Circulation

AHA FOCUSED UPDATE

2019 American Heart Association Focused Update on Advanced Cardiovascular Life Support: Use of Advanced Airways, Vasopressors, and Extracorporeal Cardiopulmonary Resuscitation During Cardiac Arrest

An Update to the American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care

ABSTRACT: The fundamentals of cardiac resuscitation include the immediate provision of high-quality cardiopulmonary resuscitation combined with rapid defibrillation (as appropriate). These mainstays of therapy set the groundwork for other possible interventions such as medications, advanced airways, extracorporeal cardiopulmonary resuscitation, and post–cardiac arrest care, including targeted temperature management, cardiorespiratory support, and percutaneous coronary intervention. Since 2015, an increased number of studies have been published evaluating some of these interventions, requiring a reassessment of their use and impact on survival from cardiac arrest. This 2019 focused update to the American Heart Association advanced cardiovascular life support guidelines summarizes the most recent published evidence for and recommendations on the use of advanced airways, vasopressors, and extracorporeal cardiopulmonary resuscitation during cardiac arrest. It includes revised recommendations for all 3 areas, including the choice of advanced airway devices and strategies during cardiac arrest (eg, bag-mask ventilation, supraglottic airway, or endotracheal intubation), the training and retraining required, the administration of standard-dose epinephrine, and the decisions involved in the application of extracorporeal cardiopulmonary resuscitation and its potential impact on cardiac arrest survival.

Ashish R. Panchal, MD, PhD, Chair
Katherine M. Berg, MD
Karen G. Hirsch, MD
Peter J. Kudenchuk, MD, FAHA
Marina Del Rios, MD, MSc
José G. Cabañas, MD, MPH
Mark S. Link, MD, FAHA
Michael C. Kurz, MD, MS, FAHA
Paul S. Chan, MD, MSc
Peter T. Morley, MBBS, FAHA
Mary Fran Hazinski, RN, MSN, FAHA
Michael W. Donnino, MD

Key Words: AHA Scientific Statements ■ advanced cardiac life support ■ airway management ■ cardiopulmonary resuscitation ■ extracorporeal membrane oxygenation ■ heart arrest ■ vasoconstrictor agents

https://www.ahajournals.org/journal/circ

This 2019 focused update to the American Heart Association advanced cardiovascular life support (ACLS) guidelines for cardiopulmonary resuscitation (CPR) and emergency cardiovascular care is based on the evidence identified in systematic reviews and the resulting "2019 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science With Treatment Recommendations" from the International Liaison Committee on Resuscitation (ILCOR).[1] The draft advanced life support Consensus on Science With Treatment Recommendations was posted online for public comment,[2–4] and a summary containing the final wording of the Consensus on Science With Treatment Recommendations has been published simultaneously with this focused update.[1]

The expert writing group for this 2019 ACLS focused update reviewed both the 2019 Consensus on Science With Treatment Recommendations web-based documents and the studies included in the systematic reviews.[5–7] The writing group discussion and evidence reviews were conducted in light of the structure and resources of the out-of-hospital and in-hospital resuscitation systems and the providers who use these ACLS guidelines. In addition, the writing group determined Classes of Recommendation and Levels of Evidence (Table) according to the most recent recommendations of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines[8] by using the process detailed in the "2015 American Heart Association Guidelines Update for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care."[9]

This 2019 document updates the recommendations for use of advanced airways, vasopressors, and extracorporeal CPR (ECPR) during cardiac arrest only. These updates are in addition to those published in the 2017 and 2018 guidelines focused updates.[10,11] All other recommendations and algorithms published in "Part 7: Adult Advanced Cardiovascular Life Support" in the 2015 AHA guidelines update[12] and "Part 8: Adult Advanced Cardiovascular Life Support" in the "2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care"[13] remain the official recommendations of the American Heart Association Emergency Cardiovascular Care Science Subcommittee and writing groups.

USE OF ADVANCED AIRWAYS IN CARDIAC ARREST

To use advanced airways effectively, healthcare providers must maintain their knowledge and skills through frequent practice. Airway management during cardiac arrest usually begins with a basic strategy such as bag-mask ventilation (BMV). In addition to BMV, it may be helpful for providers to master an advanced airway strategy and a second (backup) strategy for use if they are unable to establish the first-choice airway adjunct.

Once an advanced airway is inserted, providers should immediately perform a thorough assessment to ensure that the airway device is properly positioned and effective. This assessment should minimize interruption of chest compressions. Assessment by physical examination consists of visualizing chest expansion bilaterally and listening over the epigastrium (breath sounds should not be heard) and the lung fields bilaterally (breath sounds should be equal and adequate). A device should also be used to confirm correct placement (see the Endotracheal Intubation Versus BMV—Updated 2019 section).

Providers should observe a persistent capnographic waveform with ventilation to confirm and monitor endotracheal tube (ETT) placement in the field, in the transport vehicle, on arrival at the hospital, and after any patient transfer to reduce the risk of unrecognized tube misplacement or displacement.

The use of capnography to confirm and monitor correct placement of supraglottic airways (SGAs) has undergone limited evaluation, and its utility will depend on airway design.[14,15] However, effective ventilation through an SGA device should result in a capnograph waveform during CPR and after return of spontaneous circulation (ROSC).

Once an advanced airway is in place during cardiac arrest, the providers performing CPR should no longer deliver cycles of CPR (ie, compressions interrupted by pauses for ventilation). Instead, the compressing provider should give continuous chest compressions at a rate of 100 to 120 per minute without pauses for ventilation. Ventilation is then provided at a rate of 10 breaths per minute (1 breath every 6 seconds). Asynchronous breaths are delivered unless ventilation can only be delivered successfully when compressions are paused. Providers should avoid delivering excessive ventilation during CPR because doing so can compromise venous return and cardiac output and decrease cerebral blood flow by causing direct vasoconstriction.[16]

Choice of an Advanced Airway—Updated 2019

BMV without an advanced airway device may not allow adequate ventilation in all patients during resuscitation from cardiac arrest and does not protect against pulmonary aspiration of orogastric secretions. As a result, advanced airway devices are frequently placed by providers during CPR. However, placement of an advanced airway during active compressions is challenging, often requiring interruption of chest compressions. Emergent intubation may result in a

Circulation. 2019;140:00–00. DOI: 10.1161/CIR.0000000000000732

Table. Applying Class of Recommendation and Level of Evidence to Clinical Strategies, Interventions, Treatments, or Diagnostic Testing in Patient Care (Updated August 2015)*

CLASS (STRENGTH) OF RECOMMENDATION	LEVEL (QUALITY) OF EVIDENCE‡
CLASS 1 (STRONG) — **Benefit >>> Risk** **Suggested phrases for writing recommendations:** • Is recommended • Is indicated/useful/effective/beneficial • Should be performed/administered/other • Comparative-Effectiveness Phrases†: – Treatment/strategy A is recommended/indicated in preference to treatment B – Treatment A should be chosen over treatment B	**LEVEL A** • High-quality evidence‡ from more than 1 RCT • Meta-analyses of high-quality RCTs • One or more RCTs corroborated by high-quality registry studies
CLASS 2a (MODERATE) — **Benefit >> Risk** **Suggested phrases for writing recommendations:** • Is reasonable • Can be useful/effective/beneficial • Comparative-Effectiveness Phrases†: – Treatment/strategy A is probably recommended/indicated in preference to treatment B – It is reasonable to choose treatment A over treatment B	**LEVEL B-R (Randomized)** • Moderate-quality evidence‡ from 1 or more RCTs • Meta-analyses of moderate-quality RCTs
CLASS 2b (WEAK) — **Benefit ≥ Risk** **Suggested phrases for writing recommendations:** • May/might be reasonable • May/might be considered • Usefulness/effectiveness is unknown/unclear/uncertain or not well-established	**LEVEL B-NR (Nonrandomized)** • Moderate-quality evidence‡ from 1 or more well-designed, well-executed nonrandomized studies, observational studies, or registry studies • Meta-analyses of such studies
CLASS 3: No Benefit (MODERATE) (Generally, LOE A or B use only) — **Benefit = Risk** **Suggested phrases for writing recommendations:** • Is not recommended • Is not indicated/useful/effective/beneficial • Should not be performed/administered/other	**LEVEL C-LD (Limited Data)** • Randomized or nonrandomized observational or registry studies with limitations of design or execution • Meta-analyses of such studies • Physiological or mechanistic studies in human subjects
Class 3: Harm (STRONG) — **Risk > Benefit** **Suggested phrases for writing recommendations:** • Potentially harmful • Causes harm • Associated with excess morbidity/mortality • Should not be performed/administered/other	**LEVEL C-EO (Expert Opinion)** • Consensus of expert opinion based on clinical experience

COR and LOE are determined independently (any COR may be paired with any LOE).

A recommendation with LOE C does not imply that the recommendation is weak. Many important clinical questions addressed in guidelines do not lend themselves to clinical trials. Although RCTs are unavailable, there may be a very clear clinical consensus that a particular test or therapy is useful or effective.

* The outcome or result of the intervention should be specified (an improved clinical outcome or increased diagnostic accuracy or incremental prognostic information).

† For comparative-effectiveness recommendations (COR 1 and 2a; LOE A and B only), studies that support the use of comparator verbs should involve direct comparisons of the treatments or strategies being evaluated.

‡ The method of assessing quality is evolving, including the application of standardized, widely-used, and preferably validated evidence grading tools; and for systematic reviews, the incorporation of an Evidence Review Committee.

COR indicates Class of Recommendation; EO, expert opinion; LD, limited data; LOE, Level of Evidence; NR, nonrandomized; R, randomized; and RCT, randomized controlled trial.

malpositioned ETT or device. An ILCOR-commissioned systematic review[7] evaluated the effects on overall cardiac arrest survival and neurological outcome when providers used an advanced airway device such as an ETT or SGA compared with BMV and other airway management strategies during attempted resuscitation for out-of-hospital cardiac arrest (OHCA) and in-hospital cardiac arrest (IHCA).

Evidence Summary—Updated 2019

Endotracheal Intubation Versus BMV

One large randomized controlled trial (RCT) of 2043 subjects with OHCA compared BMV (with predefined potential rescue intubation) with endotracheal intubation (ETI) in a physician-based system.[17] The success rate of ETI in this study was 98%, illustrating what appears to be a relatively optimal setting for the potential success of ETI as an intervention. Within that context, there were no overall differences in 28-day survival (relative risk [RR], 1.02 [95% CI, 0.71–1.47]) or 28-day survival with favorable neurological function (RR, 1.03 [95% CI, 0.68–1.55]) between groups treated with ETI and with BMV.[17]

In addition to the randomized controlled study by Jabre et al,[17] the systematic review identified a number of observational studies evaluating the use of BMV compared with ETI.[7] Many of these studies suggested an association of ETI with worse outcome, but selection bias and confounding severely limit the certainty

of the data.[7] Confounding by indication is also problematic because ETI is more likely to be used in patients with more severe disease. Almost all studies had resuscitation or immortal time bias, which are forms of bias/confounding that can occur in observational studies evaluating an intervention if timing is not taken into account. The systematic review by Granfeldt et al,[7] the work of Donnino et al,[18] and the analysis by Lévesque et al[19] provide further information.

SGA Devices

Two large RCTs compared the use of an SGA strategy with an ETI placement strategy in non–physician-based emergency medical services systems.[20,21] There was significant heterogeneity in design across studies, precluding pooling of data. One RCT of 9296 subjects compared insertion of the i-gel (from Intersurgical Ltd, Berkshire, UK) SGA with ETI, finding no difference in survival (RR, 0.95 [95% CI, 0.82–1.10]) or survival with good neurological outcome (RR, 0.92 [95% CI, 0.77–1.09]) at hospital discharge.[20] The other RCT enrolled 3004 patients with OHCA and compared ETI with insertion of the laryngeal tube (from VBM Medizintechnik GmbH, Sulz am Neckar, Germany), finding both higher survival to hospital discharge (RR, 1.34 [95% CI, 1.07–1.68]; 27 more patients per 1000 [95% CI, 6–48]) and higher survival to hospital discharge with good neurological outcome (RR, 1.42 [95% CI, 1.07–1.89]; 21 more patients per 1000 [95% CI, 3–38]) at hospital discharge when the laryngeal tube was used.[21]

Although the Jabre et al[17] study illustrated high rates of ETI success (98%), the Benger et al[20] and Wang et al[21] studies were conducted in settings with much lower success rates. Specifically, the reported ETI success rate in the Benger et al trial was 69% and in the Wang et al trial was 52%. In addition, the definition of intubation success rate also differed among these trials. Similar to the method used in the systematic review,[7] we treated these trials as occurring in settings with historically high or low intubation success. With a historically lower success rate of ETI, the results of these latter studies may not accurately reflect the effectiveness of ETI compared with SGA devices.

Recommendations—Updated 2019

1. **Either BMV or an advanced airway strategy may be considered during CPR for adult cardiac arrest in any setting (*Class 2b; Level of Evidence B-R*).**
2. **If an advanced airway is used, the SGA can be used for adults with OHCA in settings with low tracheal intubation success rate or minimal training opportunities for ETT placement (*Class 2a; Level of Evidence B-R*).**
3. **If an advanced airway is used, either the SGA or ETT can be used for adults with OHCA in settings with high tracheal intubation success rates or optimal training opportunities for ETT placement (*Class 2a; Level of Evidence B-R*).**
4. **If an advanced airway is used in the in-hospital setting by expert providers trained in these procedures, either the SGA or ETT can be used (*Class 2a; Level of Evidence B-R*).**
5. **Frequent experience or frequent retraining is recommended for providers who perform ETI (*Class 1; Level of Evidence B-NR*).**
6. **Emergency medical services systems that perform prehospital intubation should provide a program of ongoing quality improvement to minimize complications and to track overall SGA and ETT placement success rates (*Class 1; Level of Evidence C-EO*).**

The RCTs included in this evaluation allowed for provider deviation based on clinical judgement, and a number of protocol deviations were, in fact, reported. It is impossible to assess the individual potential patient benefit (or harm) that guided each decision to place an advanced airway. Patient and provider characteristics can influence outcome on a case-by-case basis. For example, a provider with poor ETI skills would likely serve the patient better by not attempting ETI. Likewise, for a patient with witnessed in-hospital ventricular fibrillation, providers should prioritize immediate CPR with defibrillation as the definitive therapy over delaying defibrillation to allow placement of an advanced airway. In contrast, a patient with hypoxic-driven arrest with copious vomitus in the airway may require qualified providers to consider rapid ETI. Therefore, the ultimate decision on both the type and timing of an advanced airway will require consideration of a host of patient and provider characteristics that are not easily defined in a global recommendation. On the basis of these challenges, there is a specific need to better understand how patient characteristics interface with rescuer training, experience, technical tools, and skills to address and overcome specific challenges for advanced airway management during resuscitation.

Recommendations for advanced airway placement during cardiac arrest presume that the provider has the initial training and skills and the ongoing experience to insert the airway and to verify proper position with minimal interruption in chest compressions. BMV ventilation also requires skill and proficiency. Thus, the choice of BMV instead of advanced airway insertion will be determined by the skill and experience of the provider and the patient needs. An important aspect of all these airway management decisions must be a clear and distinct plan for situations in which the initial airway device fails.

Circulation. 2019;140:00–00. DOI: 10.1161/CIR.0000000000000732

The rationale for tracking the overall success rate for systems performing ETI is to make informed decisions as to whether practice should allow this procedure or move toward the use of an SGA for patients in cardiac arrest; recommendations will vary depending on the overall success rate in a given system. Furthermore, frequent experience and training are important to maintain high overall success rates for airway management and should be part of a system of ongoing quality improvement. At this time, there is insufficient evidence to make a specific recommendation about the ideal frequency of retraining. This is a knowledge gap that must be addressed in future investigations.

USE OF VASOPRESSORS IN CARDIAC ARREST

In 2018, ILCOR commissioned a systematic review and meta-analysis of vasopressor use during cardiac arrest as part of the focused update process to evaluate the published literature. This ILCOR systematic review, published in 2019,[5] addresses the use of the vasopressors epinephrine and vasopressin during cardiac arrest. The new recommendations in this 2019 ACLS focused update apply only to the use of these vasopressors for cardiac resuscitation.

Evidence Summary: Standard-Dose Epinephrine—Updated 2019

Epinephrine has been hypothesized to have beneficial effects during cardiac arrest primarily because of its α-adrenergic (ie, vasoconstrictor) effects. These effects can increase coronary and cerebral perfusion pressure during CPR. The value and safety of the β-adrenergic effects of epinephrine are controversial because they may increase myocardial oxygen demand and reduce subendocardial perfusion and may be proarrhythmic. Similarly, the α-adrenergic effects of the drug may cause vasoconstriction at a microvascular level, resulting in greater tissue ischemia.

The ACLS recommendations in the 2010 guidelines[13] and the 2015 AHA guidelines update[12] state that it is reasonable to consider administering a 1-mg dose of intravenous/intraosseous epinephrine every 3 to 5 minutes during adult CPR. At the time of the 2015 evidence evaluation, 1 RCT[22] demonstrated that epinephrine increased ROSC and hospital admission, but this trial was stopped early and was therefore underpowered to detect any differences in longer-term survival or good neurological outcome.[22]

Two RCTs[22,23] were identified in the 2019 systematic review that evaluated the effects of epinephrine in OHCA.[5] There were also a number of nonrandomized comparative studies, but high risk of bias and heterogeneity of design precluded combining them into a meta-analysis.[5]

The 2 RCTs[22,23] comparing use of epinephrine (up to 10 standard doses of 1 mg every 3–5 minutes) with placebo during cardiac arrest were included in a meta-analysis. In the pooled analyses, the use of epinephrine for patients with any initial rhythm significantly increased survival to hospital discharge (RR, 1.44 [95% CI, 1.11–1.86]; 10 more per 1000 [95% CI, 2–19]), survival to hospital admission (RR, 2.88 [95% CI, 2.57–3.22]; 156 more per 1000 [95% CI, 131–185]), and ROSC (RR, 3.09 [95% CI, 2.82–3.39]; 243 more per 1000 [95% CI, 211–277]).[5] However, there was no significant difference between groups in survival to hospital discharge with a favorable neurological outcome.

Only the larger, more recent RCT (PARAMEDIC 2 [A Randomized Trial of Epinephrine in Out-of-Hospital Cardiac Arrest]) looked at survival beyond hospital discharge, although the number of survivors was small. In this study, epinephrine improved survival at 30 days (RR, 1.40 [95% CI, 1.07–1.84]; 9 more per 1000 [95% CI, 2–18]). Although there was an increase in survivors with poor neurological function at discharge in the epinephrine group, there was no difference in survival with favorable or unfavorable neurological outcome at the 3-month time point. In fact, the difference in survival with favorable neurological outcome approached significance in the epinephrine group (RR, 1.30 [95% CI, 0.94–1.80]; 5 more per 1000 [95% CI, 1 fewer–13 more]).[23]

Epinephrine Effect and Arrest Rhythms

There may be a difference in epinephrine effect on favorable neurological outcomes on the basis of arrest rhythm. In the PARAMEDIC 2 trial, among those with nonshockable rhythm treated with epinephrine, the increase in survival with favorable neurological outcome at 3 months approached statistical significance (RR, 3.03 [95% CI, 0.98–9.38]; 3 more per 1000 [95% CI, 0 fewer–11 more]).[24] There was no difference in this outcome for those with shockable rhythms.

The systematic review also analyzed short-term outcomes in a pooled analysis of the 2 RCTs on the basis of presenting rhythm.[5] Such subgroup analysis, although informative, has limitations because the number of patients is small, so the analysis is underpowered, and accordingly, conclusions are less definitive than overall findings. In this analysis, epinephrine improved survival to hospital discharge in those with nonshockable rhythms (RR, 2.56 [95% CI, 1.37–4.80]; 6 more per 1000 [95% CI, 1–15]) but not in those with shockable rhythms. Epinephrine increased ROSC in patients with both nonshockable (RR, 4.45 [95% CI, 3.91–5.08]; 254 more per 1000 [95% CI, 214–301]) and shockable (RR, 1.68 [95% CI, 1.48–1.92]; 185 more per 1000 [95% CI, 130–250]) rhythms.[22,23] There was a statistically

significant interaction between epinephrine and initial rhythm, suggesting that epinephrine may be effective for nonshockable rhythms.[5]

Recommendation: Standard-Dose Epinephrine—Updated 2019

1. **We recommend that epinephrine be administered to patients in cardiac arrest (*Class 1; Level of Evidence B-R*). On the basis of the protocol used in clinical trials, it is reasonable to administer 1 mg every 3 to 5 minutes (*Class 2a; Level of Evidence C-LD*).**

The strength of the recommendation is based on the significant difference in 30-day survival and survival to hospital discharge, as well as the short-term outcomes of ROSC and survival to hospital admission. Although epinephrine has not been shown definitively to improve survival with favorable neurological outcome, this outcome was difficult to assess given the small number of evaluable subjects at the 3-month time point. However, results suggest possible benefit, particularly for patients with initial nonshockable rhythm. Although the PARAMEDIC 2 trial did not report any increase in long-term survival with unfavorable neurological outcome, there was an increase in short-term survival with unfavorable neurological outcome.[23] The very low survival rate with favorable neurological outcome at discharge (1.9%–2.2%) in this study[23] may not be generalizable to other healthcare systems or locations where survival may be higher; therefore, the impact of epinephrine could vary. Variations in post–cardiac arrest care may also have a substantial impact on outcomes of patients with OHCA who survive to hospital admission.[25] The significant improvements in ROSC, short-term survival, long-term survival, and potentially good neurological outcome support a strong recommendation for epinephrine despite some remaining uncertainty about the overall impact on neurological outcome.

The systematic review identified no RCTs testing epinephrine versus placebo in IHCA.[5] It is unclear in what way the results from the OHCA studies apply to IHCA; the potential impact of variations in timing of drug administration, presenting rhythms, and presence of immediately reversible factors also is unclear. Time to drug is markedly shorter in IHCA, suggesting that epinephrine may be more likely to be beneficial, particularly for nonshockable rhythms, but this remains unknown. Conversely, witnessed arrests, particularly if shockable, may be treatable without epinephrine, especially if a reversible cause is identified.

Finally, these evaluations did not address the potential importance of the mode of delivery of epinephrine (intraosseous versus intravenous) and whether a threshold dose of benefit or harm exists for epinephrine. These knowledge gaps need to be addressed and are important avenues for future research.

Evidence Summary: Standard Dose Epinephrine Versus High-Dose Epinephrine—Reviewed

High doses of epinephrine are generally defined as doses in the range of 0.1 to 0.2 mg/kg. In theory, higher doses of epinephrine may increase coronary perfusion pressure, resulting in increased ROSC and survival after cardiac arrest. However, the adverse effects of higher doses of epinephrine in the post–cardiac arrest period may negate potential advantages during the intra-arrest period. In the 2010 guidelines, the use of high-dose epinephrine was not recommended except in special circumstances such as for β-blocker or calcium channel blocker overdose or when titrated to real-time physiologically monitored parameters.[13] In 2015, ILCOR evaluated the use of high-dose epinephrine compared with standard doses,[25] and the 2015 AHA guidelines update recommended against its use with a strength of Class 3: No Benefit.[12]

A number of trials comparing high-dose with standard-dose epinephrine found that high-dose epinephrine failed to result in improvement in survival to discharge with favorable neurological outcome (ie, Cerebral Performance Category score 1–2),[26,27] survival to discharge,[26–30] or survival to hospital admission.[26,27,29,31] Some studies reported higher rates of short-term ROSC with high-dose epinephrine.[26–31]

For the 2019 review, ILCOR determined that unless new studies were identified that were not considered in the 2015 review on this topic, this comparison would not be rereviewed. In a systematic search, no new studies were identified; therefore, the 2015 recommendation remains unchanged.

Recommendation: Standard-Dose Epinephrine Versus High-Dose Epinephrine—Unchanged

1. **High-dose epinephrine is not recommended for routine use in cardiac arrest (*Class 3: No Benefit; Level of Evidence B-R*).**

Evidence Summary: Vasopressin Versus Epinephrine—Updated 2019

Vasopressin is a nonadrenergic peripheral vasoconstrictor that also causes coronary and renal vasoconstriction. Vasopressin was removed from the American Heart Association Adult Cardiac Arrest Algorithm in 2015 when initial trials[32,33] failed to demonstrate significant benefit for vasopressin compared with or in addition to epinephrine.

Circulation. 2019;140:00–00. DOI: 10.1161/CIR.0000000000000732

The 2019 vasopressor systematic review[5] identified 3 RCTs[32–34] that were evaluated in a meta-analysis and 1 additional trial not pooled,[35] comparing initial vasopressin with initial epinephrine during CPR. There was no significant difference between groups in any of the outcomes. The certainty of this evidence was low to very low as a result of heterogeneity in study design and imprecision resulting from small sample sizes.

Recommendation: Vasopressin Versus Epinephrine—Updated 2019

1. **Vasopressin may be considered in a cardiac arrest but offers no advantage as a substitute for epinephrine in cardiac arrest (*Class 2b; Level of Evidence C-LD*).**

The RCTs comparing initial vasopressin with initial epinephrine have failed to show any outcome benefit from the use of vasopressin compared with epinephrine. These trials were typically small, and even when combined in a meta-analysis, they do not approach the sample size that would be necessary to conclude definitively that vasopressin offers no benefit. There is evidence that epinephrine improves survival compared with placebo, and there is no such evidence for vasopressin compared with placebo. Because there is also no evidence that vasopressin is superior to epinephrine, it seems appropriate to use only epinephrine during cardiac arrest, thus maintaining greater simplicity for providers in the treatment algorithm and in the drugs required. It should be noted that the combination of vasopressin and steroids during cardiac arrest was not evaluated in the 2019 vasopressors update.

Evidence Summary: Epinephrine in Combination With Vasopressin Versus Epinephrine Only—Updated 2019

Three RCTs[36–38] were evaluated in a meta-analysis comparing the use of initial epinephrine plus vasopressin with epinephrine only during CPR.[5] There was no significant difference between groups for any of the outcomes. The low to very low certainty of evidence was the result of heterogeneity in study design, some inconsistency in results between studies, and imprecision resulting from smaller sample sizes. One other RCT was available for analysis and was not included in the meta-analysis because of a significant number of patients receiving epinephrine before randomization.[35]

Recommendation: Epinephrine in Combination With Vasopressin Versus Epinephrine Only—Updated 2019

1. **Vasopressin in combination with epinephrine may be considered during cardiac arrest but offers no advantage as a substitute for epinephrine alone (*Class 2b; Level of Evidence C-LD*).**

The RCTs comparing the combination of vasopressin and epinephrine with epinephrine alone have failed to show any benefit from the addition of vasopressin to epinephrine. However, these trials were typically small, and even when combined in a meta-analysis, they do not approach the sample size that would be necessary to conclude definitively that vasopressin offers no additional benefit. Because there is no evidence that vasopressin provides additional benefit when added to epinephrine, the consensus of the writing group was that the use of epinephrine alone as a vasopressor during cardiac arrest will maintain simplicity in the cardiac arrest treatment algorithm and the drugs required.

Evidence Summary: Timing of Epinephrine Administration—Updated 2019

No RCTs have directly investigated the optimal timing of epinephrine administration. Sixteen observational studies were identified on this topic, the majority of which were in patients with OHCA and all of which were deemed to have critical risk of bias, precluding a meta-analysis. Ten of these studies[18,39–47] compared early (variably defined as 1–3, <5, <10, 5–18, and 5–20 minutes) and late administration of the first dose of epinephrine. All found higher rates of ROSC when epinephrine was administered early. Differences in survival to hospital discharge and favorable neurological outcome were additionally limited by very low event rates and inconsistent results across studies. Four studies[48–51] evaluated time to first dose of epinephrine as a continuous variable, finding slightly lower odds of ROSC per 1-minute delay in epinephrine administration. Earlier treatment may encompass many variables apart from time itself. Among these, a higher level of overall performance by care providers (eg, high-quality CPR, rapid vascular access, improved team performance, and rapid airway management) could improve the overall efficiency of the resuscitation effort, for which the timing of epinephrine may merely serve as a surrogate.

Although neither of the RCTs comparing epinephrine with placebo evaluated the timing of epinephrine administration, the protocol in both cases was to administer epinephrine as soon as possible for nonshockable rhythms and after the third shock for shockable rhythms.[22,23]

Recommendations: Timing of Epinephrine Administration—Updated 2019

1. **With respect to timing, for cardiac arrest with a nonshockable rhythm, it is reasonable**

to administer epinephrine as soon as feasible (*Class 2a; Level of Evidence C-LD*).

2. **With respect to timing, for cardiac arrest with a shockable rhythm, it may be reasonable to administer epinephrine after initial defibrillation attempts have failed (*Class 2b; Level of Evidence C-LD*).**

The lack of other competing beneficial interventions for nonshockable rhythms and the higher rates of ROSC and survival with epinephrine in nonshockable rhythms form the basis of the Class 2a recommendation for epinephrine administration as soon as feasible for arrest with nonshockable rhythms. In circumstances in which a reversible cause of nonshockable arrest (eg, asphyxia) is identified and addressed immediately, the use and optimal timing of epinephrine may differ. For shockable rhythms, provision of high-quality CPR and defibrillation should be the immediate care priorities, and the optimal timing of epinephrine is less clear. The 2 available RCTs administered epinephrine after the third shock for those with initial shockable rhythms. Whether giving epinephrine earlier for these shockable rhythms would be beneficial, or even harmful, is unknown.

EXTRACORPOREAL CPR

Note: The evidence and recommendations for the use of extracorporeal membrane oxygenation during CPR (ECPR) addressed in this ACLS focused update are also included in "Part 6: Alternative Techniques and Ancillary Devices for Cardiopulmonary Resuscitation" in the 2015 AHA guidelines update.[52] The following section updates the content related to ECPR in the ACLS guidelines but also should be used to update Part 6 of the 2015 AHA guidelines update.[52]

For these guidelines, the term *ECPR* refers to the initiation of cardiopulmonary bypass during the resuscitation of a patient in cardiac arrest. This involves the cannulation of a large vein and artery and initiation of venoarterial extracorporeal circulation and oxygenation (Figure). The goal of ECPR is to support end-organ perfusion while potentially reversible conditions are addressed. ECPR is a complex intervention that requires a highly trained team, specialized equipment, and multidisciplinary support within a healthcare system.

Evidence Summary—Updated 2019

In 2018, ILCOR commissioned a systematic review as part of the focused update process to evaluate the published evidence on ECPR; this review was published in 2018.[6] Studies were included in the systematic review if they involved >5 patients in the ECPR group, reported the timing of ECPR in relation to the cardiac arrest, and were randomized trials, nonrandomized controlled trials, or observational studies (cohort and case-control studies) that included a control group.

ECPR for OHCA

There are no RCTs on the use of ECPR for OHCA. Fifteen observational studies were identified that included patients from Asia, Europe, and North America with median ages from 46 to 59 years who were enrolled between 1999 and 2015. Some studies included overlapping cohorts or time frames. The studies varied in inclusion criteria and ECPR setting, ranging in size from 31 to 955 patients, including 3398 patients in total. Five of the studies included only patients with witnessed cardiac arrest and short no-flow times.[53–57] Most studies also required a cardiac cause of the arrest,[53,55–62] and many limited the patient age to a maximum of 75 years.[53,54,57,61,62]

The studies were analyzed by outcome, with short- and long-term neurological outcomes and survival outcomes synthesized separately. Eight studies with 1294 patients evaluated short-term favorable neurological outcome at hospital discharge or 1 month,[54,57–59,61–64] and 6 studies with 1303 patients evaluated long-term favorable neurological outcomes (3 months, 6 months, and 1 year).[55–57,59,60,63] In all studies, favorable neurological outcome was defined as a Cerebral Performance Category score of 1 or 2. Data were available from 12 studies of 2739 patients that evaluated survival to hospital discharge or 1 month[53–55,57–60,63–67] and 6 studies of 1212 patients that reported long-term survival.[53,55,57,59,60,63]

All studies were found to have very serious risk of bias, caused primarily by confounding.[6] In addition, across studies, there was significant heterogeneity in study design, and for the outcome of survival, there was significant inconsistency in the results. The overall certainty of evidence was thus rated by the reviewers as very low across all outcomes, and no meta-analyses were performed. Because the only available evidence consists of nonrandomized studies, the reported findings should be considered associated with rather than caused by the intervention.

Subject to the significant limitations listed above, the majority of studies reported improved neurological outcome associated with ECPR. In 3 studies, ECPR was associated with improved favorable neurological outcome at both short-term and long-term follow-up,[57,59,63] and in 3 additional studies that did not include long-term follow-up, ECPR was also associated with improved short-term favorable neurological outcome.[54,61,62] Two studies showed no benefit on short-term neurological outcome associated with ECPR,[58,64] and 3 studies reported beneficial effect on long-term neurological outcome associated with ECPR.[55,56,60]

Two studies reported short-term and long-term survival benefit associated with ECPR,[59,60] and 1 study reported long-term survival benefit associated with ECPR

Circulation. 2019;140:00–00. DOI: 10.1161/CIR.0000000000000732

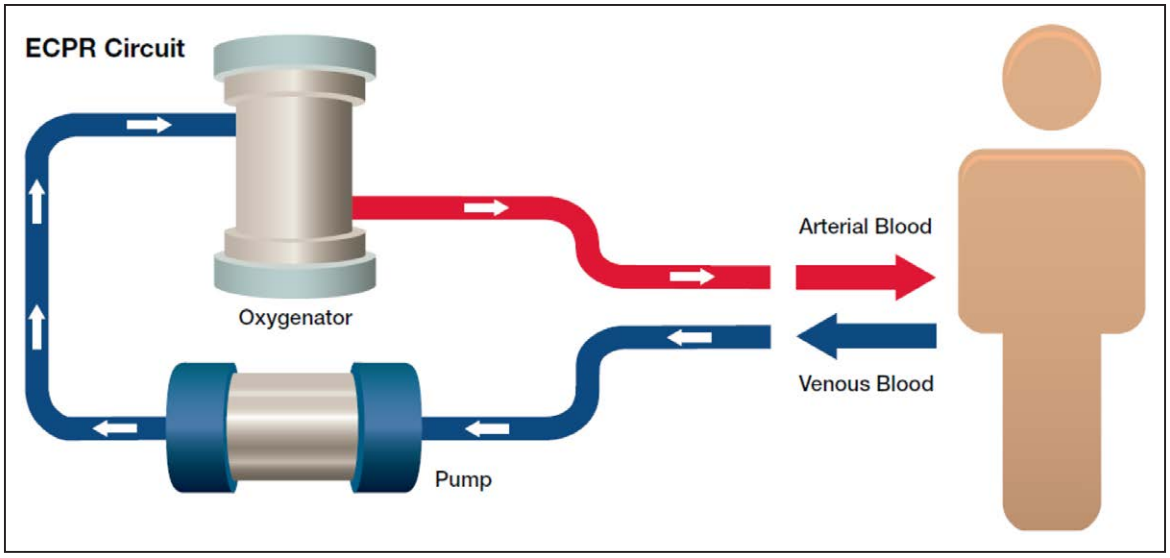

Figure. Schematic depiction of the components of an extracorporeal membrane oxygenator circuit used for extracorporeal cardiopulmonary resuscitation (ECPR).
Components include venous cannula, a pump, an oxygenator, and arterial cannula.

but, interestingly, did not demonstrate a benefit for the outcome of short-term survival.[55] The use of ECPR was not associated with short-term survival benefit in 9 studies[54,55,57,58,63–67] and was not associated with long-term survival in 2 studies.[57,63] One study noted the association of lower rates of both short-term and long-term survival with ECPR.[53]

ECPR for IHCA

There are no RCTs of the use of ECPR for IHCA. Seven observational studies were reviewed. These studies included patients from Asia and Europe with median ages from 57 to 72 years who were enrolled between 2001 and 2013. Some of the studies include overlapping cohorts or time frames. Study cohorts ranged from 20 to 353 patients, including a total of 705 patients. The studies varied in inclusion criteria such as cause of cardiac arrest, and many limited the patient enrollment age to a maximum of 75 or 80 years.[68–71] When only nonrandomized studies are available, any results are considered to be associated or not associated with the intervention and not caused by the intervention.

The studies were analyzed by outcome, with short-term and long-term neurological outcomes and survival outcomes synthesized separately. Data from 4 studies in 619 patients reported both short-term favorable neurological outcome (hospital discharge or 1 month) and long-term favorable neurological outcomes (3 months, 6 months, and 1 year) associated with ECPR.[69–72] In all studies, favorable neurological outcome was defined as a Cerebral Performance Category score of 1 to 2. Five studies of 685 patients reported survival to hospital discharge or 1 month and long-term survival.[68–70,72,73]

All studies were assessed as having a very serious risk of bias, resulting primarily from confounding. The overall certainty of evidence was rated by the reviewers as very low for all outcomes.[6] Given these assessments and the heterogeneity of results, individual studies were difficult to interpret, and no meta-analyses were performed.

In 3 studies, ECPR was not associated with beneficial effects for short- or long-term neurological outcomes,[68,69,72] whereas 1 study[70] reported associated short- and long-term neurological outcome benefit. Four studies demonstrated no increase in short- or long-term survival associated with ECPR,[68,69,72,73] with only 1 study[70] reporting improvement in these outcomes.

Recommendations—Updated 2019

1. **There is insufficient evidence to recommend the routine use of ECPR for patients with cardiac arrest.**
2. **ECPR may be considered for selected patients as rescue therapy when conventional CPR efforts are failing in settings in which it can be expeditiously implemented and supported by skilled providers (*Class 2b; Level of Evidence C-LD*).**

Despite many studies reporting favorable outcomes with the use of ECPR, the vast majority of the studies are from single centers with varying inclusion criteria and settings, with decisions to perform ECPR made on a case-by-case basis. Clinical and patient factors that influence a decision to pursue ECPR may also influence outcome. For this and other reasons, the included studies were all assessed to have a critical risk of bias as a result of confounding. In addition, the heterogeneity across studies reduced their external validity (generalizability). All of these factors precluded the performance of meta-analyses.[6] Although there is currently

no evidence to clearly define what should constitute selected patients, most of the studies analyzed in the systematic review included younger patients with fewer comorbidities.[6] For example, a young subject without comorbidities with a sudden arrest secondary to presumed cardiac arrhythmia may be considered a better candidate than an elderly patient with a metastatic malignancy and cardiac arrest. Clearly, more data are needed from studies of higher methodological quality, including randomized trials. Data are also needed to address the complexities of cost-effectiveness, resource allocation, and ethics surrounding the use of ECPR in resuscitation.

ARTICLE INFORMATION

The American Heart Association makes every effort to avoid any actual or potential conflicts of interest that may arise as a result of an outside relationship or a personal, professional, or business interest of a member of the writing panel. Specifically, all members of the writing group are required to complete and submit a Disclosure Questionnaire showing all such relationships that might be perceived as real or potential conflicts of interest.

This document was approved by the American Heart Association Science Advisory and Coordinating Committee on July 19, 2019, and the American Heart Association Executive Committee on August 9, 2019.

The American Heart Association requests that this document be cited as follows: Panchal AR, Berg KM, Hirsch KG, Kudenchuk PJ, Del Rios M, Cabañas JG, Link MS, Kurz MC, Chan PS, Morley PT, Hazinski MF, Donnino MW. 2019 American Heart Association focused update on advanced cardiovascular life support: use of advanced airways, vasopressors, and extracorporeal cardiopulmonary resuscitation during cardiac arrest: an update to the American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation.* 2019;140:eXXX–eXXX. doi: 10.1161/CIR.0000000000000732.

Copies: This document is available on the website of the American Heart Association (professional.heart.org). A copy of the document is available at https://professional.heart.org/statements by using either "Search for Guidelines & Statements" or the "Browse by Topic" area. To purchase additional reprints, call 843-216-2533 or e-mail kelle.ramsay@wolterskluwer.com.

The expert peer review of AHA-commissioned documents (eg, scientific statements, clinical practice guidelines, systematic reviews) is conducted by the AHA Office of Science Operations. For more on AHA statements and guidelines development, visit https://professional.heart.org/statements. Select the "Guidelines & Statements" drop-down menu, then click "Publication Development."

Disclosures

Writing Group Disclosures

Writing Group Member	Employment	Research Grant	Other Research Support	Speakers' Bureau/ Honoraria	Expert Witness	Ownership Interest	Consultant/ Advisory Board	Other
Ashish R. Panchal	The Ohio State University Wexner Medical Center	None	None	None	None	None	None	None
Katherine M. Berg	Beth Israel Deaconess Medical Center	NIH (cardiac arrest clinical trial grant [study drug is thiamine], not related to guidelines)*	None	None	None	None	None	None
José G. Cabañas	Wake County Emergency Medical Services	None	None	None	None	None	None	None
Paul S. Chan	Mid America Heart Institute and the University of Missouri–Kansas City	NHLBI†	None	None	None	None	None	None
Marina Del Rios	University of Illinois at Chicago College of Medicine	NIH (receives 6% salary support for hypertension research)*	None	None	None	None	None	None
Michael W. Donnino	Beth Israel Deaconess Medical Center	None	None	None	None	None	None	None
Mary Fran Hazinski	Vanderbilt University School of Nursing	None	None	None	None	None	American Heart Association Emergency Cardiovascular Care Programs†	None
Karen G. Hirsch	Stanford University	American Heart Association (research support for post–cardiac arrest research)*	None	None	None	None	None	None
Peter J. Kudenchuk	University of Washington Medical Center	NIH/NHLBI/NINDS (PI at University of Washington for SIREN Network)*	None	None	None	None	None	None
Michael C. Kurz	University of Alabama at Birmingham	Zoll Medical Foundation†; Zoll Medical Corp†; NIH (research grants, both received and pending)†	None	Zoll Medical Corp†	None	Rapid Oxygen Corp*	Zoll Medical Corp*	None

(*Continued*)

Writing Group Disclosures Continued

Writing Group Member	Employment	Research Grant	Other Research Support	Speakers' Bureau/ Honoraria	Expert Witness	Ownership Interest	Consultant/ Advisory Board	Other
Mark S. Link	UT Southwestern Medical Center	None	None	None	None	None	None	None
Peter T. Morley	University of Melbourne Clinical School, Royal Melbourne Hospital (Australia)	None	None	None	None	None	None	None

This table represents the relationships of writing group members that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all members of the writing group are required to complete and submit. A relationship is considered to be "significant" if (a) the person receives $10 000 or more during any 12-month period, or 5% or more of the person's gross income; or (b) the person owns 5% or more of the voting stock or share of the entity, or owns $10 000 or more of the fair market value of the entity. A relationship is considered to be "modest" if it is less than "significant" under the preceding definition.

*Modest.

†Significant.

Reviewer Disclosures

Reviewer	Employment	Research Grant	Other Research Support	Speakers' Bureau/ Honoraria	Expert Witness	Ownership Interest	Consultant/ Advisory Board	Other
Janet E. Bray	Monash University (Australia)	None	None	None	None	None	None	None
Alan C. Heffner	Atrium Health	None	None	The Difficult Airway Course Faculty*	Medicolegal review of cases involving cardiac arrest*	None	None	None
Bryan McNally	Emory University	Cardiac Arrest Registry to Enhance Survival (CARES receives funding from American Red Cross and American Heart Association)†	None	None	None	None	None	None
Robert D. Nelson	Wake Forest University	None	None	None	None	None	None	None
Joseph P. Ornato	Virginia Commonwealth University Health System	None	None	None	None	None	None	None
Mary Ann Peberdy	Virginia Commonwealth University	None	None	None	None	None	None	None
Thomas Rea	University of Washington	Federal pending grant (pending grant to further investigate airway techniques)*	None	None	None	None	None	None

This table represents the relationships of reviewers that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all reviewers are required to complete and submit. A relationship is considered to be "significant" if (a) the person receives $10 000 or more during any 12-month period, or 5% or more of the person's gross income; or (b) the person owns 5% or more of the voting stock or share of the entity, or owns $10 000 or more of the fair market value of the entity. A relationship is considered to be "modest" if it is less than "significant" under the preceding definition.

*Modest.

†Significant.

REFERENCES

1. Soar J, Maconochie I, Wyckoff MH, Olasveengen TM, Singletary EM, Greif R, Aickin R, Bhanji F, Donnino MW, Mancini ME, et al. 2019 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science With Treatment Recommendations: summary from the Basic Life Support; Advanced Life Support; Pediatric Life Support; Neonatal Life Support; Education, Implementation, and Teams; and First Aid Task Forces. *Circulation*. 2019;140:XXX–XXX. doi: 10.1161/CIR.0000000000000734
2. Soar J, Nicholson TC, Parr MJ, Berg KM, Böttiger BW, Callaway CW, Deakin CD, Drennan I, Neumar RW, O'Neil BJ, et al. Advanced airway management during adult cardiac arrest: Consensus on Science With Treatment Recommendations. International Liaison Committee on Resuscitation (ILCOR) Advanced Life Support Task Force. April 4, 2019. https://costr.ilcor.org/document/advanced-airway-management-during-adult-cardiac-arrest. Accessed August 23, 2019.
3. Welsford M, Berg KM, Neumar RW, Paiva EF, Andersen LW, Böttiger BW, Callaway CW, Deakin CD, Drennan I, Kleinman M, et al. Vasopressors in adult cardiac arrest: Consensus on Science With Treatment Recommendations. International Liaison Committee on Resuscitation (ILCOR) Advanced Life Support Task Force. April 4, 2019. https://costr.ilcor.org/document/vasopressors-in-adult-cardiac-arrest. Accessed August 23, 2019.
4. Donnino MW, Andersen LW, Deakin CD, Berg KM, Böttiger BW, Callaway CW, Drennan I, Neumar RW, Nicholson TC, O'Neil BJ, et al. Extracorporeal cardiopulmonary resuscitation (ECPR) for cardiac arrest–adults: Consensus on Science With Treatment Recommendations. International Liaison Committee on Resuscitation (ILCOR) Advanced Life Support Task Force. March 21, 2019. https://costr.ilcor.org/document/extracorporeal-cardiopulmonary-resuscitation-ecpr-for-cardiac-arrest-adults. Accessed August 23, 2019.

5. Holmberg MJ, Issa MS, Moskowitz A, Morley P, Welsford M, Neumar RW, Paiva EF, Coker A, Hansen CK, Andersen LW, et al; on behalf of the International Liaison Committee on Resuscitation Advanced Life Support Task Force Collaborators. Vasopressors during adult cardiac arrest: a systematic review and meta-analysis. *Resuscitation.* 2019;139:106–121. doi: 10.1016/j.resuscitation.2019.04.008
6. Holmberg MJ, Geri G, Wiberg S, Guerguerian AM, Donnino MW, Nolan JP, Deakin CD, Andersen LW; International Liaison Committee on Resuscitation's (ILCOR) Advanced Life Support and Pediatric Task Forces. Extracorporeal cardiopulmonary resuscitation for cardiac arrest: a systematic review. *Resuscitation.* 2018;131:91–100. doi: 10.1016/j.resuscitation.2018.07.029
7. Granfeldt A, Avis SR, Nicholson TC, Holmberg MJ, Moskowitz A, Coker A, Berg KM, Parr MJ, Donnino MW, Soar J, et al; on behalf of the International Liaison Committee on Resuscitation Advanced Life Support Task Force Collaborators. Advanced airway management during adult cardiac arrest: a systematic review. *Resuscitation*. 2019;133–143:139.
8. Halperin JL, Levine GN, Al-Khatib SM, Birtcher KK, Bozkurt B, Brindis RG, Cigarroa JE, Curtis LH, Fleisher LA, Gentile F, et al. Further evolution of the ACC/AHA Clinical Practice Guideline Recommendation Classification System: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation.* 2016;133:1426–1428. doi: 10.1161/CIR.0000000000000312
9. Morrison LJ, Gent LM, Lang E, Nunnally ME, Parker MJ, Callaway CW, Nadkarni VM, Fernandez AR, Billi JE, Egan JR, et al. Part 2: evidence evaluation and management of conflicts of Interest: 2015 American Heart Association Guidelines Update for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation*. 2015;132(suppl 2):S368-S382. doi: 10.1161/CIR.0000000000000253
10. Kleinman ME, Goldberger ZD, Rea T, Swor RA, Bobrow BJ, Brennan EE, Terry M, Hemphill R, Gazmuri RJ, Hazinski MF, et al. 2017 American Heart Association focused update on adult basic life support and cardiopulmonary resuscitation quality: an update to the American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care [published correction appears in *Circulation*. 2018;137:e14]. *Circulation*. 2018;137:e7–e13. doi: 10.1161/CIR.0000000000000539
11. Panchal AR, Berg KM, Kudenchuk PJ, Del Rios M, Hirsch KG, Link MS, Kurz MC, Chan PS, Cabañas JG, Morley PT, et al. 2018 American Heart Association focused update on advanced cardiovascular life support use of antiarrhythmic drugs during and immediately after cardiac arrest: an update to the American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation.* 2018;138:e740–e749. doi: 10.1161/CIR.0000000000000613
12. Link MS, Berkow LC, Kudenchuk PJ, Halperin HR, Hess EP, Moitra VK, Neumar RW, O'Neil BJ, Paxton JH, Silvers SM, et al. Part 7: adult advanced cardiovascular life support: 2015 American Heart Association Guidelines Update for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care [published correction appears in *Circulation*. 2015;132:e385]. *Circulation*. 2015;132(suppl 2):S444–S464. doi: 10.1161/CIR.0000000000000261
13. Neumar RW, Otto CW, Link MS, Kronick SL, Shuster M, Callaway CW, Kudenchuk PJ, Ornato JP, McNally B, Silvers SM, et al. Part 8: adult advanced cardiovascular life support: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care [published corrections appear in *Circulation*. 2011;123:e236 and *Circulation*. 2013;128:e480]. *Circulation*. 2010;122:S729–S767. doi: 10.1161/CIRCULATIONAHA.110.970988
14. Frascone RJ, Russi C, Lick C, Conterato M, Wewerka SS, Griffith KR, Myers L, Conners J, Salzman JG. Comparison of prehospital insertion success rates and time to insertion between standard endotracheal intubation and a supraglottic airway. *Resuscitation.* 2011;82:1529–1536. doi: 10.1016/j.resuscitation.2011.07.009
15. Vithalani VD, Vlk S, Davis SQ, Richmond NJ. Unrecognized failed airway management using a supraglottic airway device. *Resuscitation.* 2017;119:1–4. doi: 10.1016/j.resuscitation.2017.07.019
16. Aufderheide TP, Sigurdsson G, Pirrallo RG, Yannopoulos D, McKnite S, von Briesen C, Sparks CW, Conrad CJ, Provo TA, Lurie KG. Hyperventilation-induced hypotension during cardiopulmonary resuscitation. *Circulation.* 2004;109:1960–1965. doi: 10.1161/01.CIR.0000126594.79136.61
17. Jabre P, Penaloza A, Pinero D, Duchateau FX, Borron SW, Javaudin F, Richard O, de Longueville D, Bouilleau G, Devaud ML, et al. Effect of bag-mask ventilation vs endotracheal intubation during cardiopulmonary resuscitation on neurological outcome after out-of-hospital cardiorespiratory arrest: a randomized clinical trial. *JAMA.* 2018;319:779–787. doi: 10.1001/jama.2018.0156
18. Donnino MW, Salciccioli JD, Howell MD, Cocchi MN, Giberson B, Berg K, Gautam S, Callaway C; American Heart Association's Get With The Guidelines–Resuscitation Investigators. Time to administration of epinephrine and outcome after in-hospital cardiac arrest with non-shockable rhythms: retrospective analysis of large in-hospital data registry. *BMJ.* 2014;348:g3028. doi: 10.1136/bmj.g3028
19. Lévesque LE, Hanley JA, Kezouh A, Suissa S. Problem of immortal time bias in cohort studies: example using statins for preventing progression of diabetes. *BMJ.* 2010;340:b5087. doi: 10.1136/bmj.b5087
20. Benger JR, Kirby K, Black S, Brett SJ, Clout M, Lazaroo MJ, Nolan JP, Reeves BC, Robinson M, Scott LJ, et al. Effect of a strategy of a supraglottic airway device vs tracheal intubation during out-of-hospital cardiac arrest on functional outcome: the AIRWAYS-2 randomized clinical trial. *JAMA.* 2018;320:779–791. doi: 10.1001/jama.2018.11597
21. Wang HE, Schmicker RH, Daya MR, Stephens SW, Idris AH, Carlson JN, Colella MR, Herren H, Hansen M, Richmond NJ, et al. Effect of a strategy of initial laryngeal tube insertion vs endotracheal intubation on 72-hour survival in adults with out-of-hospital cardiac arrest: a randomized clinical trial. *JAMA.* 2018;320:769–778. doi: 10.1001/jama.2018.7044
22. Jacobs IG, Finn JC, Jelinek GA, Oxer HF, Thompson PL. Effect of adrenaline on survival in out-of-hospital cardiac arrest: a randomised double-blind placebo-controlled trial. *Resuscitation*. 2011;82:1138–1143. doi: 10.1016/j.resuscitation.2011.06.029
23. Perkins GD, Ji C, Deakin CD, Quinn T, Nolan JP, Scomparin C, Regan S, Long J, Slowther A, Pocock H, et al; PARAMEDIC2 Collaborators. A randomized trial of epinephrine in out-of-hospital cardiac arrest. *N Engl J Med.* 2018;379:711–721. doi: 10.1056/NEJMoa1806842
24. Perkins GD, Kenna C, Ji C, Deakin CD, Nolan JP, Quinn T, Fothergill R, Gunson I, Pocock H, Rees N, et al. The effects of adrenaline in out of hospital cardiac arrest with shockable and non-shockable rhythms: findings from the PACA and PARAMEDIC-2 randomised controlled trials. *Resuscitation*. 2019;140:55–63. doi: 10.1016/j.resuscitation.2019.05.007
25. Callaway CW, Soar J, Aibiki M, Böttiger BW, Brooks SC, Deakin CD, Donnino MW, Drajer S, Kloeck W, Morley PT, et al; on behalf of the Advanced Life Support Chapter Collaborators. Part 4: advanced life support: 2015 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science With Treatment Recommendations. *Circulation*. 2015;132(suppl 1):S84–S145. doi: 10.1161/CIR.0000000000000273
26. Callaham M, Madsen CD, Barton CW, Saunders CE, Pointer J. A randomized clinical trial of high-dose epinephrine and norepinephrine vs standard-dose epinephrine in prehospital cardiac arrest. *JAMA.* 1992;268:2667–2672.
27. Gueugniaud PY, Mols P, Goldstein P, Pham E, Dubien PY, Deweerdt C, Vergnion M, Petit P, Carli P. A comparison of repeated high doses and repeated standard doses of epinephrine for cardiac arrest outside the hospital. European Epinephrine Study Group. *N Engl J Med.* 1998;339:1595–1601. doi: 10.1056/NEJM199811263392204
28. Stiell IG, Hebert PC, Weitzman BN, Wells GA, Raman S, Stark RM, Higginson LA, Ahuja J, Dickinson GE. High-dose epinephrine in adult cardiac arrest. *N Engl J Med.* 1992;327:1045–1050. doi: 10.1056/NEJM199210083271502
29. Brown CG, Martin DR, Pepe PE, Stueven H, Cummins RO, Gonzalez E, Jastremski M. A comparison of standard-dose and high-dose epinephrine in cardiac arrest outside the hospital: the Multicenter High-Dose Epinephrine Study Group. *N Engl J Med.* 1992;327:1051–1055. doi: 10.1056/NEJM199210083271503
30. Sherman BW, Munger MA, Foulke GE, Rutherford WF, Panacek EA. High-dose versus standard-dose epinephrine treatment of cardiac arrest after failure of standard therapy. *Pharmacotherapy.* 1997;17:242–247.
31. Choux C, Gueugniaud PY, Barbieux A, Pham E, Lae C, Dubien PY, Petit P. Standard doses versus repeated high doses of epinephrine in cardiac arrest outside the hospital. *Resuscitation.* 1995;29:3–9.
32. Lindner KH, Dirks B, Strohmenger HU, Prengel AW, Lindner IM, Lurie KG. Randomised comparison of epinephrine and vasopressin in patients with out-of-hospital ventricular fibrillation. *Lancet.* 1997;349:535–537. doi: 10.1016/S0140-6736(97)80087-6
33. Wenzel V, Krismer AC, Arntz HR, Sitter H, Stadlbauer KH, Lindner KH; European Resuscitation Council Vasopressor during Cardiopulmonary Resuscitation Study Group. A comparison of vasopressin and epinephrine for out-of-hospital cardiopulmonary resuscitation. *N Engl J Med.* 2004;350:105–113. doi: 10.1056/NEJMoa025431
34. Mukoyama T, Kinoshita K, Nagao K, Tanjoh K. Reduced effectiveness of vasopressin in repeated doses for patients undergoing prolonged

cardiopulmonary resuscitation. *Resuscitation.* 2009;80:755–761. doi: 10.1016/j.resuscitation.2009.04.005
35. Ong ME, Tiah L, Leong BS, Tan EC, Ong VY, Tan EA, Poh BY, Pek PP, Chen Y. A randomised, double-blind, multi-centre trial comparing vasopressin and adrenaline in patients with cardiac arrest presenting to or in the emergency department. *Resuscitation.* 2012;83:953–960. doi: 10.1016/j.resuscitation.2012.02.005
36. Callaway CW, Hostler D, Doshi AA, Pinchalk M, Roth RN, Lubin J, Newman DH, Kelly LJ. Usefulness of vasopressin administered with epinephrine during out-of-hospital cardiac arrest. *Am J Cardiol.* 2006;98: 1316–1321. doi: 10.1016/j.amjcard.2006.06.022
37. Gueugniaud PY, David JS, Chanzy E, Hubert H, Dubien PY, Mauriaucourt P, Bragança C, Billères X, Clotteau-Lambert MP, Fuster P, et al. Vasopressin and epinephrine vs. epinephrine alone in cardiopulmonary resuscitation. *N Engl J Med.* 2008;359:21–30. doi: 10.1056/NEJMoa0706873
38. Ducros L, Vicaut E, Soleil C, Le Guen M, Gueye P, Poussant T, Mebazaa A, Payen D, Plaisance P. Effect of the addition of vasopressin or vasopressin plus nitroglycerin to epinephrine on arterial blood pressure during cardiopulmonary resuscitation in humans. *J Emerg Med.* 2011;41:453–459. doi: 10.1016/j.jemermed.2010.02.030
39. Tanaka H, Takyu H, Sagisaka R, Ueta H, Shirakawa T, Kinoshi T, Takahashi H, Nakagawa T, Shimazaki S, Ong Eng Hock M. Favorable neurological outcomes by early epinephrine administration within 19 minutes after EMS call for out-of-hospital cardiac arrest patients. *Am J Emerg Med.* 2016;34:2284–2290. doi: 10.1016/j.ajem.2016.08.026
40. Hayashi Y, Iwami T, Kitamura T, Nishiuchi T, Kajino K, Sakai T, Nishiyama C, Nitta M, Hiraide A, Kai T. Impact of early intravenous epinephrine administration on outcomes following out-of-hospital cardiac arrest. *Circ J.* 2012;76:1639–1645.
41. Cantrell CL Jr, Hubble MW, Richards ME. Impact of delayed and infrequent administration of vasopressors on return of spontaneous circulation during out-of-hospital cardiac arrest. *Prehosp Emerg Care.* 2013;17:15–22. doi: 10.3109/10903127.2012.702193
42. Hansen M, Schmicker RH, Newgard CD, Grunau B, Scheuermeyer F, Cheskes S, Vithalani V, Alnaji F, Rea T, Idris AH, et al; on behalf of the Resuscitation Outcomes Consortium Investigators. Time to epinephrine administration and survival from nonshockable out-of-hospital cardiac arrest among children and adults. *Circulation.* 2018;137:2032–2040. doi: 10.1161/CIRCULATIONAHA.117.033067
43. Koscik C, Pinawin A, McGovern H, Allen D, Media DE, Ferguson T, Hopkins W, Sawyer KN, Boura J, Swor R. Rapid epinephrine administration improves early outcomes in out-of-hospital cardiac arrest. *Resuscitation.* 2013;84:915–920. doi: 10.1016/j.resuscitation.2013.03.023
44. Nakahara S, Tomio J, Nishida M, Morimura N, Ichikawa M, Sakamoto T. Association between timing of epinephrine administration and intact neurologic survival following out-of-hospital cardiac arrest in Japan: a population-based prospective observational study. *Acad Emerg Med.* 2012;19:782–792. doi: 10.1111/j.1553-2712.2012.01387.x
45. Patel KK, Spertus JA, Khariton Y, Tang Y, Curtis LH, Chan PS; on behalf of the American Heart Association's Get With The Guidelines–Resuscitation Investigators. Association between prompt defibrillation and epinephrine treatment with long-term survival after in-hospital cardiac arrest. *Circulation.* 2018;137:2041–2051. doi: 10.1161/CIRCULATIONAHA.117.030488
46. Sagisaka R, Tanaka H, Takyu H, Ueta H, Tanaka S. Effects of repeated epinephrine administration and administer timing on witnessed out-of-hospital cardiac arrest patients. *Am J Emerg Med.* 2017;35:1462–1468. doi: 10.1016/j.ajem.2017.04.052
47. Ueta H, Tanaka H, Tanaka S, Sagisaka R, Takyu H. Quick epinephrine administration induces favorable neurological outcomes in out-of-hospital cardiac arrest patients. *Am J Emerg Med.* 2017;35:676–680. doi: 10.1016/j.ajem.2016.12.066
48. Ewy GA, Bobrow BJ, Chikani V, Sanders AB, Otto CW, Spaite DW, Kern KB. The time dependent association of adrenaline administration and survival from out-of-hospital cardiac arrest. *Resuscitation.* 2015;96:180–185. doi: 10.1016/j.resuscitation.2015.08.011
49. Homma Y, Shiga T, Funakoshi H, Miyazaki D, Sakurai A, Tahara Y, Nagao K, Yonemoto N, Yaguchi A, Morimura N; SOS-KANTO Study Group. Association of the time to first epinephrine administration and outcomes in out-of-hospital cardiac arrest: SOS-KANTO 2012 study. *Am J Emerg Med.* 2019;37:241–248. doi: 10.1016/j.ajem.2018.05.037
50. Hubble MW, Johnson C, Blackwelder J, Collopy K, Houston S, Martin M, Wilkes D, Wiser J. Probability of return of spontaneous circulation as a function of timing of vasopressor administration in out-of-hospital cardiac arrest. *Prehosp Emerg Care.* 2015;19:457–463. doi: 10.3109/10903127.2015.1005262
51. Hubble MW, Tyson C. Impact of early vasopressor administration on neurological outcomes after prolonged out-of-hospital cardiac arrest. *Prehosp Disaster Med.* 2017;32:297–304. doi: 10.1017/S1049023X17000115
52. Brooks SC, Anderson ML, Bruder E, Daya MR, Gaffney A, Otto CW, Singer AJ, Thiagarajan RR, Travers AH. Part 6: alternative techniques and ancillary devices for cardiopulmonary resuscitation: 2015 American Heart Association Guidelines Update for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation.* 2015;132:S436–S443. doi: 10.1161/CIR.0000000000000260
53. Cesana F, Avalli L, Garatti L, Coppo A, Righetti S, Calchera I, Scanziani E, Cozzolino P, Malafronte C, Mauro A, et al. Effects of extracorporeal cardiopulmonary resuscitation on neurological and cardiac outcome after ischaemic refractory cardiac arrest. *Eur Heart J Acute Cardiovasc Care.* 2018;7:432–441. doi: 10.1177/2048872617737041
54. Choi DH, Kim YJ, Ryoo SM, Sohn CH, Ahn S, Seo DW, Lim JY, Kim WY. Extracorporeal cardiopulmonary resuscitation among patients with out-of-hospital cardiac arrest. *Clin Exp Emerg Med.* 2016;3:132–138. doi: 10.15441/ceem.16.145
55. Maekawa K, Tanno K, Hase M, Mori K, Asai Y. Extracorporeal cardiopulmonary resuscitation for patients with out-of-hospital cardiac arrest of cardiac origin: a propensity-matched study and predictor analysis. *Crit Care Med.* 2013;41:1186–1196. doi: 10.1097/CCM.0b013e31827ca4c8
56. Schober A, Sterz F, Herkner H, Wallmueller C, Weiser C, Hubner P, Testori C. Emergency extracorporeal life support and ongoing resuscitation: a retrospective comparison for refractory out-of-hospital cardiac arrest. *Emerg Med J.* 2017;34:277–281. doi: 10.1136/emermed-2015-205232
57. Siao FY, Chiu CC, Chiu CW, Chen YC, Chen YL, Hsieh YK, Lee CH, Wu CT, Chou CC, Yen HH. Managing cardiac arrest with refractory ventricular fibrillation in the emergency department: conventional cardiopulmonary resuscitation versus extracorporeal cardiopulmonary resuscitation. *Resuscitation.* 2015;92:70–76. doi: 10.1016/j.resuscitation.2015.04.016
58. Hase M, Tsuchihashi K, Fujii N, Nishizato K, Kokubu N, Nara S, Kurimoto Y, Hashimoto A, Uno K, Miura T, et al. Early defibrillation and circulatory support can provide better long-term outcomes through favorable neurological recovery in patients with out-of-hospital cardiac arrest of cardiac origin. *Circ J.* 2005;69:1302–1307.
59. Sakamoto T, Morimura N, Nagao K, Asai Y, Yokota H, Nara S, Hase M, Tahara Y, Atsumi T; SAVE-J Study Group. Extracorporeal cardiopulmonary resuscitation versus conventional cardiopulmonary resuscitation in adults with out-of-hospital cardiac arrest: a prospective observational study. *Resuscitation.* 2014;85:762–768. doi: 10.1016/j.resuscitation.2014.01.031
60. Tanno K, Itoh Y, Takeyama Y, Nara S, Mori K, Asai Y. Utstein style study of cardiopulmonary bypass after cardiac arrest. *Am J Emerg Med.* 2008;26:649–654. doi: 10.1016/j.ajem.2007.09.019
61. Yannopoulos D, Bartos JA, Martin C, Raveendran G, Missov E, Conterato M, Frascone RJ, Trembley A, Sipprell K, John R, et al. Minnesota Resuscitation Consortium's advanced perfusion and reperfusion cardiac life support strategy for out-of-hospital refractory ventricular fibrillation. *J Am Heart Assoc.* 2016;5 doi: 10.1161/JAHA.116.003732
62. Yannopoulos D, Bartos JA, Raveendran G, Conterato M, Frascone RJ, Trembley A, John R, Connett J, Benditt DG, Lurie KG, et al. Coronary artery disease in patients with out-of-hospital refractory ventricular fibrillation cardiac arrest. *J Am Coll Cardiol.* 2017;70:1109–1117. doi: 10.1016/j.jacc.2017.06.059
63. Kim SJ, Jung JS, Park JH, Park JS, Hong YS, Lee SW. An optimal transition time to extracorporeal cardiopulmonary resuscitation for predicting good neurological outcome in patients with out-of-hospital cardiac arrest: a propensity-matched study. *Crit Care.* 2014;18:535. doi: 10.1186/s13054-014-0535-8
64. Poppe M, Weiser C, Holzer M, Sulzgruber P, Datler P, Keferböck M, Zeiner S, Lobmeyr E, van Tulder R, Ziegler A, et al. The incidence of "load&go" out-of-hospital cardiac arrest candidates for emergency department utilization of emergency extracorporeal life support: a one-year review. *Resuscitation.* 2015;91:131–136. doi: 10.1016/j.resuscitation.2015.03.003
65. Agostinucci JM, Ruscev M, Galinski M, Gravelo S, Petrovic T, Carmeaux C, Haouache H, Roussin F, Adnet F, Lapostolle F. Out-of-hospital use of an automated chest compression device: facilitating access to extracorporeal

life support or non-heart-beating organ procurement. *Am J Emerg Med.* 2011;29:1169–1172. doi: 10.1016/j.ajem.2010.06.029

66. Lee SH, Jung JS, Lee KH, Kim HJ, Son HS, Sun K. Comparison of extracorporeal cardiopulmonary resuscitation with conventional cardiopulmonary resuscitation: is extracorporeal cardiopulmonary resuscitation beneficial? *Korean J Thorac Cardiovasc Surg.* 2015;48:318–327. doi: 10.5090/kjtcs.2015.48.5.318
67. Venturini JM, Retzer E, Estrada JR, Friant J, Beiser D, Edelson D, Paul J, Blair J, Nathan S, Shah AP. Mechanical chest compressions improve rate of return of spontaneous circulation and allow for initiation of percutaneous circulatory support during cardiac arrest in the cardiac catheterization laboratory. *Resuscitation.* 2017;115:56–60. doi: 10.1016/j.resuscitation.2017.03.037
68. Lin JW, Wang MJ, Yu HY, Wang CH, Chang WT, Jerng JS, Huang SC, Chou NK, Chi NH, Ko WJ, et al. Comparing the survival between extracorporeal rescue and conventional resuscitation in adult in-hospital cardiac arrests: propensity analysis of three-year data. *Resuscitation.* 2010;81:796–803. doi: 10.1016/j.resuscitation.2010.03.002
69. Chen YS, Lin JW, Yu HY, Ko WJ, Jerng JS, Chang WT, Chen WJ, Huang SC, Chi NH, Wang CH, et al. Cardiopulmonary resuscitation with assisted extracorporeal life-support versus conventional cardiopulmonary resuscitation in adults with in-hospital cardiac arrest: an observational study and propensity analysis. *Lancet.* 2008;372:554–561. doi: 10.1016/S0140-6736(08)60958-7
70. Shin TG, Choi JH, Jo IJ, Sim MS, Song HG, Jeong YK, Song YB, Hahn JY, Choi SH, Gwon HC, et al. Extracorporeal cardiopulmonary resuscitation in patients with inhospital cardiac arrest: a comparison with conventional cardiopulmonary resuscitation. *Crit Care Med.* 2011;39:1–7. doi: 10.1097/CCM.0b013e3181feb339
71. Shin TG, Jo IJ, Sim MS, Song YB, Yang JH, Hahn JY, Choi SH, Gwon HC, Jeon ES, Sung K, et al. Two-year survival and neurological outcome of in-hospital cardiac arrest patients rescued by extracorporeal cardiopulmonary resuscitation. *Int J Cardiol.* 2013;168:3424–3430. doi: 10.1016/j.ijcard.2013.04.183
72. Blumenstein J, Leick J, Liebetrau C, Kempfert J, Gaede L, Groß S, Krug M, Berkowitsch A, Nef H, Rolf A, et al. Extracorporeal life support in cardiovascular patients with observed refractory in-hospital cardiac arrest is associated with favourable short and long-term outcomes: a propensity-matched analysis. *Eur Heart J Acute Cardiovasc Care.* 2016;5:13–22. doi: 10.1177/2048872615612454
73. Chou TH, Fang CC, Yen ZS, Lee CC, Chen YS, Ko WJ, Wang CH, Wang SS, Chen SC. An observational study of extracorporeal CPR for in-hospital cardiac arrest secondary to myocardial infarction. *Emerg Med J.* 2014;31:441–447. doi: 10.1136/emermed-2012-202173

American Heart Association.

Circulation