Buick JE, Wallner C, Aickin R, Meaney R, de Caen A, Maconochie IK, Skifars M,
14 Welsford M; on behalf of the International Liaison Committee on Resuscitation Pediatric Life
15 Support Task Force. Pediatric targeted temperature management post cardiac arrest: a systematic
16 review with meta-analysis. *TBA*. TBA;
- 17 8. Welsford M, Nishiyama C, Shortt C, Isayama T, Dawson JA, Weiner G, Roehr CC,
18 Wyckoff MH, Rabi Y; on behalf of the International Liaison Committee on Resuscitation
19 Neonatal Life Support Task Force. Room air for initiating term newborn resuscitation: a
20 systematic review with meta-analysis. *Pediatrics*. 2019;143. doi: 10.1542/peds.2018-1825
- 21 9. Welsford M, Nishiyama C, Shortt C, Weiner G, Roehr CC, Isayama T, Dawson JA,
22 Wyckoff MH, Rabi Y; on behalf of the International Liaison Committee on Resuscitation

- 1 Neonatal Life Support Task Force. Initial oxygen use for preterm newborn resuscitation: a
2 systematic review with meta-analysis. *Pediatrics*. 2019;143. doi: 10.1542/peds.2018-1828
- 3 10. Yeung J, Matsuyama T, Bray J, Reynolds J, Skrifvars MB. Does care at a cardiac arrest
4 centre improve outcome after out-of-hospital cardiac arrest? A systematic review. *Resuscitation*.
5 2019;137:102–115. doi: 10.1016/j.resuscitation.2019.02.006
- 6 11. Jensen JL, Ohshimo S, Cassan P, Meyran D, Greene J, Ng KG, Singletary E, Zideman D.
7 Immediate interventions for presyncope of vasovagal or orthostatic origin: a systematic review.
8 *Prehosp Emerg Care*. 2019:1–63. doi: 10.1080/10903127.2019.1605431
- 9 12. International Liaison Committee on Resuscitation (ILCOR). ILCOR home page.
- 10 13. Perkins GD, Travers AH, Berg RA, Castren M, Considine J, Escalante R, Gazmuri RJ,
11 Koster RW, Lim SH, Nation KJ, Olasveengen TM, Sakamoto T, Sayre MR, Sierra A, Smyth
12 MA, Stanton D, Vaillancourt C; on behalf of the Basic Life Support Chapter Collaborators. Part
13 3: adult basic life support and automated external defibrillation: 2015 International Consensus on
14 Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science with Treatment
15 Recommendations. *Resuscitation*. 2015;95:e43–e69. doi: 10.1016/j.resuscitation.2015.07.041
- 16 14. Travers AH, Perkins GD, Berg RA, Castren M, Considine J, Escalante R, Gazmuri RJ,
17 Koster RW, Lim SH, Nation KJ, Olasveengen TM, Sakamoto T, Sayre MR, Sierra A, Smyth
18 MA, Stanton D, Vaillancourt C; on behalf of the Basic Life Support Chapter Collaborators. Part
19 3: adult basic life support and automated external defibrillation: 2015 International Consensus on
20 Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science With Treatment
21 Recommendations. *Circulation*. 2015;132(suppl 1):S51–S83. doi:
22 10.1161/CIR.0000000000000272

- 1 15. Olasveengen TM, Mancini ME, Vaillancourt C, Brooks SC, Castren M, Chung SP,
2 Couper K, Dainty KN, Escalante R, Gazmuri RJ, Hatanaka T, Kudenchuk PJ, Lim SH, Nikolaou
3 N, Nishiyama C, Perkins GD, Ristagno G, Smyth MA, Morley P. Emergency care: dispatcher
4 instruction in CPR. 2018.
- 5 16. US National Library of Medicine. ClinicalTrials.gov database.
- 6 17. Culley LL, Clark JJ, Eisenberg MS, Larsen MP. Dispatcher-assisted telephone CPR:
7 common delays and time standards for delivery. *Ann Emerg Med.* 1991;20:362–366
- 8 18. Song KJ, Shin SD, Park CB, Kim JY, Kim DK, Kim CH, Ha SY, Eng Hock Ong M,
9 Bobrow BJ, McNally B. Dispatcher-assisted bystander cardiopulmonary resuscitation in a
10 metropolitan city: a before-after population-based study. *Resuscitation.* 2014;85:34–41. doi:
11 10.1016/j.resuscitation.2013.06.004
- 12 19. Stipulante S, Tubes R, El Fassi M, Donneau AF, Van Troyen B, Hartstein G, D'Orio V,
13 Ghuysen A. Implementation of the ALERT algorithm, a new dispatcher-assisted telephone
14 cardiopulmonary resuscitation protocol, in non-Advanced Medical Priority Dispatch System
15 (AMPDS) Emergency Medical Services centres. *Resuscitation.* 2014;85:177–181. doi:
16 10.1016/j.resuscitation.2013.10.005
- 17 20. Vaillancourt C, Verma A, Trickett J, Crete D, Beaudoin T, Nesbitt L, Wells GA, Stiell
18 IG. Evaluating the effectiveness of dispatch-assisted cardiopulmonary resuscitation instructions.
19 *Acad Emerg Med.* 2007;14:877–883. doi: 10.1197/j.aem.2007.06.021
- 20 21. Harjanto S, Na MX, Hao Y, Ng YY, Doctor N, Goh ES, Leong BS, Gan HN, Chia MY,
21 Tham LP, Cheah SO, Shahidah N, Ong ME; on behalf of the PAROS study group. A before-after
22 interventional trial of dispatcher-assisted cardio-pulmonary resuscitation for out-of-hospital

- 1 cardiac arrests in Singapore. *Resuscitation*. 2016;102:85–93. doi:
2 10.1016/j.resuscitation.2016.02.014
- 3 22. Besnier E, Damm C, Jardel B, Veber B, Compere V, Dureuil B. Dispatcher-assisted
4 cardiopulmonary resuscitation protocol improves diagnosis and resuscitation recommendations
5 for out-of-hospital cardiac arrest. *Emerg Med Australas*. 2015;27:590–596. doi: 10.1111/1742-
6 6723.12493
- 7 23. Bång A, Biber B, Isaksson L, Lindqvist J, Herlitz J. Evaluation of dispatcher-assisted
8 cardiopulmonary resuscitation. *Eur J Emerg Med*. 1999;6:175–183
- 9 24. Kuisma M, Boyd J, Väyrynen T, Repo J, Nousila-Wiik M, Holmström P. Emergency call
10 processing and survival from out-of-hospital ventricular fibrillation. *Resuscitation*. 2005;67:89–
11 93. doi: 10.1016/j.resuscitation.2005.04.008
- 12 25. Akahane M, Ogawa T, Tanabe S, Koike S, Horiguchi H, Yasunaga H, Imamura T.
13 Impact of telephone dispatcher assistance on the outcomes of pediatric out-of-hospital cardiac
14 arrest. *Crit Care Med*. 2012;40:1410–1416. doi: 10.1097/CCM.0b013e31823e99ae
- 15 26. Goto Y, Maeda T, Goto Y. Impact of dispatcher-assisted bystander cardiopulmonary
16 resuscitation on neurological outcomes in children with out-of-hospital cardiac arrests: a
17 prospective, nationwide, population-based cohort study. *J Am Heart Assoc*. 2014;3:e000499. doi:
18 10.1161/JAHA.113.000499
- 19 27. Japanese Circulation Society Resuscitation Science Study Group. Chest-compression-
20 only bystander cardiopulmonary resuscitation in the 30:2 compression-to-ventilation ratio era:
21 nationwide observational study. *Circ J*. 2013;77:2742–2750
- 22 28. Hiltunen PV, Silfvast TO, Jäntti TH, Kuisma MJ, Kurola JO; on behalf of the
23 FINNRESUSCI Prehospital Study Group. Emergency dispatch process and patient outcome in

- 1 bystander-witnessed out-of-hospital cardiac arrest with a shockable rhythm. *Eur J Emerg Med.*
2 2015;22:266–272. doi: 10.1097/MEJ.0000000000000151
- 3 29. Fukushima H, Panczyk M, Hu C, Dameff C, Chikani V, Vadeboncoeur T, Spaite DW,
4 Bobrow BJ. Description of abnormal breathing is associated with improved outcomes and
5 delayed telephone cardiopulmonary resuscitation instructions. *J Am Heart Assoc.*
6 2017;6:e005058. doi: 10.1161/JAHA.116.005058
- 7 30. Moriwaki Y, Tahara Y, Kosuge T, Suzuki N. The effect of telephone advice on
8 cardiopulmonary resuscitation (CPR) on the rate of bystander CPR in out-of-hospital
9 cardiopulmonary arrest in a typical urban area *Hong Kong J Emerg Med.* 2016;23:220–226. doi:
10 <https://doi.org/10.1177/102490791602300403> .
- 11 31. Ro YS, Shin SD, Song KJ, Hong KJ, Ahn KO, Kim DK, Kwak YH. Effects of
12 dispatcher-assisted cardiopulmonary resuscitation on survival outcomes in infants, children, and
13 adolescents with out-of-hospital cardiac arrests. *Resuscitation.* 2016;108:20–26. doi:
14 10.1016/j.resuscitation.2016.08.026
- 15 32. Takahashi H, Sagisaka R, Natsume Y, Tanaka S, Takyu H, Tanaka H. Does dispatcher-
16 assisted CPR generate the same outcomes as spontaneously delivered bystander CPR in Japan?
17 *Am J Emerg Med.* 2018;36:384–391. doi: 10.1016/j.ajem.2017.08.034
- 18 33. Wu Z, Panczyk M, Spaite DW, Hu C, Fukushima H, Langlais B, Sutter J, Bobrow BJ.
19 Telephone cardiopulmonary resuscitation is independently associated with improved survival
20 and improved functional outcome after out-of-hospital cardiac arrest. *Resuscitation.*
21 2018;122:135–140. doi: 10.1016/j.resuscitation.2017.07.016
- 22 34. Ro YS, Shin SD, Lee YJ, Lee SC, Song KJ, Ryoo HW, Ong MEH, McNally B, Bobrow
23 B, Tanaka H, Myklebust H, Birkenes TS. Effect of dispatcher-assisted cardiopulmonary

- 1 resuscitation program and location of out-of-hospital cardiac arrest on survival and neurologic
2 outcome. *Ann Emerg Med.* 2017;69:52.e1–61.e1. doi: 10.1016/j.annemergmed.2016.07.028
- 3 35. Chang I, Lee SC, Shin SD, Song KJ, Ro YS, Park JH, Kong SY. Effects of dispatcher-
4 assisted bystander cardiopulmonary resuscitation on neurological recovery in paediatric patients
5 with out-of-hospital cardiac arrest based on the pre-hospital emergency medical service response
6 time interval. *Resuscitation.* 2018;130:49–56. doi: 10.1016/j.resuscitation.2018.06.029
- 7 36. Viereck S, Møller TP, Ersbøll AK, Bækgaard JS, Claesson A, Hollenberg J, Folke F,
8 Lippert FK. Recognising out-of-hospital cardiac arrest during emergency calls increases
9 bystander cardiopulmonary resuscitation and survival. *Resuscitation.* 2017;115:141–147. doi:
10 10.1016/j.resuscitation.2017.04.006
- 11 37. Shah M, Bartram C, Irwin K, Vellano K, McNally B, Gallagher T, Swor R. Evaluating
12 dispatch-assisted CPR using the CARES registry. *Prehosp Emerg Care.* 2018;22:222–228. doi:
13 10.1080/10903127.2017.1376133
- 14 38. Rea TD, Eisenberg MS, Culley LL, Becker L. Dispatcher-assisted cardiopulmonary
15 resuscitation and survival in cardiac arrest. *Circulation.* 2001;104:2513–2516
- 16 39. Chang I, Ro YS, Shin SD, Song KJ, Park JH, Kong SY. Association of dispatcher-
17 assisted bystander cardiopulmonary resuscitation with survival outcomes after pediatric out-of-
18 hospital cardiac arrest by community property value. *Resuscitation.* 2018;132:120–126. doi:
19 10.1016/j.resuscitation.2018.09.008
- 20 40. Takei Y, Kamikura T, Nishi T, Maeda T, Sakagami S, Kubo M, Inaba H. Recruitments of
21 trained citizen volunteering for conventional cardiopulmonary resuscitation are necessary to
22 improve the outcome after out-of-hospital cardiac arrests in remote time-distance area: a

- 1 nationwide population-based study. *Resuscitation*. 2016;105:100–108. doi:
2 10.1016/j.resuscitation.2016.05.021
- 3 41. Lewis M, Stubbs BA, Eisenberg MS. Dispatcher-assisted cardiopulmonary resuscitation:
4 time to identify cardiac arrest and deliver chest compression instructions. *Circulation*.
5 2013;128:1522–1530. doi: 10.1161/CIRCULATIONAHA.113.002627
- 6 42. Dami F, Heymann E, Pasquier M, Fuchs V, Carron PN, Hugli O. Time to identify cardiac
7 arrest and provide dispatch-assisted cardio-pulmonary resuscitation in a criteria-based dispatch
8 system. *Resuscitation*. 2015;97:27–33. doi: 10.1016/j.resuscitation.2015.09.390
- 9 43. Oman G, Bury G. Use of telephone CPR advice in Ireland: uptake by callers and delays
10 in the assessment process. *Resuscitation*. 2016;102:6–10. doi:
11 10.1016/j.resuscitation.2016.02.006
- 12 44. Eisenberg MS, Cummins RO, Litwin P, Hallstrom AP, Hearne T. Dispatcher
13 cardiopulmonary resuscitation instruction via telephone. *Crit Care Med*. 1985;13:923–924
- 14 45. Park JH, Ro YS, Shin SD, Song KJ, Hong KJ, Kong SY. Dispatcher-assisted bystander
15 cardiopulmonary resuscitation in rural and urban areas and survival outcomes after out-of-
16 hospital cardiac arrest. *Resuscitation*. 2018;125:1–7. doi: 10.1016/j.resuscitation.2018.01.026
- 17 46. Gotz J, Petutschnigg B, Wasler A, Wran-Schumer D, Hansak P. Bystander resuscitation
18 as a measure of success [in German]. *Notfall Rettungsmed*. 2017;20:470–476
- 19 47. Hasselqvist-Ax I, Riva G, Herlitz J, Rosenqvist M, Hollenberg J, Nordberg P, Ringh M,
20 Jonsson M, Axelsson C, Lindqvist J, Karlsson T, Svensson L. Early cardiopulmonary
21 resuscitation in out-of-hospital cardiac arrest. *N Engl J Med*. 2015;372:2307–2315. doi:
22 10.1056/NEJMoa1405796

- 1 48. Soar J, Callaway CW, Aibiki M, Böttiger BW, Brooks SC, Deakin CD, Donnino MW,
2 Drajer S, Kloeck W, Morley PT, Morrison LJ, Neumar RW, Nicholson TC, Nolan JP, Okada K,
3 O'Neil BJ, Paiva EF, Parr MJ, Wang TL, Witt J; on behalf of the Advanced Life Support Chapter
4 Collaborators. Part 4: advanced life support: 2015 International Consensus on Cardiopulmonary
5 Resuscitation and Emergency Cardiovascular Care Science with Treatment Recommendations.
6 *Resuscitation*. 2015;95:e71–e120. doi: 10.1016/j.resuscitation.2015.07.042
- 7 49. Andersen LW, Granfeldt A, Callaway CW, Bradley SM, Soar J, Nolan JP, Kurth T,
8 Donnino MW; on behalf of the the American Heart Association's Get With The Guidelines–
9 Resuscitation Investigators. Association between tracheal intubation during adult in-hospital
10 cardiac arrest and survival. *JAMA*. 2017;317:494–506. doi: 10.1001/jama.2016.20165
- 11 50. McMullan J, Gerecht R, Bonomo J, Robb R, McNally B, Donnelly J, Wang HE; on
12 behalf of the CARES Surveillance Group. Airway management and out-of-hospital cardiac arrest
13 outcome in the CARES registry. *Resuscitation*. 2014;85:617–622. doi:
14 10.1016/j.resuscitation.2014.02.007
- 15 51. Bengier JR, Kirby K, Black S, Brett SJ, Clout M, Lazaroo MJ, Nolan JP, Reeves BC,
16 Robinson M, Scott LJ, Smartt H, South A, Stokes EA, Taylor J, Thomas M, Voss S, Wordsworth
17 S, Rogers CA. Effect of a strategy of a supraglottic airway device vs tracheal intubation during
18 out-of-hospital cardiac arrest on functional outcome: the AIRWAYS-2 randomized clinical
19 trial. *JAMA*. 2018;320:779–791. doi: 10.1001/jama.2018.11597
- 20 52. Jabre P, Penaloza A, Pinero D, Duchateau FX, Borron SW, Javaudin F, Richard O, de
21 Longueville D, Bouilleau G, Devaud ML, Heidet M, Lejeune C, Fauroux S, Greingor JL,
22 Manara A, Hubert JC, Guihard B, Vermeylen O, Lievens P, Auffret Y, Maisondieu C, Huet S,
23 Claessens B, Lapostolle F, Javaud N, Reuter PG, Baker E, Vicaut E, Adnet F. Effect of bag-

- 1 mask ventilation vs endotracheal intubation during cardiopulmonary resuscitation on
2 neurological outcome after out-of-hospital cardiorespiratory arrest: a randomized clinical trial.
3 *JAMA*. 2018;319:779–787. doi: 10.1001/jama.2018.0156
- 4 53. Wang HE, Schmicker RH, Daya MR, Stephens SW, Idris AH, Carlson JN, Colella MR,
5 Herren H, Hansen M, Richmond NJ, Puyana JCJ, Aufderheide TP, Gray RE, Gray PC, Verkest
6 M, Owens PC, Brienza AM, Sternig KJ, May SJ, Sopko GR, Weisfeldt ML, Nichol G. Effect of
7 a strategy of initial laryngeal tube insertion vs endotracheal intubation on 72-hour survival in
8 adults with out-of-hospital cardiac arrest: a randomized clinical trial. *JAMA*. 2018;320:769–778.
9 doi: 10.1001/jama.2018.7044
- 10 54. Goldenberg IF, Champion BC, Siebold CM, McBride JW, Long LA. Esophageal gastric
11 tube airway vs endotracheal tube in prehospital cardiopulmonary arrest. *Chest*. 1986;90:90–96
- 12 55. Staudinger T, Brugger S, Röggl M, Rintelen C, Atherton GL, Johnson JC, Frass M.
13 Comparison of the Combitube with the endotracheal tube in cardiopulmonary resuscitation in the
14 prehospital phase [in German]. *Wien Klin Wochenschr*. 1994;106:412–415
- 15 56. Rumball CJ, MacDonald D. The PTL, Combitube, laryngeal mask, and oral airway: a
16 randomized prehospital comparative study of ventilatory device effectiveness and cost-
17 effectiveness in 470 cases of cardiorespiratory arrest. *Prehosp Emerg Care*. 1997;1:1–10
- 18 57. Rabitsch W, Schellongowski P, Staudinger T, Hofbauer R, Dufek V, Eder B, Raab H,
19 Thell R, Schuster E, Frass M. Comparison of a conventional tracheal airway with the Combitube
20 in an urban emergency medical services system run by physicians. *Resuscitation*. 2003;57:27–32
- 21 58. Maignan M, Koch FX, Kraemer M, Lehodey B, Viglino D, Monnet MF, Pham D, Roux
22 C, Genty C, Rolland C, Bosson JL, Danel V, Debaty G. Impact of laryngeal tube use on chest

- 1 compression fraction during out-of-hospital cardiac arrest: a prospective alternate month study.
2 *Resuscitation*. 2015;93:113–117. doi: 10.1016/j.resuscitation.2015.06.002
- 3 59. Ono Y, Hayakawa M, Maekawa K, Mizugaki A, Katabami K, Wada T, Sawamura A,
4 Gando S. Should laryngeal tubes or masks be used for out-of-hospital cardiac arrest patients? *Am*
5 *J Emerg Med*. 2015;33:1360–1363. doi: 10.1016/j.ajem.2015.07.043
- 6 60. Benger J, Coates D, Davies S, Greenwood R, Nolan J, Rhys M, Thomas M, Voss S.
7 Randomised comparison of the effectiveness of the laryngeal mask airway supreme, i-gel and
8 current practice in the initial airway management of out of hospital cardiac arrest: a feasibility
9 study. *Br J Anaesth*. 2016;116:262–268. doi: 10.1093/bja/aev477
- 10 61. Fiala A, Lederer W, Neumayr A, Egger T, Neururer S, Toferer E, Baubin M, Paal P.
11 EMT-led laryngeal tube vs. face-mask ventilation during cardiopulmonary resuscitationa
12 multicenter prospective randomized trial. *Scand J Trauma Resusc Emerg Med*. 2017;25:104. doi:
13 10.1186/s13049-017-0446-1
- 14 62. Callaway CW, Soar J, Aibiki M, Böttiger BW, Brooks SC, Deakin CD, Donnino MW,
15 Drajer S, Kloeck W, Morley PT, Morrison LJ, Neumar RW, Nicholson TC, Nolan JP, Okada K,
16 O'Neil BJ, Paiva EF, Parr MJ, Wang TL, Witt J; on behalf of the Advanced Life Support Chapter
17 Collaborators. Part 4: advanced life support: 2015 International Consensus on Cardiopulmonary
18 Resuscitation and Emergency Cardiovascular Care Science With Treatment Recommendations.
19 *Circulation*. 2015;132(suppl 1):S84–S145. doi: 10.1161/CIR.0000000000000273
- 20 63. Pearson JW, Redding JS. Epinephrine in cardiac resuscitation. *Am Heart J*. 1963;66:210–
21 214
- 22 64. Redding JS, Pearson JW. Resuscitation from ventricular fibrillation: drug therapy. *JAMA*.
23 1968;203:255–260

- 1 65. Perkins GD, Ji C, Deakin CD, Quinn T, Nolan JP, Scomparin C, Regan S, Long J,
2 Slowther A, Pocock H, Black JJM, Moore F, Fothergill RT, Rees N, O'Shea L, Docherty M,
3 Gunson I, Han K, Charlton K, Finn J, Petrou S, Stallard N, Gates S, Lall R; PARAMEDIC2
4 Collaborators. A randomized trial of epinephrine in out-of-hospital cardiac arrest. *N Engl J Med.*
5 2018;379:711–721. doi: 10.1056/NEJMoa1806842
- 6 66. Jacobs IG, Finn JC, Jelinek GA, Oxeer HF, Thompson PL. Effect of adrenaline on
7 survival in out-of-hospital cardiac arrest: a randomised double-blind placebo-controlled trial.
8 *Resuscitation.* 2011;82:1138–1143. doi: 10.1016/j.resuscitation.2011.06.029
- 9 67. Perkins et al. In the larger, more recent trial, the subgroup with nonshockable rhythms
10 showed no difference in survival to 3 months with favorable or unfavorable neurological
11 outcome. *TBA.* In press;
- 12 68. Lindner KH, Dirks B, Strohmenger HU, Pregel AW, Lindner IM, Lurie KG.
13 Randomised comparison of epinephrine and vasopressin in patients with out-of-hospital
14 ventricular fibrillation. *Lancet.* 1997;349:535–537. doi: 10.1016/S0140-6736(97)80087-6
- 15 69. Wenzel V, Krismer AC, Arntz HR, Sitter H, Stadlbauer KH, Lindner KH; European
16 Resuscitation Council Vasopressor during Cardiopulmonary Resuscitation Study Group. A
17 comparison of vasopressin and epinephrine for out-of-hospital cardiopulmonary resuscitation. *N*
18 *Engl J Med.* 2004;350:105–113. doi: 10.1056/NEJMoa025431
- 19 70. Mukoyama T, Kinoshita K, Nagao K, Tanjoh K. Reduced effectiveness of vasopressin in
20 repeated doses for patients undergoing prolonged cardiopulmonary resuscitation. *Resuscitation.*
21 2009;80:755–761. doi: 10.1016/j.resuscitation.2009.04.005

- 1 71. Stiell IG, Hebert PC, Weitzman BN, Wells GA, Raman S, Stark RM, Higginson LA,
2 Ahuja J, Dickinson GE. High-dose epinephrine in adult cardiac arrest. *N Engl J Med*.
3 1992;327:1045–1050. doi: 10.1056/NEJM199210083271502
- 4 72. Callaway CW, Hostler D, Doshi AA, Pinchalk M, Roth RN, Lubin J, Newman DH, Kelly
5 LJ. Usefulness of vasopressin administered with epinephrine during out-of-hospital cardiac
6 arrest. *Am J Cardiol*. 2006;98:1316–1321. doi: 10.1016/j.amjcard.2006.06.022
- 7 73. Gueugniaud PY, David JS, Chanzy E, Hubert H, Dubien PY, Mauriaucourt P, Bragança
8 C, Billères X, Clotteau-Lambert MP, Fuster P, Thiercelin D, Debaty G, Ricard-Hibon A, Roux P,
9 Espesson C, Querellou E, Ducros L, Ecollan P, Halbout L, Savary D, Guillaumée F, Maupoint R,
10 Capelle P, Bracq C, Dreyfus P, Nouguier P, Gache A, Meurisse C, Boulanger B, Lae C, Metzger
11 J, Raphael V, Beruben A, Wenzel V, Guinhouya C, Vilhelm C, Marret E. Vasopressin and
12 epinephrine vs. epinephrine alone in cardiopulmonary resuscitation. *N Engl J Med*. 2008;359:21–
13 30. doi: 10.1056/NEJMoa0706873
- 14 74. Ducros L, Vicaut E, Soleil C, Le Guen M, Gueye P, Poussant T, Mebazaa A, Payen D,
15 Plaisance P. Effect of the addition of vasopressin or vasopressin plus nitroglycerin to epinephrine
16 on arterial blood pressure during cardiopulmonary resuscitation in humans. *J Emerg Med*.
17 2011;41:453–459. doi: 10.1016/j.jemermed.2010.02.030
- 18 75. Stiell IG, Hébert PC, Wells GA, Vandemheen KL, Tang AS, Higginson LA, Dreyer JF,
19 Clement C, Battram E, Watpool I, Mason S, Klassen T, Weitzman BN. Vasopressin versus
20 epinephrine for inhospital cardiac arrest: a randomised controlled trial. *Lancet*. 2001;358:105–
21 109. doi: 10.1016/S0140-6736(01)05328-4
- 22 76. Conrad SA, Broman LM, Taccone FS, Lorusso R, Malferteiner MV, Pappalardo F, Di
23 Nardo M, Belliato M, Grazioli L, Barbaro RP, McMullan DM, Pellegrino V, Brodie D, Bembea

- 1 MM, Fan E, Mendonca M, Diaz R, Bartlett RH. The Extracorporeal Life Support Organization
2 Maastricht Treaty for Nomenclature in Extracorporeal Life Support: a position paper of the
3 Extracorporeal Life Support Organization. *Am J Respir Crit Care Med*. 2018;198:447–451. doi:
4 10.1164/rccm.201710-2130CP
- 5 77. Agostinucci JM, Ruscev M, Galinski M, Gravelo S, Petrovic T, Carmeaux C, Haouache
6 H, Roussin F, Adnet F, Lapostolle F. Out-of-hospital use of an automated chest compression
7 device: facilitating access to extracorporeal life support or non-heart-beating organ procurement.
8 *Am J Emerg Med*. 2011;29:1169–1172. doi: 10.1016/j.ajem.2010.06.029
- 9 78. Cesana F, Avalli L, Garatti L, Coppo A, Righetti S, Calchera I, Scanziani E, Cozzolino P,
10 Malafrente C, Mauro A, Soffici F, Sulmina E, Bozzon V, Maggioni E, Foti G, Achilli F. Effects
11 of extracorporeal cardiopulmonary resuscitation on neurological and cardiac outcome after
12 ischaemic refractory cardiac arrest. *Eur Heart J Acute Cardiovasc Care*. 2018;7:432–441. doi:
13 10.1177/2048872617737041
- 14 79. Choi DH, Kim YJ, Ryoo SM, Sohn CH, Ahn S, Seo DW, Lim JY, Kim WY.
15 Extracorporeal cardiopulmonary resuscitation among patients with out-of-hospital cardiac arrest.
16 *Clin Exp Emerg Med*. 2016;3:132–138. doi: 10.15441/ceem.16.145
- 17 80. Hase M, Tsuchihashi K, Fujii N, Nishizato K, Kokubu N, Nara S, Kurimoto Y,
18 Hashimoto A, Uno K, Miura T, Ura N, Asai Y, Shimamoto K. Early defibrillation and
19 circulatory support can provide better long-term outcomes through favorable neurological
20 recovery in patients with out-of-hospital cardiac arrest of cardiac origin. *Circ J*. 2005;69:1302–
21 1307
- 22 81. Kim SJ, Jung JS, Park JH, Park JS, Hong YS, Lee SW. An optimal transition time to
23 extracorporeal cardiopulmonary resuscitation for predicting good neurological outcome in

- 1 patients with out-of-hospital cardiac arrest: a propensity-matched study. *Crit Care*. 2014;18:535.
2 doi: 10.1186/s13054-014-0535-8
- 3 82. Lee SH, Jung JS, Lee KH, Kim HJ, Son HS, Sun K. Comparison of extracorporeal
4 cardiopulmonary resuscitation with conventional cardiopulmonary resuscitation: is
5 extracorporeal cardiopulmonary resuscitation beneficial? *Korean J Thorac Cardiovasc Surg*.
6 2015;48:318–327. doi: 10.5090/kjtcs.2015.48.5.318
- 7 83. Maekawa K, Tanno K, Hase M, Mori K, Asai Y. Extracorporeal cardiopulmonary
8 resuscitation for patients with out-of-hospital cardiac arrest of cardiac origin: a propensity-
9 matched study and predictor analysis. *Crit Care Med*. 2013;41:1186–1196. doi:
10 10.1097/CCM.0b013e31827ca4c8
- 11 84. Poppe M, Weiser C, Holzer M, Sulzgruber P, Datler P, Keferböck M, Zeiner S, Lobmeyr
12 E, van Tulder R, Ziegler A, Glück H, Meixner M, Schrattenbacher G, Maszar H, Zajicek A,
13 Sterz F, Schober A. The incidence of "load&go" out-of-hospital cardiac arrest candidates for
14 emergency department utilization of emergency extracorporeal life support: a one-year review.
15 *Resuscitation*. 2015;91:131–136. doi: 10.1016/j.resuscitation.2015.03.003
- 16 85. Sakamoto T, Morimura N, Nagao K, Asai Y, Yokota H, Nara S, Hase M, Tahara Y,
17 Atsumi T; and the SAVE-J Study Group. Extracorporeal cardiopulmonary resuscitation versus
18 conventional cardiopulmonary resuscitation in adults with out-of-hospital cardiac arrest: a
19 prospective observational study. *Resuscitation*. 2014;85:762–768. doi:
20 10.1016/j.resuscitation.2014.01.031
- 21 86. Schober A, Sterz F, Herkner H, Wallmueller C, Weiser C, Hubner P, Testori C.
22 Emergency extracorporeal life support and ongoing resuscitation: a retrospective comparison for

- 1 refractory out-of-hospital cardiac arrest. *Emerg Med J*. 2017;34:277–281. doi:
2 10.1136/emered-2015-205232
- 3 87. Siao FY, Chiu CC, Chiu CW, Chen YC, Chen YL, Hsieh YK, Lee CH, Wu CT, Chou
4 CC, Yen HH. Managing cardiac arrest with refractory ventricular fibrillation in the emergency
5 department: conventional cardiopulmonary resuscitation versus extracorporeal cardiopulmonary
6 resuscitation. *Resuscitation*. 2015;92:70–76. doi: 10.1016/j.resuscitation.2015.04.016
- 7 88. Tanno K, Itoh Y, Takeyama Y, Nara S, Mori K, Asai Y. Utstein style study of
8 cardiopulmonary bypass after cardiac arrest. *Am J Emerg Med*. 2008;26:649–654. doi:
9 10.1016/j.ajem.2007.09.019
- 10 89. Venturini JM, Retzer E, Estrada JR, Friant J, Beiser D, Edelson D, Paul J, Blair J, Nathan
11 S, Shah AP. Mechanical chest compressions improve rate of return of spontaneous circulation
12 and allow for initiation of percutaneous circulatory support during cardiac arrest in the cardiac
13 catheterization laboratory. *Resuscitation*. 2017;115:56–60. doi:
14 10.1016/j.resuscitation.2017.03.037
- 15 90. Yannopoulos D, Bartos JA, Martin C, Raveendran G, Missov E, Conterato M, Frascione
16 RJ, Trembley A, Sipprell K, John R, George S, Carlson K, Brunsvold ME, Garcia S,
17 Aufderheide TP. Minnesota Resuscitation Consortium's advanced perfusion and reperfusion
18 cardiac life support strategy for out-of-hospital refractory ventricular fibrillation. *J Am Heart*
19 *Assoc*. 2016;5. doi: 10.1161/JAHA.116.003732
- 20 91. Yannopoulos D, Bartos JA, Raveendran G, Conterato M, Frascione RJ, Trembley A, John
21 R, Connett J, Benditt DG, Lurie KG, Wilson RF, Aufderheide TP. Coronary artery disease in
22 patients with out-of-hospital refractory ventricular fibrillation cardiac arrest. *J Am Coll Cardiol*.
23 2017;70:1109–1117. doi: 10.1016/j.jacc.2017.06.059

- 1 92. Blumenstein J, Leick J, Liebetrau C, Kempfert J, Gaede L, Gross S, Krug M,
2 Berkowitsch A, Nef H, Rolf A, Arlt M, Walther T, Hamm CW, Mollmann H. Extracorporeal life
3 support in cardiovascular patients with observed refractory in-hospital cardiac arrest is associated
4 with favourable short and long-term outcomes: a propensity-matched analysis. *Eur Heart J Acute*
5 *Cardiovasc Care*. 2016;5:13–22. doi: 10.1177/2048872615612454
- 6 93. Chen YS, Lin JW, Yu HY, Ko WJ, Jerng JS, Chang WT, Chen WJ, Huang SC, Chi NH,
7 Wang CH, Chen LC, Tsai PR, Wang SS, Hwang JJ, Lin FY. Cardiopulmonary resuscitation with
8 assisted extracorporeal life-support versus conventional cardiopulmonary resuscitation in adults
9 with in-hospital cardiac arrest: an observational study and propensity analysis. *Lancet*.
10 2008;372:554–561. doi: 10.1016/S0140-6736(08)60958-7
- 11 94. Cho YH, Kim WS, Sung K, Jeong DS, Lee YT, Park PW, Kim DK. Management of
12 cardiac arrest caused by acute massive pulmonary thromboembolism: importance of
13 percutaneous cardiopulmonary support. *ASAIO J*. 2014;60:280–283. doi:
14 10.1097/MAT.0000000000000063
- 15 95. Lin JW, Wang MJ, Yu HY, Wang CH, Chang WT, Jerng JS, Huang SC, Chou NK, Chi
16 NH, Ko WJ, Wang YC, Wang SS, Hwang JJ, Lin FY, Chen YS. Comparing the survival
17 between extracorporeal rescue and conventional resuscitation in adult in-hospital cardiac arrests:
18 propensity analysis of three-year data. *Resuscitation*. 2010;81:796–803. doi:
19 10.1016/j.resuscitation.2010.03.002
- 20 96. Shin TG, Choi JH, Jo IJ, Sim MS, Song HG, Jeong YK, Song YB, Hahn JY, Choi SH,
21 Gwon HC, Jeon ES, Sung K, Kim WS, Lee YT. Extracorporeal cardiopulmonary resuscitation in
22 patients with inhospital cardiac arrest: a comparison with conventional cardiopulmonary
23 resuscitation. *Crit Care Med*. 2011;39:1–7. doi: 10.1097/CCM.0b013e3181feb339

- 1 97. Chou TH, Fang CC, Yen ZS, Lee CC, Chen YS, Ko WJ, Wang CH, Wang SS, Chen SC.
2 An observational study of extracorporeal CPR for in-hospital cardiac arrest secondary to
3 myocardial infarction. *Emerg Med J*. 2014;31:441–447. doi: 10.1136/emered-2012-202173
- 4 98. Shin TG, Jo IJ, Sim MS, Song YB, Yang JH, Hahn JY, Choi SH, Gwon HC, Jeon ES,
5 Sung K, Lee YT, Choi JH. Two-year survival and neurological outcome of in-hospital cardiac
6 arrest patients rescued by extracorporeal cardiopulmonary resuscitation. *Int J Cardiol*.
7 2013;168:3424–3430. doi: 10.1016/j.ijcard.2013.04.183
- 8 99. Ro YS, Shin SD, Song KJ, Hong SO, Kim YT, Cho SI. Bystander cardiopulmonary
9 resuscitation training experience and self-efficacy of age and gender group: a nationwide
10 community survey. *Am J Emerg Med*. 2016;34:1331–1337. doi: 10.1016/j.ajem.2015.12.001
- 11 100. Bohm K, Vaillancourt C, Charette ML, Dunford J, Castrén M. In patients with out-of-
12 hospital cardiac arrest, does the provision of dispatch cardiopulmonary resuscitation instructions
13 as opposed to no instructions improve outcome: a systematic review of the literature.
14 *Resuscitation*. 2011;82:1490–1495. doi: 10.1016/j.resuscitation.2011.09.004
- 15 101. Leong BS. Bystander CPR and survival. *Singapore Med J*. 2011;52:573–575
- 16 102. Lerner EB, Rea TD, Bobrow BJ, Acker JE, 3rd, Berg RA, Brooks SC, Cone DC, Gay M,
17 Gent LM, Mears G, Nadkarni VM, O'Connor RE, Potts J, Sayre MR, Swor RA, Travers AH; on
18 behalf of the American Heart Association Emergency Cardiovascular Care Committee and the
19 Council on Cardiopulmonary, Critical Care, Perioperative and Resuscitation. Emergency medical
20 service dispatch cardiopulmonary resuscitation prearrival instructions to improve survival from
21 out-of-hospital cardiac arrest: a scientific statement from the American Heart Association.
22 *Circulation*. 2012;125:648–655. doi: 10.1161/CIR.0b013e31823ee5fc

- 1 103. Olasveengen TM, de Caen AR, Mancini ME, Maconochie IK, Aickin R, Atkins DL, Berg
2 RA, Bingham RM, Brooks SC, Castrén M, Chung SP, Considine J, Couto TB, Escalante R,
3 Gazmuri RJ, Guerguerian AM, Hatanaka T, Koster RW, Kudenchuk PJ, Lang E, Lim SH,
4 Løfgren B, Meaney PA, Montgomery WH, Morley PT, Morrison LJ, Nation KJ, Ng KC,
5 Nadkarni VM, Nishiyama C, Nuthall G, Ong GY, Perkins GD, Reis AG, Ristagno G, Sakamoto
6 T, Sayre MR, Schexnayder SM, Sierra AF, Singletary EM, Shimizu N, Smyth MA, Stanton D,
7 Tijssen JA, Travers A, Vaillancourt C, Van de Voorde P, Hazinski MF, Nolan JP; on behalf of
8 the ILCOR Collaborators. 2017 International Consensus on Cardiopulmonary Resuscitation and
9 Emergency Cardiovascular Care Science With Treatment Recommendations Summary.
10 *Circulation*. 2017;136:e424–e440. doi: 10.1161/CIR.0000000000000541
- 11 104. Nuthall G, Van de Voorde P, Atkins DL, Aickin RP, Bingham R, Couto TB, de Caen
12 AR, Guerguerian A-M, Meaney PA, Nadkarni VM, Ng KC, Nuthall GA, Ong GYK, Reis AG,
13 Schexnayder SM, Shimizu NS, Tijssen JA, Lavonas EJ, Ohshimo S, Nation K, Nolan J,
14 Morrison L, Maconochie IK. Advanced airway interventions in pediatric cardiac arrest–
15 Paediatric Consensus on Science with Treatment Recommendations 2019.
- 16 105. Gausche M, Lewis RJ, Stratton SJ, Haynes BE, Gunter CS, Goodrich SM, Poore PD,
17 McCollough MD, Henderson DP, Pratt FD, Seidel JS. Effect of out-of-hospital pediatric
18 endotracheal intubation on survival and neurological outcome: a controlled clinical trial. *JAMA*.
19 2000;283:783–790
- 20 106. Andersen LW, Raymond TT, Berg RA, Nadkarni VM, Grossestreuer AV, Kurth T,
21 Donnino MW; on behalf of the American Heart Association’s Get With The Guidelines–
22 Resuscitation Investigators. Association between tracheal intubation during pediatric in-hospital
23 cardiac arrest and survival. *JAMA*. 2016;316:1786–1797. doi: 10.1001/jama.2016.14486

- 1 107. Hansen ML, Lin A, Eriksson C, Daya M, McNally B, Fu R, Yanez D, Zive D, Newgard
2 C; and the CARES surveillance group. A comparison of pediatric airway management
3 techniques during out-of-hospital cardiac arrest using the CARES database. *Resuscitation*.
4 2017;120:51–56. doi: 10.1016/j.resuscitation.2017.08.015
- 5 108. Ohashi-Fukuda N, Fukuda T, Doi K, Morimura N. Effect of prehospital advanced airway
6 management for pediatric out-of-hospital cardiac arrest. *Resuscitation*. 2017;114:66–72. doi:
7 10.1016/j.resuscitation.2017.03.002
- 8 109. Abe T, Nagata T, Hasegawa M, Hagihara A. Life support techniques related to survival
9 after out-of-hospital cardiac arrest in infants. *Resuscitation*. 2012;83:612–618. doi:
10 10.1016/j.resuscitation.2012.01.024
- 11 110. Aijian P, Tsai A, Knopp R, Kallsen GW. Endotracheal intubation of pediatric patients by
12 paramedics. *Ann Emerg Med*. 1989;18:489–494
- 13 111. Deasy C, Bernard SA, Cameron P, Jaison A, Smith K, Harriss L, Walker T, Masci K,
14 Tibballs J. Epidemiology of paediatric out-of-hospital cardiac arrest in Melbourne, Australia.
15 *Resuscitation*. 2010;81:1095–1100. doi: 10.1016/j.resuscitation.2010.04.029
- 16 112. Del Castillo J, López-Herce J, Matamoros M, Cañadas S, Rodríguez-Calvo A, Cecchetti
17 C, Rodríguez-Nunez A, Álvarez AC; the Iberoamerican Pediatric Cardiac Arrest Study Network
18 RIBEPCI. Long-term evolution after in-hospital cardiac arrest in children: prospective
19 multicenter multinational study. *Resuscitation*. 2015;96:126–134. doi:
20 10.1016/j.resuscitation.2015.07.037
- 21 113. Guay J, Lortie L. An evaluation of pediatric in-hospital advanced life support
22 interventions using the pediatric Utstein guidelines: a review of 203 cardiorespiratory arrests.
23 *Can J Anaesth*. 2004;51:373–378. doi: 10.1007/BF03018242

- 1 114. Pitetti R, Glustein JZ, Bhende MS. Prehospital care and outcome of pediatric out-of-
2 hospital cardiac arrest. *Prehosp Emerg Care*. 2002;6:283–290
- 3 115. Sirbaugh PE, Pepe PE, Shook JE, Kimball KT, Goldman MJ, Ward MA, Mann DM. A
4 prospective, population-based study of the demographics, epidemiology, management, and
5 outcome of out-of-hospital pediatric cardiopulmonary arrest. *Ann Emerg Med*. 1999;33:174–184
- 6 116. Tham LP, Wah W, Phillips R, Shahidah N, Ng YY, Shin SD, Nishiuchi T, Wong KD, Ko
7 PC, Khunklai N, Naroo GY, Ong MEH. Epidemiology and outcome of paediatric out-of-hospital
8 cardiac arrests: a paediatric sub-study of the Pan-Asian resuscitation outcomes study (PAROS).
9 *Resuscitation*. 2018;125:111–117. doi: 10.1016/j.resuscitation.2018.01.040
- 10 117. Fink EL, Prince DK, Kaltman JR, Atkins DL, Austin M, Warden C, Hutchison J, Daya
11 M, Goldberg S, Herren H, Tijssen JA, Christenson J, Vaillancourt C, Miller R, Schmicker RH,
12 Callaway CW; on behalf of the Resuscitation Outcomes Consortium. Unchanged pediatric out-
13 of-hospital cardiac arrest incidence and survival rates with regional variation in North America.
14 *Resuscitation*. 2016;107:121–128. doi: 10.1016/j.resuscitation.2016.07.244
- 15 118. Tijssen JA, Prince DK, Morrison LJ, Atkins DL, Austin MA, Berg R, Brown SP,
16 Christenson J, Egan D, Fedor PJ, Fink EL, Meckler GD, Osmond MH, Sims KA, Hutchison JS;
17 on behalf of the Resuscitation Outcomes Consortium. Time on the scene and interventions are
18 associated with improved survival in pediatric out-of-hospital cardiac arrest. *Resuscitation*.
19 2015;94:1–7. doi: 10.1016/j.resuscitation.2015.06.012
- 20 119. Friedrich JO, Adhikari NK, Beyene J. Inclusion of zero total event trials in meta-analyses
21 maintains analytic consistency and incorporates all available data. *BMC Med Res Methodol*.
22 2007;7:5. doi: 10.1186/1471-2288-7-5

- 1 120. Fink EL, Clark RS, Kochanek PM, Bell MJ, Watson RS. A tertiary care center's
2 experience with therapeutic hypothermia after pediatric cardiac arrest. *Pediatr Crit Care Med*.
3 2010;11:66–74. doi: 10.1097/PCC.0b013e3181c58237
- 4 121. de Caen AR, Maconochie IK, Aickin R, Atkins DL, Biarent D, Guerguerian AM,
5 Kleinman ME, Kloeck DA, Meaney PA, Nadkarni VM, Ng KC, Nuthall G, Reis AG, Shimizu N,
6 Tibballs J, Veliz Pintos R; on behalf of the Pediatric Basic Life Support and Pediatric Advanced
7 Life Support Chapter Collaborators. Part 6: pediatric basic life support and pediatric advanced
8 life support: 2015 International Consensus on Cardiopulmonary Resuscitation and Emergency
9 Cardiovascular Care Science With Treatment Recommendations. *Circulation*. 2015;132(suppl
10 1):S177–S1203. doi: 10.1161/CIR.0000000000000275
- 11 122. Guerguerian AM, de Caen AR, Aickin RP, Tijssen JA, Atkins DL, Bingham R, Couto
12 TB, Meaney PA, Nadkarni VM, Ng KC, Nuthall GA, Ong GYK, Reis AG, Schexnayder SM,
13 Shimizu NS, Van de Voorde P, Morley PT, Rabi Y, Andersen LW, Deakin CD, Maconochie IK.
14 Extracorporeal cardiopulmonary resuscitation (ECPR) for cardiac arrest – Pediatric Consensus
15 on Science with Treatment Recommendations 2019;2019.
- 16 123. Lasa JJ, Rogers RS, Localio R, Shults J, Raymond T, Gaies M, Thiagarajan R, Laussen
17 PC, Kilbaugh T, Berg RA, Nadkarni V, Topjian A. Extracorporeal cardiopulmonary resuscitation
18 (E-CPR) during pediatric in-hospital cardiopulmonary arrest is associated with improved
19 survival to discharge: a report from the American Heart Association's Get With The Guidelines-
20 Resuscitation (GWTG-R) Registry. *Circulation*. 2016;133:165–176. doi:
21 10.1161/CIRCULATIONAHA.115.016082
- 22 124. Ortmann L, Prophan P, Gossett J, Schexnayder S, Berg R, Nadkarni V, Bhutta A; on
23 behalf of the American Heart Association's Get With the Guidelines–Resuscitation Investigators.

- 1 Outcomes after in-hospital cardiac arrest in children with cardiac disease: a report from Get With
2 the Guidelines–Resuscitation. *Circulation*. 2011;124:2329–2337. doi:
3 10.1161/CIRCULATIONAHA.110.013466
- 4 125. Alsoufi B, Al-Radi OO, Nazer RI, Gruenwald C, Foreman C, Williams WG, Coles JG,
5 Caldarone CA, Bohn DG, Van Arsdell GS. Survival outcomes after rescue extracorporeal
6 cardiopulmonary resuscitation in pediatric patients with refractory cardiac arrest. *J Thorac*
7 *Cardiovasc Surg*. 2007;134:952–959. doi: 10.1016/j.jtcvs.2007.05.054
- 8 126. Turek JW, Andersen ND, Lawson DS, Bonadonna D, Turley RS, Peters MA, Jaggars J,
9 Lodge AJ. Outcomes before and after implementation of a pediatric rapid-response
10 extracorporeal membrane oxygenation program. *Ann Thorac Surg*. 2013;95:2140–2146. doi:
11 10.1016/j.athoracsur.2013.01.050
- 12 127. del Nido PJ, Dalton HJ, Thompson AE, Siewers RD. Extracorporeal membrane
13 oxygenator rescue in children during cardiac arrest after cardiac surgery. *Circulation*.
14 1992;86(suppl):II300–II304
- 15 128. Dalton HJ, Siewers RD, Fuhrman BP, Del Nido P, Thompson AE, Shaver MG, Dowhy
16 M. Extracorporeal membrane oxygenation for cardiac rescue in children with severe myocardial
17 dysfunction. *Crit Care Med*. 1993;21:1020–1028
- 18 129. Duncan BW, Ibrahim AE, Hraska V, del Nido PJ, Laussen PC, Wessel DL, Mayer JE Jr,
19 Bower LK, Jonas RA. Use of rapid-deployment extracorporeal membrane oxygenation for the
20 resuscitation of pediatric patients with heart disease after cardiac arrest. *J Thorac Cardiovasc*
21 *Surg*. 1998;116:305–311

- 1 130. Mahle WT, Forbess JM, Kirshbom PM, Cuadrado AR, Simsic JM, Kanter KR. Cost-
2 utility analysis of salvage cardiac extracorporeal membrane oxygenation in children. *J Thorac*
3 *Cardiovasc Surg*. 2005;129:1084–1090. doi: 10.1016/j.jtcvs.2004.08.012
- 4 131. Lowry AW, Morales DL, Graves DE, Knudson JD, Shamszad P, Mott AR, Cabrera AG,
5 Rossano JW. Characterization of extracorporeal membrane oxygenation for pediatric cardiac
6 arrest in the United States: analysis of the kids' inpatient database. *Pediatr Cardiol*.
7 2013;34:1422–1430. doi: 10.1007/s00246-013-0666-8
- 8 132. Aickin RP, de Caen AR, Atkins DL, Bingham R, Couto TB, Guerguerian A-M, Hazinski
9 MF, Lavonas E, Meaney PA, Nadkarni VM, Ng KC, Nuthall GA, Ohshimo S, Ong GYK, Reis
10 AG, Schexnayder SM, Scholefield Barney, Shimizu NS, Tijssen JA, Van de Voorde P, Buick JE,
11 Welsford M, Maconochie I; on behalf of the International Liaison Committee on Resuscitation
12 Pediatric Life Support Task Force. Pediatric targeted temperature management post cardiac
13 arrest 2019.
- 14 133. Varni JW. The PedsQL Measurement Model for the Quality of Life Inventory.
- 15 134. Raat H, Landgraf JM, Oostenbrink R, Moll HA, Essink-Bot ML. Reliability and validity
16 of the Infant and Toddler Quality of Life Questionnaire (ITQOL) in a general population and
17 respiratory disease sample. *Qual Life Res*. 2007;16:445–460. doi: 10.1007/s11136-006-9134-8
- 18 135. Moler FW, Silverstein FS, Holubkov R, Slomine BS, Christensen JR, Nadkarni VM,
19 Meert KL, Browning B, Pemberton VL, Page K, Gildea MR, Scholefield BR, Shankaran S,
20 Hutchison JS, Berger JT, Ofori-Amanfo G, Newth CJ, Topjian A, Bennett KS, Koch JD, Pham
21 N, Chanani NK, Pineda JA, Harrison R, Dalton HJ, Alten J, Schleien CL, Goodman DM,
22 Zimmerman JJ, Bhalala US, Schwarz AJ, Porter MB, Shah S, Fink EL, McQuillen P, Wu T,
23 Skellett S, Thomas NJ, Nowak JE, Baines PB, Pappachan J, Mathur M, Lloyd E, van der Jagt

- 1 EW, Dobyns EL, Meyer MT, Sanders RC Jr, Clark AE, Investigators DJ, Jobot TT. Therapeutic
2 hypothermia after in-hospital cardiac arrest in children. *N Engl J Med*. 2017;376:318–329. doi:
3 10.1056/NEJMoa1610493
- 4 136. Moler FW, Silverstein FS, Holubkov R, Slomine BS, Christensen JR, Nadkarni VM,
5 Meert KL, Clark AE, Browning B, Pemberton VL, Page K, Shankaran S, Hutchison JS, Newth
6 CJ, Bennett KS, Berger JT, Topjian A, Pineda JA, Koch JD, Schleien CL, Dalton HJ, Ofori-
7 Amanfo G, Goodman DM, Fink EL, McQuillen P, Zimmerman JJ, Thomas NJ, van der Jagt EW,
8 Porter MB, Meyer MT, Harrison R, Pham N, Schwarz AJ, Nowak JE, Alten J, Wheeler DS,
9 Bhalala US, Lidsky K, Lloyd E, Mathur M, Shah S, Wu T, Theodorou AA, Sanders RC, Jr.,
10 Dean JM, Investigators TT. Therapeutic hypothermia after out-of-hospital cardiac arrest in
11 children. *N Engl J Med*. 2015;372:1898–1908. doi: 10.1056/NEJMoa1411480
- 12 137. Chang I, Kwak YH, Shin SD, Ro YS, Lee EJ, Ahn KO, Kim do K. Therapeutic
13 hypothermia and outcomes in paediatric out-of-hospital cardiac arrest: a nationwide
14 observational study. *Resuscitation*. 2016;105:8–15. doi: 10.1016/j.resuscitation.2016.04.021
- 15 138. Cheng HH, Rajagopal SK, Sansevere AJ, McDavitt E, Wigmore D, Mecklosky J, Andren
16 K, Williams KA, Danehy A, Soul JS. Post-arrest therapeutic hypothermia in pediatric patients
17 with congenital heart disease. *Resuscitation*. 2018;126:83–89. doi:
18 10.1016/j.resuscitation.2018.02.022
- 19 139. Lin JJ, Hsia SH, Wang HS, Chiang MC, Lin KL. Therapeutic hypothermia associated
20 with increased survival after resuscitation in children. *Pediatr Neurol*. 2013;48:285–290. doi:
21 10.1016/j.pediatrneurol.2012.12.021
- 22 140. Lin JJ, Lin CY, Hsia SH, Wang HS, Chiang MC, Lin KL; the iCNS Group. 72-h
23 therapeutic hypothermia improves neurological outcomes in paediatric asphyxial out-of-hospital

- 1 cardiac arrest—an exploratory investigation. *Resuscitation*. 2018;133:180–186. doi:
2 10.1016/j.resuscitation.2018.08.019
- 3 141. Scholefield BR, Morris KP, Duncan HP, Perkins GD, Gosney J, Skone R, Sanders V,
4 Gao F. Evolution, safety and efficacy of targeted temperature management after pediatric cardiac
5 arrest. *Resuscitation*. 2015;92:19–25. doi: 10.1016/j.resuscitation.2015.04.007
- 6 142. Torres-Andres F, Fink EL, Bell MJ, Sharma MS, Yablonsky EJ, Sanchez-de-Toledo J.
7 Survival and long-term functional outcomes for children with cardiac arrest treated with
8 extracorporeal cardiopulmonary resuscitation. *Pediatr Crit Care Med*. 2018;19:451–458. doi:
9 10.1097/PCC.0000000000001524
- 10 143. Doherty DR, Parshuram CS, Gaboury I, Hoskote A, Lacroix J, Tucci M, Joffe A, Choong
11 K, Farrell R, Bohn DJ, Hutchison JS; on behalf of the Canadian Critical Care Trials Group.
12 Hypothermia therapy after pediatric cardiac arrest. *Circulation*. 2009;119:1492–1500. doi:
13 10.1161/CIRCULATIONAHA.108.791384
- 14 144. Moler FW, Hutchison JS, Nadkarni VM, Silverstein FS, Meert KL, Holubkov R, Page K,
15 Slomine BS, Christensen JR, Dean JM; and the Therapeutic Hypothermia After Pediatric Cardiac
16 Arrest Out-of-Hospital Trial Investigators. Targeted temperature management after pediatric
17 cardiac arrest due to drowning: outcomes and complications. *Pediatr Crit Care Med*.
18 2016;17:712–720. doi: 10.1097/PCC.0000000000000763
- 19 145. Saugstad OD. Room air resuscitation—two decades of neonatal research. *Early Hum Dev*.
20 2005;81:111–116. doi: 10.1016/j.earlhumdev.2004.10.009
- 21 146. Lorente-Pozo S, Parra-Llorca A, Núñez-Ramiro A, Cernada M, Hervás D, Boronat N,
22 Sandoval J, Vento M. The oxygen load supplied during delivery room stabilization of preterm

- 1 infants modifies the DNA methylation profile. *J Pediatr.* 2018;202:70–76. doi:
2 10.1016/j.jpeds.2018.07.009
- 3 147. Perlman JM, Wyllie J, Kattwinkel J, Atkins DL, Chameides L, Goldsmith JP, Guinsburg
4 R, Hazinski MF, Morley C, Richmond S, Simon WM, Singhal N, Szyld E, Tamura M, Velaphi
5 S; on behalf of the Neonatal Resuscitation Chapter Collaborators. Part 11: Neonatal
6 resuscitation: 2010 International Consensus on Cardiopulmonary Resuscitation and Emergency
7 Cardiovascular Care Science With Treatment Recommendations. *Circulation.* 2010;122(suppl
8 2):S516–S538. doi: 10.1161/CIRCULATIONAHA.110.971127
- 9 148. Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, Norris S, Falck-Ytter Y,
10 Glasziou P, DeBeer H, Jaeschke R, Rind D, Meerpohl J, Dahm P, Schünemann HJ. GRADE
11 guidelines: 1. Introduction—GRADE evidence profiles and summary of findings tables. *J Clin*
12 *Epidemiol.* 2011;64:383–394. doi: 10.1016/j.jclinepi.2010.04.026
- 13 149. Perlman JM, Wyllie J, Kattwinkel J, Wyckoff MH, Aziz K, Guinsburg R, Kim HS, Liley
14 HG, Mildenhall L, Simon WM, Szyld E, Tamura M, Velaphi S; on behalf of the Neonatal
15 Resuscitation Chapter Collaborators. Part 7: Neonatal Resuscitation: 2015 International
16 Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science
17 With Treatment Recommendations. *Circulation.* 2015;132 (suppl 1):S204–S241. doi:
18 10.1161/CIR.0000000000000276
- 19 150. Sarnat HB, Sarnat MS. Neonatal encephalopathy following fetal distress: a clinical and
20 electroencephalographic study. *Arch Neurol.* 1976;33:696–705.
- 21 151. Isayama T, Dawson JA, Roehr CC, Rabi Y, Weiner GM, Aziz K, Kapadia VS, de
22 Almeida MF, Trevisanuto D, Mildenhall L, Liley HG, Hosono S, Kim HS, Szyld E, Perlman JM,

- 1 Velaphi S, Guinsburg R, Welsford M, Nishiyama C, Wyllie JP, Wyckoff MH. Initial oxygen
2 concentration for term neonatal resuscitation. 2019.
- 3 152. Ramji S, Ahuja S, Thirupuram S, Rootwelt T, Rooth G, Saugstad OD. Resuscitation of
4 asphyxic newborn infants with room air or 100% oxygen. *Pediatr Res*. 1993;34:809–812. doi:
5 10.1203/00006450-199312000-00023
- 6 153. Saugstad OD, Rootwelt T, Aalen O. Resuscitation of asphyxiated newborn infants with
7 room air or oxygen: an international controlled trial: the Resair 2 study. *Pediatrics*. 1998;102:e1.
- 8 154. Vento M, Asensi M, Sastre J, Lloret A, Garcia-Sala F, Viña J. Oxidative stress in
9 asphyxiated term infants resuscitated with 100% oxygen. *J Pediatr*. 2003;142:240–246
- 10 155. Ramji S, Rasaily R, Mishra PK, Narang A, Jayam S, Kapoor AN, Kambo I, Mathur A,
11 Saxena BN. Resuscitation of asphyxiated newborns with room air or 100% oxygen at birth: a
12 multicentric clinical trial. *Indian Pediatr*. 2003;40:510–517.
- 13 156. Bajaj N, Udani RH, Nanavati RN. Room air vs. 100 per cent oxygen for neonatal
14 resuscitation: a controlled clinical trial. *J Trop Pediatr*. 2005;51:206–211. doi:
15 10.1093/tropej/fmh086
- 16 157. Vento M, Sastre J, Asensi MA, Viña J. Room-air resuscitation causes less damage to
17 heart and kidney than 100% oxygen. *Am J Respir Crit Care Med*. 2005;172:1393–1398. doi:
18 10.1164/rccm.200412-1740OC
- 19 158. Toma AI, Nanea M, Scheiner M, Mitu R, Petrescu I, Matu E. Effects of the gas used in
20 the resuscitation of the newborn in the post-resuscitation haemodynamics. *Asfixia Perinatale*
21 *Primul Congres National de Neonatologie*. 2006:33–44

- 1 159. Saugstad OD, Ramji S, Irani SF, El-Meneza S, Hernandez EA, Vento M, Talvik T,
2 Solberg R, Rootwelt T, Aalen OO. Resuscitation of newborn infants with 21% or 100% oxygen:
3 follow-up at 18 to 24 months. *Pediatrics*. 2003;112:296–300
- 4 160. Kapadia V, Wyckoff MH. Oxygen therapy in the delivery room: what is the right dose?
5 *Clin Perinatol*. 2018;45:293–306. doi: 10.1016/j.clp.2018.01.014
- 6 161. International Committee for the Classification of Retinopathy of Prematurity. The
7 International Classification of Retinopathy of Prematurity revisited. *Arch Ophthalmol*.
8 2005;123:991–999. doi: 10.1001/archophth.123.7.991
- 9 162. Walsh MC, Kliegman RM. Necrotizing enterocolitis: treatment based on staging criteria.
10 *Pediatr Clin North Am*. 1986;33:179–201
- 11 163. Higgins RD, Jobe AH, Koso-Thomas M, Bancalari E, Viscardi RM, Hartert TV, Ryan
12 RM, Kallapur SG, Steinhorn RH, Konduri GG, Davis SD, Thebaud B, Clyman RI, Collaco JM,
13 Martin CR, Woods JC, Finer NN, Raju TNK. Bronchopulmonary dysplasia: Executive summary
14 of a workshop. *J Pediatr*. 2018;197:300–308. doi: 10.1016/j.jpeds.2018.01.043
- 15 164. Papile LA, Burstein J, Burstein R, Koffler H. Incidence and evolution of subependymal
16 and intraventricular hemorrhage: a study of infants with birth weights less than 1,500 gm. *J*
17 *Pediatr*. 1978;92:529–534
- 18 165. Lundstrøm KE, Pryds O, Greisen G. Oxygen at birth and prolonged cerebral
19 vasoconstriction in preterm infants. *Arch Dis Child Fetal Neonatal Ed*. 1995;73:F81–F86.
- 20 166. Wang CL, Anderson C, Leone TA, Rich W, Govindaswami B, Finer NN. Resuscitation
21 of preterm neonates by using room air or 100% oxygen. *Pediatrics*. 2008;121:1083–1089. doi:
22 10.1542/peds.2007-1460

- 1 167. Vento M, Moro M, Escrig R, Arruza L, Villar G, Izquierdo I, Roberts LJ II, Arduini A,
2 Escobar JJ, Sastre J, Asensi MA. Preterm resuscitation with low oxygen causes less oxidative
3 stress, inflammation, and chronic lung disease. *Pediatrics*. 2009;124:e439–e449. doi:
4 10.1542/peds.2009-0434
- 5 168. Rabi Y, Singhal N, Nettel-Aguirre A. Room-air versus oxygen administration for
6 resuscitation of preterm infants: the ROAR study. *Pediatrics*. 2011;128:e374–e381. doi:
7 10.1542/peds.2010-3130
- 8 169. Armanian AM, Badiie Z. Resuscitation of preterm newborns with low concentration
9 oxygen versus high concentration oxygen. *J Res Pharm Pract*. 2012;1:25–29. doi: 10.4103/2279-
10 042X.99674
- 11 170. Kapadia VS, Chalak LF, Sparks JE, Allen JR, Savani RC, Wyckoff MH. Resuscitation of
12 preterm neonates with limited versus high oxygen strategy. *Pediatrics*. 2013;132:e1488–e1496.
13 doi: 10.1542/peds.2013-0978
- 14 171. Aguar M, Escobar J, Kuligowski J, Inondo M, Izquierdo M, Nunez A, et al. Preterm
15 babies randomly assigned to be blindly resuscitated with higher (60%) vs. lower (30%) initial
16 F_{iO_2} : effects on oxidative stress and mortality. Abstract presented at the 2013 Pediatric Academic
17 Societies Annual Meeting; Vancouver, BC.
- 18 172. Rook D, Schierbeek H, Vento M, Vlaardingerbroek H, van der Eijk AC, Longini M,
19 Buonocore G, Escobar J, van Goudoever JB, Vermeulen MJ. Resuscitation of preterm infants
20 with different inspired oxygen fractions. *J Pediatr*. 2014;164:1322–1326. doi:
21 10.1016/j.jpeds.2014.02.019
- 22 173. Oei JL, Saugstad OD, Lui K, Wright IM, Smyth JP, Craven P, Wang YA, McMullan R,
23 Coates E, Ward M, Mishra P, De Waal K, Travadi J, See KC, Cheah IG, Lim CT, Choo YM,

- 1 Kamar AA, Cheah FC, Masoud A, Tarnow-Mordi W. Targeted oxygen in the resuscitation of
2 preterm infants, a randomized clinical trial. *Pediatrics*. 2017;139.:e20161452. doi:
3 10.1542/peds.2016-1452
- 4 174. Harling AE, Beresford MW, Vince GS, Bates M, Yoxall CW. Does the use of 50%
5 oxygen at birth in preterm infants reduce lung injury? *Arch Dis Child Fetal Neonatal Ed*.
6 2005;90:F401–F405. doi: 10.1136/adc.2004.059287
- 7 175. Dawson JA, Kamlin CO, Wong C, te Pas AB, O'Donnell CP, Donath SM, Davis PG,
8 Morley CJ. Oxygen saturation and heart rate during delivery room resuscitation of infants <30
9 weeks' gestation with air or 100% oxygen. *Arch Dis Child Fetal Neonatal Ed*. 2009;94:F87–F91.
10 doi: 10.1136/adc.2008.141341
- 11 176. Rabi Y, Lodha A, Soraisham A, Singhal N, Barrington K, Shah PS. Outcomes of preterm
12 infants following the introduction of room air resuscitation. *Resuscitation*. 2015;96:252–259.
13 doi: 10.1016/j.resuscitation.2015.08.012
- 14 177. Soraisham AS, Rabi Y, Shah PS, Singhal N, Synnes A, Yang J, Lee SK, Lodha AK.
15 Neurodevelopmental outcomes of preterm infants resuscitated with different oxygen
16 concentration at birth. *J Perinatol*. 2017;37:1141–1147. doi: 10.1038/jp.2017.83
- 17 178. Kapadia VS, Lal CV, Kakkilaya V, Heyne R, Savani RC, Wyckoff MH. Impact of the
18 Neonatal Resuscitation Program–recommended low oxygen strategy on outcomes of infants born
19 preterm. *J Pediatr*. 2017;191:35–41. doi: 10.1016/j.jpeds.2017.08.074
- 20 179. Roehr CC, Weiner GM, Isayama T, Dawson JA, Rabi Y, Kapadia VS, de Almeida MF,
21 Trevisanuto D, Mildenhall L, Liley HG, Hosono S, Kim HS, Szyld E, Perlman JM, Aziz K,
22 Velaphi S, Guinsburg R, Welsford M, Nishiyama C, Wyllie JP, Wyckoff MH. Initial oxygen
23 concentration for preterm neonatal resuscitation. 2019.

- 1 180. Boronat N, Aguar M, Rook D, Iriondo M, Brugada M, Cernada M, Nuñez A, Izquierdo
2 M, Cubells E, Martinez M, Parra A, van Goudoever H, Vento M. Survival and
3 neurodevelopmental outcomes of preterms resuscitated with different oxygen fractions.
4 *Pediatrics*. 2016;138. doi: 10.1542/peds.2016-1405
- 5 181. Thamrin V, Saugstad OD, Tarnow-Mordi W, Wang YA, Lui K, Wright IM, De Waal K,
6 Travadi J, Smyth JP, Craven P, McMullan R, Coates E, Ward M, Mishra P, See KC, Cheah IGS,
7 Lim CT, Choo YM, Kamar AA, Cheah FC, Masoud A, Oei JL. Preterm infant outcomes after
8 randomization to initial resuscitation with F_{iO_2} 0.21 or 1.0. *J Pediatr*. 2018;201:55.e1–61.e1. doi:
9 10.1016/j.jpeds.2018.05.053
- 10 182. Munkeby BH, Børke WB, Bjornland K, Sikkeland LI, Borge GI, Halvorsen B, Saugstad
11 OD. Resuscitation with 100% O_2 increases cerebral injury in hypoxemic piglets. *Pediatr Res*.
12 2004;56:783–790. doi: 10.1203/01.PDR.0000141988.89820.E3
- 13 183. Matsuyama T, Kiyohara K, Kitamura T, Nishiyama C, Nishiuchi T, Hayashi Y,
14 Kawamura T, Ohta B, Iwami T. Hospital characteristics and favourable neurological outcome
15 among patients with out-of-hospital cardiac arrest in Osaka, Japan. *Resuscitation*. 2017;110:146–
16 153. doi: 10.1016/j.resuscitation.2016.11.009
- 17 184. Tagami T, Hirata K, Takeshige T, Matsui J, Takinami M, Satake M, Satake S, Yui T,
18 Itabashi K, Sakata T, Tosa R, Kushimoto S, Yokota H, Hiramata H. Implementation of the fifth
19 link of the chain of survival concept for out-of-hospital cardiac arrest. *Circulation*.
20 2012;126:589–597. doi: 10.1161/CIRCULATIONAHA.111.086173
- 21 185. Bhanji F, Finn JC, Lockey A, Monsieurs K, Frengley R, Iwami T, Lang E, Ma MH,
22 Mancini ME, McNeil MA, Greif R, Billi JE, Nadkarni VM, Bigham B; on behalf of the
23 Education, Implementation, and Teams Chapter Collaborators. Part 8: education,

- 1 implementation, and teams: 2015 International Consensus on Cardiopulmonary Resuscitation
2 and Emergency Cardiovascular Care Science With Treatment Recommendations. *Circulation*.
3 2015;132(suppl 1):S242–S268. doi: 10.1161/CIR.0000000000000277
- 4 186. Finn JC, Bhanji F, Lockey A, Monsieurs K, Frengley R, Iwami T, Lang E, Ma MH,
5 Mancini ME, McNeil MA, Greif R, Billi JE, Nadkarni VM, Bigham B; on behalf of the
6 Education, Implementation, and Teams Chapter Collaborators. Part 8: education,
7 implementation, and teams: 2015 International Consensus on Cardiopulmonary Resuscitation
8 and Emergency Cardiovascular Care Science with Treatment Recommendations. *Resuscitation*.
9 2015;95:e203–e224. doi: 10.1016/j.resuscitation.2015.07.046
- 10 187. Yeung J, Bray J, Reynolds J, Matsuyama T, Skrifvars M, Lang E, Singletary E, Lockey
11 A, Pellegrino J, Gilfoyle E, Duff J, M H, Monsieurs K, Breckwoldt J, Iwami T, Bigham B,
12 Okamoto D, Ma M, Ong M, Bhanji F, Greif R; on behalf of the ALS and EIT Task Forces.
13 Cardiac arrest centers versus non-cardiac arrest centers—adults. 2019.
- 14 188. Seiner J, Polasek R, Lejsek J, Strycek M, Karasek J. Cardiac arrest center—one-year
15 experience of the Regional Hospital Liberec. *Cor et Vasa*. 2018;60:;60:e234–e238
- 16 189. Kragholm K, Malta Hansen C, Dupre ME, Xian Y, Strauss B, Tyson C, Monk L, Corbett
17 C, Fordyce CB, Pearson DA, Fosbøl EL, Jollis JG, Abella BS, McNally B, Granger CB. Direct
18 transport to a percutaneous cardiac intervention center and outcomes in patients with out-of-
19 hospital cardiac arrest. *Circ Cardiovasc Qual Outcomes*. 2017;10:e003414. doi:
20 10.1161/CIRCOUTCOMES.116.003414
- 21 190. Spaite DW, Bobrow BJ, Stolz U, Berg RA, Sanders AB, Kern KB, Chikani V, Humble
22 W, Mullins T, Stapczynski JS, Ewy GA; on behalf of the Arizona Cardiac Receiving Center
23 Consortium. Statewide regionalization of postarrest care for out-of-hospital cardiac arrest:

- 1 association with survival and neurologic outcome. *Ann Emerg Med.* 2014;64:496–506. doi:
2 10.1016/j.annemergmed.2014.05.028
- 3 191. Couper K, Kimani PK, Gale CP, Quinn T, Squire IB, Marshall A, Black JJM, Cooke
4 MW, Ewings B, Long J, Perkins GD. Patient, health service factors and variation in mortality
5 following resuscitated out-of-hospital cardiac arrest in acute coronary syndrome: analysis of the
6 Myocardial Ischaemia National Audit Project. *Resuscitation.* 2018;124:49–57. doi:
7 10.1016/j.resuscitation.2018.01.011
- 8 192. Søholm H, Kjaergaard J, Bro-Jeppesen J, Hartvig-Thomsen J, Lippert F, Køber L,
9 Nielsen N, Engsig M, Steensen M, Wanscher M, Karlens FM, Hassager C. Prognostic
10 implications of level-of-care at tertiary heart centers compared with other hospitals after
11 resuscitation from out-of-hospital cardiac arrest. *Circ Cardiovasc Qual Outcomes.* 2015;8:268–
12 276. doi: 10.1161/CIRCOUTCOMES.115.001767
- 13 193. Harnod D, Ma MHM, Chang WH, Chang RE, Chang CH. Mortality factors in out-of-
14 hospital cardiac arrest patients: a nationwide population-based study in Taiwan. *Int J*
15 *Gerontology.* 2013;7:216–220
- 16 194. Elmer J, Callaway CW, Chang CH, Madaras J, Martin-Gill C, Nawrocki P, Seaman
17 KAC, Sequeira D, Traynor OT, Venkat A, Walker H, Wallace DJ, Guyette FX. Long-term
18 outcomes of out-of-hospital cardiac arrest care at regionalized centers. *Ann Emerg Med.*
19 2019;73:29–39. doi: 10.1016/j.annemergmed.2018.05.018
- 20 195. Elmer J, Rittenberger JC, Coppler PJ, Guyette FX, Doshi AA, Callaway CW; and the
21 Pittsburgh Post-Cardiac Arrest Service. Long-term survival benefit from treatment at a specialty
22 center after cardiac arrest. *Resuscitation.* 2016;108:48–53. doi:
23 10.1016/j.resuscitation.2016.09.008

- 1 196. Brooks SC, Scales DC, Pinto R, Dainty KN, Racz EM, Gaudio M, Amaral AC, Gray SH,
2 Friedrich JO, Chapman M, Dorian P, Fam N, Fowler RA, Hayes CW, Baker A, Crystal E,
3 Madan M, Rubenfeld G, Smith OM, Morrison LJ. The postcardiac arrest consult team: impact on
4 hospital care processes for out-of-hospital cardiac arrest patients. *Crit Care Med.* 2016;44:2037–
5 2044. doi: 10.1097/CCM.0000000000001863
- 6 197. Andrew E, Nehme Z, Wolfe R, Bernard S, Smith K. Long-term survival following out-
7 of-hospital cardiac arrest. *Heart.* 2017;103:1104–1110. doi: 10.1136/heartjnl-2016-310485
- 8 198. Mumma BE, Diercks DB, Wilson MD, Holmes JF. Association between treatment at an
9 ST-segment elevation myocardial infarction center and neurologic recovery after out-of-hospital
10 cardiac arrest. *Am Heart J.* 2015;170:516–523. doi: 10.1016/j.ahj.2015.05.020
- 11 199. Tranberg T, Lippert FK, Christensen EF, Stengaard C, Hjort J, Lassen JF, Petersen F,
12 Jensen JS, Back C, Jensen LO, Ravkilde J, Bøtker HE, Terkelsen CJ. Distance to invasive heart
13 centre, performance of acute coronary angiography, and angioplasty and associated outcome in
14 out-of-hospital cardiac arrest: a nationwide study. *Eur Heart J.* 2017;38:1645–1652. doi:
15 10.1093/eurheartj/ehx104
- 16 200. Cournoyer A, Notebaert É, de Montigny L, Ross D, Cossette S, Londei-Leduc L, Iseppon
17 M, Lamarche Y, Sokoloff C, Potter BJ, Vadeboncoeur A, Larose D, Morris J, Daoust R, Chauny
18 JM, Piette É, Paquet J, Cavayas YA, de Champlain F, Segal E, Albert M, Guertin MC, Denault
19 A. Impact of the direct transfer to percutaneous coronary intervention-capable hospitals on
20 survival to hospital discharge for patients with out-of-hospital cardiac arrest. *Resuscitation.*
21 2018;125:28–33. doi: 10.1016/j.resuscitation.2018.01.048
- 22 201. Lick CJ, Aufderheide TP, Niskanen RA, Steinkamp JE, Davis SP, Nygaard SD,
23 Bemenderfer KK, Gonzales L, Kalla JA, Wald SK, Gillquist DL, Sayre MR, Osaki Holm SY,

- 1 Oakes DA, Provo TA, Racht EM, Olsen JD, Yannopoulos D, Lurie KG. Take Heart America: a
2 comprehensive, community-wide, systems-based approach to the treatment of cardiac arrest. *Crit*
3 *Care Med.* 2011;39:26–33. doi: 10.1097/CCM.0b013e3181fa7ce4
- 4 202. Stub D, Smith K, Bray JE, Bernard S, Duffy SJ, Kaye DM. Hospital characteristics are
5 associated with patient outcomes following out-of-hospital cardiac arrest. *Heart.* 2011;97:1489–
6 1494. doi: 10.1136/hrt.2011.226431
- 7 203. Chocron R, Bougouin W, Beganton F, Juvin P, Loeb T, Adnet F, Lecarpentier E,
8 Lamhaut L, Jost D, Marijon E, Cariou A, Jouven X, Dumas F. Are characteristics of hospitals
9 associated with outcome after cardiac arrest? Insights from the Great Paris registry.
10 *Resuscitation.* 2017;118:63–69. doi: 10.1016/j.resuscitation.2017.06.019
- 11 204. Lai CY, Lin FH, Chu H, Ku CH, Tsai SH, Chung CH, Chien WC, Wu CH, Chu CM,
12 Chang CW. Survival factors of hospitalized out-of-hospital cardiac arrest patients in Taiwan: a
13 retrospective study. *PLoS One.* 2018;13:e0191954. doi: 10.1371/journal.pone.0191954
- 14 205. Søholm H, Wachtell K, Nielsen SL, Bro-Jeppesen J, Pedersen F, Wanscher M, Boesgaard
15 S, Møller JE, Hassager C, Kjaergaard J. Tertiary centres have improved survival compared to
16 other hospitals in the Copenhagen area after out-of-hospital cardiac arrest. *Resuscitation.*
17 2013;84:162–167. doi: 10.1016/j.resuscitation.2012.06.029
- 18 206. McKenzie N, Williams TA, Ho KM, Inoue M, Bailey P, Celenza A, Fatovich D, Jenkins
19 I, Finn J. Direct transport to a PCI-capable hospital is associated with improved survival after
20 adult out-of-hospital cardiac arrest of medical aetiology. *Resuscitation.* 2018;128:76–82. doi:
21 10.1016/j.resuscitation.2018.04.039
- 22 207. Patterson T, Perkins GD, Joseph J, Wilson K, Van Dyck L, Robertson S, Nguyen H,
23 McConkey H, Whitbread M, Fothergill R, Nevett J, Dalby M, Rakhit R, MacCarthy P, Perera D,

- 1 Nolan JP, Redwood SR. A Randomised tRial of Expedited transfer to a cardiac arrest centre for
2 non-ST elevation ventricular fibrillation out-of-hospital cardiac arrest: the ARREST pilot
3 randomised trial. *Resuscitation*. 2017;115:185–191. doi: 10.1016/j.resuscitation.2017.01.020
4 208. Geri G, Gilgan J, Wu W, Vijendira S, Ziegler C, Drennan IR, Morrison L, Lin S. Does
5 transport time of out-of-hospital cardiac arrest patients matter? A systematic review and meta-
6 analysis. *Resuscitation*. 2017;115:96–101. doi: 10.1016/j.resuscitation.2017.04.003
7 209. Bartoletti A, Fabiani P, Bagnoli L, Cappelletti C, Cappellini M, Nappini G, Gianni R,
8 Lavacchi A, Santoro GM. Physical injuries caused by a transient loss of consciousness: main
9 clinical characteristics of patients and diagnostic contribution of carotid sinus massage. *Eur*
10 *Heart J*. 2008;29:618-624. doi: 10.1093/eurheartj/ehm563
11 210. Jensen JL, Cassan P, Meyran D, Ng KC, Ohshimo S, Singletary EM, Zideman DA,
12 Epstein JL, Bendall J, Berry DC, Carlson JN, Chang WT, Charlton NP, Hood NA, Markenson
13 DS, Woodin JA, Swain JM, Sakamoto T, Lang E; on behalf of the International Liaison
14 Committee on Resuscitation (ILCOR) First Aid Task Force and Pediatric Task Force. First aid
15 interventions for presyncope Consensus on Science With Treatment Recommendations. 2019.
16 211. Brignole M, Croci F, Menozzi C, Solano A, Donateo P, Oddone D, Puggioni E, Lolli G.
17 Isometric arm counter-pressure maneuvers to abort impending vasovagal syncope. *J Am Coll*
18 *Cardiol*. 2002;40:2053–2059
19 212. Alizadeh A, Peighambari M, Keikhavani A, Emkanjoo Z, Rad M, Ghadrdoost B,
20 Khabazian M. The role of acute physical maneuver in preventing vasovagal syncope: a
21 randomized clinical trial. *Clinic Cardia Electrophysiology*. 2016;1:e5348

- 1 213. Clarke DA, Medow MS, Taneja I, Ocon AJ, Stewart JM. Initial orthostatic hypotension
2 in the young is attenuated by static handgrip. *J Pediatr*. 2010;156:1019–1022. doi:
3 10.1016/j.jpeds.2010.01.035
- 4 214. Krediet CT, van Dijk N, Linzer M, van Lieshout JJ, Wieling W. Management of
5 vasovagal syncope: controlling or aborting faints by leg crossing and muscle tensing.
6 *Circulation*. 2002;106:1684–1689
- 7 215. Krediet CT, Go-Schön IK, van Lieshout JJ, Wieling W. Optimizing squatting as a
8 physical maneuver to prevent vasovagal syncope. *Clin Auton Res*. 2008;18:179–186. doi:
9 10.1007/s10286-008-0481-0
- 10 216. Kim KH, Cho JG, Lee KO, Seo TJ, Shon CY, Lim SY, Yun KH, Sohn IS, Hong YJ, Park
11 HW, Kim JH, Kim W, Ahn YK, Jeong MH, Park JC, Kang JC. Usefulness of physical
12 maneuvers for prevention of vasovagal syncope. *Circ J*. 2005;69:1084-1088
- 13 217. Croci F, Brignole M, Menozzi C, Solano A, Donateo P, Oddone D, Puggioni E, Lolli G.
14 Efficacy and feasibility of isometric arm counter-pressure manoeuvres to abort impending
15 vasovagal syncope during real life. *Europace*. 2004;6:287–291. doi: 10.1016/j.eupc.2004.03.008
16
17