

# Part 4: Advanced Life Support

## 2015 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science With Treatment Recommendations

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### Introduction

The International Liaison Committee on Resuscitation (ILCOR) Advanced Life Support (ALS) Task Force performed detailed systematic reviews based on the recommendations of the Institute of Medicine of the National Academies<sup>1</sup> and using the methodological approach proposed by the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) Working Group.<sup>2</sup> Questions to be addressed (using the PICO [population, intervention, comparator, outcome] format)<sup>3</sup> were prioritized by ALS Task Force members (by voting). Prioritization criteria included awareness of significant new data and new controversies or questions about practice. Questions about topics no longer relevant to contemporary practice or where little new research has occurred were given lower priority. The ALS Task Force prioritized 42 PICO questions for review. With the assistance of information specialists, a detailed search for relevant articles was performed in each of 3 online databases (PubMed, Embase, and the Cochrane Library).

By using detailed inclusion and exclusion criteria, articles were screened for further evaluation. The reviewers for each question created a reconciled risk of bias assessment for each of the included studies, using state-of-the-art tools: Cochrane for randomized controlled trials (RCTs),<sup>4</sup> Quality Assessment of Diagnostic Accuracy Studies (QUADAS)-2 for studies of diagnostic accuracy,<sup>5</sup> and GRADE for observational studies that inform both therapy and prognosis questions.<sup>6</sup>

GRADE evidence profile tables<sup>7</sup> were then created to facilitate an evaluation of the evidence in support of each of the critical and important outcomes. The quality of the evidence (or confidence in the estimate of the effect) was categorized as

high, moderate, low, or very low,<sup>8</sup> based on the study methodologies and the 5 core GRADE domains of risk of bias, inconsistency, indirectness, imprecision, and other considerations (including publication bias).<sup>9</sup>

These evidence profile tables were then used to create a written summary of evidence for each outcome (the consensus on science statements). Whenever possible, consensus-based treatment recommendations were then created. These recommendations (designated as strong or weak) were accompanied by an overall assessment of the evidence and a statement from the task force about the values, preferences, and task force insights that underlie the recommendations. Further details of the methodology that underpinned the evidence evaluation process are found in "Part 2: Evidence Evaluation and Management of Conflicts of Interest."

The task force preselected and ranked outcome measures that were used as consistently as possible for all PICO questions. Longer-term, patient-centered outcomes were considered more important than process variables and shorter-term outcomes. For most questions, we used the following hierarchy starting with the most important: long-term survival with neurologically favorable survival, long-term survival, short-term survival, and process variable. In general, *long-term* was defined as from hospital discharge to 180 days or longer, and *short-term* was defined as shorter than to hospital discharge. For certain questions (eg, related to defibrillation or confirmation of tracheal tube position), process variables such as termination of fibrillation and correct tube placement were important. A few questions (eg, organ donation) required unique outcomes.

The International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science

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With Treatment Recommendations (CoSTR) statements in this Part are organized in the approximate sequence of interventions for a patient: defibrillation, airway, oxygenation and ventilation, circulatory support, monitoring during cardiopulmonary resuscitation (CPR), drugs during CPR, and special circumstances. We also include statements for postresuscitation care, prognostication of neurologic outcome, and organ donation.

#### Defibrillation Strategies for Ventricular Fibrillation (VF) or Pulseless Ventricular Tachycardia (pVT)

- Biphasic waveform (ALS 470)
- Pulsed biphasic waveform (ALS 470)
- First-shock energy (ALS 470)
- Single shock versus stacked shocks (ALS 470)
- Fixed versus escalating defibrillation energy levels (ALS 470)
- Recurrent VF (ALS 470)

#### Airway, Oxygenation, and Ventilation

- Oxygen dose during CPR (ALS 889)
- Basic versus advanced airway (ALS 783)
- Supraglottic airways (SGAs) versus tracheal intubation (ALS 714)
- Confirmation of correct tracheal tube placement (ALS 469)
- Ventilation rate during continuous chest compressions (ALS 808)

#### Circulatory Support During CPR

- Impedance threshold device (ITD) (ALS 579)
- Mechanical CPR devices (ALS 782)
- Extracorporeal CPR (ECPR) versus manual or mechanical CPR (ALS 723)

#### Physiological Monitoring During CPR

- End-tidal carbon dioxide (ETCO<sub>2</sub>) to predict outcome of cardiac arrest (ALS 459)
- Monitoring physiological parameters during CPR (ALS 656)
- Ultrasound during CPR (ALS 658)

#### Drugs During CPR

- Epinephrine versus placebo (ALS 788)
- Epinephrine versus vasopressin (ALS 659)
- Epinephrine versus vasopressin in combination with epinephrine (ALS 789)
- Standard-dose epinephrine (SDE) versus high-dose epinephrine (HDE) (ALS 778)
- Timing of administration of epinephrine (ALS 784)
- Steroids for cardiac arrest (ALS 433)
- Antiarrhythmic drugs for cardiac arrest (ALS 428)

#### Cardiac Arrest in Special Circumstances

- Cardiac arrest during pregnancy (ALS 436)
- Lipid therapy for cardiac arrest (ALS 834)
- Opioid toxicity (ALS 441)
- Cardiac arrest associated with pulmonary embolism (PE) (ALS 435)
- Cardiac arrest during coronary catheterization (ALS 479)

#### Postresuscitation Care

- Oxygen dose after return of spontaneous circulation (ROSC) in adults (ALS 448)
- Postresuscitation ventilation strategy (ALS 571)
- Postresuscitation hemodynamic support (ALS 570)
- Postresuscitation antiarrhythmic drugs (ALS 493)
- Targeted temperature management (ALS 790)
- Timing of induced hypothermia (ALS 802)
- Prevention of fever after cardiac arrest (ALS 879)
- Postresuscitation seizure prophylaxis (ALS 431)
- Seizure treatment (ALS 868)
- Glucose control after resuscitation (ALS 580)
- Prognostication in comatose patients treated with hypothermic targeted temperature management (TTM) (ALS 450)
- Prognostication in the absence of TTM (ALS 713)
- Organ donation (ALS 449)

The 2010 CoSTR statements<sup>10,11</sup> that have not been addressed in 2015 are listed under the relevant section.

### Summary of ALS Treatment Recommendations

The systematic reviews showed that the quality of evidence for many ALS interventions is low or very low, and this led to predominantly weak recommendations. For some issues, despite a low quality of evidence, the values and preferences of the task force led to a strong recommendation. This was especially so when there was consensus that not doing so could lead to harm. In addition, treatment recommendations were left unchanged unless there were compelling reasons not to do so. The rationale for any change is addressed in the values, preferences, and insights that follow treatment recommendations. The most important developments and recommendations in ALS since the 2010 ILCOR review are as follows:

#### Defibrillation strategies for VF or pVT:

- There were no major developments since 2010. We suggest if the first shock is not successful and the defibrillator is capable of delivering shocks of higher energy, it is reasonable to increase the energy for subsequent shocks.

#### Airway, oxygenation, and ventilation:

- We suggest using the highest possible inspired oxygen concentration during CPR.
- There was equipoise between the choice of an advanced airway or a bag-mask device for airway management during CPR, and the choice between a SGA or tracheal tube as the initial advanced airway during CPR.
- The role of waveform capnography during ALS was emphasized, including its use to confirm and to continuously monitor the position of a tracheal tube during CPR.

#### Circulatory support during CPR:

- We recommend against the routine use of the ITD in addition to conventional CPR but could not achieve consensus for or against the use of the ITD when used together with active compression-decompression (ACD) CPR.

- We suggest against the routine use of automated mechanical chest compression devices but suggest they are a reasonable alternative to use in situations where sustained high-quality manual chest compressions are impractical or compromise provider safety.
- We suggest ECPR is a reasonable rescue therapy for select patients with cardiac arrest when initial conventional CPR is failing in settings where this can be implemented.

#### Physiological monitoring during CPR:

- Physiological measurement in addition to clinical signs and electrocardiographic monitoring has the potential to help guide interventions during ALS.
- We have not made a recommendation for any particular physiological measure to guide CPR, because the available evidence would make any estimate of effect speculative.
- We recommend against using  $\text{ETCO}_2$  cutoff values alone as a mortality predictor or for the decision to stop a resuscitation attempt.
- We suggest that if cardiac ultrasound can be performed without interfering with standard advanced cardiovascular life support (ACLS) protocol, it may be considered as an additional diagnostic tool to identify potentially reversible causes.

#### Drugs during CPR:

- We suggest SDE (defined as 1 mg) be administered to patients in cardiac arrest after considering the observed benefit in short-term outcomes (ROSC and admission to hospital) and our uncertainty about the benefit or harm on survival to discharge and neurologic outcome. Our statement is not intended to change current practice until there are high-quality data on long-term outcomes.
- We suggest the use of amiodarone in adult patients with refractory VF/pVT to improve rates of ROSC. Our statement is not intended to change current practice until there are high-quality data on long-term outcomes.

#### Cardiac arrest in special circumstances:

- The systematic review found very-low-quality evidence for specific interventions for ALS in the pregnant woman. We suggest delivery of the fetus by perimortem cesarean delivery for women in cardiac arrest in the second half of pregnancy.
- The lack of comparative studies led to the task force being unable to make any evidence-based treatment recommendation about the use of intravenous (IV) lipid emulsion to treat toxin-induced cardiac arrest.
- We recommend the use of naloxone by IV, intramuscular, subcutaneous, intraosseous (IO), or intranasal routes in respiratory arrest associated with opioid toxicity but make no recommendation regarding the modification of standard ALS in opioid-induced cardiac arrest.

#### Postresuscitation care:

- We recommend avoiding hypoxia in adults with ROSC after cardiac arrest.

- We suggest avoiding hyperoxia in adults with ROSC after cardiac arrest.
- We suggest the use of 100% inspired oxygen until the arterial oxygen saturation or the partial pressure of arterial oxygen can be measured reliably in adults with ROSC after cardiac arrest.
- We suggest maintaining  $\text{Paco}_2$  within a normal physiological range as part of a post-ROSC bundle of care.
- We suggest hemodynamic goals (eg, mean arterial pressure [MAP], systolic blood pressure [SBP]) be considered during postresuscitation care and as part of any bundle of postresuscitation interventions.
- We recommend selecting and maintaining a constant target temperature between 32°C and 36°C for those patients in whom temperature control is used.
- We recommend TTM as opposed to no TTM for adults with out-of-hospital cardiac arrest (OHCA) with an initial shockable rhythm who remain unresponsive after ROSC.
- We suggest TTM as opposed to no TTM for adults with OHCA with an initial nonshockable rhythm who remain unresponsive after ROSC.
- We suggest TTM as opposed to no TTM for adults with in-hospital cardiac arrest (IHCA) with any initial rhythm who remain unresponsive after ROSC.
- We suggest that if TTM is used, duration should be at least 24 hours.
- We recommend against routine use of prehospital cooling with rapid infusion of large volumes of cold IV fluid immediately after ROSC.
- We suggest prevention and treatment of fever in persistently comatose adults after completion of TTM between 32°C and 36°C.
- We suggest against routine seizure prophylaxis in post-cardiac arrest patients.
- We recommend the treatment of seizures in post-cardiac arrest patients.
- We suggest no modification of standard glucose management protocols for adults with ROSC after cardiac arrest.
- Comatose patients treated with TTM:
  - We suggest against the use of clinical criteria alone before 72 hours after ROSC to estimate prognosis.
  - We suggest prolonging the observation of clinical signs when interference from residual sedation or paralysis is suspected, so that the possibility of incorrectly predicting poor outcome is minimized.
  - We recommend that the earliest time to prognosticate a poor neurologic outcome is 72 hours after ROSC, and should be extended longer if the residual effect of sedation and/or paralysis confounds the clinical examination.
  - We suggest that multiple modalities of testing (clinical exam, neurophysiological measures, imaging, or blood markers) be used to estimate prognosis instead of relying on single tests or findings.
- We recommend that all patients who have restoration of circulation after CPR and who subsequently progress to death be evaluated for organ donation.

## Defibrillation Strategies for VF or pVT

The task force restricted its review to new studies since the 2010 CoSTR<sup>12,13</sup> and topics not reviewed in 2010. There are no major differences between the recommendations made in 2015 and those made in 2010. The PICO questions have been grouped into (1) waveforms, (2) first-shock energy, (3) single shock versus 3 shocks, (4) fixed versus escalating energy levels, and (5) refribrillation. In reviewing these, shock success is usually defined as termination of VF 5 seconds after the shock.

Consensus on science and treatment recommendations for the use of automated external defibrillators can be found in “Part 3: Adult Basic Life Support and Automated External Defibrillation,” and for infants or children requiring defibrillation in “Part 6: Pediatric Basic Life Support and Pediatric Advanced Life Support.”

### Biphasic Waveform (ALS 470)

Among adults who are in VF or pVT in any setting (P), does any specific defibrillation strategy, such as biphasic waveform (I), compared with standard management (or other defibrillation strategy), such as monophasic waveform (C), change survival with favorable neurologic/functional outcome at discharge, 30 days, 60 days, 180 days, and/or 1 year; survival only at discharge, 30 days, 60 days, 180 days, and/or 1 year; ROSC; termination of arrhythmia (O)?

#### Introduction

All newly manufactured defibrillators currently deliver shocks using biphasic waveforms. Although it has not been shown conclusively in randomized clinical studies that biphasic defibrillators save more lives than monophasic defibrillators, biphasic defibrillators achieve higher first-shock success rates at lower energy levels and appear to cause less postshock myocardial dysfunction.<sup>12,13</sup>

#### Consensus on Science

No new randomized trials of biphasic waveforms since 2010 were identified.

#### Treatment Recommendation

We recommend that a biphasic waveform (biphasic truncated exponential [BTE] or rectilinear-biphasic [RLB]) is used for both atrial and ventricular arrhythmias in preference to a monophasic waveform (strong recommendation, very-low-quality evidence). In the absence of biphasic defibrillators, monophasic defibrillators are acceptable.

#### Values, Preferences, and Task Force Insights

In making this strong recommendation, we place a high value on the reported higher first-shock success rate for termination of fibrillation with a biphasic waveform, the potential for less postshock myocardial dysfunction, and the existing 2010 CoSTR.<sup>12,13</sup> The task force acknowledges that many emergency medical services (EMS) systems and hospitals around the world continue to use older monophasic devices.

### Pulsed Biphasic Waveform (ALS 470)

Among adults who are in VF or pVT in any setting (P), does any specific defibrillation strategy, such as pulsed biphasic waveform (I), compared with standard management (or

other defibrillation strategy) (C), change survival with favorable neurologic/functional outcome at discharge, 30 days, 60 days, 180 days, and/or 1 year; survival only at discharge, 30 days, 60 days, 180 days, and/or 1 year; ROSC; termination of arrhythmia (O)?

#### Introduction

The pulsed biphasic waveform that is used in clinical practice had not previously been reviewed in 2010. The single published study<sup>14</sup> of this waveform used a non-impedance compensated waveform (ie, the current delivered is not adjusted for the impedance of the chest), whereas the waveform in clinical use is an impedance-compensated waveform (ie, the current delivered is adjusted for the impedance of the chest).

#### Consensus on Science

For the critical outcome of **survival to hospital discharge**, very-low-quality evidence (downgraded for very serious risk of bias and serious indirectness) from 1 cohort study (ie, no control group)<sup>14</sup> with a total of 104 patients that used a 130 J-130 J-180 J pulsed biphasic waveform protocol documented a survival rate of 9.8%. This compares with a weighted average BTE survival rate of 33.1% at 150 to 200 J.<sup>14</sup>

For the important outcome of **termination of fibrillation**, the same very-low-quality evidence (downgraded for very serious risk of bias and serious indirectness) from 1 cohort study<sup>14</sup> with a total of 104 patients documented first-shock termination rates at 130 J of 90.4% with a pulsed biphasic waveform, comparable with BTE waveforms (weighted average 91.8%) at 150 to 200 J.<sup>14</sup>

#### Treatment Recommendation

We recommend following the manufacturer’s instructions for first and subsequent shock energy levels for the pulsed biphasic waveform (strong recommendation, very-low-quality evidence).

#### Values, Preferences, and Task Force Insights

In making this strong recommendation, we have placed a high value on following the manufacturer’s guidance in the absence of high-quality data to suggest otherwise. The available very-low-quality data showing the efficacy of a non-impedance compensated pulsed biphasic waveform do not enable direct comparison with other biphasic waveforms. In addition, no clinical studies attest to the efficacy of this waveform in its current impedance-compensated form.

### First-Shock Energy (ALS 470)

Among adults who are in VF or pVT in any setting (P), does any specific defibrillation strategy, such as specific first-shock energy level (I), compared with standard management (or other defibrillation strategy), such as a different first-shock energy level (C), change survival with favorable neurologic/functional outcome at discharge, 30 days, 60 days, 180 days, and/or 1 year; survival only at discharge, 30 days, 60 days, 180 days, and/or 1 year; ROSC; termination of arrhythmia (O)?

#### Introduction

In 2010, it was concluded that it was reasonable to start at a selected energy level of 150 to 200 J for a BTE waveform, and no lower than 120 J for an RLB waveform for defibrillation of



VF/pVT cardiac arrest, acknowledging that the evidence was limited.<sup>12,13</sup>

### **Consensus on Science**

For the important outcome of **termination of VF/pVT**, low-quality evidence (downgraded for imprecision and risk of bias, respectively) from a post hoc report from an RCT and a cohort study showed a first-shock success rate of 73 of 86 (85%) and 79 of 90 (87.8%), respectively, when using a 120 J initial shock with an RLB waveform.<sup>15,16</sup>

### **Treatment Recommendations**

We recommend an initial biphasic shock energy of 150 J or greater for BTE waveforms, and 120 J or greater for RLB waveforms (strong recommendation, very-low-quality evidence). If a monophasic defibrillator is used, we recommend an initial monophasic shock energy of 360 J (strong recommendation, very-low-quality evidence).

### **Values, Preferences, and Task Force Insights**

In making these strong recommendations, the working group was keen to acknowledge manufacturer's instructions and recognize that evidence for the optimal first-shock energy level was lacking. We also considered that although monophasic defibrillators are no longer manufactured, they are still used in many countries.

### **Single Shock Versus Stacked Shocks (ALS 470)**

Among adults who are in VF or pVT in any setting (P), does any specific defibrillation strategy, such as a single shock (I), compared with standard management (or other defibrillation strategy), such as 3 stacked shocks (C), change survival with favorable neurologic/functional outcome at discharge, 30 days, 60 days, 180 days, and/or 1 year; survival only at discharge, 30 days, 60 days, 180 days, and/or 1 year; ROSC; termination of arrhythmia (O)?

### **Introduction**

In 2010, it was recommended that when defibrillation was required, a single shock should be provided with immediate resumption of chest compressions after the shock.<sup>12,13</sup> This recommendation was made for 2 reasons: (1) in an attempt to minimize perishock interruptions to chest compressions, and (2) because it was thought that with the greater efficacy of biphasic shocks, if a biphasic shock failed to defibrillate, a further period of chest compressions could be beneficial. It was acknowledged that there was no clinical evidence to support improved outcomes from this strategy.

### **Consensus on Science**

For the critical outcome of **survival to 1 year**, we have identified low-quality evidence (downgraded for serious risk of bias and serious indirectness) from 1 RCT enrolling 845 OHCA patients showing no difference in single versus 3 stacked shocks (odds ratio [OR], 1.64; 95% confidence interval [CI], 0.53–5.06).<sup>17</sup>

For the critical outcome of **survival to hospital discharge**, we have identified low-quality evidence (downgraded for serious risk of bias and serious indirectness) from 1 RCT enrolling 845 OHCA patients showing no difference in single versus 3 stacked shocks (OR, 1.29; 95% CI, 0.85–1.96).<sup>17</sup>

For the critical outcome of **survival to hospital admission**, we have identified very-low-quality evidence (downgraded for serious risk of bias and serious indirectness) from 1 RCT enrolling 845 OHCA patients showing no difference in single versus 3 stacked shocks (OR, 1.02; 95% CI, 0.78–1.34).<sup>17</sup>

For the critical outcome of **ROSC**, we have identified low-quality evidence (downgraded for serious risk of bias and serious indirectness) from 1 RCT enrolling 845 OHCA patients showing no difference in single versus 3 stacked shocks (OR, 0.94; 95% CI, 0.72–1.23).<sup>17</sup>

For the important outcome of **recurrence of VF** (refibrillation), we have identified low-quality evidence (downgraded for serious risk of bias, serious indirectness, and serious imprecision) from 1 RCT enrolling 136 OHCA patients showing no difference in single versus 3 stacked shocks (OR, 1.00; 95% CI, 0.47–2.13).<sup>18</sup>

### **Treatment Recommendation**

We recommend a single-shock strategy when defibrillation is required (strong recommendation, low-quality evidence).

### **Values, Preferences, and Task Force Insights**

In making this strong recommendation, the task force has placed a greater value on not changing current practice and minimizing interruptions in chest compressions whilst acknowledging that studies since 2010 have not shown that any specific shock strategy is of benefit for any survival end point. There is no conclusive evidence that a single-shock strategy is of benefit for ROSC or recurrence of VF compared with 3 stacked shocks, but in view of the evidence suggesting that outcome is improved by minimizing interruptions to chest compressions, we continue to recommend single shocks. The task force is aware that there are some circumstances (eg, witnessed, monitored VF cardiac arrest with defibrillator immediately available) when 3 rapid stacked shocks could be considered.

### **Fixed Versus Escalating Defibrillation Energy Levels (ALS 470)**

Among adults who are in VF or pVT in any setting (P), does any specific defibrillation strategy, such as fixed shock energy level (I), compared with standard management (or other defibrillation strategy), such as escalating shock energy level (C), change survival with favorable neurologic/functional outcome at discharge, 30 days, 60 days, 180 days, and/or 1 year; survival only at discharge, 30 days, 60 days, 180 days, and/or 1 year; ROSC; termination of arrhythmia (O)?

### **Introduction**

In 2010, we recommended that for second and subsequent biphasic shocks, the same initial energy level was acceptable, but that it was reasonable to increase the energy level when possible (ie, with manual defibrillators).<sup>12,13</sup>

### **Consensus on Science**

For the critical outcome of **survival with favorable neurologic outcome at hospital discharge**, we identified very-low-quality evidence (downgraded for serious risk of bias, serious imprecision, and serious indirectness) from 1 RCT enrolling 221 OHCA patients showing no benefit of one strategy over the other (OR, 0.78; 95% CI, 0.34–1.78).<sup>19</sup>

For the critical outcome of **survival to hospital discharge**, we have identified very-low-quality evidence (downgraded for serious risk of bias, serious imprecision, and serious indirectness) from 1 RCT enrolling 221 OHCA patients showing no benefit of one strategy over the other (OR, 1.06; 95% CI, 0.52–2.16).<sup>19</sup>

For the critical outcome of **ROSC**, we have identified very-low-quality evidence (downgraded for serious risk of bias, serious imprecision, and serious indirectness) from 1 RCT enrolling 221 OHCA patients showing no benefit of one strategy over the other (OR, 1.095; 95% CI, 0.65–1.86).<sup>19</sup>

### **Treatment Recommendation**

We suggest if the first shock is not successful and the defibrillator is capable of delivering shocks of higher energy, it is reasonable to increase the energy for subsequent shocks (weak recommendation, very-low-quality evidence).

### **Values, Preferences, and Task Force Insights**

In making this recommendation, we have considered that an escalating shock energy may prevent the risk of refrillation (see **ALS 470**). We also consider this to be in line with current practices where rescuers will escalate shock energy if initial defibrillation attempts fail and the defibrillator is capable of delivering a higher shock energy.

### **Recurrent VF (Refrillation) (ALS 470)**

Among adults who are in VF or pVT in any setting (P), does any specific defibrillation strategy (I), compared with standard management (or other defibrillation strategy) (C), improve termination of refrillation (O)?

### **Introduction**

Refrillation is common and occurs in the majority of patients after initial first-shock termination of VF.<sup>20</sup> Refrillation was not specifically addressed in 2010 guidelines. Distinct from refractory VF, defined as fibrillation that persists after 1 or more shocks, recurrence of fibrillation is usually defined as recurrence of VF during a documented cardiac arrest, occurring after initial termination of VF while the patient remains under the care of the same providers (usually out-of-hospital).

### **Consensus on Science**

For the important outcome of **termination of refrillation**, low-quality evidence (downgraded for serious risk of bias) from 2 observational studies<sup>16,21</sup> with a total of 191 cases of initial fibrillation showed termination rates of subsequent refrillation were unchanged when using fixed 120 or 150 J shocks, respectively, and another observational study<sup>20</sup> (downgraded for confounding factors) with a total of 467 cases of initial fibrillation showed termination rates of refrillation declined when using repeated 200 J shocks, unless an increased energy level (360 J) was selected.

### **Treatment Recommendation**

We suggest an escalating defibrillation energy protocol to prevent refrillation (weak recommendation, low-quality evidence).

### **Values, Preferences, and Task Force Insights**

In making this weak recommendation, we considered the lack of studies showing myocardial injury from biphasic

waveforms, making it reasonable to consider increasing defibrillation energy levels when delivering shocks for refrillation if the energy dose delivered by the defibrillator can be increased. It is unclear from current studies whether repeated episodes of VF are more resistant to defibrillation and require a higher energy level or whether a fixed energy level is adequate.

### **Defibrillation Knowledge Gaps**

- Considering that defibrillation is one of the few interventions that improves outcome from cardiac arrest, high-quality studies of optimal defibrillation strategies are sparse.
- The dose response curves for defibrillation of shockable rhythms is unknown and the initial shock energy, subsequent shock energies, and maximum shock energies for each waveform are unknown. In particular, the strategy of delivering shock energy at maximum defibrillation output to improve current defibrillation efficacy rates remains unanswered.
- Studies of optimal defibrillation energies for refrillation are contradictory, and it remains unclear whether refrillation is a different form of fibrillation that requires the same or higher energy levels for successful termination of fibrillation.
- The selected energy is a poor comparator for assessing different waveforms, as impedance compensation and subtleties in waveform shape result in a different transmural current between devices for any given selected energy. The optimal energy levels may ultimately vary between different manufacturers and associated waveforms.
- We would encourage manufacturers to undertake high-quality clinical trials to support their defibrillation strategy recommendations. Caution is also urged in attributing the outcomes observed to any one portion of the elements of bundled care.
- The task force did not address the topic of hands-on defibrillation strategies, its efficacy, and safety, although we realize it is a topic of interest for future studies.

### **2010 CoSTR Defibrillation Topics Not Reviewed in 2015**

- CPR before defibrillation
- Self-adhesive defibrillation pads compared with paddles
- Placement of paddles/pads
- Size of paddles/pads
- Composition of conductive material
- Biphasic compared with monophasic defibrillation waveform
- Multiphasic compared with biphasic defibrillation waveform
- Waveforms, energy levels, and myocardial damage
- Shock using manual versus semiautomatic mode
- Cardioversion strategy in atrial fibrillation
- Pacing (eg, transcutaneous, transvenous, needle, and fist)
- Implantable cardioverter-defibrillator or pacemaker
- Predicting success of defibrillation and outcome (VF waveform analysis)

- Defibrillation in the immediate vicinity of supplementary oxygen
- Algorithm for transition from shockable to nonshockable rhythm

### Airway, Oxygenation, and Ventilation

The use of supplementary oxygen (when it is available) during CPR is accepted practice, but in other circumstances (eg, acute myocardial infarction), there is increasing evidence that administration of high-concentration oxygen may be harmful.

The optimal strategy for managing the airway has yet to be determined, but several observational studies have challenged the premise that tracheal intubation improves outcomes. Options for airway management can be categorized broadly into bag-mask ventilation with simple airway adjuncts, SGAs, and tracheal intubation. In this section, we present the evidence for the use of oxygen and airway devices during CPR, for how to confirm correct tracheal tube placement, and for ventilation rate once an advanced airway device (either a tracheal tube or SGA) has been inserted.

#### Oxygen Dose During CPR (ALS 889)

In adults with cardiac arrest in any setting (P), does administering a maximal oxygen concentration (eg, 100% by face mask or closed circuit) (I), compared with no supplementary oxygen (eg, 21%) or a reduced oxygen concentration (eg, 40%–50%) (C), change survival with favorable neurologic/functional outcome at discharge, 30 days, 60 days, 180 days, and/or 1 year; survival only at discharge, 30 days, 60 days, 180 days, and/or 1 year; ROSC (O)?

#### Introduction

It has generally been considered appropriate to administer 100% oxygen, whenever available, during cardiac arrest; however, in some other medical emergencies, the use of 100% is now being challenged.

#### Consensus on Science

There are no adult human studies that directly compare maximal inspired oxygen with any other inspired oxygen concentration.

For the critical outcome of **survival to hospital discharge with favorable neurologic outcome** (Cerebral Performance Category [CPC] 1 or 2), we identified very-low-quality evidence (downgraded for very serious risk of bias, very serious indirectness, and serious imprecision) from 1 observational study<sup>22</sup> enrolling 145 OHCA patients who had a Pao<sub>2</sub> measured during CPR that showed no difference between an intermediate Pao<sub>2</sub> and low Pao<sub>2</sub> (11/83 [13.3%] versus 1/32 [3.1%]; relative risk [RR], 4.2; 95% CI, 0.57–31.52; *P*=0.16), or between a high Pao<sub>2</sub> and low Pao<sub>2</sub> (7/30 [23.3%] versus 1/32 [3.1%]; RR, 7.45; 95% CI, 0.98–57.15; *P*=0.053).

For the important outcome of **ROSC**, we identified very-low-quality evidence (downgraded for very serious risk of bias, very serious indirectness, and serious imprecision) from 1 observational study<sup>22</sup> enrolling 145 OHCA patients who had a Pao<sub>2</sub> measured during CPR that showed improved ROSC in those with a higher Pao<sub>2</sub>: intermediate Pao<sub>2</sub> versus low Pao<sub>2</sub> (47/83 [56.6%] versus 7/32 [21.9%]; RR, 2.59; 95%

CI, 1.31–5.12; *P*=0.006); high Pao<sub>2</sub> versus low Pao<sub>2</sub> (25/30 [83.3%] versus 7/32 [21.9%]; RR, 3.81; 95% CI, 1.94–7.48; *P*=0.0001); high Pao<sub>2</sub> versus intermediate Pao<sub>2</sub> (25/30 [83.3%] versus 47/83 [56.6%]; RR, 1.47; 95% CI, 1.15–1.88; *P*=0.002).

In the single identified study,<sup>22</sup> all patients had tracheal intubation and received 100% inspired oxygen during CPR. The worse outcomes associated with a low Pao<sub>2</sub> during CPR could be an indication of illness severity.

#### Treatment Recommendation

We suggest the use of the highest possible inspired oxygen concentration during CPR (weak recommendation, very-low-quality evidence).

#### Values, Preferences, and Task Force Insights

In making this recommendation, we have considered the limited available evidence and the need to correct tissue hypoxia during CPR, and see no reason to change the current treatment recommendation.

#### Knowledge Gaps

- The optimal arterial or tissue oxygen targets during CPR are unknown.
- A method of reliably monitoring oxygen targets during CPR has not been established.
- The feasibility of controlling inspired oxygen concentration during CPR remains unclear.
- Prospective clinical trials may be warranted to explore different inspired oxygen concentrations during CPR.
- The role and feasibility of alternatives to oxygen/air mixtures during CPR are unknown.

#### Basic Versus Advanced Airway (ALS 783)

Among adults who are in cardiac arrest in any setting (P), does insertion of an advanced airway (tracheal tube or SGA) (I), compared with basic airway (bag-mask device with or without oropharyngeal airway) (C), change survival with favorable neurologic/functional outcome at discharge, 30 days, 60 days, 180 days, and/or 1 year; survival only at discharge, 30 days, 60 days, 180 days, and/or 1 year; ROSC; CPR parameters; development of aspiration pneumonia (O)?

#### Introduction

The optimal approach to managing the airway during cardiac arrest has been unclear, and several recent observational studies have challenged the assumption that advanced airways are necessarily superior to basic airway techniques.

#### Consensus on Science

##### All Advanced Airways (I) Versus Bag-Mask Device (C)

For the critical outcome of **1-year survival**, we have identified very-low-quality evidence (downgraded for very serious risk of bias, indirectness and imprecision, and serious inconsistency) from 1 observational study of 1278 OHCA patients showing a similar unadjusted rate of survival with insertion of an advanced airway (tracheal tube, esophageal obturator airway [EOA] or laryngeal mask airway [LMA]) compared with a bag-mask device (3.7% versus 5.6%; OR, 0.65; 95% CI, 0.4–1.1).<sup>23</sup>



For the critical outcome of **favorable neurologic survival at 1 month**, we have identified very-low-quality evidence (downgraded for very serious risk of bias and indirectness, and serious inconsistency) from 1 observational study of 648 549 OHCAs showing a lower unadjusted rate of survival with insertion of an advanced airway (tracheal tube, LMA, laryngeal tube, or Combitube) compared with management with a bag-mask device (1.1% versus 2.9%; OR, 0.38; 95% CI, 0.36–0.39).<sup>24</sup> When adjusted for all known variables, the OR was 0.32 (95% CI, 0.30–0.33).

For the critical outcome of **favorable neurologic survival to hospital discharge**, we have identified very-low-quality evidence (downgraded for very serious risk of bias and indirectness, and serious inconsistency) from 1 observational study of 10 691 OHCAs showing a lower unadjusted rate of survival with insertion of an advanced airway (tracheal tube, LMA, laryngeal tube, or Combitube) compared with management with a bag-mask device (5.3% versus 18.6%; OR, 0.25; 95% CI, 0.2–0.3).<sup>25</sup> In an analysis of 3398 propensity-matched patients from the same study, the OR for favorable neurologic survival at hospital discharge (bag-mask device versus advanced airway) adjusted for all variables was 4.19 (95% CI, 3.09–5.70).

For the critical outcome of **survival to hospital discharge**, we have identified very-low-quality evidence (downgraded for very serious risk of bias and indirectness, and serious inconsistency) from 2 observational studies: 1 of 10 691 OHCAs showed a lower unadjusted rate of survival with insertion of an advanced airway (tracheal tube or LMA) compared with a bag-mask device (7.7% versus 21.9%; OR, 0.30; 95% CI, 0.3–0.3)<sup>25</sup>; 1 of 5278 OHCAs showed a similar unadjusted rate of survival with insertion of an advanced airway (tracheal tube or LMA) compared with a bag-mask device (6.6% versus 7.0%; OR, 0.94; 95% CI, 0.7–1.3).<sup>26</sup>

#### *Tracheal Intubation (I) Versus Bag-Mask Device (C)*

For the critical outcome of **favorable neurologic survival at 1 month**, we have identified very-low-quality evidence (downgraded for very serious risk of bias and indirectness, and serious inconsistency) from 1 observational study of 409 809 OHCAs showing a lower unadjusted rate of survival with tracheal intubation compared with a bag-mask device (1.0% versus 2.9%; OR, 0.35; 95% CI, 0.31–0.38).<sup>24</sup> In an analysis of 357 228 propensity-matched patients from the same study, the OR for favorable neurologic survival at 1 month (tracheal intubation versus bag-mask device) adjusted for all variables was 0.42 (95% CI, 0.34–0.53).

For the critical outcome of **survival at 1 month**, we have identified very-low-quality evidence (downgraded for very serious risk of bias and indirectness, and serious inconsistency) from 2 observational studies. One of 409 809 OHCAs showed a lower unadjusted rate of survival with tracheal intubation compared with a bag-mask device (4.2% versus 5.3%; OR, 0.77; 95% CI, 0.74–0.81).<sup>24</sup> In an analysis of 357 228 propensity-matched patients from the same study, the OR for survival at 1 month (tracheal intubation versus bag-mask device) adjusted for all variables was 0.88 (95% CI, 0.79–0.98). Another study of 10 783 OHCAs also showed a lower unadjusted rate of survival with tracheal intubation compared

with a bag-mask device (3.6% versus 6.4%; OR, 0.54; 95% CI, 0.5–0.7).<sup>27</sup>

For the critical outcome of **favorable neurologic survival to hospital discharge**, we have identified very-low-quality evidence (downgraded for very serious risk of bias and indirectness, and serious inconsistency) from 1 observational study of 7520 OHCAs showing a lower unadjusted rate of survival with tracheal intubation compared with a bag-mask device (5.4% versus 18.6%; OR, 0.25; 95% CI 0.2–0.3).<sup>25</sup>

For the critical outcome of **survival to hospital discharge**, we have identified very-low-quality evidence (downgraded for very serious risk of bias, indirectness, and imprecision, and serious inconsistency) from 6 observational studies. One observational study of 7520 OHCAs showed a lower unadjusted rate of survival with tracheal intubation compared with a bag-mask device (8.3% versus 21.9%; OR, 0.25; 95% CI, 0.2–0.3).<sup>25</sup> One study of 4887 OHCAs showed a similar unadjusted rate of survival with insertion of a tracheal tube compared with a bag-mask device (8.0% versus 7.0%; OR, 1.16; 95% CI, 0.7–1.9).<sup>26</sup> Among 496 propensity-matched OHCAs in the same study, the OR for survival to discharge (tracheal intubation versus bag-mask device) was 1.44 (95% CI, 0.66–3.15).<sup>26</sup> One observational study of 1158 OHCAs showed a lower unadjusted rate of survival with tracheal intubation compared with a bag-mask device (3.7% versus 10.8%; OR, 0.32; 95% CI, 0.2–0.6).<sup>28</sup> One observational study of 8651 OHCAs showed a lower unadjusted rate of survival with tracheal intubation compared with a bag-mask device (3.7% versus 9.1%; OR, 0.41; 95% CI, 0.3–0.5).<sup>29</sup> One observational study of 1142 OHCAs showed a lower unadjusted rate of survival with tracheal intubation compared with a bag-mask device (6.3% versus 28.6%; OR, 0.17; 95% CI, 0.1–0.2).<sup>30</sup>

#### *Supraglottic Airways (I) Versus Bag-Mask Device (C)*

For the critical outcome of **favorable neurologic survival at 1 month**, we have identified very-low-quality evidence (downgraded for very serious risk of bias and indirectness, and serious inconsistency) from 1 observational study of 607 387 OHCAs showing a lower unadjusted rate of survival with insertion of an SGA (LMA, laryngeal tube, or Combitube) compared with a bag-mask device (1.1% versus 2.9%; OR, 0.38; 95% CI, 0.37–0.40).<sup>24</sup> In an analysis of 357 228 propensity-matched patients from the same study, the OR for favorable neurologic survival at 1 month (SGA versus bag-mask device) adjusted for all variables was 0.36 (95% CI, 0.33–0.40).

For the critical outcome of **favorable neurologic survival to hospital discharge**, we have identified very-low-quality evidence (downgraded for very serious risk of bias and indirectness, and serious inconsistency) from 1 observational study of 5039 OHCAs showing a lower unadjusted rate of survival with an SGA compared with a bag-mask device (5.2% versus 18.6%; OR, 0.24; 95% CI, 0.2–0.3).<sup>25</sup>

For the critical outcome of **survival to hospital discharge**, we have identified very-low-quality evidence (downgraded for very serious risk of bias, indirectness, and imprecision, and serious inconsistency) from 2 observational studies. One observational study of 5039 OHCAs showed a lower unadjusted rate of survival with an SGA compared with a bag-mask device (6.7% versus 21.9%; OR, 0.26; 95% CI,



0.2–0.3).<sup>25</sup> Another study of 262 OHCAs also showed a lower unadjusted rate of survival with an SGA compared with a bag-mask device (0.0% versus 10.7%).<sup>28</sup>

#### *Laryngeal Mask Airway (I) Versus Bag-Mask Device (C)*

For the critical outcome of **survival to hospital discharge**, we have identified very-low-quality evidence (downgraded for very serious risk of bias, indirectness, and imprecision, and serious inconsistency) from 1 observational study of 5028 OHCAs showing a similar unadjusted rate of survival with insertion of an LMA compared with a bag-mask device (5.6% versus 7.0%; OR, 0.80; 95% CI, 0.5–1.2).<sup>26</sup> Among 772 propensity-matched OHCAs in the same study, the OR for survival to discharge (LMA versus bag-mask device) was 0.45 (95% CI, 0.25–0.82).<sup>26</sup>

#### **Treatment Recommendation**

We suggest using either an advanced airway or a bag-mask device for airway management during CPR (weak recommendation, very-low-quality evidence) for cardiac arrest in any setting.

#### **Values, Preferences, and Task Force Insights**

In the absence of sufficient data obtained from studies of IHCA, it is necessary to extrapolate from data derived from OHCA.

The type of airway used may depend on the skills and training of the healthcare provider. Tracheal intubation may result in unrecognized esophageal intubation and increased hands-off time in comparison with insertion of an SGA or a bag-mask device. Both a bag-mask device and an advanced airway are frequently used in the same patient as part of a stepwise approach to airway management, but this has not been formally assessed.

#### **Knowledge Gaps**

- There are no RCTs of initial airway management during cardiac arrest.
- The type and duration of training required for each device is unknown.
- During cardiac arrest, is a stepwise approach to airway management commonly used? It is not clear how this can be studied rigorously.

### **SGAs Versus Tracheal Intubation (ALS 714)**

Among adults who are in cardiac arrest in any setting (P), does SGA insertion as first advanced airway (I), compared with insertion of a tracheal tube as first advanced airway (C), change survival with favorable neurologic/functional outcome at discharge, 30 days, 60 days, 180 days, and/or 1 year; survival only at discharge, 30 days, 60 days, 180 days, and/or 1 year; ROSC; CPR parameters; development of aspiration pneumonia (O)?

#### **Introduction**

SGAs are generally considered easier to insert than tracheal tubes are, and their use in cardiac arrest has been increasing.

#### **Consensus on Science**

##### *SGAs (Combitube, LMA, Laryngeal Tube) Versus Tracheal Intubation*

For the critical outcome of **favorable neurologic survival**, we have identified very-low-quality evidence (downgraded

for very serious concerns about risk of bias, inconsistency, and indirectness) from 1 observational study of 5377 OHCAs showing no difference between tracheal intubation and insertion of a SGA (adjusted OR, 0.71; 95% CI, 0.39–1.30),<sup>31</sup> from 1 observational study of 281 522 OHCAs showing higher rates of favorable neurologic outcome between insertion of an SGA and tracheal intubation (OR, 1.11; 95% CI, 1.0–1.2),<sup>24</sup> and from 2 studies showing higher rates of favorable neurologic outcome between tracheal intubation and insertion of an SGA (8701 OHCAs: adjusted OR, 1.44; 95% CI, 1.10–1.88<sup>25</sup> and 10455 OHCAs: adjusted OR, 1.40; 95% CI, 1.04–1.89).<sup>32</sup>

##### *SGAs (EOA and LMA) Versus Tracheal Intubation*

For the critical outcome of **neurologically favorable 1-month survival**, we have identified very-low-quality evidence (downgraded for very serious risk of bias, inconsistency, indirectness, and imprecision) from 1 observational study of 138 248 OHCAs that showed higher rates of neurologically favorable 1-month survival with tracheal intubation compared with insertion of an EOA or LMA (OR, 0.89; 95% CI, 0.8–1.0).<sup>33</sup>

For the critical outcome of **1-month survival**, we have identified very-low-quality evidence (downgraded for very serious concerns about risk of bias, inconsistency, indirectness, and imprecision) from 1 observational study that showed no difference in 1-month survival between tracheal intubation and insertion of an EOA of an LMA (OR, 0.75; 95% CI, 0.3–1.9)<sup>23</sup> and very-low-quality evidence (downgraded for very serious risk of bias, inconsistency, indirectness, and imprecision) from another observation study that showed higher 1-month survival with tracheal intubation compared with insertion of an EOA of an LMA (OR, 1.03; 95% CI, 0.9–1.1).<sup>33</sup>

##### *LMA (I) Versus Tracheal Intubation (C)*

For the critical outcome of **survival to hospital discharge**, we have identified very-low-quality evidence (downgraded for very serious risk of bias, inconsistency, indirectness, and imprecision) from 1 observational study of 641 OHCAs that showed lower rates of survival to hospital discharge with insertion of an LMA compared with tracheal tube (OR, 0.69; 95% CI, 0.4–1.3).<sup>26</sup>

##### *Esophageal Gastric Tube Airway (I) Versus Tracheal Intubation (C)*

For the critical outcome of **survival to hospital discharge**, we have identified very-low-quality evidence (downgraded for very serious risk of bias and imprecision) from 1 RCT enrolling 175 OHCAs showing no difference between esophageal gastric tube airway and tracheal intubation (OR, 1.19; 95% CI, 0.5–3.0).<sup>34</sup>

##### *Combitube (I) Versus Tracheal Intubation (C)*

For the critical outcome of **survival to hospital discharge**, we have identified very-low-quality evidence (downgraded for very serious risk of bias, inconsistency, indirectness, and imprecision) from 1 RCT enrolling 173 OHCAs that showed no difference between Combitube and tracheal intubation (OR, 2.38; 95% CI, 0.5–12.1)<sup>35</sup> and very-low-quality evidence from 1 observational study of 5822 OHCAs that showed no difference between tracheal intubation by paramedics, and Combitube insertion by emergency medical technicians (adjusted OR, 1.02; 95% CI, 0.79–1.30).<sup>36</sup>

### Treatment Recommendation

We suggest using either an SGA or tracheal tube as the initial advanced airway during CPR (weak recommendation, very-low-quality evidence) for cardiac arrest in any setting.

### Values, Preferences, and Task Force Insights

In the absence of sufficient data obtained from studies of IHCA, it is necessary to extrapolate from data derived from OHCA.

The type of airway used may depend on the skills and training of the healthcare provider. Tracheal intubation requires considerably more training and practice. Tracheal intubation may result in unrecognized esophageal intubation and increased hands-off time in comparison with insertion of an SGA. Both an SGA and tracheal tube are frequently used in the same patients as part of a stepwise approach to airway management, but this has not been formally assessed.

### Knowledge Gaps

- There are no RCTs of initial airway management during cardiac arrest.
- The type and duration of training required for each device is unknown.
- During the management of cardiac arrest, is a stepwise approach to airway management commonly used? It is not clear how this can be studied rigorously.

## Confirmation of Correct Tracheal Tube Placement (ALS 469)

Among adults who are in cardiac arrest, needing/with an advanced airway during CPR in any setting (P), does use of devices (eg, waveform capnography, CO<sub>2</sub> detection device, esophageal detector device, or tracheal ultrasound) (I), compared with not using devices (C), change placement of the tracheal tube in the trachea and above the carina, or success of intubation (O)?

### Introduction

Unrecognized esophageal intubation is a serious complication of attempted tracheal intubation during CPR. There are several potential methods for confirming correct placement of a tracheal tube: capnography and detection of CO<sub>2</sub>, use of an esophageal detection device, and tracheal ultrasound.

### Consensus on Science

#### Waveform Capnography

For the important outcome of **detection of correct placement of a tracheal tube during CPR**, we identified very-low-quality evidence (downgraded for risk of bias and indirectness) from 1 observational study<sup>37</sup> showing that the use of waveform capnography compared with no waveform capnography in 153 critically ill patients (51 with cardiac arrest) decreased the occurrence of unrecognized esophageal intubation on hospital arrival from 23% to 0% (OR, 29; 95% CI, 4–122).

For the important outcome of **detection of correct placement of a tracheal tube during CPR**, we identified low-quality evidence (downgraded for serious risk of bias and imprecision) from 3 observational studies<sup>38–40</sup> with 401 patients and 1 randomized study<sup>41</sup> including 48 patients that showed

that the specificity for waveform capnography to detect correct tracheal placement was 100% (95% CI, 87%–100%). The sensitivity was 100% in 1 study<sup>38,39</sup> when waveform capnography was used in the prehospital setting immediately after intubation, and esophageal intubation was less common than the average (1.5%). The sensitivity was between 65% and 68% in the other 3 studies<sup>39–41</sup> when the device was used in OHCA patients after intubation in the emergency department (ED). The difference may be related to prolonged resuscitation with compromised or nonexistent pulmonary blood flow. Based on the pooled sensitivity/specificity from these studies and assumed esophageal intubation prevalence of 4.5%, the false-positive rate (FPR) of waveform capnography was 0% (95% CI, 0%–0.6%).

#### Colorimetric CO<sub>2</sub> Detection Devices

For the important outcome of **detection of correct placement of a tracheal tube during CPR**, we identified very-low-quality evidence (downgraded for risk of bias and indirectness) from 7 observational studies<sup>38,42–47</sup> including 1119 patients that evaluated the diagnostic accuracy of colorimetric CO<sub>2</sub> devices. The specificity was 97% (95% CI, 84%–99%), the sensitivity was 87% (95% CI, 85%–89%), and the FPR was 0.3% (95% CI, 0%–1%).

#### Esophageal Detection Devices

For the important outcome of **detection of correct placement of a tracheal tube during CPR**, we identified very-low-quality evidence (downgraded for risk of bias, indirectness, inconsistency, and a strong suspicion of publication bias) from 4 observational studies<sup>39,40,43,48</sup> including 228 patients, low-quality evidence (downgraded for risk of bias and indirectness) from 1 randomized study<sup>41</sup> including 48 patients, and very-low-quality evidence (downgraded for risk of bias, indirectness, inconsistency, and a strong suspicion of publication bias) from 1 observational study<sup>50</sup> including 168 patients that evaluated esophageal detection devices. The pooled specificity was 92% (95% CI, 84%–96%), the pooled sensitivity was 88% (95% CI, 84%–192%), and the FPR was 0.2% (95% CI, 0%–0.6%). Low-quality evidence (downgraded for risk of bias and suspected publication bias) from 1 observational study<sup>41</sup> showed no statistically significant difference between the performance of a bulb (sensitivity 71%, specificity 100%) and a syringe (sensitivity 73%, specificity 100%)-type esophageal detection devices in the detection of tracheal placement of a tracheal tube.

#### Ultrasound for Tracheal Tube Detection

For the important outcome of **detection of correct placement of a tracheal tube during CPR**, we identified low-quality evidence (downgraded for suspicion of publication bias and indirectness) from 3 observational studies<sup>51–53</sup> including 254 patients in cardiac arrest that evaluated the use of ultrasound to detect tracheal tube placement. The pooled specificity was 90% (95% CI, 68%–98%), the sensitivity was 100% (95% CI, 98%–100%), and the FPR was 0.8% (95% CI, 0.2%–2.6%).

### Treatment Recommendations

We recommend using waveform capnography to confirm and continuously monitor the position of a tracheal tube during CPR in addition to clinical assessment (strong recommendation, low-quality evidence).

We recommend that if waveform capnography is not available, a nonwaveform CO<sub>2</sub> detector, esophageal detector device, or ultrasound in addition to clinical assessment is an alternative (strong recommendation, low-quality evidence).

#### **Values, Preferences, and Task Force Insights**

In making these strong recommendations, and despite the low-quality evidence, we place a high value on avoiding unrecognized esophageal intubation. The mean incidence of unrecognized esophageal intubation in cardiac arrest was 4.3% (range, 0%–14%) in the 11 studies we assessed. Unrecognized esophageal placement of an advanced airway is associated with a very high mortality. We, therefore, place value on recommending devices with a low FPR (ie, the device indicates tracheal placement but the tube is in the esophagus).

In addition, waveform capnography is given a strong recommendation, because it may have other potential uses during CPR (eg, monitoring ventilation rate, assessing quality of CPR).

#### **Knowledge Gaps**

- The evidence is limited on the value of CO<sub>2</sub> devices after prolonged cardiac arrest.
- There are very few studies comparing the practical implications (cost, timeliness) of these devices.
- The use of ultrasound requires further studies.

### **Ventilation Rate During Continuous Chest Compression (ALS 808)**

Among adults with cardiac arrest with a secure airway receiving chest compressions (in any setting, and with standard tidal volume) (P), does a ventilation rate of 10 breaths/min (I), compared with any other ventilation rate (C), change survival with favorable neurologic/functional outcome at discharge, 30 days, 60 days, 180 days, and/or 1 year; survival only at discharge, 30 days, 60 days, 180 days, and/or 1 year; ROSC (O)?

#### **Introduction**

Hyperventilation during CPR has been shown to be harmful, but once an advanced airway has been placed, the optimal ventilation rate remains uncertain.

#### **Consensus on Science**

We did not identify any evidence to address the critical outcomes of survival with favorable neurologic/functional outcome at discharge, 30 days, 60 days, 180 days, and/or 1 year; survival at discharge, 30 days, 60 days, 180 days, and/or 1 year.

We identified very-low-quality evidence (downgraded for very serious risk of bias and indirectness, and serious inconsistency and imprecision) from 10 animal studies<sup>54–63</sup> and 1 human observational study<sup>64</sup> that does not enable us to estimate with confidence the effect of a ventilation rate of 10/min compared with any other rate for the important outcome of ROSC.

#### **Treatment Recommendation**

We suggest a ventilation rate of 10 breaths/min in adults with cardiac arrest with a secure airway receiving continuous chest compressions (weak recommendation, very-low-quality evidence).

#### **Values, Preferences, and Task Force Insights**

In making this recommendation, we have valued the need to suggest a ventilation rate that is already in use. We note that the Australian and New Zealand Committee on Resuscitation (ANZCOR) currently recommends a ventilation rate of 6 to 10 breaths/min and would see no reason for this to change. We did not assess effect of tidal volume and any other ventilation variables during CPR and have therefore not addressed these in the treatment recommendation.

#### **Knowledge Gaps**

- Ventilation rates lower than 10/min need to be assessed during ALS.
- We do not know the ideal tidal volume and any other ventilation variables during CPR.

### **2010 CoSTR Topics Not Reviewed in 2015**

- Oropharyngeal and nasopharyngeal adjuncts
- Monitoring ventilator parameters during CPR
- Thoracic impedance to confirm airway placement
- Cricoid pressure
- Automatic ventilators versus manual ventilation during CPR

### **Circulatory Support During CPR**

The ALS Task Force reviewed the evidence for 3 technologies for which there have been significant developments since 2010: (1) the ITD, (2) automated mechanical chest compression devices, and (3) ECP. All are already in use in some settings, have strong proponents for their use, and have cost implications for their implementation such that there was considerable debate in reaching a consensus on science and treatment recommendation. In addition, some studies of these technologies had support and involvement of device manufacturers. Some of this debate is presented in the narrative that follows each treatment recommendation.

#### **Impedance Threshold Device (ALS 579)**

Among adults who are in cardiac arrest in any setting (P), does use of an inspiratory ITD during CPR (I), compared with no ITD (C), change survival with favorable neurologic/functional outcome at discharge, 30 days, 60 days, 180 days, and/or 1 year; survival only at discharge, 30 days, 60 days, 180 days, and/or 1 year; ROSC (O)?

#### **Introduction**

The ITD is designed to reduce the intrathoracic pressure during the decompression phase of chest compression. There is some evidence the ITD increases blood flow during CPR. The ITD has been studied during conventional CPR and during ACD CPR.

#### **Consensus on Science**

*ITD Plus Conventional CPR (I) Versus Conventional CPR (C)*

For the critical outcome of **neurologically favorable survival at hospital discharge** (assessed with modified Rankin Scale



[mRS] score of 3 or less), there was 1 RCT<sup>65</sup> of high quality in 8718 OHCA that was unable to demonstrate a clinically significant benefit from the addition of the ITD to conventional CPR (RR, 0.97; 95% CI, 0.82–1.15).

For the critical outcome of **survival to hospital discharge**, there was 1 RCT<sup>65</sup> of high quality in 8718 OHCA that was unable to demonstrate a clinically significant benefit from the addition of the ITD to conventional CPR (RR, 1; 95% CI, 0.87–1.15).

#### *ITD Plus ACD CPR (I) Versus ACD CPR (C)*

For the critical outcome of **neurologically favorable survival**, there were no studies identified that compared the use of ITD with ACD CPR with ACD CPR in cardiac arrests.

For the critical outcome of **survival to hospital discharge**, there were 2 RCTs<sup>66,67</sup> of very low quality (downgraded for serious imprecision and very serious indirectness because of pre-2000 resuscitation practices) that were unable to demonstrate a clinically significant benefit from the addition of the ITD to ACD CPR in a total of 421 OHCA (RR, 0.91; 95% CI, 0.07–12.7<sup>66</sup> and RR, 1.25; 95% CI, 0.5–3.1).<sup>67</sup>

#### *ITD Plus ACD CPR (I) Versus Conventional CPR (C)*

For the critical outcome of **neurologically favorable survival** (CPC  $\leq 2$ ) at 12 months, there was 1 publication reporting results from a randomized study<sup>68</sup> of very low quality (downgraded for very serious risk of bias and serious imprecision) in 2738 OHCA that was unable to demonstrate a clinically significant benefit from the addition of the ITD to ACD CPR (when compared with conventional CPR: RR, 1.34; 95% CI, 0.97–1.85).

For the critical outcome of **neurologically favorable survival at hospital discharge**, there was 1 RCT<sup>68</sup> that incorporated the presumed cardiac etiology subset published in 2011<sup>69</sup> of very low quality (downgraded for very serious risk of bias, serious inconsistency, and serious imprecision) in 2738 OHCA that was unable to demonstrate a clinically significant benefit (using CPC  $\leq 2$ ) from the addition of the ITD to ACD CPR (when compared with conventional CPR: RR, 1.28; 95% CI, 0.98–1.69). Similar data (neurologically intact survival at hospital discharge) were also reported that used mRS of 3 or less, and were unable to demonstrate a clinically significant benefit (lower CI was 3 more/1000 in Frascone [number needed to treat, NNT, of 333] and 6 more/1000 [NNT of 167] in Aufderheide).<sup>68,69</sup>

For the critical outcome of **survival to 12 months**, there were 2 publications reporting results from a single randomized study,<sup>68</sup> which incorporated the presumed cardiac etiology subset published in 2011,<sup>69</sup> of very low quality (downgraded for very serious risk of bias and serious imprecision) in 2738 OHCA that was unable to demonstrate a clinically significant benefit from the addition of the ITD to ACD CPR (when compared with conventional CPR): Frascone: RR, 1.39 (95% CI, 1.04–1.85; lower CI was 2 more/1000; NNT, 500); Aufderheide: RR, 1.49 (95% CI, 1.05–2.12; lower CI was 4 more/1000; NNT, 250).

For the critical outcome of **survival to hospital discharge**, there were 3 publications reporting results from 2 randomized studies<sup>69,70</sup> (which incorporated the presumed cardiac etiology subset published in Aufderheide<sup>69</sup>) of very

low quality (downgraded for very serious risk of bias, serious indirectness, and serious imprecision) in a total of 2948 OHCA that were unable to demonstrate a clinically significant benefit from the addition of the ITD to ACD CPR (when compared with conventional CPR): Frascone: RR, 1.17 (95% CI, 0.94–1.45); Aufderheide: RR, 1.26 (95% CI, 0.96–1.66); Wolcke: RR, 1.41 (95% CI, 0.75–2.66).

#### *Treatment Recommendation*

We recommend against the routine use of the ITD in addition to conventional CPR (strong recommendation, high-quality evidence).

A consensus recommendation could not be reached for the use of the ITD when used together with ACD CPR.

#### *Values, Preferences, and Task Force Insights*

In making a recommendation against the routine use of the ITD alone, we place a higher value on not allocating resources to an ineffective intervention over any yet-to-be-proven benefit for critical or important outcomes.

Because of the concern about allocating resources to an intervention with equivocal benefit for critical or important outcomes, a consensus recommendation could not be reached for ITD combined with ACD CPR. The task force thought that the decision on use of the ITD plus ACD combination should be left to individual Council guidelines.

Public comments posted online were reviewed and considered by the task force, specifically regarding the use of the ITD and ACD CPR combination and the task force's interpretation of the data from 2 publications from the same study<sup>68,69</sup> using the GRADE process, and how the data from these studies had been analyzed and interpreted. The task force received feedback from the investigator(s) of this study in the public commenting period and in an open session. In addition, it considered an editorial on the analysis of this study<sup>71</sup> and discussed the publications<sup>68,69</sup> and their clinical significance in its closed sessions. The NNTs were discussed and the use of the CI closest to unity as a measure of study precision. It was also noted that the critical and important endpoints for this and the other ALS PICO questions were agreed *a priori* and posted for public commenting before searches took place, hence the difference in our hierarchy of outcomes compared with the actual primary and secondary outcomes reported in the study that made up the 2 publications. The task force appreciated the challenges of studying a combined intervention and conducting a large cardiac arrest study. There was also discussion of the involvement of the manufacturer in the design and reporting of the study and that sponsorship of drug and device studies by manufacturers can lead to more favorable results and conclusions.<sup>72</sup> There was considerable debate on this topic in both closed and open task force sessions such that a consensus could not be achieved by the task force on a treatment recommendation for the use of the ITD when used together with ACD CPR.

#### *Knowledge Gaps*

- Optimal compression and ventilation rates for ITD CPR and ACD plus ITD CPR may or may not be different from those for conventional CPR.

- The independent effects of ITD and ACD CPR are uncertain.
- Effectiveness studies should examine other geographical settings and populations.

### Mechanical CPR Devices (ALS 782)

Among adults who are in cardiac arrest in any setting (P), do automated mechanical chest compression devices (I), compared with standard manual chest compressions (C), change survival with favorable neurologic/functional outcome at discharge, 30 days, 60 days, 180 days, and/or 1 year; survival only at discharge, 30 days, 60 days, 180 days, and/or 1 year; ROSC (O)?

#### Introduction

Providing high-quality manual CPR is tiring, and there is evidence that CPR quality deteriorates with time. Mechanical CPR devices may enable the delivery of high-quality CPR for a sustained period, but at the time of writing the 2010 CoSTR, their impact on outcome was unclear.

#### Consensus on Science

For the critical outcome of **survival to 1 year**, we identified moderate-quality evidence (downgraded for serious risk of bias) from 1 cluster RCT<sup>73</sup> using the Lund University Cardiac Arrest System (LUCAS) device showing no benefit or harm when compared with manual chest compressions (5.4% versus 6.2%; RR, 0.87; 95% CI, 0.68–1.11).

For the critical outcomes of **survival at 180 days with good neurologic outcome** and **survival at 30 days with favorable neurologic outcome**, we identified moderate-quality evidence (downgraded for serious risk of bias) from 1 RCT<sup>74</sup> using a LUCAS device and enrolling 2589 OHCA patients that did not show benefit or harm when compared with manual chest compressions at 180 days (8.5% versus 7.6%; RR, 1.11; 95% CI, 0.86–1.45) or 30 days (7.3% versus 8.1%; RR, 1.11; 95% CI, 0.84–1.45).

For the critical outcome of **survival to 180 days**, we identified moderate-quality evidence (downgraded for serious risk of bias) from 1 RCT<sup>74</sup> using a LUCAS device enrolling 2589 OHCA patients showing no benefit or harm when compared with manual chest compressions where quality of chest compressions in the manual arm was not measured (8.5% versus 8.1%; RR, 1.06; 95% CI, 0.81–1.41).

For the critical outcome of **survival to hospital discharge with favorable neurologic outcome** (defined as CPC 1–2 or mRS 0–3), we have identified moderate-quality evidence (downgraded for serious risk of bias) from 3 RCTs enrolling 7582 OHCA patients showing variable results.<sup>74–76</sup> One study<sup>75</sup> (n=767) showed harm with the use of a load-distributing band mechanical chest compression device compared with manual chest compressions (7.5% of patients in the control group versus 3.1% in the intervention group;  $P=0.006$ ; RR, 0.41; 95% CI, 0.21–0.79). Two other RCTs<sup>74,76</sup> (n=6820), one using a load-distributing band and the other using a LUCAS, did not show benefit or harm when compared with manual chest compressions: load-distributing band study: 4.14% survival in the intervention group versus 5.25% for manual compressions (RR, 0.79; 95% CI, 0.60–1.03); LUCAS: 8.31%

intervention versus 7.76% manual compressions (RR, 1.07; 95% CI, 0.83–1.39).

For the critical outcome of **survival to hospital discharge**, we identified moderate-quality evidence (downgraded for serious risk of bias) from 5 RCTs<sup>74–78</sup> enrolling 7734 OHCA patients and 150 IHCA patients showing heterogeneous results. One study of patients with IHCA<sup>77</sup> (n=150) showed benefit with use of a piston device compared with manual chest compressions (32.9% versus 14.7%;  $P=0.02$ ; RR, 2.21; 95% CI, 1.17–4.17). Two other RCTs<sup>74,78</sup> of LUCAS did not show benefit or harm (9.0% versus 9.15%; RR, 0.98; 95% CI, 0.77–1.25 and 8.0% versus 9.72%; RR, 0.82; 95% CI, 0.29–2.33, respectively, for LUCAS versus manual compressions). One large RCT<sup>76</sup> (n=4231) using a load-distributing band device showed equivalence when compared with high-quality manual chest compressions (9.34% versus 10.93%; RR, 0.85; 95% CI, 0.71–1.02).

For the critical outcome of **survival to 30 days**, we identified moderate-quality evidence (downgraded for serious risk of bias) from 2 RCTs<sup>73,74</sup> (n=7060) using the LUCAS device showing no benefit or harm when compared with manual chest compressions and where quality of compressions in the manual arm was not measured (6.3% versus 6.85%; RR, 0.92; 95% CI, 0.73–1.16 and 8.82% versus 8.07%; RR, 1.02; 95% CI, 0.97–1.31, respectively).

For the important outcome of **ROSC**, we identified low-quality evidence (downgraded for serious risk of bias and serious inconsistency) from 7 RCTs enrolling 11 638 cardiac arrest patients (IHCA and OHCA).<sup>73,74,76–80</sup> Two studies<sup>77,79</sup> (n=167) showed benefit with mechanical chest compression devices compared with manual compressions: 14.29% versus 0% (RR, not applicable) and 55.26% versus 37.84% (RR, 1.46; 95% CI, 1.02–2.08), respectively. One study<sup>76</sup> (n=4231) showed harm with mechanical devices; however, there was no adjustment for interim analyses: 28.59% versus 32.32% (RR, 0.88; 95% CI, 0.81–0.97). Four studies<sup>73,74,78,80</sup> (n=7240) did not show benefit or harm when compared with manual chest compressions: 47.06% versus 17.75% (RR, 2.67; 95% CI, 0.85–8.37), 31.60% versus 31.39% (RR, 1.01; 95% CI, 0.92–1.10), 35.38% versus 34.60% (RR, 1.02; 95% CI, 0.92–1.14), and 40.54% versus 31.94% (RR, 1.27; 95% CI, 0.82–1.96), respectively.

#### Treatment Recommendations

We suggest against the routine use of automated mechanical chest compression devices to replace manual chest compressions (weak recommendation, moderate-quality evidence).

We suggest that automated mechanical chest compression devices are a reasonable alternative to high-quality manual chest compressions in situations where sustained high-quality manual chest compressions are impractical or compromise provider safety (weak recommendation, low-quality evidence).

#### Values, Preferences, and Task Force Insights

The task force placed value on ensuring high-quality chest compressions with adequate depth, rate, and minimal interruptions, regardless of whether they are delivered by machine or human. The task force also considered that application of a mechanical chest compression device without a focus on

minimizing interruptions in compressions and delay to defibrillation could cause harm.

In making a recommendation for mechanical compression devices for use in some settings, we place value on the results from a large, high-quality RCT<sup>76</sup> showing equivalence between very-high-quality manual chest compressions and mechanical chest compressions delivered with a load-distributing band in a setting with rigorous training and CPR quality monitoring. Also, the task force acknowledges the existence of situations where sustained high-quality manual chest compressions may not be practical. Examples include CPR in a moving ambulance where provider safety is at risk, the need for prolonged CPR where provider fatigue may impair high-quality manual compressions (eg, hypothermic arrest), and CPR during certain procedures (eg, coronary angiography or preparation for ECPR).

Our task force agreed that there was an adequate amount of data generated from RCTs for the systematic review to exclude observational studies. We agreed that despite the availability of several observational studies comparing manual and mechanical chest compressions, the inherent risk of bias related to patient selection, group allocation, and uncontrolled confounders supports a decision to exclude them from the process of developing this CoSTR statement.

We conducted a universal literature search for RCTs studying any type of automated mechanical chest compression device. Prior to initiating the review, we planned to parse the data by device type if an effect specific to device was observed in the analysis. Although we did not undertake a formal analysis by device, there were no obvious device-specific effects observed.

The task force did consider some data that are not included in the evidence profile tables or CoSTR statement. Specifically, the PARAMEDIC (prehospital randomized assessment of a mechanical compression device in cardiac arrest) study<sup>73</sup> showed an association between mechanical chest compressions and worse survival with good neurologic outcome (CPC 1–2) at 3 months (adjusted OR, 0.72; 95% CI, 0.52–0.99). This was not included in our consensus on science, because survival with good neurologic outcome at 90 days was not an *a priori* outcome identified by the group.

After assessing the evidence, there was much debate over the ultimate wording of our recommendation. Some members thought a weak recommendation supporting mechanical chest compression devices as a reasonable alternative to manual chest compressions was most appropriate, whereas others thought a recommendation against the routine use of mechanical chest compression devices was more appropriate. There was general agreement that the bulk of evidence reviewed suggests no significant difference or equivalence between mechanical and manual chest compressions related to critical and important clinical outcomes. The task force weighed this with the data from a few studies suggesting a negative association between mechanical chest compression and outcomes as well as the potential resource implications associated with implementation of mechanical devices in any setting. With these factors in mind, the task force concluded that available clinical evidence did not support a recommendation for broad and universal implementation of mechanical

chest compression devices across all clinical settings in favor of high-quality manual chest compressions.

Public comments provided online were reviewed by the task force. Comments suggested that we consider special circumstances where mechanical chest compressions may be more practical than the continued provision of high-quality chest compression and circumstances where provider safety might be improved with the use of mechanical versus manual chest compressions. Delivery of manual compressions in a moving ambulance by an unrestrained provider was seen as a particularly unsafe situation. Mechanical devices may allow providers to remain seated and restrained in this situation while chest compressions continue. Accordingly, we have included a treatment recommendation to address these situations not directly addressed in the literature reviewed but deemed to represent reasonable situations for the use of this technology.

### Knowledge Gaps

- Are mechanical chest compression devices superior to manual chest compressions in special situations such as the moving ambulance, prolonged CPR, or during procedures such as coronary angiography?
- Are there certain subgroups of patients who may benefit differentially from mechanical or manual chest compressions (eg, shockable versus nonshockable initial rhythm)?
- Is one type of mechanical chest compression device superior to another with respect to important clinical outcomes?

### ECPR Versus Manual or Mechanical CPR (ALS 723)

Among adults who are in cardiac arrest in any setting (P), does the use of ECPR techniques (including extracorporeal membrane oxygenation or cardiopulmonary bypass) (I), compared with manual CPR or mechanical CPR (C), change survival with favorable neurologic/functional outcome at discharge, 30 days, 60 days, 180 days, and/or 1 year; survival only at discharge, 30 days, 60 days, 180 days, and/or 1 year; ROSC (O)?

#### Introduction

Extracorporeal techniques require vascular access and a circuit with a pump and oxygenator and can provide a circulation of oxygenated blood to restore tissue perfusion. This has the potential to buy time for restoration of an adequate spontaneous circulation and treatment of reversible underlying conditions. This is commonly called extracorporeal life support (ECLS), and more specifically ECPR when done during cardiac arrest. These techniques are increasingly being used for OHCA. We considered ECLS for IHCA and OHCA separately.

#### Consensus on Science

##### ECPR for IHCA

For the critical outcome of **favorable functional survival at 180 days or 1 year after IHCA**, we identified very-low-quality evidence (downgraded for risk of bias from selection of cases for ECPR, crossover in treatments, and imprecision)



from 2 non-RCTs,<sup>81,82</sup> comparing 144 patients treated with ECPR to 434 patients treated with conventional CPR. At 180 days, favorable outcome increased with ECPR (RR, 3.78; 95% CI, 2.26–6.31), even in propensity-matched samples.<sup>82</sup> At 1 year, favorable outcome was not different with ECPR (RR, 1.72; 95% CI, 0.74–4.01).

For the critical outcome of **survival to 30, 180 days, or 1 year after IHCA**, we identified very-low-quality evidence (downgraded for risk of bias from selection of cases for ECPR, crossover in treatments, and imprecision) from 2 non-RCTs,<sup>81,82</sup> comparing 144 patients treated with ECPR to 434 patients treated with conventional CPR. These studies found improved survival at 30 days (RR, 2.25; 95% CI, 1.28–3.96) and 180 days (RR, 2.81; 95% CI, 1.79–4.39 and RR, 2.50; 95% CI, 1.31–4.80), but not 1 year (RR, 1.92; 95% CI, 0.88–4.15). A propensity-matched sample found improved survival at 180 days<sup>82</sup> (RR, 3.20; 95% CI, 1.25–8.18).

For the important outcome of **favorable functional survival at hospital discharge after IHCA**, we identified very-low-quality evidence (downgraded for risk of bias from selection of cases for ECPR, crossover in treatments, and imprecision) from 2 non-RCTs,<sup>81,82</sup> comparing 144 patients treated with ECPR to 434 patients treated with conventional CPR. These studies found improved favorable outcome with ECPR (RR, 2.23; 95% CI, 1.11–4.52 and adjusted RR, 3.63; 95% CI, 2.18–6.02), even in propensity-matched samples (RR, 4.67; 95% CI, 1.41–15.41).<sup>82</sup>

For the important outcome of **survival to hospital discharge after IHCA**, we identified very-low-quality evidence (downgraded for risk of bias from selection of cases for ECPR, crossover in treatments, and imprecision) from 2 non-RCTs,<sup>81,82</sup> comparing 144 patients treated with ECPR to 434 patients treated with conventional CPR. These studies found improved survival to hospital discharge in the entire cohort (RR, 2.33; 95% CI, 1.23–4.38 and RR, 2.81; 95% CI, 1.85–4.26). One of these studies found improved survival to hospital discharge in propensity-matched samples (RR, 3.17; 95% CI, 1.36–7.37).<sup>82</sup>

#### *ECPR for OHCA*

For the critical outcome of **favorable functional survival at 30, 90, or 180 days after OHCA**, we identified very-low-quality evidence from 2 non-RCTs (downgraded for risk of bias for selection of cases for ECPR and imprecision), comparing 311 patients treated with ECPR to 312 patients treated with conventional CPR.<sup>83,84</sup> One study reported increased favorable outcome with ECPR at 30 days (RR, 7.92; 95% CI, 2.46–25.48) and 180 days (RR, 4.34; 95% CI, 1.71–11.00).<sup>84</sup> The other study reported increased favorable outcome at 90 days (RR, 5.48; 95% CI, 1.52–19.84), but this association was not present in the propensity-matched sample (RR, 3.50; 95% CI, 0.81–15.16).<sup>83</sup>

For the critical outcome of **survival to 30, 90, or 180 days after OHCA**, we identified very-low-quality evidence (downgraded for risk of bias from selection of cases for ECPR and imprecision) from 2 non-RCTs, comparing 311 patients treated with ECPR to 312 patients treated with conventional CPR.<sup>83,84</sup> One study reported increased survival with ECPR

at 30 days (RR, 3.94; 95% CI, 2.24–6.92) and 180 days (RR, 5.42; 95% CI, 2.65–11.09),<sup>84</sup> and the other study reported increased survival with ECPR at 90 days (RR, 6.17; 95% CI, 2.37–16.07), even in a propensity-matched sample (RR, 4.50; 95% CI, 1.08–18.69).<sup>83</sup>

For the important outcome of **favorable functional survival at hospital discharge after OHCA**, we identified no comparative studies.

For the important outcome of **survival to hospital discharge after OHCA**, we identified very-low-quality evidence (downgraded for risk of bias from selection of cases for ECPR and imprecision) from 1 non-RCT comparing 53 patients treated with ECPR to 109 patients treated with conventional CPR.<sup>83</sup> Survival to hospital discharge was higher in patients treated with ECPR (RR, 4.99; 95% CI, 2.21–11.30), though not in propensity matched samples (RR, 3.00; 95% CI, 0.92–9.74).

#### *Treatment Recommendation*

We suggest ECPR is a reasonable rescue therapy for selected patients with cardiac arrest when initial conventional CPR is failing in settings where this can be implemented (weak recommendation, very-low-quality evidence).

#### *Values, Preferences, and Task Force Insights*

In making this weak recommendation, we note that the published series used selected patients for ECPR and that guidelines for clinical practice should apply to similar populations. Published comparative studies are limited by the bias created when experienced clinicians select the best candidates to receive ECPR, perhaps using unmeasured variables. We acknowledge that ECPR is a complex intervention that requires considerable resource and training that is not universally available, but put value on an intervention that may be successful in individuals where usual CPR techniques have failed. In addition, ECPR can buy time for another treatment such as coronary angiography and percutaneous coronary intervention (PCI).

#### *Knowledge Gaps*

- Controlled clinical trials are needed to assess the effect of ECPR versus traditional CPR on clinical outcomes in patients with cardiac arrest.
- What is the optimal flow rate for ECPR in the treatment for cardiac arrest?
- Which subgroups of patients can benefit most from a strategy of ECPR?
- What type of patients should be considered for ECPR?
- What role, if any, should prehospital ECPR play in resuscitating patients from OHCA?
- What is the optimal target temperature for patients on ECPR after cardiac arrest?
- What are reliable prognostic factors for patients treated with ECPR after cardiac arrest?

#### **2010 CoSTR Topics Not Reviewed in 2015**

- Interposed abdominal compression CPR
- ACD CPR
- Open-chest CPR

## Physiological Monitoring During CPR

The ability to monitor real-time physiological variables and obtain ultrasound images during CPR, in addition to clinical signs and electrocardiographic monitoring, has the potential to enable rescuers to tailor ALS interventions. Strategies for physiological monitoring include the use of ETCO<sub>2</sub>, arterial pressure, central venous pressure (enabling monitoring of coronary perfusion pressure and aortic diastolic pressure), and cerebral oximetry (regional cerebral oxygenation).

### ETCO<sub>2</sub> to Predict Outcome of Cardiac Arrest (ALS 459)

Among adults who are in cardiac arrest in any setting (P), does any ETCO<sub>2</sub> level value, when present (I), compared with any ETCO<sub>2</sub> level below that value (C), change survival with favorable neurologic/functional outcome at discharge, 30 days, 60 days, 180 days, and/or 1 year; survival only at discharge, 30 days, 60 days, 180 days, and/or 1 year; ROSC (O)?

#### Introduction

ETCO<sub>2</sub> is the partial pressure of CO<sub>2</sub> at the end of an exhaled breath. It reflects cardiac output (CO) and pulmonary blood flow, as CO<sub>2</sub> is transported by the venous system to the right side of the heart and then pumped to the lungs by the right ventricle. During CPR, ETCO<sub>2</sub> values are low, reflecting the low CO generated by chest compression. Although ETCO<sub>2</sub> values higher than 10 mmHg have been correlated to ROSC,<sup>85–89</sup> there is uncertainty if any ETCO<sub>2</sub> value measured during CPR can reliably predict survival or survival with good neurologic outcome.

#### Consensus on Science

We did not identify any evidence to address the critical outcome of **neurologically intact survival**.

For the critical outcome of **survival at discharge**, we have identified low-quality evidence (downgraded for serious risk of bias and serious imprecision) from 1 observational study enrolling 127 patients<sup>90</sup> showing a correlation with initial ETCO<sub>2</sub> 10 mmHg (1.33 kPa) or greater when compared with less than 10 mmHg (OR, 11.4; 95% CI, 1.4–90.2).

For the critical outcome of **survival at discharge**, we have identified low-quality evidence (downgraded for serious risk of bias and serious imprecision) from 1 observational study enrolling 127 patients<sup>90</sup> showing a correlation with 20 minutes of ETCO<sub>2</sub> 20 mmHg (2.67 kPa) or greater when compared with less than 20 mmHg (OR, 20.0; 95% CI, 2.0–203.3).

For the important outcome of **ROSC**, we have identified moderate-quality evidence (downgraded for serious risk of bias) from 3 observational studies enrolling 302 patients<sup>90–92</sup> showing a correlation with initial ETCO<sub>2</sub> 10 mmHg or greater when compared with less than 10 mmHg (OR, 10.7; 95% CI, 5.6–20.3).

For the important outcome of **ROSC**, we have identified very-low-quality evidence (downgraded for very serious risk of bias, serious inconsistency, and serious imprecision) from 3 observational studies enrolling 367 patients<sup>90,93,94</sup> showing correlation with 20 minutes ETCO<sub>2</sub> 10 mmHg or greater when compared with less than 10 mmHg (OR, 181.6; 95% CI, 40.1–822.6).

### Treatment Recommendations

We recommend against using ETCO<sub>2</sub> cutoff values alone as a mortality predictor or for the decision to stop a resuscitation attempt (strong recommendation, low-quality evidence).

We suggest that an ETCO<sub>2</sub> 10 mmHg or greater measured after tracheal intubation or after 20 minutes of resuscitation may be a predictor of ROSC (weak recommendation, low-quality evidence).

We suggest that an ETCO<sub>2</sub> 10 mmHg or greater measured after tracheal intubation or an ETCO<sub>2</sub> 20 mmHg or greater measured after 20 minutes of resuscitation may be a predictor of survival to discharge (weak recommendation, moderate-quality evidence).

### Values, Preferences, and Task Force Insights

In making the strong recommendations against using a specific ETCO<sub>2</sub> cutoff value alone as a mortality predictor or for the decision to stop a resuscitation attempt, we have put a higher value on not relying on a single variable (ETCO<sub>2</sub>) and cutoff value when their usefulness in actual clinical practice, and variability according to the underlying cause of cardiac arrest, has not been established and there are considerable knowledge gaps.

The task force was concerned that the etiology (eg, asphyxia, PE) of cardiac arrest could affect ETCO<sub>2</sub> values, and that there was a risk of self-fulfilling prophecy if specific threshold values were followed. There was concern about the accuracy of ETCO<sub>2</sub> values measured during CPR. During open discussions there were requests that the ILCOR recommendation be far more prescriptive to prevent futile and prolonged resuscitation attempts.

### Knowledge Gaps

- The effects on ETCO<sub>2</sub> of timing, etiology of arrest, ventilation rate, and chest compression quality are not fully understood.
- The role of ETCO<sub>2</sub> with a bag-mask device or SGA requires further study.
- Are ETCO<sub>2</sub> values measured during CPR accurate?
- The ETCO<sub>2</sub> cutoff values to reliably predict short- and long-term outcomes is not known.

### Monitoring Physiological Parameters During CPR (ALS 656)

Among adults who are in cardiac arrest in any setting (P), does the use of physiological feedback regarding CPR quality (eg, arterial lines, ETCO<sub>2</sub> monitoring, SpO<sub>2</sub> waveforms, or others) (I), compared with no feedback (C), change survival with favorable neurologic/functional outcome at discharge, 30 days, 60 days, 180 days, and/or 1 year; survival only at discharge, 30 days, 60 days, 180 days, and/or 1 year; ROSC; change in physiologic values by modifications in CPR (O)?

#### Introduction

Several physiological variables such as ETCO<sub>2</sub>, coronary perfusion pressure, aortic diastolic pressure, and cerebral oximetry measurements have been used to assess and guide the quality of CPR.

**Consensus on Science**

We found no studies that addressed the critical and important outcomes.

For the outcome of **change in physiologic values by modifications in CPR**, we identified 13 observational studies that provided very-low-quality evidence (downgraded for serious risk of bias, serious inconsistency, serious indirectness, and serious imprecision) comparing different CPR techniques (standard, lower sternal, active compression-decompression, intra-abdominal compression, mechanical thumper, ITD, band chest compression, load-distributing band, vest CPR) with the use of physiologic monitoring (arterial line, ET $\text{CO}_2$ , oxygen saturation as measured by pulse oximetry ( $\text{SpO}_2$ ), coronary perfusion pressure, cerebral oximetry, near-infrared spectroscopy) in 469 subjects.<sup>66,80,95–105</sup> Differences were detected between different CPR techniques, although this was not consistent across different modalities. Given the heterogeneity of CPR techniques used across studies, data could not be pooled. There were no studies that were found that used physiologic feedback to evaluate CPR quality.

**Treatment Recommendation**

We make no treatment recommendation for any particular physiological measure to guide CPR, because the available evidence would make any estimate of effect speculative.

**Values, Preferences, and Task Force Insights**

In making no recommendation, we have placed high value on the lack of evidence and the need for further studies in this area.

**Knowledge Gaps**

- Studies of the effect of using physiologic feedback to evaluate CPR quality and modifications in CPR technique are required.
- Studies that measure the effect of physiological monitoring to guide resuscitation on ROSC and survival with good neurologic outcome are required.

**Ultrasound During CPR (ALS 658)**

Among adults who are in cardiac arrest in any setting (P), does use of ultrasound (including echocardiography or other organ assessments) during CPR (I), compared with conventional CPR and resuscitation without use of ultrasound (C), change survival with favorable neurologic/functional outcome at discharge, 30 days, 60 days, 180 days, and/or 1 year; survival only at discharge, 30 days, 60 days, 180 days, and/or 1 year; ROSC (O)?

**Introduction**

Ultrasound has been increasingly used as a diagnostic and prognostic tool for critically ill patients, particularly in intensive care units (ICUs).<sup>106</sup> Specific protocols for evaluation during CPR enable assessment of myocardial contractility and may help identify potentially treatable causes, such as hypovolemia, pneumothorax, pulmonary thromboembolism, or restrictive pericardial effusion, without interfering in patient care.<sup>107</sup>

**Consensus on Science**

For the critical outcome of **survival**, we identified 1 observational study.<sup>108</sup> The evidence was downgraded for very

high risk of bias (significant confounding, selection bias) and imprecision (small sample size). Therefore, we concluded that the data do not provide enough evidence to address the PICO question.

For the important outcome of **ROSC**, we identified very-low-quality evidence (downgraded for imprecision [small sample size] and very high risk of bias [no information about randomization allocation, lack of blinding, lack of blinding in outcome assessors]) from 1 RCT investigating the use of cardiac ultrasound during ACLS, compared with no use of cardiac ultrasound during ACLS in adult patients with pulseless electrical activity arrest.<sup>109</sup> This study enrolled 100 patients in a convenience sample and reported ROSC for at least 10 seconds in 34% of patients in the ultrasound group versus 28% in the group with no ultrasound ( $P=0.52$ ).

**Treatment Recommendations**

We suggest that if cardiac ultrasound can be performed without interfering with standard ACLS protocol, it may be considered as an additional diagnostic tool to identify potentially reversible causes (weak recommendation, very-low-quality evidence).

**Values, Preferences, and Task Force Insights**

In making this recommendation we have placed a higher value on the potential harm from interruptions in chest compressions. There is currently inadequate evidence to evaluate whether there is any benefit of cardiac ultrasound during ACLS. Although this was not specifically part of the question, the task force discussed the importance of the need for an individual trained in ultrasound during resuscitation to minimize interruption in chest compression. The task force agreed there will be circumstances where ultrasound identification of a potentially reversible cause of cardiac arrest or 'pseudo' pulseless electrical activity may be useful.

**Knowledge Gaps**

It remains unclear if the addition of ultrasound during ACLS improves outcomes:

- All data are from OHCA. All data are from non-VF patients, primarily assessing pulseless electrical activity.
- A systematic review of the diagnostic utility of ultrasound should be done. There are some articles investigating whether ultrasound findings predict probability of survival.
- Pretest probability (suspicion of an ultrasound-detectable etiology) is important for choosing to do ultrasound, because ultrasound will interfere to some extent with CPR.
- It is unknown if the findings of ultrasound during CPR are correctly interpreted, because images are compared with findings from patients with pulse (eg, right ventricular dilation occurs in all cardiac arrest, separate from PE).
- It remains unclear if the addition of ultrasound during CPR improves outcomes. The vast majority of literature on ultrasound during cardiac arrest has focused on the prognostic value of cardiac ultrasound findings. Randomized trials investigating whether use of ultrasound during CPR has an effect on patient outcomes are needed.



## Drugs During CPR

In 2010, ILCOR reduced routine drug administration in adult cardiac arrest to vasopressor and antiarrhythmic drugs. The science was insufficient to comment on critical outcomes such as survival to discharge and survival to discharge with good neurologic outcome with either vasopressors or antiarrhythmic drugs. There was also insufficient evidence to comment on the best time to give drugs to optimize outcome. The task force made a decision to include only RCTs in this systematic review and meta-analysis. Where the number of RCTs was few, we looked for recent published systematic reviews or where there were no recent reviews, expanded the search to include observational studies.

### Epinephrine Versus Placebo (ALS 788)

Among adults who are in cardiac arrest in any setting (P), does the use of epinephrine (I), compared with placebo or not using epinephrine (C), change survival with favorable neurologic/functional outcome at discharge, 30 days, 60 days, 180 days, and/or 1 year; survival only at discharge, 30 days, 60 days, 180 days, and/or 1 year; ROSC (O)?

#### Introduction

Since 2010, there have been 2 randomized drug trials in cardiac arrest: one compared drugs with no drugs<sup>110</sup> and another compared epinephrine with placebo.<sup>111</sup> The Olasveengen trial compared a bundle of drugs given intravenously to a control group of patients randomized to no intravenous access and, therefore, no drugs. A post hoc subgroup analysis of the trial comparing those patients who did or did not receive epinephrine<sup>112</sup> revealed an advantage with epinephrine for admission to hospital but suggested an association with harm for the outcomes of survival to discharge and functional survival as measured by CPC. The Olasveengen original trial<sup>110</sup> was excluded from our review; however, the post hoc subgroup analysis was included in the systematic review of observational and randomized trials, which we have used to comment on the body of work defined by adjusted and unadjusted observational studies.<sup>113</sup>

#### Consensus on Science

For all 4 long-term and short-term outcomes, we found 1 underpowered RCT that provided low-quality evidence (downgraded for selection and ascertainment bias) comparing SDE with placebo<sup>111</sup> in 534 subjects.

For the critical outcome of **survival to discharge**, there was uncertain benefit or harm of SDE over placebo (RR, 2.12; 95% CI, 0.75–6.02;  $P=0.16$ ; absolute risk reduction [ARR], 2.14%; 95% CI, –0.91% to 5.38%, or 21 more patients/1000 survived with epinephrine [95% CI, 9 fewer patients/1000 to 54 more patients/1000 survived with epinephrine]).

For the critical outcome of **survival to discharge with good neurologic outcome** (defined as CPC of 1–2), there was uncertain benefit or harm of SDE over placebo (RR, 1.73; 95% CI, 0.59–5.11;  $P=0.32$ ; ARR, 1.4%; 95% CI, –1.5% to 4.5%, which translates to 14 more patients/1000 survived with a CPC score of 1 or 2 with epinephrine [95% CI, 15 fewer patients/1000 to 45 more patients/1000 survived with a CPC score of 1 or 2 when given epinephrine]).

For the important outcome of **survival to admission**, patients who received SDE had higher rates of survival to admission (RR, 1.95; 95% CI, 1.34–2.84;  $P=0.0004$ ; ARR, 12%; 95% CI, 5.7%–18.9%, which translates to 124 more patients/1000 survived to admission with epinephrine [95% CI, 57–189 more patients/1000 survived to admission]).

For the important outcome of **ROSC in the prehospital setting**, 151 more patients/1000 achieved ROSC with epinephrine (95% CI, 90–212 more patients/1000 achieved ROSC with epinephrine) when compared with those who received placebo (RR, 2.80; 95% CI, 1.78–4.41;  $P<0.00001$ ; ARR, 15%; 95% CI, 9%–21%).

While observational studies were excluded from the primary evidence evaluation, the task force did make some comparison of the randomized trial data with prior conclusions drawn from large observational data sets. Using the analysis published by Patanwala<sup>113</sup> in 2014 when the Jacobs trial<sup>111</sup> is compared with adjusted observational trials<sup>114,115</sup> for the critical outcome of **survival to discharge and functional survival with a CPC of 1 or 2**, in settings with very low survival rates after cardiac arrest, 4.7% OHCA<sup>114</sup> and 14% IHCA,<sup>115</sup> in the OHCA setting, the use of epinephrine was associated with worse outcomes for survival to discharge (5.4% with epinephrine versus 4.7% without epinephrine; unadjusted OR, 1.15; 95% CI, 1.07–1.53; adjusted OR, 0.46; 95% CI, 0.42–0.51) and for functional survival (1.4% with epinephrine versus 2.2% without epinephrine; unadjusted OR, 0.61; 95% CI, 0.53–0.71%; adjusted OR, 0.31; 95% CI, 0.26–0.36).<sup>114</sup> In the in-hospital setting, the use of epinephrine was not significantly associated with either survival to discharge (OR, 1.16; 95% CI, 0.52–2.58) or functional survival (CPC, 1–2; OR, 0.43; 95% CI, 0.08–2.29).

#### Treatment Recommendation

We suggest SDE be administered to patients in cardiac arrest (weak recommendation, very-low-quality evidence).

#### Values, Preferences, and Task Force Insights

We make this statement after considering the observed benefit in short-term outcomes (ROSC and admission to hospital) and our uncertainty about the benefit or harm on survival to discharge and neurologic outcome given the limitations of the observational studies. Our statement is not intended to change current practice until there are high-quality data on long-term outcomes. We have considered 1 mg to be the standard dose of epinephrine.

#### Knowledge Gaps

- Dose response and placebo-controlled efficacy trials are needed to evaluate the use of epinephrine in cardiac arrest. We are aware of an ongoing randomized study of epinephrine (adrenaline) versus placebo for OHCA in the United Kingdom (PARAMEDIC 2: The Adrenaline Trial, ISRCTN73485024).

### Epinephrine Versus Vasopressin (ALS 659)

Among adults who are in cardiac arrest in any setting (P), does use of epinephrine (I), compared with vasopressin (C), change survival to 30 days with good neurologic outcome, survival to 30 days, survival to hospital discharge with good neurologic outcome, survival to hospital discharge, ROSC (O)?

**Consensus on Science**

A single RCT<sup>116</sup> (n=336) of low quality (downgraded for high risk of bias) compared multiple doses of SDE with multiple doses of standard-dose vasopressin in the ED after OHCA. Much of the methodology is unclear, and there was 37% post-randomization exclusion. The primary outcome measure was a CPC score of 1 or 2; however, neither the sample size estimate nor power calculation were included in the article.

For the critical outcome of **survival to discharge with favorable neurologic outcome** (CPC 1 or 2), there was no advantage with vasopressin (RR, 0.68; 95% CI, 0.25–1.82;  $P=0.44$  or ARR,  $-1.6$ ; 95% CI,  $-6$  to 2.4, which translates to 16 fewer patients/1000 surviving with CPC 1 or 2 with vasopressin [95% CI, 60 fewer patients/1000 to 24 more patients/1000 survive with CPC 1 or 2]).

For the critical outcome of **survival to discharge**, RR was 0.68 (95% CI, 0.25–1.82;  $P=0.44$  or ARR, 1.8%; 95% CI,  $-3.1$  to 6.7, which translates to 18 more patients/1000 surviving to discharge with vasopressin [95% CI, 31 fewer patients/1000 surviving to discharge with vasopressin to 67 more patients/1000 surviving to discharge]).

For the important outcome of **ROSC**, there was no observed advantage with vasopressin (RR, 0.93; 95% CI, 0.66–1.31;  $P=0.67$ ).

**Treatment Recommendations**

We suggest vasopressin should not be used instead of epinephrine in cardiac arrest (weak recommendation, low-quality evidence).

We suggest that those settings already using vasopressin instead of epinephrine can continue to do so (weak recommendation, low-quality evidence).

**Values, Preferences, and Task Force Insights**

The recommendation considers the fact that vasopressin is already used in some settings, and the available data do not indicate any reason to stop using vasopressin if current treatment protocols already include vasopressin instead of epinephrine. Conversely, there is also no evidence to indicate that settings that use epinephrine should switch to using vasopressin.

**Knowledge Gaps**

- Until high-quality, adequately powered trials are completed comparing epinephrine with placebo, trials involving vasopressin are not required unless as a third arm against epinephrine and placebo.

**Epinephrine Versus Vasopressin in Combination With Epinephrine (ALS 789)**

Among adults who are in cardiac arrest in any setting (P), does use of both vasopressin and epinephrine (I), compared with using epinephrine alone (C), change survival with favorable neurologic/functional outcome at discharge, 30 days, 60 days, 180 days, and/or 1 year; survival only at discharge, 30 days, 60 days, 180 days, and/or 1 year; ROSC (O)?

**Consensus on Science**

For the critical outcome of **survival to hospital discharge with CPC of 1 or 2**, we found very-low-quality evidence (downgraded for very serious bias and serious imprecision)

from 3 RCTs<sup>117–119</sup> (n=2402) comparing SDE with vasopressin and epinephrine combination therapy that showed no superiority with vasopressin and epinephrine combination (RR, 1.32; 95% CI, 0.88–1.98 and ARR, 0.5%; 95% CI,  $-0.2\%$  to 1.3%, which translates to 5 more patients/1000 [95% CI, 2 fewer patients/1000 to 13 more/1000] surviving to hospital discharge with a CPC of 1 or 2 with vasopressin in combination with epinephrine).

For the critical outcome of **survival to hospital discharge**, we found very-low-quality evidence (downgraded for very serious bias and serious imprecision) from 5 RCTs<sup>117–121</sup> (n=2438) comparing SDE to vasopressin and epinephrine combination therapy that did not show superiority with vasopressin and epinephrine combination therapy in survival to discharge (RR, 1.12; 95% CI, 0.84–1.49;  $P=0.45$  and ARR,  $-0.17\%$ ; 95% CI,  $-1.3$  to 1, which translates to 2 fewer patients/1000 [95% CI, 13 fewer patients/1000 to 10 more/1000] surviving to hospital discharge with vasopressin in combination with epinephrine).

For the important outcome of **survival to admission**, we found moderate-quality evidence (downgraded for serious bias) from 5 RCTs<sup>117–121</sup> (n=2438) showing no significant differences in survival to hospital admission with vasopressin and epinephrine combination therapy (RR, 0.88; 95% CI, 0.73–1.06;  $P=0.17$ ).

For the important outcome of **ROSC**, we found moderate-quality evidence (downgraded for serious bias) from 6 RCTs<sup>117–122</sup> showing no ROSC advantage with vasopressin and epinephrine combination therapy (RR, 0.96; 95% CI, 0.89–1.04;  $P=0.31$ ).

**Treatment Recommendation**

We suggest against adding vasopressin to SDE during cardiac arrest (weak recommendation, moderate-quality evidence).

**Values, Preferences, and Task Force Insights**

In making this recommendation, we preferred to avoid the additional expense and implementation issues required to add a drug (vasopressin) that has no evidence of additional benefit for patients.

**Knowledge Gaps**

- Until high-quality, adequately powered trials are completed comparing epinephrine with placebo, trials involving vasopressin in combination with epinephrine are not required unless as a third arm against epinephrine and placebo.

**SDE Versus HDE (ALS 778)**

In adult patients in cardiac arrest in any setting (P), does HDE (at least 0.2 mg/kg or 5 mg bolus dose) (I), compared with SDE (1 mg bolus dose) (C), change survival to 180 days with good neurologic outcome, survival to 180 days, survival to hospital discharge with good neurologic outcome, survival to hospital discharge, ROSC (O)?

**Consensus on Science**

For the critical outcome of **survival to hospital discharge with CPC 1 or 2**, we found very-low-quality evidence (downgraded for very serious indirectness and serious imprecision) from 2 RCTs comparing SDE with HDE<sup>123,124</sup> (n=1920) and

cumulative RR that did not show any CPC 1 or 2 survival to discharge advantage with HDE (RR, 1.2; 95% CI, 0.74–1.96; ARR, –0.4%, 95% CI, –1.2 to 0.5, which translates to 3 fewer patients/1000 surviving to discharge with a CPC score of 1 or 2 [95% CI, 12 fewer to 5 more patients/1000 surviving to discharge with a CPC score of 1–2]).

For the critical outcome of **survival to hospital discharge**, we found very-low-quality evidence (downgraded for very serious indirectness and serious imprecision) from 5 RCTs comparing SDE with HDE<sup>123–127</sup> (n=2859) that did not show any survival to discharge advantage with HDE (RR, 0.97; 95% CI, 0.71–1.32; ARR, –0.1%; 95% CI, –0.1 to 0.7, which translated to 1 fewer patient/1000 surviving to discharge with HDE [95% CI, 10 fewer patients/1000 to 7 more patients/1000]).

For the important outcome of **survival to hospital admission**, we found low-quality evidence (downgraded for very serious indirectness) from 4 RCTs comparing SDE with HDE<sup>123–125,128</sup> (n=2882) showing a survival to hospital admission advantage with HDE (RR, 1.15; 95% CI, 1.0–1.32).

For the important outcome of **ROSC**, we found low-quality evidence (downgraded for very serious indirectness) from 6 RCTs comparing SDE with HDE<sup>123–128</sup> (n=3130) showing a ROSC advantage with HDE (RR, 1.17; 95% CI, 1.03–1.34).

### Treatment Recommendation

We suggest against the routine use of HDE in cardiac arrest (weak recommendation, low-quality evidence).

### Values, Preferences, and Task Force Insights

In making this statement, we acknowledge that HDE improves short-term outcomes but note that the low-quality evidence failed to show an improvement in the critical outcomes of survival and neurologic outcome. The absolute magnitude of effects of HDE versus SDE on ROSC (RR, 1.17; 95% CI, 1.03–1.34) and admission to hospital (RR, 1.15; 95% CI, 1.0–1.32) are modest. These HDE studies were published in the 1990s, and since then care and outcomes for cardiac arrest have changed dramatically, making it hard to interpret the relevance of these results for current care.

### Knowledge Gaps

- Until high-quality, well-powered trials are completed comparing epinephrine with placebo, trials addressing dose response of epinephrine are not required except as a third arm embedded in an epinephrine-versus-placebo trial.

### Timing of Administration of Epinephrine (ALS 784)

Among adults who are in cardiac arrest in any setting (P), does early epinephrine delivery by IV or IO route (eg, less than 10 minutes after the beginning of resuscitation) (I), compared with delayed timing of epinephrine delivery (eg, more than 10 minutes after the beginning of resuscitation) (C), change survival with favorable neurologic/functional outcome at discharge, 30 days, 60 days, 180 days, and/or 1 year; survival only at discharge, 30 days, 60 days, 180 days, and/or 1 year; ROSC (O)?

### Consensus on Science

#### In-Hospital Cardiac Arrest

For IHCA, for the critical outcome of **survival to hospital discharge**, there was 1 observational study<sup>129</sup> of low quality

(downgraded for serious risk of bias and upgraded for dose-response effect) in 25 095 IHCA patients with a nonshockable rhythm that showed an improved outcome with early administration of adrenaline: compared with reference interval of 1 to 3 minutes, adjusted OR for survival to discharge was 0.91 (95% CI, 0.82–1.00) when epinephrine was given after 4 to 6 minutes, 0.74 (95% CI, 0.63–0.88) when given after 7 to 9 minutes, and 0.63 (95% CI, 0.52–0.76) when given at more than 9 minutes after onset of arrest.

For IHCA, for the critical outcome of **neurologically favorable survival at hospital discharge** (assessed with CPC 1 or 2), there was 1 observational study<sup>129</sup> of low quality (downgraded for serious risk of bias and upgraded for dose-response effect) in 25 095 patients with IHCA with a nonshockable rhythm that showed an improved outcome from early administration of adrenaline: compared with reference interval of 1 to 3 minutes, adjusted OR was 0.93 (95% CI, 0.82–1.06) with epinephrine given after 4 to 7 minutes, 0.77 (95% CI, 0.62–0.95) when given after 7 to 9 minutes, and 0.68 (95% CI, 0.53–0.86) when given at more than 9 minutes after onset of arrest.

For IHCA, for the important outcome of **ROSC**, there was 1 observational study<sup>129</sup> of low quality (downgraded for serious risk of bias and upgraded for dose-response effect) in 25 095 patients with IHCA with a nonshockable rhythm that showed an improved outcome from early administration of adrenaline: adjusted OR compared with reference interval of 1 to 3 minutes of 0.90 (95% CI, 0.85–0.94) when given after 4 to 7 minutes, 0.81 (95% CI, 0.74–0.89) when given after 7 to 9 minutes, and 0.70 (95% CI, 0.61–0.75) when given after 9 minutes.

No studies were identified that looked specifically at the effect of timing on administration of epinephrine after IHCA with an initial shockable rhythm.

#### Out-of-Hospital Cardiac Arrest

For the critical outcome of **neurologically favorable survival at hospital discharge** (assessed with CPC 1 or 2), there was very-low-quality evidence (downgraded for risk of bias, inconsistency, indirectness, and imprecision) from 4 observational studies<sup>130–133</sup> involving more than 262 556 OHCAs, showing variable benefit from early administration of epinephrine. One study of 1556 OHCAs who had achieved ROSC<sup>130</sup> demonstrated an association between the administration of epinephrine and worse CPC, but shorter times of administration were associated with less negative effects: adjusted OR of 0.54 (95% CI, 0.32–0.91) for good CPC with epinephrine at less than 9 minutes versus no prehospital epinephrine, and adjusted OR of 0.17 (95% CI, 0.09–0.34) for epinephrine at more than 22 minutes.

Another study enrolling 209 577 OHCAs<sup>131</sup> did not show any significant difference in **1-month CPC 1 or 2** with epinephrine given in less than 9 minutes compared with no epinephrine (OR, 0.71; 95% CI, 0.54–0.92 and OR, 0.95; 95% CI, 0.62–1.37).

Another study enrolling 3161 subjects<sup>132</sup> showed an association with improved 1-month neurologic outcome in VF/pVT OHCA with early epinephrine (at 10 minutes or less from EMS call to administration) compared with no



epinephrine (OR, 6.34; 95% CI, 1.49–27.02). A fourth study enrolling more than 49 000 cases<sup>133</sup> demonstrated a nonsignificant association with improved neurologic survival with early epinephrine (less than 10 minutes from EMS-initiated CPR): OR of 1.39 (95% CI, 1.08–1.78) versus OR of 2.01 (95% CI, 0.96–4.22).

For the critical outcome of **survival to hospital discharge after OHCA**, there was very-low-quality evidence (downgraded for risk of bias, inconsistency, indirectness, and imprecision), from 4 observational studies<sup>127,131,133,134</sup> enrolling more than 420 000 OHCA that showed variable effect from early administration of adrenaline. Goto<sup>131</sup> showed no significant difference in 1-month survival for shockable rhythms, but improved 1-month survival for shockable rhythms with epinephrine at less than 9 minutes (OR, 0.95; 95% CI, 0.77–1.16 and OR, 1.78; 95% CI, 1.5–2.1). Another study<sup>133</sup> showed an association with improved survival with early epinephrine (less than 10 minutes from EMS CPR): for arrests of cardiac origin: OR, 1.73 (95% CI, 1.46–2.04); for noncardiac origin: OR, 1.89 (95% CI, 1.37–2.61). A third study<sup>134</sup> did not show any overall survival benefit for early epinephrine compared with late (epinephrine at more or less than 10 minutes): OR, 0.91 (95% CI, 0.35–2.37).

For the important outcome of **ROSC**, there was very-low-quality evidence (downgraded for risk of bias, indirectness, and imprecision) from 4 observational studies<sup>127,131,134,135</sup> of more than 210 000 OHCA showing an association with improved outcome and early administration of adrenaline. One study<sup>135</sup> showed increased ROSC for patients receiving the first vasopressor dose early (less than 10 versus more than 10 minutes after EMS call): OR, 1.91 (95% CI, 1.01–3.63).

Another study<sup>131</sup> showed an association with improved ROSC for epinephrine given at less than 9 minutes after arrest versus none (for nonshockable rhythms: OR, 8.83; 95% CI, 8.01–9.73; for shockable rhythms: OR, 1.45; 95% CI, 1.20–1.75). A third study<sup>134</sup> showed an association with improved ROSC for early epinephrine versus late (more or less than 10 minutes after EMS call): OR, 1.78 (95% CI, 1.15–2.74).

The design flaws for most of the observational OHCA studies included the use of a “no epinephrine” control group as the comparator, thus not allowing for actual estimates of the effect of timing, and the lack of known timing of epinephrine administration upon arrival in the ED. The relationship of timing of defibrillation to timing of epinephrine is unknown for studies including shockable rhythms. These design issues make the question of timing of epinephrine difficult to interpret in the OHCA setting despite attempts to control for other confounders.

### **Treatment Recommendation**

For cardiac arrest with an initial nonshockable rhythm, we suggest that if epinephrine is to be administered, it is given as soon as feasible after the onset of the arrest (weak recommendation, low-quality evidence).

For cardiac arrest with an initial shockable rhythm, we found insufficient evidence to make a treatment suggestion regarding the timing of administration of epinephrine, particularly in relation to defibrillation, and the optimal

timing may vary for different groups of patients and different circumstances.

### **Values, Preferences, and Task Force Insights**

In making the recommendation for nonshockable rhythms, we place a higher value on being able to modify a current (standard) treatment at minimal cost.

For shockable rhythms, we place a higher value on early defibrillation than on administration of epinephrine but did not think there is sufficient evidence to make a treatment recommendation. Although we acknowledge that the pathophysiology of IHCA and OHCA is likely to be different, we were confident that the same recommendations could apply to both settings.

### **Knowledge Gaps**

- Until high-quality, well-powered trials are completed comparing epinephrine with placebo, trials addressing the timing of epinephrine doses are not required except as a third arm embedded in an epinephrine-versus-placebo trial.

### **Steroids for Cardiac Arrest (ALS 433)**

Among adults who are in cardiac arrest in any setting (P), does corticosteroid or mineralocorticoid administration during CPR (I), compared with not using steroids (C), change survival with favorable neurologic/functional outcome at discharge, 30 days, 60 days, 180 days, and/or 1 year; survival only at discharge, 30 days, 60 days, 180 days, and/or 1 year; ROSC (O)?

### **Introduction**

We identified studies that assessed the use of methylprednisolone, hydrocortisone, or dexamethasone during CPR. Studies usually bundled the steroid with other vasoactive drugs. All studies examined either IHCA or OHCA. Because the pathophysiology and epidemiology of IHCA and OHCA are so different, we considered these situations separately.

### **Consensus on Science**

#### *In-Hospital Cardiac Arrest*

For the critical outcome of **survival to discharge with favorable neurologic outcome**, there was low-quality evidence (downgraded for indirectness and for imprecision) from 1 RCT<sup>136</sup> in 268 patients with IHCA that showed improved outcome with methylprednisolone, vasopressin, and epinephrine during cardiac arrest, and hydrocortisone in those with post-ROSC shock compared with only epinephrine and placebo (18/130 [13.9%] versus 7/138 [5.1%]; RR, 2.94; 95% CI, 1.16–6.50, which translates to 98 more/1000 surviving with good neurologic outcome [95% CI, from 8–279 more/1000 surviving with good neurologic outcome]).

For the critical outcome of **survival to discharge**, there was low-quality evidence (downgraded for indirectness and for imprecision) from 1 RCT<sup>137</sup> of 100 patients with IHCA that showed improved outcome with the combination of methylprednisolone, vasopressin, and epinephrine during cardiac arrest and hydrocortisone after ROSC for those with shock, compared with the use of only epinephrine and placebo (9/48 [19%] versus 2/52 [4%]; RR, 4.87; 95% CI, 1.17–13.79, which

translates to 149 more/1000 surviving to discharge [95% CI, 7–492 more/1000 surviving to discharge]).

For the important outcome of **ROSC**, there was low-quality evidence (downgraded for indirectness and imprecision) from 2 RCTs<sup>136,137</sup> involving 368 patients with IHCA showing improved outcome with the use of methylprednisolone and vasopressin in addition to epinephrine, compared with the use of placebo and epinephrine alone (combined RR, 1.34; 95% CI, 1.21–1.43, which translates to 130–267 more achieving ROSC with the combination of methylprednisolone, vasopressin, and epinephrine during cardiac arrest, compared with the use of only epinephrine and placebo [95% CI, 130–267 more achieving ROSC]).

#### *Out-of-Hospital Cardiac Arrest*

For the critical outcome of **survival to discharge**, there was very-low-quality evidence (downgraded for risk of bias, indirectness, and imprecision) from 1 RCT and 1 observational study<sup>138,139</sup> showing no association with benefit with the use of steroids. Paris had no long-term survivors and Tsai showed survival to discharge in 8% (3/36) receiving hydrocortisone compared with 10% (6/61) receiving placebo ( $P=0.805$ ).

For the important outcome of **ROSC**, we found very-low-quality evidence from 1 RCT<sup>138</sup> and 1 observational study<sup>139</sup> with a combined total of 183 patients. The RCT<sup>138</sup> showed no improvement in ROSC (and ICU admission) with dexamethasone given during cardiac arrest compared with placebo (5.4% [2/37] versus 8.7% [4/46]), but the observational study<sup>139</sup> showed an association with improved ROSC with hydrocortisone compared with no hydrocortisone (58% versus 38%;  $P=0.049$ ).

#### **Treatment Recommendation**

For IHCA, the task force was unable to reach a consensus recommendation for or against the use of steroids in cardiac arrest.

We suggest against the routine use of steroids during CPR for OHCA (weak recommendation, very-low-quality evidence).

#### **Values, Preferences, and Task Force Insights**

In making this recommendation for IHCA, it was noted that there were no studies assessing the effect of the addition of steroids alone to standard treatment for IHCA. Also, although the triple-agent drug regimen appears to suggest an association with improved outcome, the population studied had very rapid ALS, a high incidence of asystolic cardiac arrest, and low baseline survival compared with other IHCA studies, so some of the observed effects might be peculiar to the population studied.

In making this recommendation for OHCA, we considered the cost and distraction from the addition of treatments for which there is very low confidence in any effect. The different recommendation for OHCA and IHCA was influenced by the physiological differences between these conditions, such as the incidence of sepsis, adrenal insufficiency from critical illness, and cardiovascular etiologies.

#### **Knowledge Gaps**

- It is unclear which aspect of bundled treatments such as epinephrine, vasopressin, and steroids are related to

any observed treatment effect. The alternative possibility is that bundled treatments require synergistic action, because other studies with each agent (vasopressin and steroids) have failed to find the same effect.

- Confidence in the treatment effects from bundled treatments will increase if confirmed in further studies.

### **Antiarrhythmic Drugs for Cardiac Arrest (ALS 428)**

Among adults who are in cardiac arrest in any setting (P), does administration of antiarrhythmic drugs (eg, amiodarone, lidocaine, other) (I), compared with not using antiarrhythmic drugs (no drug or placebo) (C), change survival with favorable neurologic/functional outcome at discharge, 30 days, 60 days, 180 days, and/or 1 year; survival only at discharge, 30 days, 60 days, 180 days, and/or 1 year; ROSC (O)?

#### **Introduction**

Antiarrhythmic drugs can be used during cardiac arrest for refractory ventricular dysrhythmias. *Refractory VF/pVT* is defined differently in many trials but generally refers to failure to terminate VF/pVT with 3 stacked shocks, or with the first shock. In an ongoing clinical trial from which results are not yet available, refractory VF refers to “persistent or recurrent VF/pVT after 1 or more shocks.”<sup>140</sup>

#### **Consensus on Science**

Comparative data on the use of antiarrhythmic drugs were identified for amiodarone, lidocaine, magnesium, and nifekalant. The data reviewed for magnesium only addressed the use of this drug for undifferentiated VF/pVT and not the treatment of *torsades de pointes* or known hypomagnesemic patients. Nifekalant is only available in certain regions.

#### *Amiodarone (I) Versus No Amiodarone (C)*

For the critical outcome of **survival with favorable neurologic/functional outcome at discharge**, there was moderate-quality evidence (downgraded due to serious risk of indirectness) from 1 RCT involving 504 OHCA patients, which detected no difference with administration of amiodarone (300 mg after 1 mg of adrenaline) compared with no drug (7.3% versus 6.6%;  $P$ =not significant [NS]; RR, 1.11; 95% CI, 0.59–2.10).<sup>141</sup>

For the critical outcome of **survival at discharge**, there was moderate-quality evidence (downgraded due to serious risk of indirectness) from 1 RCT involving 504 OHCA patients that detected no difference with the administration of amiodarone (300 mg after 1 mg of adrenaline) compared with no drug (13.4% versus 13.2%;  $P$ =NS; RR, 1.02; 95% CI, 0.65–1.59).<sup>141</sup>

For the important outcome of **ROSC**, there was moderate-quality evidence (downgraded due to serious risk of indirectness) from 1 RCT involving 504 OHCA patients that showed higher ROSC with administration of amiodarone (300 mg after 1 mg of adrenaline) compared with no drug (64% versus 41%;  $P=0.03$ ; RR, 1.55; 95% CI, 1.31–1.85).<sup>141</sup>

#### *Lidocaine (I) Versus No Lidocaine (C)*

For the critical outcome of **survival at discharge**, there was very-low-quality evidence (downgraded for very serious risk

of bias and serious indirectness) from 2 retrospective observational studies that did not detect a difference with treatment. In 290 OHCA patients, rates of survival with administration of lidocaine (50 mg, repeatable up to 200 mg) or with no drug did not differ (14% versus 8%;  $P=NS$ ).<sup>142</sup> In 116 OHCA patients, survival with administration of lidocaine (100 mg) compared with no drug did not differ (11% versus 2%;  $P=NS$ ).<sup>143</sup>

For the important outcome of **ROSC**, there was very-low-quality evidence (downgraded for very serious risk of bias and serious indirectness) from 2 retrospective observational single-center studies, which showed conflicting results. In 290 OHCA patients, rates of ROSC were not different after administration of lidocaine (50 mg, repeatable up to 200 mg) compared with no drug (45% versus 23%;  $P<0.001$ ).<sup>142</sup> In 116 OHCA patients who had OHCA with VF refractory to 3 shocks, a similar rate of ROSC was documented with administration of lidocaine (100 mg) compared with no drug (55% versus 54%;  $P=NS$ ).<sup>143</sup>

#### *Magnesium (I) Versus No Magnesium (C)*

For the critical outcome of **survival with favorable neurologic/functional outcome at discharge**, there was low-quality evidence (downgraded for serious risk of imprecision and indirectness) from 1 single-center RCT of 156 IHCA patients with all initial rhythms (50% in VF/pVT), which showed similar survival with favorable neurologic outcome with administration of magnesium (2 g [8 mmol] bolus followed by infusion of 8 g [32 mmol] in 24 hours) compared with no drugs (favorable return to independent living 14.5% versus 7.5%;  $P=NS$ ; RR, 1.93; 95% CI, 0.75–4.96; median Glasgow Coma Scale [GCS] score at hospital discharge 15 [interquartile range, 15–15] versus 15 [interquartile range, 15–15];  $P=NS$ ).<sup>144</sup>

For the critical outcome of **survival at discharge**, there was low-quality evidence (downgraded for serious risk of imprecision and indirectness) from 4 RCTs, which showed no differences in outcome with treatment. One single-center RCT of 156 IHCA patients with all initial rhythms (50% in VF/pVT) showed similar survival with administration of magnesium (2 g [8 mmol] bolus followed by infusion of 8 g [32 mmol] in 24 hours) compared with no drugs (21% versus 21%;  $P=NS$ ; adjusted OR, 1.22; 95% CI, 0.53–2.81).<sup>144</sup> One single-center trial of 67 OHCA patients with all rhythms and ongoing CPR at ED arrival detected no difference with administration of magnesium (5 g [20 mmol] bolus) compared with no drugs (1 versus 0 patients;  $P=0.46$ ).<sup>145</sup>

A multicenter study of 109 OHCA patients with VF did not detect a difference in survival with administration of magnesium (2 g [8 mmol] bolus) compared with no drugs (3.6% versus 3.7%;  $P=1.0$ ; unadjusted RR of increased survival, 0.98; 95% CI, 0.53–2.81).<sup>146</sup> A single-center trial of 105 OHCA patients with VF did not detect a difference in survival with administration of magnesium (2 g [8 mmol] bolus, repeatable once) compared with no drugs (4% versus 2%;  $P=0.99$ ).<sup>147</sup>

For the important outcome of **ROSC**, there was low-quality evidence (downgraded for serious risk of imprecision and indirectness) from 3 RCTs that did not detect a difference with treatment. One single-center trial of 67 OHCA patients with all rhythms and ongoing CPR at ED arrival detected no difference with administration of magnesium (5 g [20 mmol] bolus)

compared with no drugs (23% versus 22%;  $P=0.97$ ).<sup>145</sup> A multicenter study of 109 OHCA patients with VF did not detect difference in ROSC rates with administration of magnesium (2 g [8 mmol] bolus) compared with no drugs (25% versus 19%;  $P=0.39$ ).<sup>146</sup> A single-center trial of 105 OHCA patients with VF did not detect a difference in ROSC rates with administration of magnesium (2 g [8 mmol] bolus, repeatable once) compared with no drugs (17% versus 13%;  $P=0.56$ ).<sup>147</sup>

#### *Nifekalant (I) Versus No Nifekalant (C)*

For the critical outcome of **survival at discharge**, there was very-low-quality evidence (downgraded for very serious risk of bias, very serious indirectness, and imprecision) from 1 retrospective single-center observational study of 63 patients with cardiac arrest upon or during hospitalization, which found improved survival with administration of nifekalant (loading dose 0.27 mg/kg followed by infusion of 0.26 mg/kg/h) compared with no drug in historic controls (OR for cardiac death, 0.26; 95% CI, 0.07–0.95;  $P=0.041$ ).<sup>148</sup>

#### *Treatment Recommendations*

We suggest the use of amiodarone in adult patients with refractory VF/pVT to improve rates of ROSC (weak recommendation, moderate-quality evidence).

We suggest the use of lidocaine or nifekalant as an alternative to amiodarone in adult patients with refractory VF/pVT (weak recommendation, very-low-quality evidence).

We recommend against the routine use of magnesium in adult patients (strong recommendation, low-quality evidence).

#### *Values, Preferences, and Task Force Insights*

In making these recommendations, we considered the reported beneficial effects of amiodarone on the important outcome of survival to hospital admission. We acknowledged that there was the uncertainty about any beneficial or harmful effects of these drugs on the critical outcomes of survival or favorable neurologic survival. Although the evidence supporting their use is weaker, in making a recommendation for lidocaine and nifekalant as alternatives to amiodarone, the task force recognized that amiodarone is not available or currently used in some countries. The small quantity of new data made the task force place value on not changing current clinical practice.

#### *Knowledge Gaps*

- There is a need for sufficiently powered RCTs to detect a difference in survival to hospital discharge or favorable neurologic outcomes.
- A potential source of bias reducing confidence in prior trials of amiodarone is use of the polysorbate solvent for the drug. This solvent is known to reduce blood pressure, and its use as placebo may have created a bias for worse outcomes in placebo groups. Future studies should account for this effect or use other solvents.
- There is an ongoing trial comparing amiodarone to lidocaine and to placebo designed and powered to evaluate for functional survival.<sup>140</sup>
- No data address how to select a second-line agent when VF/pVT is refractory to the first drug.



## 2010 CoSTR Topics Not Reviewed in 2015

- IV fluids during cardiac arrest
- Drugs for atrial fibrillation
- Drugs for narrow complex tachycardia
- Drugs for monomorphic wide complex tachycardia
- Drugs for undifferentiated stable wide complex tachycardia
- Drugs for polymorphic wide complex tachycardia
- Drugs for *torsades de pointes*
- Drugs for bradycardia
- Atropine for cardiac arrest
- Calcium for cardiac arrest
- Fibrinolytics for cardiac arrest
- Buffering agents for cardiac arrest

### Cardiac Arrest in Special Circumstances

There are numerous special circumstances where additional interventions and/or modifications to ALS may be required. The ILCOR ALS Task Force prioritized 5 topics for review: (1) cardiac arrest during pregnancy, (2) lipid therapy for cardiac arrest associated with overdose, (3) opioid toxicity, (4) cardiac arrest caused by PE, and (5) cardiac arrest during coronary catheterization.

### Cardiac Arrest During Pregnancy (ALS 436)

Among pregnant women who are in cardiac arrest in any setting (P), do any specific interventions (I), compared with standard care (usual resuscitation practice) (C), change survival with favorable neurologic/functional outcome at discharge, 30 days, 60 days, 180 days, and/or 1 year; survival only at discharge, 30 days, 60 days, 180 days, and/or 1 year; ROSC (O)?

#### Introduction

The aim of this PICO review was to assess whether commonly applied additions to the standard practice of resuscitation led to improved outcomes in pregnant women. Specific emphasis was placed on uterine displacement for the purpose of decreasing aortocaval compression, and perimortem cesarean delivery as interventions to improve outcome in the mother and newborn.

#### Consensus on Science

There were no comparative studies of uterine displacement for women in cardiac arrest before delivery. No studies compared different maneuvers (eg, manual displacement versus left pelvic tilt) to achieve optimal uterine displacement for women in cardiac arrest before delivery.

Physiologic reviews and studies of uterine displacement maneuvers in nonarrest pregnant women support that uterine displacement might be physiologically beneficial for women in cardiac arrest.<sup>149</sup> Any benefit would have to be weighed against the potential interference or delay with usual resuscitation care.

For the critical outcomes of **survival with favorable neurologic/functional outcome at discharge, 30 days, 60 days, 180 days, and/or 1 year**, and **survival only at discharge, 30 days, 60 days, 180 days, and/or 1 year**, and the important outcomes of **ROSC**, we found 3 observational studies of 154 subjects collectively<sup>150–152</sup> that provided

very-low-quality evidence (downgraded for very serious risk of bias and imprecision, and serious inconsistency) comparing cardiac arrest resuscitation with or without perimortem cesarean delivery. The procedures to ascertain cases and controls in these studies were significantly different so that the pooled comparison of any of the assigned outcomes is considered inappropriate.

#### Treatment Recommendations

We suggest delivery of the fetus by perimortem cesarean delivery for women in cardiac arrest in the second half of pregnancy (weak recommendation, very-low-quality evidence).

There is insufficient evidence to define a specific time interval by which delivery should begin. High-quality usual resuscitation care and therapeutic interventions that target the most likely cause(s) of cardiac arrest remain important in this population.

There is insufficient evidence to make a recommendation regarding the use of left lateral tilt and/or uterine displacement during CPR in the pregnant patient.

#### Values, Preferences, and Task Force Insights

In making this statement, we place value on maternal and neonatal survival, on the absence of data on left lateral tilt and uterine displacement in women with cardiac arrest, and on our uncertainty about the absolute effect of either uterine displacement or perimortem delivery during CPR on any of the assigned outcomes. The task force thought not making a recommendation for or against the use of left lateral tilt or uterine tilt is unlikely to change current practice or guidelines.

#### Knowledge Gaps

- Research in the area of maternal resuscitation is lacking because cardiac arrest in pregnancy is rare. Most evidence is extrapolated from nonpregnant people, manikin or simulation studies, and case reports.
- The heterogeneous nature of the etiologies of maternal cardiac arrest, variations in gestational age and body mass index of the cases, variations in the location (eg, out-of-hospital, ED, obstetric unit), and context of arrest and personnel available to immediately respond, and absence of information about the quality of usual resuscitation care all further hamper interpretation of the limited available data.
- Systematic data collection in pregnant women who have experienced cardiac arrest will require a national or international registry and/or coordinated prospective population-level surveillance to compile a sufficiently large and robust data set to evaluate the effect of either uterine displacement or perimortem delivery on maternal ROSC, maternal survival, functionally intact maternal survival, neonatal survival, and functionally intact neonatal survival.
- A particular emphasis on cardiovascular etiologies of arrest is warranted given increasing numbers of women with congenital heart conditions having children, the increasing prevalence of cardiomyopathy among pregnant and postpartum women, and the preponderance of cardiovascular disease evident in maternal mortality surveillance reports.<sup>153</sup>

**Lipid Therapy for Cardiac Arrest (ALS 834)**

In adult patients with cardiac arrest due to suspected drug toxicity (eg, local anesthetics, tricyclic antidepressants, others) (P), does administration of IV lipid (I), compared with no IV lipid (C), change survival with favorable neurologic/functional outcome at discharge, 30 days, 60 days, 180 days, and/or 1 year; survival only at discharge, 30 days, 60 days, 180 days, and/or 1 year; ROSC (O)?

**Introduction**

Lipid therapy for cardiac arrest associated with drug toxicity, and in particular local anesthetic toxicity, is becoming increasingly common. Based on laboratory and preclinical data showing that IV administration of lipid solutions can absorb lipid-soluble drugs, studies examined whether this therapy would be useful for cardiac arrest related to drug overdose. We set out to identify studies comparing outcomes with IV lipids to no IV lipids.

**Consensus on Science**

We identified no human comparative studies in cardiac arrest and periarrest states relevant to the PICO question. Many case reports and case series described resuscitation that included administration of lipid.

**Treatment Recommendation**

We are unable to make any evidence-based treatment recommendation about the use of IV lipid emulsion to treat toxin-induced cardiac arrest.

**Values, Preferences, and Task Force Insights**

Although there are many case reports and case series of patients who were resuscitated after administration of IV lipid, the absence of any comparative data made it impossible to determine anything besides temporal association of the therapy with outcome. Despite the paucity of data, we do not wish to discourage the use of an antidote with some theoretical basis in a dire clinical situation.

**Knowledge Gaps**

- Comparisons are needed of patients with similar clinical characteristics who were treated and who were not treated with IV lipids after suspected drug toxicity.

**Opioid Toxicity (ALS 441)**

Among adults who are in cardiac arrest or respiratory arrest due to opioid toxicity in any setting (P), does any specific therapy (eg, naloxone, bicarbonate, or other drugs) (I), compared with usual ALS (C), change survival with favorable neurologic/functional outcome at discharge, 30 days, 60 days, 180 days, and/or 1 year; survival only at discharge, 30 days, 60 days, 180 days, and/or 1 year; ROSC (O)?

**Introduction**

Opioid toxicity is associated with respiratory depression that can lead to cardiorespiratory arrest. This is becoming an increasingly common cause of death in many countries.<sup>154</sup> The specific role of education and availability of naloxone for those with a high risk of opioid overdose is addressed in "Part 3: Adult Basic Life Support and Automated External Defibrillation." Here we address whether any specific

modifications to ALS are required when cardiac arrest is precipitated by opioid toxicity.

Cardiac arrest and respiratory arrest were considered separately. We sought evidence that compared results with any changes in usual resuscitation sequences or interventions in the setting of opioid overdose. Administration of the opioid antagonist naloxone was the only intervention for which literature was identified.

**Consensus on Science**

For the important outcome of **survival with favorable neurologic outcome at discharge, 30 days, 60 days, 180 days, and/or 1 year, survival only at discharge, 30 days, 60 days, 180 days, and/or 1 year, ROSC, after opioid-induced cardiac arrest**, we found no study with comparative data beyond standard ALS care.

For the important outcome of **survival with favorable neurologic outcome at discharge, 30 days, 60 days, 180 days, and/or 1 year, survival only at discharge, 30 days, 60 days, 180 days, and/or 1 year, ROSC, after opioid-induced respiratory arrest**, we found no comparative studies. There were 12 studies of which 5 compared intramuscular and intranasal routes of naloxone administration (2 RCT,<sup>156,157</sup> 3 non-RCT,<sup>158–160</sup> and 7 assessed the safety of naloxone use or were observational studies of naloxone use).<sup>161–169</sup> These studies report that naloxone is safe and effective in treatment of opioid-induced respiratory depression, that complications are rare and dose related, and that mortality is rare when patients refuse transfer after initial naloxone administration.

**Treatment Recommendation**

We recommend the use of naloxone by IV, intramuscular, subcutaneous, IO, or intranasal routes in respiratory arrest associated with opioid toxicity (strong recommendation, very-low-quality evidence). The dose of naloxone required will depend on the route.

We can make no recommendation regarding the modification of standard ALS in opioid-induced cardiac arrest.

**Values, Preferences, and Task Force Insights**

In making these recommendations, we place a high value on the potential of the opioid antagonist naloxone to reverse opioid-induced respiratory depression.

**Knowledge Gaps**

- There are no data on the use of any additional ALS therapies in opioid-induced cardiac arrest. In respiratory arrest, there is only evidence for the use of naloxone—no other adjuncts or changes in sequence of interventions. Studies of naloxone use in respiratory arrest were observational, looked at safety, or compared routes of administration.

**Cardiac Arrest Associated With PE (ALS 435)**

Among adults who are in cardiac arrest due to PE or suspected PE in any setting (P), does any specific alteration in treatment algorithm (eg, fibrinolytics, or any other) (I), compared with standard care (according to 2010 treatment algorithm) (C), change survival with favorable neurologic/functional outcome at discharge, 30 days, 60 days, 180 days, and/or 1 year; survival only at discharge, 30 days, 60 days, 180 days, and/or 1 year; ROSC (O)?

## Introduction

The possible treatments for massive PE include fibrinolytic therapy, surgical embolectomy, and percutaneous mechanical thrombectomy. Most retrospective studies do not make subgroup analysis of patients with suspected or confirmed PE. These treatments were assessed separately as therapies during cardiac arrest as a consequence of PE. The reported outcomes and follow-up of patients is very heterogeneous between studies.

## Consensus on Science

### Fibrinolysis

For the critical outcome of **survival with favorable neurologic status at 30, 90, or 180 days**, there was very-low-quality evidence (downgraded for serious imprecision) from 1 RCT comparing fibrinolytics versus placebo during cardiac arrest.<sup>170</sup> In this double-blinded RCT, 37 of the 1050 patients randomized to receive either fibrinolytic treatment (tenecteplase) or placebo during CPR had confirmed PE as primary cause of cardiac arrest. However, this study was not powered to reach significance in this small subgroup. Patients in whom PE was suspected were furthermore subject to use of open-label fibrinolysis and were not included in the trial at all. The 30-day survival in this subgroup was not statistically different ( $P=0.31$ ; RR, 7.19; 95% CI, 0.37–139.9) between tenecteplase (2/15, 13.3%) and placebo (0/22, 0%).

For the important outcome of **survival to hospital discharge**, very-low-quality evidence (downgraded for very serious risk of bias and imprecision) from 2 retrospective observational studies showed there was no difference in discharge rates: 9.5% fibrinolysis versus 4.8% control<sup>171</sup> and 19.4% fibrinolysis versus 6.7% control (RR, 2.9; 95% CI, 0.75–13.8).<sup>172</sup>

For the important outcome of **ROSC**, very-low-quality evidence from 2 studies (downgraded for very serious risk of bias) showed benefit for the use of fibrinolytic drugs compared with controls in patients with PE: ROSC was reported to be significantly higher in a retrospective analysis (81.0% fibrinolysis versus 42.9% control;  $P=0.03$ ).<sup>171</sup> In a separate study, ROSC (66.7% in fibrinolysis group versus 43.3% in control group; RR, 1.5; 95% CI, 0.8–8.6) was not different, but 24-hour survival (52.8% fibrinolysis versus 23.3% control; RR, 2.3; 95% CI, 1.1–4.7) showed favorable results for the use of fibrinolytic drugs.<sup>172</sup>

### Surgical Embolectomy

We found very-low-quality evidence (downgraded for very serious risk of publication bias) from 2 case series<sup>173,174</sup> with no control groups and a total of 21 patients requiring CPR with a 30-day survival rate of 12.5% and 71.4%, respectively.

### Percutaneous Mechanical Thrombectomy

For the important outcome of **ROSC**, very-low-quality evidence (downgraded for very serious risk of bias and very serious imprecision) from 1 case series of 7 patients with cardiac arrest with no control group,<sup>175</sup> ROSC was achieved in 6 of 7 patients (85.7%) treated with percutaneous mechanical thrombectomy.

## Treatment Recommendations

We suggest administering fibrinolytic drugs for cardiac arrest when PE is the suspected cause of cardiac arrest (weak recommendation, very-low-quality evidence).

We suggest the use of fibrinolytic drugs or surgical embolectomy or percutaneous mechanical thrombectomy for cardiac arrest when PE is the known cause of cardiac arrest (weak recommendation, very-low-quality evidence).

## Values, Preferences, and Task Force Insights

In making these recommendations, we acknowledge the use of thrombolytic drugs, surgical embolectomy or percutaneous mechanical thrombectomy, or a combination for known PE in non-cardiac arrest patients. We acknowledge the potential risk of bleeding after fibrinolysis and place value in the choice of intervention taking into account location, availability of interventions, and contraindications to fibrinolysis.

## Knowledge Gaps

- There is a paucity of data on the topic of pulmonary embolus and its diagnosis and management during cardiac arrest. Further high-quality studies are required.

## Cardiac Arrest During Coronary Catheterization (ALS 479)

Among adults who have a cardiac arrest in the cardiac catheterization laboratory (P), does any special intervention or change in care (eg, catheterization during CPR, cardiopulmonary bypass, balloon pump, different timing of shocks) (I), compared with standard resuscitation care (eg, CPR, drugs, and shocks according to 2010 treatment algorithm) (C), change survival with favorable neurologic/functional outcome at discharge, 30 days, 60 days, 180 days, and/or 1 year; survival only at discharge, 30 days, 60 days, 180 days, and/or 1 year; ROSC (O)?

## Introduction

We examined the literature for any studies comparing novel treatments during cardiac arrest that occurs during cardiac catheterization in addition to standard ALS approaches (eg, defibrillation) to cardiac arrest. The search was intended to find studies about any changes in sequence of interventions or about routine use of advanced circulatory support techniques.

## Consensus on Science

There were no comparative studies evaluating the survival benefit of mechanical CPR; however, individual noncomparative case series reported variable survival rates.

For the critical outcomes of **survival with favorable neurologic/functional outcome at discharge, 30 days, 60 days, 90 days, 180 days, and 1 year**, and the outcomes of **survival at 30 days, 60 days, 90 days, and 180 days, and 1 year**, no studies were identified.

For the critical outcomes of **survival to discharge and survival to 6 months**, and the important outcome of **ROSC**, very-low-quality evidence (downgraded for very serious imprecision and risk of bias) from 1 observational study<sup>176</sup> compared ECLS with intra-aortic balloon pump and medical therapy for cardiogenic shock during PCI for ST-segment elevation myocardial infarction. There were 21 subjects with cardiac arrest during PCI, and all survivors were in the ECLS group.

## Treatment Recommendation

We suggest the use of ECLS as a rescue treatment when initial therapy is failing for cardiac arrest that occurs during coronary



catheterization (weak recommendation, very-low-quality evidence).

### **Values, Preferences, and Task Force Insights**

In making this weak recommendation, the task force puts a higher value on usual ALS measures such as defibrillation.

We have not made a specific recommendation here regarding the use of automated mechanical chest compressions, because we found no studies that addressed this question. We have suggested previously that automated mechanical chest compression devices are a reasonable alternative to high-quality manual chest compressions in situations where sustained high-quality manual chest compressions are impractical or compromise provider safety. This earlier weak recommendation could, therefore, apply to cardiac arrest during coronary catheterization. ECLS encompasses ECPR. We have already suggested ECPR is a reasonable rescue therapy for selected patients with cardiac arrest when initial conventional CPR is failing in settings where this can be implemented.

### **Knowledge Gaps**

- There is a lack of data about specific interventions to treat cardiac arrest during coronary catheterization.

### **2010 CoSTR Topics Not Reviewed in 2015**

- Anaphylaxis and cardiac arrest
- Asthma and cardiac arrest
- Post-op cardiothoracic surgery cardiac arrest
- Cardiac tamponade
- Noncardiac etiology cardiac arrest
- Benzodiazepine toxicity
- $\beta$ -blocker toxicity
- Calcium channel blocker toxicity
- Carbon monoxide toxicity
- Cocaine toxicity
- Cyanide toxicity
- Tricyclic antidepressant toxicity
- Digoxin toxicity
- Electrolyte disturbances
- Avalanche victims

### **Postresuscitation Care**

Since 2010, there has been a considerable quantity of data published with the domain of postresuscitation care. The ILCOR ALS Task Force prioritized 9 topics for review: (1) oxygen dose after ROSC, (2) post-ROSC ventilation strategy, (3) hemodynamic support, (4) antiarrhythmic drugs, (5) TTM, (6) post-cardiac arrest seizures, (7) glucose control, (8) prognostication, and (9) organ donation.

### **Oxygen Dose After ROSC in Adults (ALS 448)**

Among adults who have ROSC after cardiac arrest in any setting (P), does an inspired oxygen concentration titrated to oxygenation (normal oxygen saturation or partial pressure of oxygen) (I), compared with the use of 100% inspired oxygen concentration (C), change survival to 30 days with good neurologic outcome, survival to hospital discharge with good neurologic outcome, improve survival, survival to 30 days, survival to hospital discharge (O)?

### **Introduction**

Previous preclinical work suggests that hyperoxia may be injurious in the post-cardiac arrest period. However, whether these findings apply to humans remains unclear. This PICO question evaluated whether titration of oxygen in post-cardiac arrest patients alters outcome.

### **Consensus on Science**

#### *30% Versus 100% Inspired Oxygen for 60 Minutes After ROSC*

For the critical outcome of **survival to hospital discharge with favorable neurologic outcome** (CPC 1 or 2), 1 RCT enrolling 32 OHCA (of which 4 excluded) patients (very-low-quality evidence, downgraded for serious risk of bias, indirectness, and imprecision)<sup>177</sup> showed no difference between 30% inspired oxygen for 60 minutes after ROSC versus 100% inspired oxygen for 60 minutes after ROSC (8/14 versus 6/14; unadjusted RR for survival, 1.33; 95% CI, 0.63–2.84).

For the critical outcome of **survival to hospital discharge**, 1 RCT (very-low-quality evidence, downgraded for small numbers, lack of blinding, indirectness, misallocation of patients)<sup>177</sup> showed no difference between 30% inspired oxygen for 60 minutes after ROSC and 100% inspired oxygen for 60 minutes after ROSC (10/14 versus 10/14; unadjusted RR for survival, 1.0; 95% CI, 0.63–1.60).

#### *Hyperoxia Versus Normoxia*

For the critical outcome of **survival to 12 months with favorable neurologic outcome** (CPC 1 or 2), 1 study<sup>178</sup> of very-low-quality evidence (downgraded for very serious risk of bias and indirectness) showed no harmful effect associated with hyperoxia during the first 24 hours of ICU care.

For the critical outcome of **survival to hospital discharge with favorable neurologic outcome** (CPC 1 or 2), 5 low-quality (downgraded as very serious bias and serious inconsistency, indirectness, confounding) observational studies showed conflicting results.<sup>179–183</sup> Two studies showed hyperoxia was worse than normoxia.<sup>179,181</sup>

Three studies reported favorable neurologic outcome as CPC 1 or 2. Very-low-quality evidence (downgraded because of very serious bias and serious inconsistency, indirectness, confounding) from a single-center study of 170 ICU patients treated with therapeutic hypothermia showed that the maximum  $Pao_2$  in the first 24 hours after arrest was associated with a worse outcome (poor neurologic status at hospital discharge; adjusted OR, 1.485; 95% CI, 1.032–2.136).<sup>181</sup> Very-low-quality evidence (downgraded because of very serious bias and serious inconsistency, indirectness, confounding) from a single-center study of 193 ICU patients showed that the first  $Pao_2$  after ROSC was not associated with outcome (hyperoxia adjusted OR for poor neurologic outcome, 1.05; 95% CI, 0.45–2.42).<sup>182</sup> Very-low-quality evidence (downgraded because of very serious bias and serious inconsistency, indirectness, confounding) from a single-center study of 184 ICU patients showed that oxygen exposure over first 24 hours of ventilation was not associated with outcome with unadjusted and adjusted outcomes (effect size cannot be estimated from data).<sup>183</sup>

Two studies used surrogate measures of favorable neurologic outcome. Very-low-quality evidence (downgraded

because of very serious bias and serious inconsistency, indirectness, confounding) from an observational study<sup>179</sup> showed worse independent functional survival at hospital discharge (hyperoxia versus normoxia, 124/1156 versus 245/1171 [29% versus 38%]; unadjusted OR, 0.45; 95% CI, 0.36–0.58). Very-low-quality evidence (downgraded because of very serious bias and serious inconsistency, indirectness, confounding) from an observational study<sup>180</sup> showed no difference in discharge to home (hyperoxia versus normoxia [27 versus 34%]; effect size cannot be estimated from data).

For the critical outcome of **survival to discharge (or survival to 30 days)**, very-low-quality evidence (downgraded because of very serious bias and serious inconsistency, indirectness, confounding) from 7 observational studies showed conflicting results.<sup>179–181,183–186</sup> Four studies showed hyperoxia worse than normoxia.<sup>179,181,183,184</sup>

One study showed a worse outcome with hyperoxia versus normoxia based on the first ICU Pao<sub>2</sub> (in-hospital mortality 63% versus 45%; adjusted OR hyperoxia exposure, 1.8; 95% CI, 1.5–2.2).<sup>179</sup> Another study showed a 100 mmHg increase in Pao<sub>2</sub> was associated with a 24% increase in mortality risk (OR, 1.24; 95% CI, 1.18–1.31).<sup>184</sup> One study showed no association between hyperoxia versus normoxia (based on the worse Pao<sub>2</sub> in first 24 hours on ICU; adjusted OR for hospital mortality, 1.2; 95% CI, 1.0–1.5).<sup>180</sup> A single-center study of 170 ICU patients treated with therapeutic hypothermia documented that the maximum Pao<sub>2</sub> in the first 24 hours after arrest was associated with a worse outcome.<sup>181</sup> Survivors had lower maximum Pao<sub>2</sub> (198 mmHg; interquartile range, 152.5–282) versus nonsurvivors (254 mmHg; interquartile range, 172–363); adjusted OR—higher Pao<sub>2</sub> increased in-hospital mortality (OR, 1.439; 95% CI, 1.028–2.015). In a data linkage study of worse Pao<sub>2</sub> (highest/lowest) in first 24 on ICU, hyperoxia was not associated with outcome (hospital mortality 47% versus 41%; adjusted OR hyperoxia versus normoxia, 1.2; 95% CI, 0.51–2.82).<sup>185</sup> Another study of 122 ICU patients showed no difference between patients with hyperoxia (Pao<sub>2</sub> greater than 300 mmHg in first 24 hours after arrest) and normoxia (22/49 versus 25/70; unadjusted OR, 0.68; 95% CI, 0.32–1.44) for 30-day survival or survival to discharge (20/49 versus 24/70; unadjusted OR, 0.76; 95% CI, 0.36–1.61).<sup>186</sup> In another study of 184 ICU patients, the 36% with severe hyperoxia had a mortality of 54%, and the presence of severe hyperoxia was associated with decreased survival in both unadjusted and adjusted analysis (adjusted OR for survival, 0.83 per hour exposure; 95% CI, 0.69–0.99).<sup>183</sup>

For the important outcome of **survival to ICU discharge**, very-low-quality evidence (downgraded because of very serious bias, serious indirectness, confounding) from 2 observational studies showed no harm from hyperoxia.<sup>185,186</sup> In a data linkage study of worse Pao<sub>2</sub> (highest/lowest) in first 24 on ICU, hyperoxia was not associated with outcome (ICU mortality 35% versus 32% for hyperoxia versus normoxia; unadjusted OR, 1.16; 95% CI, 0.56–2.40).<sup>185</sup> One observational study enrolling 122 ICU admissions patients showed no difference in survival to 30 days between patients with hyperoxia (Pao<sub>2</sub> greater than 300 mmHg in first 24 hours after arrest) and normoxia (ICU discharge 53% versus 46%; adjusted OR, 0.75; 95% CI, 0.36–1.55).<sup>186</sup>

### *Hypoxia Versus Normoxia*

For the critical outcome of **survival to discharge (or survival to 30 days)**, very-low-quality evidence (downgraded because of very serious bias and serious indirectness, confounding) from 2 of 3 observational studies showed worse outcomes with hypoxia.<sup>179,180,185</sup> One study showed a worse outcome with hypoxia versus normoxia based on the first ICU Pao<sub>2</sub> (57% versus 45%; adjusted OR hypoxia exposure, 1.3; 95% CI, 1.1–1.5).<sup>179</sup> Another study documented that hypoxia versus normoxia (based on the worse Pao<sub>2</sub> in first 24 hours on ICU) was associated with higher hospital mortality of 60% versus 47% (OR, 1.2; 95% CI, 1.1–1.4) but no difference in discharge to home (hypoxia/poor oxygen exchange versus normoxia 26% versus 24%).<sup>180</sup> In a data linkage study of worse Pao<sub>2</sub> (highest/lowest) in first 24 hours on ICU, there was no difference in outcome between hypoxia and normoxia (for in-hospital mortality, 51% versus 41%; adjusted OR hypoxia versus normoxia, 0.93; 95% CI, 0.47–1.87).<sup>185</sup>

For the important outcome of **survival to ICU discharge**, very-low-quality evidence (downgraded because of very serious bias, serious indirectness, and confounding) from 1 observational study showed hypoxia was associated with a worse outcome.<sup>185</sup> Worse Pao<sub>2</sub> (highest/lowest) in first 24 hours in ICU was associated with a worse unadjusted outcome (ICU mortality 49% versus 32% for hypoxia versus normoxia; unadjusted OR, 2.15; 95% CI, 1.23–3.77; RR, 0.74; 95% CI, 0.56–0.96).

### *Treatment Recommendations*

We recommend avoiding hypoxia in adults with ROSC after cardiac arrest in any setting (strong recommendation, very-low-quality evidence).

We suggest avoiding hyperoxia in adults with ROSC after cardiac arrest in any setting (weak recommendation, very-low-quality evidence).

We suggest the use of 100% inspired oxygen until the arterial oxygen saturation or the partial pressure of arterial oxygen can be measured reliably in adults with ROSC after cardiac arrest in any setting (weak recommendation, very-low-quality evidence).

### *Values, Preferences, and Task Force Insights*

In making these recommendations, we think, despite the very-low-quality evidence, there is likely to be far greater actual harm from hypoxia and, therefore, make a strong recommendation that hypoxia should be avoided. The evidence for harm associated with hyperoxia is of very low quality and inconsistent, hence the weak recommendation.

### *Knowledge Gaps*

- There is a lack of clinical trials evaluating titration of oxygen after ROSC.
- Observational data vary considerably on definitions of hyperoxia and the optimal timing and mechanisms for measurement (arterial oxygenation versus oxygen saturation).
- Future studies are necessary to define the optimal approach to titration of oxygen in post-cardiac arrest patients taking into account measurement as well as timing/duration.

**Postresuscitation Ventilation Strategy (ALS 571)**

Among adults with ROSC after cardiac arrest in any setting (P), does ventilation to a specific  $\text{Paco}_2$  goal (I), compared with no specific strategy or a different  $\text{Paco}_2$  goal (C), change survival at discharge, 30 days, 60 days, 180 days, and/or 1 year; survival with favorable neurologic/functional outcome at discharge, 30 days, 60 days, 180 days, and/or 1 year (O)?

**Introduction**

Post-cardiac arrest patients often have pulmonary injury and/or aspiration, and also have the added concern of ischemia-reperfusion injury to the brain. Thus, the post-cardiac arrest ventilator management may need to consider both brain and lung injury when determining specific strategies for mechanical ventilation. This PICO question addressed whether mechanical ventilation after cardiac arrest to achieve any specific  $\text{Paco}_2$  goal was superior to any other  $\text{Paco}_2$  goal.

**Consensus on Science**

No studies have specifically randomized patients to ventilation to a specific  $\text{Paco}_2$  goal.

**Hypocapnia**

For the critical outcome of **neurologically favorable survival**, 2 very-low-quality cohort studies<sup>182,187</sup> with a total of 8376 patients (downgraded for very serious concerns about risk of bias and imprecision) showed hypocapnia (less than 3.0 kPa and less than 4.7 kPa, respectively) was associated with a worse outcome. For the critical outcome of **death (or failure to be discharged home)**, 1 very-low-quality cohort study<sup>188</sup> of 6881 patients (downgraded for very serious concerns about risk of bias and imprecision) showed hypocapnia (less than 4.7 kPa) was associated with a worse outcome.

**Hypercapnia**

For the critical outcome of **neurologically favorable survival**, 3 observational cohort studies showed inconsistent associations between hypercapnia and outcome (very-low-quality evidence, downgraded for very serious concerns about risk of bias, imprecision, and inconsistency). One study<sup>182</sup> with a total of 123 patients showed worse outcome in patients ventilated to hypercapnia ( $\text{Paco}_2$  greater than 6.7 kPa). One study<sup>187</sup> with a total of 850 patients showed no difference in outcome for patients ventilated to hypercapnia ( $\text{Paco}_2$  greater than 6.0 kPa). One study<sup>178</sup> with a total of 409 patients showed better outcome for patients ventilated to hypercapnia ( $\text{Paco}_2$  5.1–10.1 kPa).

For the critical outcome of **death (or failure to be discharged home)**, 2 cohort studies showed uncertain associations with outcome (downgraded for very serious concerns about risk of bias and imprecision). One study<sup>188</sup> with a total of 16542 patients, showed no difference in outcome for patients ventilated to hypercapnia ( $\text{Paco}_2$  greater than 6.0 kPa). One study<sup>187</sup> with a total of 850 patients showed a higher mean  $\text{Paco}_2$  in survivors.

**Treatment Recommendation**

We suggest maintaining  $\text{Paco}_2$  within a normal physiological range as part of a post-ROSC bundle of care (weak recommendation, very-low-quality evidence).

**Values, Preferences, and Task Force Insights**

In making this recommendation, the task force did not find good evidence to suggest or recommend either hypercarbia or hypocarbia. In the absence of evidence to that end, combined with a potential suggestion of harm, we suggest maintaining normocarbia. Many physiological considerations may influence selection of  $\text{Paco}_2$  goals for individual patients.

**Knowledge Gaps**

- There are no randomized prospective controlled trials evaluating different  $\text{Paco}_2$  goals in post-cardiac arrest patients.
- Evaluation of optimal  $\text{Paco}_2$  goals may need to be determined in populations both with and without lung injury.

**Postresuscitation Hemodynamic Support (ALS 570)**

Among adults with ROSC after cardiac arrest in any setting (P), does titration of therapy to achieve a specific hemodynamic goal (eg, MAP greater than 65 mm Hg) (I), compared with no hemodynamic goal (C), change survival with favorable neurologic/functional outcome at discharge, 30 days, 60 days, 180 days, and/or 1 year; survival at discharge, 30 days, 60 days, 180 days, and/or 1 year (O)?

**Introduction**

In the post-cardiac arrest period, patients often have persistent tissue hypoperfusion/hemodynamic instability. The optimal approach to resuscitation of patients after cardiac arrest remains unknown.

**Consensus on Science**

There are no RCTs addressing hemodynamic goals after resuscitation.

**Titration of Therapy to Achieve a Specific Hemodynamic Goal (eg, MAP of More Than 65 mm Hg) Compared With No Hemodynamic Goal**

For the critical outcome of **survival with favorable neurologic/functional outcome**, very-low-quality evidence (downgraded for risk of bias and publication bias) from 1 multicenter retrospective nonintervention study including 8736 subjects showed post-cardiac arrest SBP less than 90 mm Hg was associated with higher mortality (65% versus 37%) and diminished discharge functional status in survivors (49% versus 38%).<sup>189</sup>

For the critical outcome of **survival**, very-low-quality evidence (downgraded for risks of bias and publication bias) from 2 retrospective single-center studies including 2282 patients showed reduced survival for patients with post-ROSC SBP less than 90 mm Hg<sup>190</sup> and less than 100 mm Hg.<sup>191</sup>

**Bundle of Therapies With a Specific Blood Pressure Target Compared With No Bundle**

For the critical outcome of **survival with favorable neurologic/functional outcome**, we found very-low-quality evidence (downgraded for risks of bias and publication bias) from 7 studies that included 813 subjects. One pre-/post-study of early goal-directed therapy of 36 patients with a MAP target greater than 80 mm Hg showed no difference in mortality or neurologic outcome at hospital discharge.<sup>192</sup>



One prospective observational study of 118 patients using historic controls showed that aiming for MAP greater than 65 mmHg increased survival to hospital discharge with a favorable neurologic outcome at 1 year in 34 of 61 (56%) versus 15 of 58 (26%) in the control period (OR, 3.61; CI, 1.66–7.84;  $P=0.001$ ).<sup>193</sup> One cohort study of 148 patients showed no difference in neurologic outcome at hospital discharge when a MAP less than 75 mmHg was a threshold for intervention.<sup>194</sup> One retrospective study of 136 patients identified groups with MAP greater than 100 mmHg or less than 100 mmHg after ROSC. Good neurologic recovery was independently and directly related to MAP measured during 2 hours after ROSC ( $r^2=0.26$ ).<sup>195</sup> One before-and-after observational study of a care bundle, including 55 subjects aiming for a MAP greater than 65 mmHg within 6 hours, showed no change of in-hospital mortality (55.2% [bundle] versus 69.2% [prebundle]) or CPC 1 or 2 (31% versus 12%).<sup>196</sup> In 1 prospective single-center observational study of 151 patients receiving a bundle of therapies where 44 (29%) experienced good neurologic outcome, a time-weighted average MAP threshold greater than 70 mmHg had the strongest association with good neurologic outcome (OR, 4.11; 95% CI, 1.34–12.66;  $P=0.014$ ).<sup>197</sup> One retrospective study of bundle therapy targeting a MAP greater than 80 mmHg in 168 patients showed survivors had higher MAPs at 1 hour (96 versus 84 mmHg), 6 hours (96 versus 90 mmHg;  $P=0.014$ ), and 24 hours (86 versus 78 mmHg) when compared with nonsurvivors. Increased requirement for vasoactive drugs was associated with mortality at all time points. Among those requiring vasoactive drugs, survivors had higher MAPs than nonsurvivors at 1 hour (97 versus 82 mmHg) and 6 hours (94 versus 87 mmHg).<sup>198</sup>

For the critical outcome of **survival**, we found very-low-quality evidence (downgraded for risks of bias and publication bias) from 2 studies including 91 patients that assessed the impact of postresuscitation goal-directed/bundles of care (including blood pressure targets) on survival. One pre-/post-study of early goal-directed therapy of 36 patients including a MAP target greater than 80 mmHg showed no difference in mortality at hospital discharge.<sup>192</sup> One pre-/postobservational study of a care bundle including 55 patients aiming for a MAP greater than 65 mmHg within 6 hours resulted in an in-hospital mortality of 55.2% (bundle) versus 69.2% (prebundle) ( $P=0.29$ ; RR, 0.80; 95% CI, 0.53–1.21).<sup>196</sup>

### Treatment Recommendations

We suggest hemodynamic goals (eg, MAP, SBP) be considered during postresuscitation care and as part of any bundle of postresuscitation interventions (weak recommendation, low-quality evidence).

There is insufficient evidence to recommend specific hemodynamic goals; such goals should be considered on an individual patient basis and are likely to be influenced by post-cardiac arrest status and pre-existing comorbidities (weak recommendation, low-quality evidence).

### Values, Preferences, and Task Force Insights

In making these recommendations, we place a higher value on the recognition that while hemodynamic goals are likely important to optimize outcome, specific targets remain

unknown and likely vary depending on individual physiology and comorbid status.

### Knowledge Gaps

- There are no prospective, randomized trials on specific hemodynamic targets or goals with respect to outcome.
- Comorbidities and the complexities of individual-based physiology should ideally be taken into account in future investigations into hemodynamic targets/goals.
- Future studies of measurement of actual blood flow and tissue perfusion, particularly cerebral perfusion, and the role of noninvasive technology are desirable.

### Postresuscitation Antiarrhythmic Drugs (ALS 493)

Among adults with ROSC after cardiac arrest in any setting (P), do prophylactic antiarrhythmic drugs given immediately after ROSC (I), compared with not giving antiarrhythmic drugs (C), change survival with favorable neurologic/functional outcome at discharge, 30 days, 60 days, 180 days, and/or 1 year; development of cardiac arrest; survival only at discharge, 30 days, 60 days, 180 days, and/or 1 year; recurrence of VF; incidence of arrhythmias (O)?

#### Introduction

After ROSC from cardiac arrest, the decision to initiate or continue therapy with antiarrhythmic medications remains uncertain. Literature was found for both  $\beta$ -blocking medications and lidocaine. We identified no studies of magnesium, amiodarone, procainamide, bretylium, or nifekalant.

#### Consensus on Science

##### $\beta$ -Blockers (I) Versus No $\beta$ -Blockers (C)

For the critical outcome of **survival at 6 months**, we have identified very-low-quality evidence (downgraded for serious risk of bias, indirectness, and imprecision) from 1 observational study of 98 patients resuscitated from OHCA showing a higher rate of survival with administration of  $\beta$ -blockers (metoprolol or bisoprolol) for 72 hours after ROSC compared with no drug (55.7% versus 21.1%;  $P<0.001$ ; RR, 2.65; 95% CI, 1.08–6.46) and after adjusting for the Utstein variables (specific OR data not available;  $P=0.002$ ).<sup>199</sup>

##### Lidocaine (I) Versus No Lidocaine (C)

For the important outcome of **recurrence of VF**, we identified very-low-quality evidence (downgraded for serious risk of bias and indirectness) from 1 observational study of 1721 patients resuscitated from OHCA showing a lower adjusted (adjusted by the Utstein variables and matched by propensity scores) rate of recurrence of VF following lidocaine bolus and/or continuous infusion immediately after ROSC compared with no drug (OR, 0.34; 95% CI, 0.26–0.44).<sup>200</sup>

For the critical outcome of **survival to hospital discharge**, we identified very-low-quality evidence (downgraded for serious risk of bias and indirectness) from 1 observational study of 1721 patients resuscitated from OHCA showing a higher rate of survival to hospital discharge after adjusting for the Utstein variables (OR, 1.49; 95% CI, 1.15–1.95) but no difference after propensity-matching analysis (OR, not reported).<sup>200</sup>

### Treatment Recommendation

We make no recommendation about the routine prophylactic use of antiarrhythmic drugs post after ROSC (GRADE used for evidence evaluation and synthesis only, very low confidence in effect estimate).

### Values, Preferences, and Task Force Insights

The available data were too limited to have any confidence in any effect, and, therefore, no recommendation is made. We also place value on avoiding known side effects of medications when the treatment effect was unproven or unknown. The studies evaluated were all observational, and no causal relation could be determined. Moreover, they were performed before changes in current practice (ie, currently amiodarone is used during cardiac arrest more than lidocaine).

### Knowledge Gaps

- There are no randomized trials for any antiarrhythmic drug in the post-cardiac arrest period.
- Patients resuscitated from VF/pVT who have received an antiarrhythmic medication during the cardiac arrest period are a specific population of interest.

### Targeted Temperature Management (Induced Hypothermia)

Post-cardiac arrest ischemia-reperfusion injury to the brain may be attenuated by induced hypothermia. Several PICO questions are addressed in this section: TTM for (a) OHCA with shockable rhythm, (b) OHCA with nonshockable rhythms, and (c) IHCA with any rhythm; the optimal target temperature; the duration of TTM; and the timing of TTM.

### Targeted Temperature Management (ALS 790)

Among patients with ROSC after cardiac arrest in any setting (P), does inducing mild hypothermia (target temperature 32°C–34°C) (I), compared with normothermia (C), change survival with favorable neurologic/functional outcome at discharge, 30 days, 60 days, 180 days, and/or 1 year; survival only at discharge, 30 days, 60 days, 180 days, and/or 1 year (O)?

### Introduction

This PICO review was divided into 2 questions. The first question evaluated whether induced hypothermia should be initiated for postarrest patients. Evidence was evaluated separately for OHCA with shockable rhythms, OHCA with nonshockable rhythms, and IHCA (all rhythms). The second question evaluated the optimal target temperature for postarrest patients.

### Consensus on Science

#### OHCA Arrest With a Shockable Rhythm

For the critical outcome of **survival with favorable neurologic outcome**, we have identified low-quality evidence (downgraded for risk of bias and imprecision) from 1 RCT<sup>201</sup> and 1 quasi-randomized trial<sup>202</sup> enrolling 275 and 77 patients, showing a benefit in patients with OHCA with VF or pVT as an initial rhythm. In these studies, cooling to 32°C to 34°C compared with no temperature management was associated

with good neurologic outcome at 6 months (RR, 1.4; 95% CI, 1.08–1.81) and survival to hospital discharge (OR, 2.65; 95% CI, 1.02–6.88). For the critical outcome of **survival**, 1 study<sup>201</sup> showed benefit in patients treated with induced hypothermia (RR for 180-day mortality, 0.74; 95% CI, 0.58–0.95), while another study found no significant difference (51% versus 68% hospital mortality; RR, 0.76; 95% CI, 0.52–1.10).<sup>202</sup>

#### OHCA With Nonshockable Rhythms

We found no RCTs comparing mild induced hypothermia (32°C–34°C) to no temperature management in patients with OHCA with pulseless electrical activity or asystole (ie, nonshockable) as the initial rhythm.

For the critical outcome of **survival with favorable neurologic outcome**, we found 3 cohort studies including a total of 1034 patients, providing overall very-low-quality evidence (downgraded for risk of bias and imprecision) for no difference in poor neurologic outcome in patients with nonshockable OHCA (adjusted pooled OR, 0.90; 95% CI, 0.45–1.82).<sup>203–205</sup>

One additional retrospective study that used a large registry, including 1830 patients, provided very-low-quality evidence (downgraded for risk of bias and imprecision) for an increase in poor neurologic outcome in patients with nonshockable OHCA (adjusted OR, 1.44; 95% CI, 1.039–2.006).<sup>206</sup> These data were not pooled with the above studies due to the lack of temperature data and limited patient information available.

For the critical outcome of **survival**, we found very-low-quality evidence (downgraded for risk of bias and imprecision) of a benefit in mortality at 6 months (OR, 0.56; 95% CI, 0.34–0.93) from one of these studies.<sup>204</sup>

#### IHCA

We found no RCTs comparing mild induced hypothermia (32°C–34°C) to no temperature management in patients with IHCA. For the critical outcome of **survival to hospital discharge**, we found very-low-quality evidence (downgraded for risk of bias and imprecision) in 1 retrospective cohort study including 8316 patients that showed no benefit in patients with IHCA of any initial rhythm who were treated with TTM versus no active temperature management (OR, 0.9; 95% CI, 0.65–1.23).<sup>207</sup>

For the critical outcome of **neurologically favorable survival**, we found very-low-quality evidence (downgraded for risk of bias and imprecision) from the same observational study showing no benefit (OR, 0.93; 95% CI, 0.65–1.32). Although we found numerous before-and-after studies on the implementation of temperature management, these data are extremely difficult to interpret in light of other changes in post-cardiac arrest care that accompanied implementation, making it impossible to isolate the effect of temperature on outcomes after cardiac arrest. For this reason, we excluded all before-and-after studies. Other observational studies with concurrent controls also represent low-quality evidence due to residual confounding and other factors. We, therefore, did not include these in the consensus on science, except for specific patient populations lacking higher quality (ie, RCT) evidence.

#### Target Temperature

For the critical outcomes of **survival and survival with favorable neurologic outcome**, we found moderate-quality

evidence (downgraded for imprecision) from 1 RCT including 939 patients. This study compared cooling to 33°C compared with tight temperature control at 36°C in adult patients with OHCA of any initial rhythm except unwitnessed asystole, and found no benefit (HR for mortality at end of trial, 1.06; 95% CI, 0.89–1.28; RR for death or poor neurologic outcome at 6 months, 1.02; 95% CI, 0.88–1.16).<sup>208</sup>

For the critical outcome of **survival with favorable neurologic outcome**, we found low-quality evidence (downgraded for risk of bias and imprecision) in 1 additional small pilot RCT enrolling 36 patients comparing 32°C with 34°C in patients with OHCA VF/pVT or asystole. This study found no benefit (neurologically intact survival 44.4% versus 11.1%;  $P=0.12$ ), although with only 36 patients it was underpowered.

### Treatment Recommendations

We recommend selecting and maintaining a constant target temperature between 32°C and 36°C for those patients in whom temperature control is used (strong recommendation, moderate-quality evidence). Whether certain subpopulations of cardiac arrest patients may benefit from lower (32°C–34°C) or higher (36°C) temperatures remains unknown, and further research may help elucidate this.

We recommend TTM as opposed to no TTM for adults with OHCA with an initial shockable rhythm who remain unresponsive after ROSC (strong recommendation, low-quality evidence).

We suggest TTM as opposed to no TTM for adults with OHCA with an initial nonshockable rhythm who remain unresponsive after ROSC (weak recommendation, very-low-quality evidence).

We suggest TTM as opposed to no TTM for adults with IHCA with any initial rhythm who remain unresponsive after ROSC (weak recommendation, very-low-quality evidence).

### Values, Preferences, and Task Force Insights

In making these recommendations, we place a higher value on the potential for increased survival with good neurologic outcome as compared with the possible risks (which appear to be minimal) and the cost of TTM. We emphasize that the mortality after cardiac arrest is high and the treatment options are limited. Although the evidence for TTM compared with no temperature management is of low quality, it is the only post-ROSC intervention that has been found to improve survival with good neurologic outcome. We have, therefore, made our recommendation strong in spite of the low-quality evidence.

### Knowledge Gaps

- There is no high-quality evidence to support or refute the use of TTM in adults with OHCA and nonshockable initial rhythm, or adults with IHCA and any initial rhythm.
- There is no evidence to support or refute specific temperature targets tailored to individual patients based on post-cardiac arrest injury severity.
- Studies including more detailed neurocognitive evaluations to determine outcome in a more granular fashion are also needed.

### Duration of TTM (ALS 791)

In patients with ROSC after cardiac arrest in any setting (P), does induction and maintenance of hypothermia for any duration other than 24 hours (I), compared with induction and maintenance of hypothermia for a duration of 24 hours (C), change survival with favorable neurologic/functional outcome at discharge, 30 days, 60 days, 180 days, and/or 1 year; survival only at discharge, 30 days, 60 days, 180 days, and/or 1 year (O)?

#### Introduction

The hypothermia trials published in 2002 used 12 hours and 24 hours of cooling,<sup>201,202</sup> which was adopted in subsequent guidelines.<sup>209</sup> The optimal duration for TTM remains unknown.

#### Consensus on Science

We found no human trials comparing different durations of TTM after cardiac arrest.

For the critical outcome of **favorable neurologic outcome**, very-low-quality evidence (downgraded for risk of bias and imprecision) from 2 observational trials found no difference in duration of hypothermia<sup>210</sup> and no difference in mortality or poor neurologic outcome with 24 hours compared with 72 hours of hypothermia.<sup>211</sup> Previous trials treated patients with 12 to 28 hours of TTM.<sup>201,202,208</sup> One trial provided strict normothermia (less than 37.5°C) after hypothermia until 72 hours after ROSC.<sup>208</sup>

#### Treatment Recommendations

We suggest that if TTM is used, duration should be at least 24 hours, as done in the 2 largest previous RCTs<sup>201,208</sup> (weak recommendation, very-low-quality evidence).

#### Values, Preferences, and Task Force Insights

In making this recommendation, we place a high value on not changing current clinical practice, which most commonly is a TTM duration of 24 hours. We further note that the 2 largest trials related to TTM both used at least 24 hours, one of which found an outcome benefit when compared with not using TTM.

#### Knowledge Gaps

- There is no direct evidence to support or refute any specific duration of TTM.
- Controlled, randomized, human trials to evaluate duration of TTM are needed.

### Timing of Induced Hypothermia (ALS 802)

Among patients with return of pulses after cardiac arrest in any setting (P), does induction of hypothermia before some time point (eg, 1 hour after ROSC or before hospital arrival) (I), compared with induction of hypothermia after that time point (C), change survival with favorable neurologic/functional outcome at discharge, 30 days, 60 days, 180 days, and/or 1 year; survival only at discharge, 30 days, 60 days, 180 days, and/or 1 year (O)?

#### Introduction

Prior recommendations suggest that cooling should be initiated as soon as possible after ROSC, but this recommendation



was based only on preclinical data and rational conjecture.<sup>209</sup> This question addressed whether early cooling was superior to delayed cooling. Early cooling was defined as prehospital cooling before hospital arrival. Because multiple trials were available, only RCTs were included.

### Consensus on Science

Five RCTs<sup>212–216</sup> used cold IV fluids after ROSC to induce hypothermia, 1 trial used cold IV fluid during resuscitation,<sup>217</sup> and 1 trial used intra-arrest intranasal cooling.<sup>218</sup> The volume of cold fluid ranged from 20 to 30 mL/kg and up to 2 L, though some patients did not receive the full amount before hospital arrival. One small feasibility trial was not included.<sup>219</sup> All 7 trials suffered from the unavoidable lack of blinding of the clinical team, and 3 also failed to blind the outcomes assessors.

For the critical outcome of **favorable neurologic outcome**, 5 trials with a total of 1867 subjects with OHCA<sup>213–216,218</sup> provided overall moderate-quality evidence (downgraded for risk of bias), showing that neurologic outcomes did not differ after initiation of induced hypothermia in the prehospital environment compared with later initiation (RR, 1.00; 95% CI, 0.95–1.06).

For the critical outcome of **mortality**, 7 trials with a total of 2237 subjects provided moderate-quality evidence (downgraded for risk of bias), showing no overall difference in mortality for patients treated with prehospital cooling (RR, 0.98; 95% CI, 0.92–1.04) compared with those who did not receive prehospital cooling. No individual trial found an effect on either poor neurologic outcome or mortality.

For the outcome of **rearrest**, 4 RCTs provided low-quality evidence (downgraded for risk of bias and inconsistency) for an increased risk among subjects who received prehospital induced hypothermia (RR, 1.22; 95% CI, 1.01–1.46).<sup>212,213,215,216</sup> This result was driven by data from the largest trial.<sup>216</sup>

For the outcome of **pulmonary edema**, 3 trials reported no pulmonary edema in any group. Two small pilot trials<sup>212,217</sup> found no difference between groups, and 1 trial showed an increase in pulmonary edema in patients who received prehospital cooling (RR, 1.34; 95% CI, 1.15–1.57).<sup>216</sup> These trials provided overall low-quality evidence (downgraded for risk of bias and inconsistency).

### Treatment Recommendations

We recommend against routine use of prehospital cooling with rapid infusion of large volumes of cold IV fluid immediately after ROSC (strong recommendation, moderate-quality evidence).

### Values, Preferences, and Task Force Insights

In making this recommendation, we place high value on not recommending an intervention with no proven benefit despite a large number of patients studied. We further note that the meta-analysis driven by the results from the largest study found also noted an increased risk of rearrest with prehospital induction of mild hypothermia using rapid infusion of cold IV fluid.<sup>216</sup> This recommendation is specific to the prehospital setting after ROSC, and we acknowledge that cold IV fluid might still be used in patients who have been further evaluated or in other settings.

### Knowledge Gaps

- Early cooling strategies, other than rapid infusion of large volumes of cold IV fluid, and cooling during CPR in the prehospital setting have not been studied adequately.
- Whether certain patient populations (eg, patients for whom transport time to a hospital is longer than average) might benefit from early cooling strategies remains unknown.

### Prevention of Fever After Cardiac Arrest (ALS 879)

Among adults with ROSC after cardiac arrest in any setting (P), does prevention of fever to maintain strict normothermia (I), compared with no fever control (C), change survival with favorable neurologic/functional outcome at discharge, 30 days, 60 days, 180 days, and/or 1 year; survival only at discharge, 30 days, 60 days, 180 days, and/or 1 year (O)?

### Introduction

Fever is associated with poor outcome in many critical illnesses with neurologic injury. Increased temperature may aggravate ischemia-reperfusion injury and neuronal damage through increased metabolic activity. We examined whether fever prevention improves outcomes in patients not receiving TTM and in patients after the use of TTM.

No interventional or observational studies were identified addressing whether fever prevention (or treatment) after cardiac arrest improves outcome. We, therefore, included studies that examined the association between fever and outcomes.

### Consensus on Science

#### Fever After ROSC Without TTM

For the critical outcomes of survival with **good neurologic/functional outcome and/or survival only**, we found very-low-quality evidence from 5 observational studies (downgraded for risk of bias and indirectness) that fever after ROSC is associated with poor outcome when TTM is not used.<sup>221–225</sup>

#### Fever After TTM

For the critical outcomes of **survival with good neurologic/functional outcome and/or survival only**, we found very-low-quality evidence from 6 observational studies (n=856) (downgraded for risk of bias and indirectness) that fever after TTM is not associated with outcome.<sup>225–230</sup> For the same critical outcomes, we also found very-low-quality evidence from 2 observational studies (n=411) (downgraded for risk of bias, inconsistency, and indirectness) that fever after TTM is associated with poor outcome.<sup>231,232</sup>

### Treatment Recommendation

We suggest prevention and treatment of fever in persistently comatose adults after completion of TTM between 32°C and 36°C (weak recommendation, very-low-quality evidence).

### Values, Preferences, and Task Force Insights

In making this recommendation, we recognize that TTM always should be used in comatose patients after cardiac arrest, and that fever will not occur during this time. Thus, fever management is primarily a concern after TTM has been completed. Despite substantial limitations of the included studies, expert opinion within the task force combined with

the fact that fever prevention is common practice for other neurologic injuries in the ICU and the relative low risk of harm associated with fever prevention prompted us to recommend in favor of fever prevention.

### Knowledge Gaps

- In the absence of RCTs, whether the prevention or treatment of fever after cardiac arrest is beneficial remains unclear.
- It is unclear how long fever prevention is necessary, and what technique (eg, external, internal, pharmacologic) is best.
- Data to date cannot distinguish whether fever causes increased neurologic injury or severe neurologic injury causes temperature dysregulation.

### Postresuscitation Seizure Prophylaxis (ALS 431)

Among adults with ROSC after cardiac arrest in any setting (P), does seizure prophylaxis (I), compared with no prophylaxis (C), reduce the incidence of seizures, or improve survival with favorable neurologic/functional outcome at discharge, 30 days, 60 days, 180 days, and/or 1 year; survival only at discharge, 30 days, 60 days, 180 days, and/or 1 year (O)?

#### Introduction

Seizures, and particularly status epilepticus (SE), are associated with poor outcomes in comatose post-cardiac arrest patients. While seizure and SE can be the result of severe brain injury caused by cardiac arrest, these disorders also have the potential to exacerbate brain injury caused by cardiac arrest. We examined whether seizure prophylaxis or effective seizure management improve outcomes of post-cardiac arrest patients.

#### Consensus on Science

For the critical outcome of **survival with favorable neurologic/functional outcome**, moderate-quality evidence (downgraded for indirectness) from 2 prospective double-blinded randomized clinical trials involving a total of 312 subjects<sup>233,234</sup> and 1 nonrandomized prospective clinical trial that used historic controls with 107 subjects<sup>235</sup> detected no benefit of seizure prophylaxis.

In 1 block randomized trial,<sup>234</sup> OHCA patients with ROSC received either placebo, diazepam, magnesium sulfate, or diazepam plus magnesium sulfate. The percentage of patients independent at 3 months was 25.3% (19/75) in the placebo group, 34.7% (26/75) in the magnesium group, 17.3% (13/75) in the diazepam group, and 17.3% (13/75) in the diazepam plus magnesium group (for magnesium: RR, 1.22; 95% CI, 0.81–1.83). After adjusting for baseline imbalances, outcomes did not differ between groups. In a trial of thiopental versus placebo within 1 hour of ROSC,<sup>233</sup> 1-year survival with good cerebral function was 15% (20/131) in the placebo group and 18% (24/131) in the thiopental group (RR, 1.20; 95% CI, 0.70–2.06). After multivariate adjustment, groups did not differ (OR, 1.18; 95% CI, 0.76–1.84). A nonrandomized clinical trial<sup>235</sup> showed no benefit of barbiturate therapy in comatose post-cardiac arrest patients using a combination of thiopental and phenobarbital when compared with historic controls. In

this study, survival to hospital discharge with favorable neurologic outcome was 38% (20/53) in the barbiturate group and 26% (14/54) in the historic control group (ARR, 11.8%; 95% CI, –5.8 to 28.5; or 118 more patients/1000; 95% CI, 58 fewer to 285 more patients/1000). One case series showed that 9 of 10 patients with anesthesia-associated cardiac arrest survived with good neurologic outcome when single-dose phenytoin was administered early after ROSC.<sup>236</sup>

For the important outcome of **seizure prevention**, we identified low-quality evidence downgraded for indirectness from 2 prospective double-blinded RCTs<sup>233,234</sup> showing no benefit of seizure prophylaxis. In 1 trial of thiopental treatment,<sup>233</sup> 21% (28/131) of control subjects and 13% (17/131) of thiopental-treated subjects had seizures (ARR, –8.4%; 95% CI, –17.5 to 0.8; 84 fewer patients/1000; 95% CI, 175 fewer to 8 more patients/1000). The incidence of seizures in a second trial<sup>234</sup> was 11.9% in all treatment groups (double placebo, magnesium plus placebo, diazepam plus placebo, and diazepam plus magnesium).

#### Treatment Recommendation

We suggest against routine seizure prophylaxis in post-cardiac arrest patients (weak recommendation, very-low-quality evidence).

#### Values, Preferences, and Task Force Insights

In making this recommendation, the task force acknowledged the lack of confidence in a treatment effect on the critical outcome of survival with good neurologic function treatment. The task force also considered that seizure prophylaxis in other forms of acute brain injuries is not associated with improved outcomes, and that most drugs have significant side effects.

#### Knowledge Gaps

- Standardized definitions for diagnosing seizures in comatose post-cardiac arrest patients have not been used.
- The utility of continuous electroencephalogram (EEG) versus intermittent EEG monitoring versus no EEG in the diagnosis and treatment of seizures in comatose post-cardiac arrest patients remains controversial due to resource utilization and lack of evidence for improved outcomes.
- There are no RCTs designed to evaluate the impact of seizure prophylaxis after ROSC on incidence of seizures and neurologic outcome.
- There are inadequate data regarding the timing, duration, dosing, and choice of antiepileptic drugs for seizure prophylaxis in comatose post-cardiac arrest patients.

### Seizure Treatment (ALS 868)

Among adults with ROSC after cardiac arrest in any setting (P), does effective seizure treatment (I), compared with no seizure control (C), change survival with favorable neurologic/functional outcome at discharge, 30 days, 60 days, 180 days, and/or 1 year; survival only at discharge, 30 days, 60 days, 180 days, and/or 1 year (O)?

#### Consensus on Science

There are no RCTs addressing this question.

For the critical outcome of **survival with favorable neurologic outcome at discharge, 30 days, 60 days, 180 days, and/or 1 year**, very-low-quality evidence (downgraded for lack of concurrent comparative data) from 3 case series<sup>237–239</sup> showed only 1/47 post-cardiac arrest patient treated for seizures or SE survived with good neurologic function. The antiepileptic drugs used were widely variable (phenytoin, levetiracetam, sodium valproate, clonazepam, propofol, and midazolam); included general anesthetics; and the drug, dose, and timing of therapy were not consistently reported. In these reports, no post-cardiac arrest patients with seizures were left untreated, providing no insight into the impact of antiepileptic drug therapy on survival or neurologic outcome. In 1 study, effective seizure control was achieved in 4/5 patients treated for seizures, and 0/5 survived with good neurologic function.<sup>239</sup> In 1 study, effective seizure control was achieved in 0/24 patients with SE, and 1/24 patients survived with good neurologic function.<sup>237</sup>

### **Treatment Recommendation**

We recommend the treatment of seizures in post-cardiac arrest patients (strong recommendation, very-low-quality evidence).

### **Values, Preferences, and Task Force Insights**

In making this recommendation, we acknowledge very low confidence in the estimated treatment effect. However, ongoing seizures have the potential to worsen brain injury, and treatment of recurrent seizures and SE is the standard of care in other patient populations.

### **Knowledge Gaps**

- Standardized definitions for diagnosing seizures in comatose post-cardiac arrest patients have not been used.
- The utility of continuous EEG versus intermittent EEG monitoring versus no EEG in the diagnosis and treatment of seizures in comatose post-cardiac arrest patients remains controversial due to resource utilization and lack of evidence for improved outcomes.
- There are no RCTs designed to evaluate the impact of seizure prophylaxis after ROSC on incidence of seizures and neurologic outcome.
- There are inadequate data regarding the timing, duration, dosing, and choice of antiepileptic drugs for seizure prophylaxis in comatose post-cardiac arrest patients.
- The threshold for treating epileptiform activity other than convulsive seizures (eg, generalized epileptiform discharges) is poorly defined.

## **Glucose Control After Resuscitation (ALS 580)**

Among adults with ROSC after cardiac arrest in any setting (P), does a specific target range for blood glucose management (eg, strict 4–6 mmol/L) (I), compared with any other target range (C), change survival with favorable neurologic/functional outcome at discharge, 30 days, 60 days, 180 days, and/or 1 year; survival only at discharge, 30 days, 60 days, 180 days, and/or 1 year (O)?

### **Introduction**

Glycemic control with insulin is now common for critically ill patients, and hyperglycemia after cardiac arrest is associated

with worse neurologic outcomes. We examined whether specific glucose values other than those selected for other critically ill patients should be targeted in patients after resuscitation from cardiac arrest.

### **Consensus on Science**

For the critical outcome of **survival to hospital discharge**, there was moderate-quality evidence (downgraded for risk of bias due to lack of blinding) from 1 RCT of 90 subjects showing reduced 30-day mortality (RR, 0.94; 95% CI, 0.53–1.68) when subjects were assigned to strict (4–6 mmol/L) versus moderate (6–8 mmol/L) glucose control.<sup>240</sup> One before-and-after observational study of 119 subjects provided very-low-quality evidence (downgraded for multiple potential confounding variables) of reduced in-hospital mortality (RR, 0.46; 95% CI, 0.28–0.76) after implementation of a bundle of care that included defined glucose management (5–8 mmol/L).<sup>193</sup> The effect of glucose management cannot be separated from the effects of other parts of the bundle.

### **Treatment Recommendation**

We suggest no modification of standard glucose management protocols for adults with ROSC after cardiac arrest (weak recommendation, moderate-quality evidence).

### **Values, Preferences, and Task Force Insights**

In making this recommendation, we considered the lack of evidence that the approach to glucose management chosen for other critical care populations should be modified for the post-cardiac arrest patients. Moreover, we noted that strict glycemic control is labor intensive, and in other populations, implementation of strict glycemic control is associated with increased episodes of hypoglycemia, which might be detrimental. Avoiding hypoglycemia was considered more important than the unproven benefits of treating moderate hyperglycemia.

### **Knowledge Gaps**

- It remains unknown whether maintaining serum glucose within a specific range or minimizing variability in post-cardiac arrest patients will improve survival and/or neurologic outcome.

## **Neurologic Prognostication**

In contemporary practice, many comatose post-cardiac arrest patients will not survive or will survive with an unfavorable neurologic outcome. In some regions, family and treating teams may limit or withdraw life-sustaining treatment when unfavorable neurologic outcomes are expected. Therefore, reliable strategies for timely prognostication are a critical component of any cardiac arrest system of care.

The decision to limit treatment of comatose post-cardiac arrest patients should never rely on a single prognostication element. The consensus of the task force was that a multimodal approach should be used in all cases, with all supplementary tests considered in the context of the clinical examination. The most reliable combination and timing for each assessment remain to be determined and require further research.

Reported reliability (FPR and 95% CIs) of any predictor of poor outcome in post-cardiac arrest patients is specific to the time points after cardiac arrest or rewarming when they are



measured. In addition, although several elements are associated with poor outcome when measured before 72 hours after ROSC, it is the consensus of the task force that decisions to limit treatments must consider that neurologic prognosis is uncertain before at least 72 hours after ROSC. We acknowledge that other non-neurological factors may contribute to decisions to limit treatment.

Separate PICO questions addressed prognostication of comatose post-cardiac arrest patients treated with hypothermic TTM and patients not treated with hypothermic TTM. This approach was chosen because hypothermic TTM can alter the natural history of coma and may also delay recovery of CNS function. Moreover, patients may be exposed to larger doses and durations of pharmacologic sedation and neuromuscular blockade to prevent or treat shivering during TTM, and the metabolism of these agents may be delayed during hypothermic TTM. Prognostic elements that are reliable in comatose post-cardiac arrest patients not treated with hypothermic TTM may be less reliable at the same time point in patients treated with TTM.

This review identified clinical signs, neurophysiological measurements, blood or cerebrospinal fluid markers, or imaging studies that had high specificity for poor neurologic outcome, defined as death, vegetative state, or severe cerebral disability (CPC 3–5). This approach was justified by the need to identify signs or measurements that might be used to justify limiting life-sustaining treatment. To quantify the specificity of the finding, we examined the FPR of each sign for predicting unfavorable neurologic outcome, with a goal of 0% FPR. The 95% CI of the FPR was calculated, and we tended to recommend a finding as useful if the FPR was less than 5%, and suggest that a finding might be useful if the FPR was less than 10%. In most cases, clinical signs and findings were considered individually, because few studies considered combinations of clinical findings.

### Prognostication in Comatose Patients Treated With Hypothermic TTM (ALS 450)

Among adults with ROSC who are treated with hypothermia (P), does any clinical variable when abnormal (eg, clinical exam, EEG, somatosensory evoked potentials [SSEPs], imaging, other) (I), compared with any clinical variable when normal (C), reliably predict death or poor neurologic outcome at discharge, 30 days, 60 days, 180 days, and/or 1 year; death only at discharge, 30 days, 60 days, 180 days, and/or 1 year (O)?

#### Consensus on Science

##### Clinical Examination

No study on clinical examination reported blinding of the treating team to the results of the index test.

For the critical outcome of **survival with unfavorable neurologic status or death at discharge**, we identified very-low-quality evidence (downgraded for very serious risk of bias and imprecision) from 4 studies on corneal reflex, pupillary reflex, motor response, GCS, or myoclonus (295 patients).<sup>238,241–243</sup>

For the critical outcome of **survival with unfavorable neurologic status or death at 90 days**, we identified

very-low-quality evidence (downgraded for very serious risk of bias and very serious imprecision) from 5 studies on corneal reflex, pupillary reflex, motor response, brainstem reflexes, or myoclonus (388 patients).<sup>244–248</sup>

For the critical outcome of **survival with unfavorable neurologic status or death at 180 days**, we identified low- or very-low-quality evidence (downgraded for very serious risk of bias and serious or very serious imprecision) from 4 studies on corneal reflex, pupillary reflex, motor response, brainstem reflexes, or myoclonus (642 patients).<sup>249–252</sup>

**Corneal Reflex.** In patients who are comatose after resuscitation from cardiac arrest and are treated with TTM, bilaterally absent corneal reflexes at 72 to 120 hours from ROSC predicted poor outcome, with 2 (0–7)% FPR and 25 (18–32)% sensitivity<sup>241,248,251,253</sup> (301 subjects; very-low-quality evidence).

**Pupillary Reflex.** Bilaterally absent pupillary light reflexes (PLR) on hospital admission predicted poor outcome, with 32 (19–48)% FPR and 86 (71–95)% sensitivity<sup>242,254</sup> (86 patients; very-low-quality evidence). Bilaterally absent PLR at 72 to 108 hours from ROSC predicted poor outcome, with 1 (0–3)% FPR and 19 (14–25)% sensitivity<sup>241,248,249,251,254</sup> (5 studies, 383 subjects; low-quality evidence downgraded for very serious bias).

**Motor Response to Pain.** On hospital admission, bilaterally absent or extensor motor responses, corresponding to a motor score 1 or 2 (M1–2) of the GCS, predicted a poor outcome, with 53 (36–68)% FPR and 92 (75–99)% sensitivity<sup>242</sup> (66 patients; very-low-quality evidence). At 36 to 108 hours from ROSC, an M1–2 predicted a poor outcome, with 70 (65–74)% sensitivity and 10 (7–15)% FPR<sup>245,247–251</sup> (635 subjects; very-low-quality evidence).

One study<sup>248</sup> indicated that both absent corneal reflexes and motor response to pain at 72 hours predicted poor outcome (CPC 4–5) more accurately in patients who did not receive any sedative drugs 12 hours or less before neurologic assessment than in those who did.

**Combination of Clinical Signs.** Bilateral absence of 1 or more brainstem reflexes (pupillary, corneal, or oculocephalic) at 36 to 72 hours from arrest predicted a poor outcome, with 8 (4–14)% FPR and 56 (48–63)% sensitivity (3 studies; 304 patients; very-low-quality evidence).<sup>246,247,255</sup> In 1 study (103 subjects; very-low-quality evidence), the combined absence of corneal reflex, PLR, and M1–2 at 72 hours from ROSC predicted poor outcome, with 0 (0–8)% FPR and 15 (7–26)% sensitivity.<sup>245</sup> In that study, the index test was used as a criterion for withdrawal of life-sustaining treatment. A GCS of 4 or less at 96 hours from ROSC predicted poor outcome, with 5 (1–15)% FPR and 46 (28–66)% sensitivity<sup>243</sup> (72 subjects; very-low-quality evidence).

**Myoclonus and Status Myoclonus.** Presence of myoclonus within 72 hours from ROSC predicted a poor outcome, with 5 (3–8)% FPR and 39 (35–44)% sensitivity (6 studies,<sup>238,246,247,249,250,252</sup> 845 subjects; very-low-quality evidence). In 1 study<sup>245</sup> (103 subjects; very-low-quality evidence),

presence of myoclonus within 7 days after ROSC predicted poor outcome, with 11 (3–26)% FPR and 54 (41–66)% sensitivity.

In 3 studies<sup>241,248,256</sup> (215 patients; low-quality evidence) presence of status myoclonus (defined as a continuous prolonged and generalized myoclonus) within 72 to 120 hours from ROSC predicted poor outcome, with 0 (0–4)% FPR and 16 (11–22)% sensitivity. However, reports of good neurologic recovery despite an early-onset, prolonged, and generalized myoclonus have been published.<sup>252,257–259</sup> In some of these cases,<sup>252,257</sup> myoclonus persisted after awakening and evolved into a chronic action myoclonus (Lance-Adams syndrome).

#### *Electrophysiology*

For the critical outcome of **survival with unfavorable neurologic status or death at discharge**, we identified very-low-quality evidence (downgraded for very serious bias and very serious imprecision) from 8 studies on short-latency SSEPs, EEG, or Bispectral Index (BIS; 571 subjects).<sup>238,241,254,256,260–262</sup>

For the critical outcome of **survival with unfavorable neurologic status or death at 30 days**, we identified 1 study on SSEPs (77 subjects; very-low-quality evidence, downgraded for serious bias and very serious imprecision).<sup>263</sup> For the critical outcome of **survival with unfavorable neurologic status or death at 60 days**, we identified 1 study on brainstem auditory evoked potentials (26 subjects; very-low-quality evidence downgraded for serious bias and very serious imprecision).<sup>264</sup>

For the critical outcome of **survival with unfavorable neurologic status or death at 90 days**, we identified 5 studies on SSEPs or EEG (362 subjects; low- or very-low-quality evidence, downgraded for serious or very serious bias and/or very serious imprecision).<sup>245–248,265</sup>

For the critical outcome of **survival with unfavorable neurologic status or death at 180 days**, we identified 10 studies on SSEPs, EEG, or BIS (566 subjects; moderate-, low-, or very-low-quality evidence downgraded for serious or very serious bias and/or very serious imprecision).<sup>249–251,266–272</sup>

For the critical outcome of **survival with unfavorable neurologic status or death at 1 year**, we identified 1 study on EEG (106 subjects; very-low-quality evidence).<sup>252</sup>

**Short Latency SSEPs.** In most prognostication studies, absence of the N20 wave after rewarming has been used—alone or in combination—as a criterion for deciding on withdrawal of life-sustaining treatment, with a consequent risk of self-fulfilling prophecy.

In patients who are comatose after resuscitation from cardiac arrest and who are treated with TTM, a bilaterally absent N20 SSEP wave during TTM predicted poor outcome, with 2 (0–4)% FPR and 28 (22–34)% sensitivity.<sup>249,263,266,271</sup> (424 subjects; moderate-quality evidence, downgraded for serious bias). A bilaterally absent N20 SSEP wave after rewarming predicted poor outcome, with 1 (0–3)% FPR (9 studies,<sup>245–251,254,261,265</sup> 629 subjects; very-low-quality evidence downgraded for very serious bias and serious inconsistency) and 45 (41–50)% sensitivity.

SSEP recording is prone to electrical interference. In 1 study,<sup>249</sup> 3 subjects with a bilaterally absent N20 during TTM rapidly recovered consciousness after rewarming and

ultimately had a good outcome. In a post hoc assessment, 2 experienced neurophysiologists reviewed blindly the original tracings and concluded that the SSEP recordings were undeterminable because of excessive noise.

**EEG.** Definitions of *burst suppression* were inconsistent among studies. Definitions of *epileptiform activity*, *electrographic seizures*, and *SE* were inconsistent among studies.

**Absence of Background Reactivity.** Absence of background reactivity on the EEG recorded during TTM predicted poor outcome, with 2 (1–7)% FPR and 63 (54–72)% sensitivity (3 studies,<sup>238,246,247</sup> 249 subjects; very-low-quality evidence downgraded for very serious bias and serious imprecision). Absence of background reactivity on the EEG recorded after rewarming predicted poor outcome, with 0 (0–3)% FPR and 62 (53–70)% sensitivity (3 studies,<sup>238,247,250</sup> 223 subjects; very-low-quality evidence downgraded for very serious bias and serious imprecision). One group of investigators provided 3 of the 4 prognostication studies on absent EEG reactivity after cardiac arrest.

**Burst Suppression.** Presence of burst suppression on initial EEG immediately after induction of TTM predicted poor outcome, with 0 (0–5)% FPR and 31 (19–44)% sensitivity (2 studies,<sup>267,268</sup> 119 subjects; very-low-quality evidence downgraded for very serious bias and serious inconsistency). Presence of burst suppression on EEG during TTM predicted poor outcome, with 6 (1–15)% FPR and 70 (56–82)% sensitivity (2 studies,<sup>247,266</sup> 107 patients; very-low-quality evidence downgraded for very serious bias, serious inconsistency, and very serious imprecision). In 1 study<sup>268</sup> (95 subjects; very-low-quality evidence) presence of burst suppression on EEG after rewarming predicted poor outcome, with 0 (0–5)% FPR and 18 (8–34)% sensitivity.

**Epileptiform Activity.** Presence of epileptiform discharges on EEG during TTM<sup>262</sup> (38 subjects) or after rewarming<sup>250</sup> (108 patients) predicted poor outcome, with 8 (0–39)% and 12 (3–31)% FPR, respectively. Quality of evidence was very low in both studies, downgraded for very serious bias and very serious imprecision. Presence of electrographic seizures with nonreactive EEG background during TTM<sup>247</sup> (61 patients), electrographic seizures during TTM<sup>262</sup> (38 subjects), or electrographic seizures both during TTM and after rewarming<sup>238</sup> (54 subjects) predicted poor outcome, with 0% FPR (95% CIs, 0–10, 0–22, and 0–9, respectively; very-low-quality evidence downgraded for very serious bias and serious or very serious imprecision).

Presence of SE during TTM<sup>273</sup> (51 subjects) or after rewarming<sup>272</sup> (30 subjects) predicted poor outcome, with 0% FPR (95% CIs, 0–22 and 0–13, respectively). However, in another study,<sup>252</sup> the presence of an SE within 72 hours from ROSC was associated with good outcome in 2 cases (FPR 6 [1–21]%). In both those patients, SE was first recorded at 40 hours or greater from ROSC (shortly after rewarming), and the EEG was reactive (very-low-quality evidence, downgraded for serious or very serious bias and very serious imprecision).

In 1 study<sup>268</sup> (95 subjects), presence of electrographic SE on a burst suppression pattern was associated with an invariably poor outcome (CPC 4–5; FPR 0 [0–5]%), while an

electrographic SE on a continuous background was still compatible with recovery of consciousness (FPR 4 [0–12]%; very-low-quality evidence downgraded for very serious bias and very serious imprecision).

**Flat or Low-Amplitude EEG.** In 1 study<sup>266</sup> (46 subjects), a flat or low-amplitude (less than 20 mcV) EEG during TTM at 24 hours from cardiac arrest predicted poor outcome, with 0 (0–11)% FPR and 40 (19–64)% sensitivity. In another study<sup>268</sup> (95 subjects), however, a flat (less than 10 mcV) EEG recorded during TTM at a median of 8 hours from cardiac arrest or immediately after rewarming was followed by recovery of consciousness (FPR 46 [32–59]% and 5 [1–15]%, respectively; very-low-quality evidence downgraded for serious or very serious bias and very serious imprecision).

**Bispectral Index.** In 1 study<sup>270</sup> (45 subjects), a lowest BIS value of 0 during TTM, corresponding to a flat or low-amplitude EEG, predicted a poor outcome, with 0 (0–6)% FPR and 50 (31–69)% sensitivity. However, in another study<sup>269</sup> (75 subjects), a lowest BIS value of 0 during TTM predicted poor outcome, with 10 (3–23)% FPR. The quality of evidence was very low (downgraded for very serious bias and very serious imprecision).

**EEG Grades.** In 1 study<sup>238</sup> (54 subjects; very-low-quality evidence), a grade 3 EEG, corresponding to 1 pattern among unreactive, burst suppression, focal or generalized seizures, generalized periodic epileptiform discharges, SE, low amplitude (10 mcV or less), or alpha-theta coma, predicted poor outcome, with 6 (1–20)% FPR during TH and 0 (0–9)% FPR after rewarming.

**Other Neurophysiological Tests.** In 1 study<sup>264</sup> (26 subjects; very-low-quality evidence), absence of brainstem auditory evoked potentials wave V during induction of TTM predicted poor outcome, with 0 (0–31)% FPR and 56 (31–78)% sensitivity. In 1 pilot study<sup>265</sup> (17 subjects; very-low-quality evidence), the bilateral absence of pain-related middle-latency cortical evoked potentials predicted poor outcome, with 0 (0–53)% FPR and 85 (55–98)% sensitivity.

#### Blood and Cerebrospinal Fluid Markers

Blood marker thresholds vary because of heterogeneous measurement techniques,<sup>274–276</sup> the presence of extraneuronal sources of biomarkers (hemolysis, non-central nervous system sources, and neuroendocrine tumors for neuron-specific enolase [NSE],<sup>277</sup> muscle and adipose tissue breakdown for S100B),<sup>278</sup> and the incomplete knowledge of the kinetics of their blood concentrations in the first few days after ROSC.

For the critical outcome of **survival with unfavorable neurologic status or death at discharge**, we identified 4 studies on NSE (354 subjects; low- or very-low-quality evidence downgraded for serious or very serious bias and very serious imprecision).<sup>241,279–281</sup> For the critical outcome of survival with unfavorable neurologic status or death at 60 days, we identified 1 study on NSE (73 subjects; very-low-quality evidence).<sup>282</sup>

For the critical outcome of **survival with unfavorable neurologic status or death at 90 days**, we identified 3 studies on NSE (248 patients, very-low-quality evidence downgraded for serious or very serious bias and very serious imprecision).<sup>246–248</sup>

For the critical outcome of **survival with unfavorable neurologic status or death at 180 days**, we identified 8 studies on NSE or S100B (810 patients; moderate-, low-, or very-low-quality evidence, downgraded for serious or very serious bias and/or serious or very serious imprecision).<sup>249,251,269,272,283–286</sup>

**NSE.** In comatose resuscitated patients who are treated with TTM, the threshold for prediction of poor outcome with 0% FPR varied between 49.6 mcg/L and 151.4 mcg/L at 24 hours from ROSC<sup>272,284,285,287</sup> (309 subjects; very-low-quality evidence, downgraded for serious or very serious bias and very serious imprecision), between 25 mcg/L and 151.5 mcg/L at 48 hours<sup>251,272,279,281,282,284–287</sup> (10 studies, 919 subjects; moderate- to very-low-quality evidence downgraded for serious or very serious bias and very serious imprecision), and between 57.2 mcg/L and 78.9 mcg/L at 72 hours<sup>280–282</sup> (193 subjects; low- or very-low-quality evidence).

Limited evidence<sup>282,284,288</sup> suggests that not only the NSE absolute concentrations but also their trends over time may have predictive value. Limited evidence<sup>284,288</sup> suggests that the discriminative value of NSE levels at 48 to 72 hours is higher than at 24 hours.

**S100B.** For S100B, the documented thresholds for a 0% FPR were 0.18 and 0.21 mcg/L at 24 hours after ROSC<sup>283,285</sup> (2 studies, total 66 subjects; very-low-quality evidence downgraded for serious or very serious bias and very serious imprecision) and 0.3 mcg/L at 48 hours (1 study, 75 subjects; very-low-quality evidence downgraded for serious or very serious bias and very serious imprecision).

#### Imaging

All studies on prognostication after cardiac arrest using imaging have a small sample size with a consequent low precision and are prone to selection bias, because the imaging studies were performed at discretion of treating physician, which may have caused a selection bias and overestimated their performance. Imaging studies depend partly on subjective human decision in identifying the region of interest to be studied and in the interpretation of results.

For the critical outcome of **survival with unfavorable neurologic status or death at discharge**, we identified 3 studies on computed tomography (CT; 273 subjects; low- or very-low-quality evidence downgraded for serious or very serious bias and serious or very serious imprecision).<sup>241,279,289</sup>

For the critical outcome of **survival with unfavorable neurologic status or death at 180 days**, we identified 6 studies on CT or magnetic resonance imaging (MRI; 246 subjects; very-low-quality evidence downgraded for serious or very serious bias and very serious imprecision).<sup>251,287,290–293</sup>

**CT Scan.** The main CT finding of global anoxic-ischemic cerebral insult after cardiac arrest is cerebral edema,<sup>294</sup> which appears as a reduction in the depth of cerebral sulci (sulcal effacement) and an attenuation of the gray matter/white matter (GM/WM) interface, due to a decreased density of the GM. This attenuation has been quantitatively measured as the ratio (GWR) between the GM and the WM densities.

In 4 studies<sup>254,279,289,290</sup> (total 276 subjects; low- or very-low-quality evidence downgraded for serious or very serious bias and very serious imprecision), a reduced GWR at



the level of the basal ganglia on brain CT performed within 2 hours from ROSC predicted an almost invariably poor outcome (FPR from 0% to 8%). Measurement techniques and thresholds for GWR varied among studies.

In 1 study<sup>241</sup> (102 subjects; low-quality evidence downgraded for serious bias and serious imprecision), a global cerebral edema on brain CT at a median of 1 day after cardiac arrest predicted poor outcome, with 0 (0–5)% FPR.

**MRI.** The main MRI finding of anoxic-ischemic cerebral injury is a hyperintensity in diffusion weighted imaging (DWI) sequences due to cytotoxic edema. Presence of DWI abnormalities in cortex or basal ganglia (1 study, 21 subjects; very-low-quality evidence) or both (2 studies, 30 subjects; very-low-quality evidence) between 2 and 6 days from ROSC was associated with poor outcome (FPR, 0%–9%). Precision of prediction, however, was very low, due to the small size of these studies.

Postischemic DWI abnormalities can be quantified using apparent diffusion coefficient (ADC). ADC values between  $700$  and  $800 \times 10^{-6}$  mm<sup>2</sup>/s are considered normal. In 1 study<sup>293</sup> (22 subjects; very-low-quality evidence downgraded for very serious bias and very serious imprecision), presence of more than 10% of brain volume with ADC less than  $650 \times 10^{-6}$  mm<sup>2</sup>/s predicted poor outcome, with 0 (0–28)% specificity. In another study,<sup>295</sup> a low ADC at the level of putamen, thalamus, or occipital cortex also predicted poor outcome, with 0% FPR (95% CIs, 0–24%). The ADC thresholds varied according to the brain area studied.

### **Treatment Recommendations**

We suggest against the use of clinical criteria alone before 72 hours after ROSC to estimate prognosis (weak recommendation, low-quality evidence).

We suggest that multiple modalities of testing (clinical exam, neurophysiological measures, imaging, or blood markers) be used to estimate prognosis instead of relying on single tests or findings (weak recommendation, low-quality evidence).

### **Clinical Examination**

We recommend using bilaterally absent PLRs or the combined absence of both pupillary and corneal reflexes at least 72 hours after ROSC to predict poor outcome in patients who are comatose after resuscitation from cardiac arrest and who are treated with TTM (strong recommendation, low-quality evidence).

We suggest against using an absent (M1) or extensor motor response to pain (M2) alone to predict poor outcome, given its high FPR. However, due to its high sensitivity, this sign may be used to identify the population with poor neurologic status needing prognostication or to predict poor outcome in combination with other more robust predictors (weak recommendation, very low-quality evidence).

We suggest against the use of myoclonus during the first 72 hours from ROSC as a predictor for prognosticating a poor neurologic outcome (weak recommendation, low-quality evidence).

We suggest that the presence of a status myoclonus during the first 72 hours from ROSC be considered at 72 hours after

ROSC (in combination with other factors) as a predictor for prognosticating a poor neurologic outcome (weak recommendation, low-quality evidence).

We suggest prolonging the observation of clinical signs when interference from residual sedation or paralysis is suspected, so that the possibility of obtaining false-positive results is minimized. We recommend that the earliest time to prognosticate a poor neurologic outcome is 72 hours after ROSC, and should be extended longer if the residual effect of sedation and/or paralysis confounds the clinical examination (weak recommendation, low-quality evidence).

### **Electrophysiology**

We recommend using bilateral absence of N20 SSEP wave measured at least 72 hours after ROSC to predict poor outcome in patients who are comatose after resuscitation from cardiac arrest and who are treated with TTM (strong recommendation, low-quality evidence).

SSEP recording requires appropriate skills and experience, and utmost care should be taken to avoid electrical interference from muscle artifacts or from the ICU environment, as well as confounding drugs. This test is only ordered in the appropriate clinical context.

We suggest using persistent absence of EEG reactivity to external stimuli at 72 hours or longer after ROSC (weak recommendation, low-quality evidence), presence of persistent burst suppression after rewarming, or intractable and persistent SE (weak recommendation, very-low-quality evidence) to predict poor outcome in patients who are comatose after resuscitation from cardiac arrest and who are treated with TTM.

We recommend against using BIS to predict poor outcome during TTM in patients who are comatose after resuscitation from cardiac arrest and are treated with TTM (strong recommendation, very-low-quality evidence).

### **Blood Markers**

We suggest using utmost care and preferably sampling at multiple serial time points (24–72 hours) when assessing NSE, to avoid false-positive results due to hemolysis (weak recommendation, very-low-quality evidence).

We suggest using serial high-serum values of NSE at 48 to 72 hours from ROSC in combination with other predictors for predicting poor neurologic outcome in patients who are comatose after cardiac arrest and who are treated with TTM (weak recommendation, very-low-quality evidence). However, no threshold-enabling prediction with 0 FPR can be recommended, and NSE levels are insufficiently specific to be used alone for estimating prognosis.

### **Imaging**

We suggest using brain imaging studies for prognostication only in centers where specific experience is available (weak recommendation, very-low-quality evidence).

We suggest using the presence of a marked reduction of the GM/WM ratio on brain CT within 2 hours after ROSC or the presence of extensive diffusion restriction on brain MRI at 2 to 6 days after ROSC in combination with other predictors for prognosticating a poor neurologic outcome in patients

who are comatose after cardiac arrest and who are treated with TTM (weak recommendation, very-low-quality evidence). Early imaging markers of poor prognosis should not prevent support for a sufficient period of time to observe other clinical features, although some extreme CT scan findings are consistent with herniation and brain death.

### Knowledge Gaps

#### Clinical Examination

- Prospective studies are needed to investigate the pharmacokinetics of sedative drugs and neuromuscular blocking drugs in post-cardiac arrest patients, especially those treated with controlled temperature.
- Studies are needed to investigate the reproducibility of clinical signs used to predict outcome in comatose postarrest patients.
- There is no universally accepted definition of *status myoclonus*. A recently proposed definition<sup>296</sup> suggests using the term *status myoclonus* to indicate a continuous and generalized myoclonus persisting for 30 minutes in comatose survivors of cardiac arrest.

#### Electrophysiology

- In most prognostication studies, results of SSEPs were not blinded and were used as a criterion for limitation or suspension of life-sustaining treatment. Blinded studies on SSEPs are needed to assess the relevance of self-fulfilling prophecies for SSEPs.
- Definitions of EEG-based predictors are inconsistent among prognostication studies. Future studies should comply with recently recommended definitions.<sup>297</sup>
- The stimulation modalities for eliciting EEG reactivity have not been standardized.

#### Blood Markers

- There is a need for standardization of the measuring techniques for NSE and S100 in cardiac arrest patients.
- Little information is available on the kinetics of the blood concentrations of biomarkers in the first few days after cardiac arrest.

#### Imaging

- Prospective studies in unselected patient populations are needed for evaluating the prognostic accuracy of imaging studies in comatose patients resuscitated from cardiac arrest.

### Prognostication in Absence of TTM (ALS 713)

Among adults who are comatose after cardiac arrest and are not treated with TTM (P), does any clinical finding when normal (eg, clinical exam, EEG, SSEPs, imaging, other) (I), compared with any clinical finding when abnormal (C), reliably predict death or poor neurologic outcome at discharge, 30 days, 60 days, 180 days, and/or 1 year; death only at discharge, 30 days, 60 days, 180 days, and/or 1 year (O)?

### Consensus on Science

No study on clinical examination reported blinding of the treating team to the results of the index test. Blinding of the treating team is very difficult to achieve for predictors based on clinical examination, which implies a risk of self-fulfilling prophecy.

For the critical outcome of **survival with unfavorable neurologic status or death at discharge**, we identified 2 studies on pupillary reflex and motor response or oculocephalic reflex (151 patients; very-low-quality evidence downgraded for very serious bias and very serious imprecision).<sup>298,299</sup>

For the critical outcome of **survival with unfavorable neurologic status or death at 30 days**, we identified 1 study on GCS (97 patients; very-low-quality evidence downgraded for very serious bias and very serious imprecision).<sup>300</sup>

For the critical outcome of **survival with unfavorable neurologic status or death at 90 days**, we identified 2 studies on corneal reflex, pupillary reflex, motor response, oculovestibular reflex, GCS, or myoclonus (97 patients; very-low-quality evidence downgraded for serious or very serious bias and serious or very serious imprecision).<sup>301,302</sup>

For the critical outcome of **survival with unfavorable neurologic status or death at 180 days**, we identified 4 studies on brainstem reflexes, motor response, or myoclonus (650 patients; very-low-quality evidence downgraded for serious or very serious bias and very serious imprecision).<sup>303–306</sup>

For the critical outcome of **survival with unfavorable neurologic status or death at 1 year**, we identified 3 studies on brainstem reflexes, motor response, GCS, or myoclonus (172 patients; very-low-quality evidence downgraded for serious or very serious bias and very serious imprecision).<sup>307–309</sup>

#### Clinical Examination

**Pupillary Reflex.** In 1 study<sup>299</sup> (98 patients; very-low-quality evidence), an absent PLR on hospital admission predicted poor outcome, with 8 (1–25)% FPR and 56 (43–67)% sensitivity. At 24 hours<sup>298,302,306</sup> (3 studies, 496 patients), 48 hours<sup>298,303,306</sup> (3 studies, 403 patients), and 72 hours<sup>298,306</sup> (2 studies, 382 patients) from ROSC, the FPRs of PLR for prediction of poor outcome were 9 (4–18)%, 4 (0–12)%, and 0 (0–8)%, respectively. Sensitivity ranged from 18 (15–23)% to 21 (17–25)%; (very-low-quality evidence, downgraded for serious or very serious bias and very serious imprecision).

**Corneal Reflex.** In patients who are comatose after resuscitation from cardiac arrest and who are not treated with TTM, an absent corneal reflex at 24 and 48 hours after ROSC predicted poor outcome, with 17 (9–27)% and 7 (2–20)% FPR. Sensitivities were 37 (32–42)% and 30 (25–35)%, respectively.<sup>302,303,306</sup> (3 studies, 497 subjects; very-low-quality evidence downgraded for very serious bias, serious inconsistency, and very serious imprecision).

**Oculovestibular Reflex.** In 2 studies<sup>302,303</sup> (65 patients; very-low-quality evidence downgraded for very serious bias, serious inconsistency, and very serious imprecision), the bilateral absence of oculovestibular reflex at 24 hours from ROSC

predicted poor outcome, with 0 (0–18)% FPR and 38 (25–53)% sensitivity. In 1 study<sup>303</sup> (19 patients; very-low-quality evidence downgraded for very serious bias and very serious imprecision), the bilateral absence of oculovestibular reflex at 48 hours from ROSC predicted poor outcome, with 0 (0–35)% FPR and 25 (5–57)% sensitivity.

**Combination of Ocular Reflexes.** In 1 study<sup>306</sup> (386 patients; very-low-quality evidence downgraded for very serious bias and very serious imprecision), the combined absence of both pupillary and corneal reflexes at 24, 48, and 72 hours from ROSC predicted a poor outcome, with 5 (1–17)%, 3 (0–17)%, and 0 (0–15)% FPR, respectively, and 13% to 14% sensitivity. In 1 study<sup>307</sup> (60 patients; very-low-quality evidence downgraded for serious bias and very serious imprecision), the absence of more than 1 among pupillary, corneal, and oculocephalic reflex at 6 to 12, 24, and 48 hours from ROSC predicted poor outcome, with 0 (0–22)% FPR.

**Motor Response to Pain.** At 24 hours from ROSC, an absent or extensor motor response, corresponding to a motor score 1 or 2 (M1–2) of the GCS, predicted a poor outcome, with 27 (12–48)% FPR and 76 (71–80)% sensitivity<sup>302,306</sup> (2 studies, 462 patients; very-low-quality evidence downgraded for serious bias, serious inconsistency, and serious imprecision). At 72 hours from ROSC, an M1–2 predicted a poor outcome, with 15 (5–31)% FPR and 39 (33–44)% sensitivity<sup>301,306</sup> (2 studies, 322 patients; very-low-quality evidence downgraded for serious bias, serious inconsistency, and very serious imprecision).

An absent extensor or abnormal flexion to pain (M1–3) predicted a poor outcome at 12, 24, and 48 hours from ROSC with 57 (37–76)%, 35 (21–52)%, and 10 (3–24)% FPR, respectively<sup>298,303,307</sup> (3 studies, 120 patients; very-low-quality evidence downgraded for very serious bias, serious inconsistency, and very serious imprecision). At 72 hours, the FPR of this sign was 6 (0–29)%<sup>298</sup> (1 study, 27 patients; very-low-quality evidence downgraded for very serious bias and very serious imprecision).

**GCS.** A GCS of 4 or less on admission, at 24 hours, and at 48 hours from ROSC predicted poor outcome, with 40 (19–64)%, 25 (5–57)%, and 0 (0–22)% FPR, respectively<sup>307,308</sup> (2 studies, 119 patients; very-low-quality evidence downgraded for serious bias and very serious imprecision). Sensitivity ranged from 54 (37–71)% to 74 (58–86)%. A GCS of 5 or less at 72 hours from ROSC predicted poor outcome, with 75 (63–86)% sensitivity and 7 (1–24)% FPR.

**Myoclonus and Status Myoclonus.** Presence of myoclonus on admission<sup>305</sup> (1 study, 107 patients; very-low-quality evidence) or at 24 hours from ROSC<sup>302</sup> (1 study, 75 patients; very-low-quality evidence) predicts a poor outcome, with 0 (0–14)% and 0 (0–5)% FPR, respectively. A status myoclonus within 24 hours, at 36 to 48 hours, and 72 hours from ROSC predicted a poor outcome, with 0 (0–7)%, 0 (0–5)%, and 0 (0–14)% FPR, respectively<sup>304,306</sup> (2 studies, 464 patients; very-low-quality evidence downgraded for very serious bias and serious imprecision). Sensitivity ranged from 2% to 29%.

### *Electrophysiology*

For the critical outcome of **survival with unfavorable neurologic status or death at discharge**, we identified 2 studies on short-latency SSEPs (63 patients; very-low-quality evidence downgraded for very serious bias and very serious imprecision)<sup>310,311</sup> and 3 studies on EEG (46 patients; very-low-quality evidence, downgraded for very serious bias and very serious imprecision).<sup>312–314</sup>

For the critical outcome of **survival with unfavorable neurologic status or death at 30 days**, we identified 2 studies on SSEPs (80 patients; very-low-quality evidence downgraded for very serious bias and very serious imprecision).<sup>315,316</sup>

For the critical outcome of **survival with unfavorable neurologic status or death at 60 days**, we identified 2 studies on EEG (54 patients; very-low-quality evidence downgraded for very serious bias and very serious imprecision).<sup>317,318</sup>

For the critical outcome of **survival with unfavorable neurologic status or death at 90 days**, we identified 2 studies on SSEPs or EEG (102 patients; very-low-quality evidence downgraded for very serious bias and very serious imprecision).<sup>302,319</sup>

For the critical outcome of **survival with unfavorable neurologic status or death at 180 days**, we identified 6 studies on SSEPs or EEG (733 patients; very-low-quality evidence downgraded for serious or very serious bias and serious or very serious imprecision).<sup>271,303,320–323</sup>

For the critical outcome of **survival with unfavorable neurologic status or death at 1 year**, we identified 6 studies on SSEPs or EEG (829 patients; low- or very-low-quality evidence downgraded for serious or very serious bias and very serious imprecision).<sup>306,307,324–327</sup>

**Short-Latency SSEPs.** Bilateral absence of the N20 wave of short-latency SSEPs predicted death or vegetative state, with 0 (0–12)% FPR as early as 8 hours from cardiac arrest. An FPR of 0% was also confirmed at 24, 48, and 72 hours after ROSC (95% CIs from 0–3 to 0–9) with consistent sensitivity (43%–46%). Among all patients in whom N20 SSEP wave was absent in the first 7 days from cardiac arrest, there was only 1 case of false-positive result.<sup>302</sup> Quality of evidence was very low in all but 1 study, downgraded for serious or very serious bias and serious or very serious imprecision.

Studies assessing the predictive value of a delayed or absent N70 SSEP from 24 hours to 72 hours after ROSC reported a false-positive prediction from 1 (0–7)% to 58 (28–85)%<sup>302,306,320,321,324</sup> (5 studies, 657 subjects; very-low-quality evidence downgraded for serious or very serious bias and serious or very serious imprecision).

Blinding of SSEP results, along with criteria for withdrawal of life-sustaining treatment, was not reported in most prognostication studies in resuscitated patients who were not treated with TTM.

**Electroencephalography.** In 1 study<sup>303</sup> (26 patients; very-low-quality evidence downgraded for serious bias and very serious imprecision), an EEG grade 3 to 5 at 24 and 48 hours predicted poor outcome (CPC 3–5), with 0% FPR (95% CIs, 0–22 and



0–24, respectively). An EEG grade 4 to 5 at 72 hours or less from ROSC predicted poor outcome, with 0 (0–11)% FPR and 44 (34–54)% sensitivity<sup>307,313,315</sup> (3 studies, 125 patients; very-low-quality evidence downgraded for very serious bias and very serious imprecision). EEG grading systems were not consistent among studies.

Presence of burst suppression within 48 hours from ROSC was compatible with recovery of consciousness (FPR 5 [0–26]%<sup>302</sup>; 1 study, 72 patients; very-low-quality evidence downgraded for very serious bias and very serious imprecision), while a burst suppression at 72 hours from ROSC predicted poor outcome, with 0 (0–11)% FPR<sup>306</sup> (1 study, 277 patients; very-low-quality evidence downgraded for very serious bias and very serious imprecision).

A low-voltage EEG (20–21 mcV or less) predicted a poor outcome, with 0 (0–15)% FPR within 48 hours from ROSC<sup>302</sup> (1 study, 72 patients; very-low-quality evidence downgraded for very serious bias and very serious imprecision) and with 0 (0–11)% FPR at 72 hours from ROSC<sup>306</sup> (1 study, 283 patients; very-low-quality evidence downgraded for very serious bias and very serious imprecision). Sensitivity was 15 (7–28)% and 31 (25–37)%, respectively.

Presence of alpha coma within 72 hours or from 1 to 7 days after ROSC was not consistently associated with poor outcome (positive predictive value, 96 [80–100]% and 88 [74–96]%)<sup>303,312,314,318,325,326</sup> (6 studies, 68 patients; very-low-quality evidence downgraded for very serious bias and very serious imprecision).

#### Blood Markers

In patients who are comatose after resuscitation from cardiac arrest and who are not treated with TTM, high concentrations of biomarkers predict a poor outcome. Advantages of biomarkers over other predictors such as EEG and clinical examination include quantitative results and likely independence from the effects of sedatives. However, the thresholds associated with 0% FPR vary between studies, and S100B thresholds are less well documented than NSE thresholds.

The main reasons for the observed variability in biomarkers' thresholds include the use of heterogeneous measurement techniques,<sup>274–276</sup> the presence of extraneuronal sources of biomarkers (hemolysis and neuroendocrine tumors for NSE,<sup>277</sup> muscle and adipose tissue breakdown for S100B),<sup>278</sup> and the incomplete knowledge of the kinetics of their blood concentrations in the first few days after ROSC.

For the critical outcome of **survival with unfavorable neurologic status or death at discharge**, we identified 2 studies on S100B (99 patients; low- or very-low-quality evidence downgraded for very serious bias and/or very serious imprecision)<sup>328,329</sup> and 1 study on NSE (73 patients; very-low-quality evidence downgraded for serious bias and very serious imprecision).<sup>280</sup>

For the critical outcome of **survival with unfavorable neurologic status or death at 90 days**, we identified 1 study on NSE (32 patients; very-low-quality evidence downgraded for very serious bias and very serious imprecision)<sup>248</sup> and 1 study on S100B (27 patients; very-low-quality

evidence downgraded for very serious bias and very serious imprecision).<sup>319</sup>

For the critical outcome of **survival with unfavorable neurologic status or death at 180 days**, we identified 3 studies on NSE or S100B (618 patients; moderate-, low-, or very-low-quality evidence downgraded for serious bias and/or serious or very serious imprecision).<sup>285,323,330</sup>

For the critical outcome of **survival with unfavorable neurologic status or death at 1 year**, we identified 2 studies on NSE or S100B (86 patients; very-low-quality evidence downgraded for very serious bias and very serious imprecision).<sup>331,332</sup>

**Neuron-Specific Enolase.** In resuscitated patients with poor neurologic outcome, the blood levels of NSE are higher than those in patients with good neurologic outcome. However, the threshold for prediction of poor outcome with 0% FPR varied between 13.3 and 47.6 mcg/L at 24 hours from ROSC<sup>285,306,319</sup> (3 studies, 332 patients; very-low-quality evidence), between 8.8 and 65 mcg/L at 48 hours<sup>285,319,330,331</sup> (4 studies, 277 patients; moderate- to very-low-quality evidence), and between 15 and 90.9 mcg/L at 72 hours<sup>280,319,331</sup> (3 studies, 301 patients; low- or very-low-quality evidence).

**S100B.** For S100B, the documented thresholds for 0% FPR ranged between 0.19 and 5.2 mcg/L at 24 hours after ROSC<sup>285,319</sup> (2 studies, total 60 patients; very-low-quality evidence) and between 0.12 and 0.8 mcg/L at 48 hours<sup>285,319,329,331</sup> (4 studies, 158 patients; very-low-quality evidence). In 1 study (27 patients; very-low-quality evidence), the threshold for prediction of poor outcome with 0% FPR at 72 hours was 0.5 mcg/L.

#### Imaging

All prognostication studies on imaging have a small sample size, and in all of them, imaging was performed at the discretion of the treating physician, which may have caused a selection bias and overestimated the performance of index tests. Another limitation is that these methods depend partly on subjective human decision in identifying the region of interest to be studied and in the interpretation of results.

For the critical outcome of **survival with unfavorable neurologic status or death at discharge**, we identified 3 studies on CT (113 patients; very-low-quality evidence)<sup>294,333,334</sup> and 2 studies on MRI (40 patients; very-low-quality evidence).<sup>316,335</sup> For the critical outcome of **survival with unfavorable neurologic status or death at 90 days**, we identified 2 studies on MRI (61 patients; low- or very-low-quality evidence).<sup>301,336</sup> For the critical outcome of **survival with unfavorable neurologic status or death at 180 days**, we identified 3 studies on MRI (34 patients; very-low-quality evidence).<sup>292,293,337</sup>

**CT Scan.** The main CT finding of global anoxic-ischemic cerebral insult after cardiac arrest is cerebral edema,<sup>294</sup> which appears as a reduction in the depth of cerebral sulci (sulcal effacement) and an attenuation of the GM/WM interface, due to a decreased density of the GM. This attenuation has been quantitatively measured as the GWR between the GM and the WM densities.

In 2 studies<sup>333,334</sup> (total 60 patients; very-low-quality evidence), a GWR between the caudate nucleus and the posterior limb of internal capsule (CN/PIC) below 1.22 within 24 hours or below 1.18 within 48 hours from ROSC predicted poor outcome, with 0 (0–28)% and 17 (0–64)% FPR, respectively. At 72 hours from ROSC, the presence of diffuse brain swelling on CT predicts a poor outcome, with 0 (0–45)% FPR and 52 (37–67)% sensitivity<sup>294</sup> (1 study, 53 patients; very-low-quality evidence).

**MRI.** The main MRI finding of anoxic-ischemic cerebral injury is a hyperintensity in DWI sequences due to cytotoxic edema. In a small study subpopulation<sup>292</sup> (12 patients; very-low-quality evidence), presence of diffuse DWI abnormalities in cortex or brainstem at a median of 80 hours from ROSC predicted poor outcome, with 0 (0–35)% FPR. In another small study<sup>337</sup> (12 patients; very-low-quality evidence), presence of extensive (cortex, basal ganglia, and cerebellum) DWI changes predicted poor outcome, with 0 (0–45)% FPR.

Postischemic DWI abnormalities can be quantified by using ADC. ADC values between  $700$  and  $800 \times 10^{-6}$  mm<sup>2</sup>/s are considered normal.<sup>335</sup> In 1 study<sup>338</sup> (80 patients; very-low-quality evidence), a whole-brain ADC less than  $665 \times 10^{-6}$  mm<sup>2</sup>/s predicted poor outcome, with 0 (0–21)% FPR and 40 (28–53)% sensitivity. In a small subset of another study<sup>293</sup> (10 patients; very-low-quality evidence), presence of more than 10% of brain volume with ADC less than  $650 \times 10^{-6}$  mm<sup>2</sup>/s predicted poor outcome, with 88 (47–100)% sensitivity and 0 (0–78)% FPR. In another study, an ADC below various thresholds at the level of putamen, thalamus, or occipital cortex at less than 120 hours from ROSC also predicted poor outcome, with 0 (0–31)% FPR. Finally, in 2 studies<sup>301,335</sup> (total 24 patients; very-low-quality evidence), the presence of extensive cortical global DWI or fluid-attenuated inversion recovery changes within 7 days from arrest predicted poor outcome, with 0 (0–78)% FPR.

### Treatment Recommendations

#### Clinical Examination

We recommend using the absence of PLR (or the combined absence of both pupillary and corneal reflexes) at 72 hours or greater from ROSC to predict poor outcome in patients who are comatose after resuscitation from cardiac arrest and who are not treated with TTM (strong recommendation, very-low-quality evidence).

We suggest against using an absent or extensor motor response to pain ( $M \leq 2$ ) alone to predict poor outcome, given its high FPR (weak recommendation, very-low-quality evidence). However, due to its high sensitivity, this sign may be used to identify the population with poor neurologic status needing prognostication or to predict poor outcome in combination with other more-robust predictors.

We suggest using the presence of myoclonus or status myoclonus within 72 hours from ROSC in combination with other predictors to predict poor outcome in comatose survivors of cardiac arrest (weak recommendation, very-low-quality evidence).

We suggest prolonging the observation of clinical signs when interference from residual sedation or paralysis is suspected, so that the possibility of obtaining false-positive results is minimized (weak recommendation, very-low-quality evidence).

#### Electrophysiology

We recommend using bilateral absence of the N20 SSEP wave within 72 hours from ROSC to predict poor outcome in patients who are comatose after cardiac arrest and who are not treated with TTM (strong recommendation, very-low-quality evidence). SSEP recording requires appropriate skills and experience, and utmost care should be taken to avoid electrical interference from muscle artifacts or from the ICU environment.

We suggest using the presence of burst suppression on EEG at 72 hours from ROSC in combination with other predictors for prognosticating a poor neurologic outcome in patients who are comatose after cardiac arrest and who are not treated with TTM (strong recommendation, very-low-quality evidence).

We suggest against using EEG grades for prognostication due to the inconsistencies in their definitions (weak recommendation, very-low-quality evidence).

We suggest against using low-voltage EEG for prognostication, given the potential interferences of technical factors on EEG amplitude (weak recommendation, very-low-quality evidence).

#### Blood Markers

We suggest using high serum values of NSE at 24 to 72 hours from ROSC in combination with other predictors for prognosticating a poor neurologic outcome in patients who are comatose after cardiac arrest and who are treated with therapeutic hypothermia (weak recommendation, very-low-quality evidence). However, no threshold-enabling prediction with 0 FPR can be recommended. We suggest using utmost care and preferably sampling at multiple time points when assessing NSE, to avoid false-positive results due to hemolysis.

#### Imaging

We suggest using the presence of a marked reduction of the GM/WM ratio on brain CT within 48 hours after ROSC or the presence of extensive reduction in diffusion on brain MRI at 2 to 6 days after ROSC only in combination with other more-established predictors for prognosticating a poor neurologic outcome in patients who are comatose after resuscitation from cardiac arrest and who are not treated with TTM (weak recommendation, very-low-quality evidence).

We suggest using brain-imaging studies for prognostication only in centers where specific experience is available (weak recommendation, very-low-quality evidence).

#### Knowledge Gaps

##### Clinical Examination

- Prospective studies are needed to investigate the pharmacokinetics of sedative drugs and neuromuscular blocking drugs in post-cardiac arrest patients, independently from treatment with TTM.

- Clinical studies are needed to evaluate the reproducibility of clinical signs used to predict outcome in comatose postarrest patients.
- There is no universally accepted definition of *status myoclonus*. A recently proposed definition suggests using the term *status myoclonus* to indicate a continuous and generalized myoclonus persisting for 30 minutes or more in comatose survivors of cardiac arrest.

### Electrophysiology

- Blinded studies on SSEPs are needed to assess the relevance of self-fulfilling prophecy for this predictor.
- The definitions of *low-voltage EEG* and *burst suppression*, and the EEG grades are inconsistent among prognostication studies. Future studies should comply with recently recommended definitions.

### Blood Markers

- There is a need for standardization of the measuring techniques for NSE and S100 in cardiac arrest patients.
- Little information is available on the kinetics of the blood concentrations of biomarkers in the first few days after cardiac arrest.

### Imaging

- Prospective studies in unselected patient populations and including evaluation of inter-rater agreement are needed to determine the prognostic accuracy of imaging studies in comatose patients resuscitated from cardiac arrest.

## 2010 CoSTR Topics Not Reviewed in 2015

- Postresuscitation hemofiltration
- IV fluids following cardiac arrest
- Neuroprotective drugs
- Postresuscitation treatment protocol

## Organ Donation (ALS 449)

In adults and children who are receiving an organ transplant in any setting (P), do organs retrieved from a donor who has had CPR (I), compared with organs retrieved from a donor who did not have CPR (C), have improved immediate graft function (30 days), 1-year graft function, or 5-year graft function (O)?

### Introduction

Resuscitation from cardiac arrest is not always successful, and many patients who are initially resuscitated from cardiac arrest will subsequently die in the hospital. Whether these nonsurviving patients can become organ donors has been debated because of the potential injury to organs during the initial cardiac arrest.

The committee reviewed experience about donation from this population that has accumulated in recent years. Two situations were separately considered. In the first, an individual who dies after being resuscitated by successful CPR may become an organ donor after brain death or having withdrawal

of life-sustaining treatment. In the second situation, an individual may die because of unsuccessful CPR in a center with a rapid response system that allows procurement of organs after unsuccessful CPR. For kidney transplants, the primary outcomes were graft function, because recipients can survive with renal replacement therapy even with graft failure. For other organs, recipient death was considered equivalent to graft failure. Only studies that allowed comparison of organs procured in these situations with other organs from non-CPR donors were selected for review.

### Consensus on Science

#### Donors With Prior CPR

Two nonrandomized studies provided low-quality evidence that the mean yield of organs procured from donors who had been resuscitated by CPR before donation was 3.9<sup>339</sup> or 2.9.<sup>340</sup>

For the important outcome of **immediate graft survival**, low-quality evidence from nonrandomized studies did not detect any worse outcome when donors have had CPR and resuscitation for adult hearts (3239 organs<sup>340-347</sup>), pediatric hearts (557 organs, 4 studies), adult lungs (1031 organs<sup>340,345,348</sup>), pediatric lungs (105 organs<sup>340</sup>), adult kidneys (5000 organs<sup>340,349</sup>), pediatric kidneys (1122 organs<sup>340,350</sup>), adult livers (2911 organs<sup>340,341</sup>), pediatric livers (689 organs<sup>340,350</sup>), adult intestines (25 organs<sup>340,351</sup>), and pediatric intestines (79 organs<sup>340</sup>).

For the important outcome of **graft survival for 1 year**, low-quality evidence from nonrandomized studies did not detect any worse outcome when donors have had CPR and resuscitation for adult hearts (3230 organs<sup>340-342,344-347</sup>), pediatric hearts (1605 organs<sup>340,350,352,353</sup>), adult lungs (1031 organs<sup>340,345,348</sup>), pediatric lungs (105 organs<sup>340</sup>), adult kidneys (5000 organs<sup>340,341</sup>), pediatric kidneys (1122 organs<sup>340</sup>), adult livers (2911 organs<sup>340,341</sup>), pediatric livers (689 organs<sup>340</sup>), adult intestines (25 organs<sup>340,351</sup>), and pediatric intestines (79 organs<sup>340</sup>).

For the important outcome of **graft survival for 5 years**, low-quality evidence from nonrandomized studies did not detect any worse outcome when donors have had CPR and resuscitation for adult hearts (3230 organs<sup>340-342,344-347</sup>), pediatric hearts (1537 organs<sup>340,353,354</sup>), adult lungs (1031 organs<sup>340,345,348</sup>), pediatric lungs (105 organs<sup>340</sup>), adult kidneys (5000 organs<sup>340,341</sup>), pediatric kidneys (1122 organs<sup>340</sup>), adult livers (2911 organs<sup>340,341</sup>), pediatric livers (689 organs<sup>340</sup>), adult intestines (25 organs<sup>340</sup>), and pediatric intestines (79 organs<sup>340</sup>).

#### Donors With Ongoing CPR (Uncontrolled Non-Heart-Beating Donors or Uncontrolled Donation After Circulatory Death)

Two nonrandomized studies provided low-quality evidence that the mean number of organs procured from donors with ongoing CPR was 1.5<sup>355</sup> and 3.2.<sup>356</sup>

For the important outcome of **immediate graft survival**, low-quality evidence from nonrandomized studies did not detect any worse outcome when organs were recovered from non-heart-beating donors with ongoing CPR compared with



other types of donors for adult kidneys (203 organs<sup>357–360</sup>) or adult livers (64 organs<sup>355,358,361,362</sup>).

For the important outcome of **graft survival for 1 year**, low-quality evidence from nonrandomized studies did not detect any worse outcome when organs were recovered from non–heart-beating donors with ongoing CPR compared with other types of donors for adult kidneys (199 organs<sup>357,358,360</sup>) or adult livers (60 organs<sup>355,358,361</sup>).

For the important outcome of **graft survival for 5 years**, low-quality evidence from nonrandomized studies did not detect any worse outcome when organs were recovered from non–heart-beating donors with ongoing CPR compared with other types of donors for adult kidneys (177 organs<sup>357,360</sup>) or adult livers (34 organs<sup>355</sup>).

### **Treatment Recommendation**

We recommend that all patients who have restoration of circulation after CPR and who subsequently progress to death be evaluated for organ donation (strong recommendation, low-quality evidence).

### **Values, Preferences, and Task Force Insights**

In making this recommendation, we consider the absence of any evidence of worse graft function from donors with antecedent CPR, the desirability of providing more organs to waiting recipients, and the absence of any risk to the donor. As in all organ donations, the function of the donated organ determines whether procurement and transplantation proceed. Therefore, there is also precaution to ensure the safety of the recipient.

### **Treatment Recommendation**

We suggest that patients who fail to have restoration of circulation after CPR and who would otherwise have termination of CPR efforts be considered candidates for kidney or liver

donation in settings where programs exist (weak recommendation, low-quality evidence).

### **Values, Preferences, and Task Force Insights**

In making this recommendation, we consider the evidence that kidney grafts obtained from donors in whom CPR failed can function at rates comparable to kidneys obtained from other donors, and that recipients can safely tolerate delayed graft function that is common with kidneys obtained in this manner. We also consider the immediate lifesaving potential of liver grafts, which offsets the potentially greater rate of long-term graft failure in livers obtained from donors with ongoing CPR.

### **Knowledge Gaps**

- The optimal methods for organ procurement after failed CPR are unknown.
- Barriers to consenting to this organ donation and the acceptability of these practices in different settings are unknown.

### **Acknowledgments**

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## Disclosures

## 2015 CoSTR Part 4: Advanced Life Support: Writing Group Disclosures

Writing Group Member	Employment	Research Grant	Other Research Support	Speakers' Bureau/Honoraria	Expert Witness	Ownership Interest	Consultant/Advisory Board	Other
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Mayuki Aibiki	Ehime University, School of Med	None	None	None	None	None	None	None
Bernd W. Böttiger	University of Cologne	None	European Resuscitation Council (ERC)†	None	None	None	None	None
Steven C. Brooks	Queen's University	Heart and Stroke Foundation of Canada†; CIHR†; NIH†	None	None	None	None	None	South Eastern Ontario Academic Medical Association†
Charles D. Deakin	Southampton University Hospital NHS Trust	Resuscitation Council UK†; National Institute for Health Research†	Resuscitation*	None	Several Coroner's cases relating to oesophageal intubation & capnography†	Prometheus Medical†	Smiths Medical*	None
Saul Drajer	Inter-American Heart Foundation	None	None	None	None	None	None	None
Walter Kloeck	Resuscitation Council of Southern Africa	None	None	None	None	None	None	None
Laurie J. Morrison	University of Toronto	NIH†; CIHR†; HSFC†	None	None	None	None	None	None
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Tonia C. Nicholson	Waikato Hospital	None	None	None	None	None	None	None
Jerry P. Nolan	Royal United Hospital, Bath	The Cardiac Arrest Individual Registry and Outcomes (CAIRO) Programme. 2013 - 2015†; NIHR Programme Development Grant (RP-DG-0612-10004) Improving Outcomes from Out of Hospital Cardiac Arrest NIHR Health Technology Assessment Programme Grant (HTA - 12/127/126) for a randomised placebo controlled trial of adrenaline for out of hospital cardiac arrest*; NIHR Health Technology Assessment Programme Grant (HTA-12/167/102) for a randomised trial of the effectiveness of a supra-glottic airway device versus tracheal intubation in the initial airway management of out of hospital cardiac arrest (AIRWAYS-2)*	None	None	None	None	None	None
Kazuo Okada	Resuscitation Council of Asia	None	None	None	None	None	None	None

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**2015 CoSTR Part 4: Advanced Life Support: Writing Group Disclosures, Continued**

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Jonathan Witt	Medical Minds	None	None	None	None	None	None	None
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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.

**Appendix**

**CoSTR Part 4: PICO Appendix**

Part	Task Force	PICO ID	Short Title	PICO Question	Evidence Reviewers
Part 4	ALS	ALS 428	Antiarrhythmic drugs for cardiac arrest	Among adults who are in cardiac arrest in any setting (P), does administration of antiarrhythmic drugs (eg, amiodarone, lidocaine, other) (I), compared with not using antiarrhythmic drugs (no drug or placebo) (C), change survival with favorable neurologic/functional outcome at discharge, 30 days, 60 days, 180 days, and/or 1 year; survival only at discharge, 30 days, 60 days, 180 days, and/or 1 year; ROSC (O)?	Katie Dainty, Thomas Pellis, Steve Lin
Part 4	ALS	ALS 431	Postresuscitation Seizure Prophylaxis	Among adults with ROSC after cardiac arrest in any setting (P), does seizure prophylaxis (I), compared with no prophylaxis (C), reduce the incidence of seizures, or improve survival with favorable neurologic/functional outcome at discharge, 30 days, 60 days, 180 days, and/or 1 year; survival only at discharge, 30 days, 60 days, 180 days, and/or 1 year (O)?	Romergrzyko Geocadin, William Stacey
Part 4	ALS	ALS 433	Steroids for Cardiac Arrest	Among adults who are in cardiac arrest in any setting (P), does corticosteroid or mineralocorticoid administration during CPR (I), compared with not using steroids (C), change survival with favorable neurologic/functional outcome at discharge, 30 days, 60 days, 180 days, and/or 1 year; survival only at discharge, 30 days, 60 days, 180 days, and/or 1 year; ROSC (O)?	Sarah Todhunter, Tonia Nicholson
Part 4	ALS	ALS 435	Cardiac Arrest Associated with Pulmonary Embolism	Among adults who are in cardiac arrest due to PE or suspected PE in any setting (P), does any specific alteration in treatment algorithm (eg, fibrinolytics, or any other) (I), compared with standard care (according to 2010 treatment algorithm) (C), change survival with favorable neurologic/functional outcome at discharge, 30 days, 60 days, 180 days, and/or 1 year; survival only at discharge, 30 days, 60 days, 180 days, and/or 1 year; ROSC (O)?	Wolfgang Wetsch, Bernd Böttiger

(Continued)



**CoSTR Part 4: PICO Appendix, Continued**

Part	Task Force	PICO ID	Short Title	PICO Question	Evidence Reviewers
Part 4	ALS	ALS 436	Cardiac Arrest during Pregnancy	Among pregnant women who are in cardiac arrest in any setting (P), do any specific interventions (I), compared with standard care (usual resuscitation practice) (C), change survival with favorable neurologic/functional outcome at discharge, 30 days, 60 days, 180 days, and/or 1 year; survival only at discharge, 30 days, 60 days, 180 days, and/or 1 year; ROSC (O)?	Carolyn Zelop, Jill Mhyre
Part 4	ALS	ALS 441	Opioid toxicity	Among adults who are in cardiac arrest or respiratory arrest due to opioid toxicity in any setting (P), does any specific therapy (eg, naloxone, bicarbonate, or other drugs) (I), compared with usual ALS (C), change survival with favorable neurologic/functional outcome at discharge, 30 days, 60 days, 180 days, and/or 1 year; survival only at discharge, 30 days, 60 days, 180 days, and/or 1 year; ROSC (O)?	Allan Mottram, Fred Severyn, Mohammed Alhelail
Part 4	ALS	ALS 448	Oxygen dose after ROSC in adults	Among adults who have ROSC after cardiac arrest in any setting (P), does an inspired oxygen concentration titrated to oxygenation (normal oxygen saturation or partial pressure of oxygen) (I), compared with the use of 100% inspired oxygen concentration (C), change survival to 30 days with good neurologic outcome, survival to hospital discharge with good neurologic outcome, improve survival, survival to 30 days, survival to hospital discharge (O)?	Jasmeet Soar, Michael Donnino
Part 4	ALS	ALS 449	Organ donation	In adults and children who are receiving an organ transplant in any setting (P), do organs retrieved from a donor who has had CPR (I), compared with organs retrieved from a donor who did not have CPR (C), have improved immediate graft function (30 days), 1-year graft function, or 5-year graft function (O)?	Stephen West, Clifton Callaway
Part 4	ALS	ALS 450	Prognostication in Comatose Patients Treated with Hypothermic TTM	Among adults with ROSC who are treated with hypothermia (P), does any clinical variable when abnormal (eg, clinical exam, EEG, somatosensory evoked potentials [SSEPs], imaging, other) (I), compared with any clinical variable when normal (C), reliably predict death or poor neurologic outcome at discharge, 30 days, 60 days, 180 days, and/or 1 year; death only at discharge, 30 days, 60 days, 180 days, and/or 1 year (O)?	Claudio Sandroni, Eyal Golan
Part 4	ALS	ALS 459	ETCO <sub>2</sub> to predict outcome of cardiac arrest	Among adults who are in cardiac arrest in any setting (P), does any ETCO <sub>2</sub> level value, when present (I), compared with any ETCO <sub>2</sub> level below that value (C), change survival with favorable neurologic/functional outcome at discharge, 30 days, 60 days, 180 days, and/or 1 year; survival only at discharge, 30 days, 60 days, 180 days, and/or 1 year; ROSC (O)?	Brian O'Neil, Edison Paiva
Part 4	ALS	ALS 469	Confirmation of Correct Tracheal Tube Placement	Among adults who are in cardiac arrest, needing/with an advanced airway, in any setting (P), does use of devices (eg, 1. waveform capnography, 2. CO <sub>2</sub> detection device, 3. esophageal detector device, or 4. tracheal ultrasound) (I), compared with not using devices (C), change placement of the ET tube between the vocal cords and the carina, success of intubation (O)?	Sarah Heikal, Markus Skrifvars
Part 4	ALS	ALS 470	Defibrillation Strategies for Ventricular Fibrillation (VF) or Pulseless Ventricular Tachycardia (pVT)	Among adults who are in ventricular fibrillation or pulseless ventricular tachycardia in any setting (P), does any specific defibrillation strategy (eg, 1. energy dose, or 2. shock waveform) (I), compared with standard management (or other defibrillation strategy) (C), change Survival with Favorable neurological/functional outcome at discharge, 30 days, 60 days, 180 days and/or 1 year, Survival only at discharge, 30 days, 60 days, 180 days and/or 1 year, ROSC, termination of arrhythmia (O)?	Giuseppe Ristagno, Charles Deakin

(Continued)

**CoSTR Part 4: PICO Appendix, Continued**

Part	Task Force	PICO ID	Short Title	PICO Question	Evidence Reviewers
Part 4	ALS	<a href="#">ALS 479</a>	Cardiac Arrest During Coronary Catheterization	Among adults who have a cardiac arrest in the cardiac catheterization laboratory (P), does any special intervention or change in care (eg, catheterization during CPR, cardiopulmonary bypass, balloon pump, different timing of shocks) (I), compared with standard resuscitation care (eg, CPR, drugs, and shocks according to 2010 treatment algorithm) (C), change survival with favorable neurologic/functional outcome at discharge, 30 days, 60 days, 180 days, and/or 1 year; survival only at discharge, 30 days, 60 days, 180 days, and/or 1 year; ROSC (O)?	Ian Drennan, Peter Kudenchuk
Part 4	ALS	<a href="#">ALS 493</a>	Postresuscitation Antiarrhythmic Drugs	Among adults with ROSC after cardiac arrest in any setting (P), do prophylactic antiarrhythmic drugs given immediately after ROSC (I), compared with not giving antiarrhythmic drugs (C), change survival with favorable neurologic/functional outcome at discharge, 30 days, 60 days, 180 days, and/or 1 year; development of cardiac arrest; survival only at discharge, 30 days, 60 days, 180 days, and/or 1 year; recurrence of VF; incidence of arrhythmias (O)?	Thomas Pellis, Steve Lin
Part 4	ALS	<a href="#">ALS 570</a>	Postresuscitation Hemodynamic Support	Among adults with ROSC after cardiac arrest in any setting (P), does titration of therapy to achieve a specific hemodynamic goal (eg, MAP greater than 65 mm Hg) (I), compared with no hemodynamic goal (C), change survival with favorable neurologic/functional outcome at discharge, 30 days, 60 days, 180 days, and/or 1 year; survival at discharge, 30 days, 60 days, 180 days, and/or 1 year (O)?	Michael Fries, Michael Parr
Part 4	ALS	<a href="#">ALS 571</a>	Postresuscitation Ventilation Strategy	Among adults with ROSC after cardiac arrest in any setting (P), does ventilation to a specific $P_{aCO_2}$ goal (I), compared with no specific strategy or a different $P_{aCO_2}$ goal (C), change survival at discharge, 30 days, 60 days, 180 days, and/or 1 year; survival with favorable neurologic/functional outcome at discharge, 30 days, 60 days, 180 days, and/or 1 year (O)?	Asger Granfeldt, Bo Lofgren
Part 4	ALS	<a href="#">ALS 579</a>	Impedance threshold device	Among adults who are in cardiac arrest in any setting (P), does use of an inspiratory ITD during CPR (I), compared with no ITD (C), change survival with favorable neurologic/functional outcome at discharge, 30 days, 60 days, 180 days, and/or 1 year; survival only at discharge, 30 days, 60 days, 180 days, and/or 1 year; ROSC (O)?	Peter Morley, Jasmeet Soar
Part 4	ALS	<a href="#">ALS 580</a>	Glucose Control After Resuscitation	Among adults with ROSC after cardiac arrest in any setting (P), does a specific target range for blood glucose management (eg, strict 4–6 mmol/L) (I), compared with any other target range (C), change survival with favorable neurologic/functional outcome at discharge, 30 days, 60 days, 180 days, and/or 1 year; survival only at discharge, 30 days, 60 days, 180 days, and/or 1 year (O)?	Janice Zimmerman, Jonathon Sullivan
Part 4	ALS	<a href="#">ALS 656</a>	Monitoring Physiological Parameters During CPR	Among adults who are in cardiac arrest in any setting (P), does the use of physiological feedback regarding CPR quality (eg, arterial lines, $ETCO_2$ monitoring, $SpO_2$ waveforms, or others) (I), compared with no feedback (C), change survival with favorable neurologic/functional outcome at discharge, 30 days, 60 days, 180 days, and/or 1 year; survival only at discharge, 30 days, 60 days, 180 days, and/or 1 year; ROSC; change in physiologic values by modifications in CPR (O)?	Amit Chopra, Natalie Wong

(Continued)

CoSTR Part 4: PICO Appendix, *Continued*

Part	Task Force	PICO ID	Short Title	PICO Question	Evidence Reviewers
Part 4	ALS	ALS 658	Ultrasound during CPR	Among adults who are in cardiac arrest in any setting (P), does use of ultrasound (including echocardiography or other organ assessments) during CPR (I), compared with conventional CPR and resuscitation without use of ultrasound (C), change survival with favorable neurologic/functional outcome at discharge, 30 days, 60 days, 180 days, and/or 1 year; survival only at discharge, 30 days, 60 days, 180 days, and/or 1 year; ROSC (O)?	Katherine Berg, Lars Wiuff Andersen
Part 4	ALS	ALS 659	Epinephrine Versus Vasopressin	Among adults who are in cardiac arrest in any setting (P), does use of epinephrine (I), compared with vasopressin (C), change survival to 30 days with good neurologic outcome, survival to 30 days, survival to hospital discharge with good neurologic outcome, survival to hospital discharge, ROSC (O)?	Laurie Morrison, Clifton Callaway, Steve Lin
Part 4	ALS	ALS 713	Prognostication in Absence of TTM	Among adults who are comatose after cardiac arrest and are not treated with TTM (P), does any clinical finding when normal (eg, clinical exam, EEG, SSEPs, imaging, other) (I), compared with any clinical finding when abnormal (C), reliably predict death or poor neurologic outcome at discharge, 30 days, 60 days, 180 days, and/or 1 year; death only at discharge, 30 days, 60 days, 180 days, and/or 1 year (O)?	Claudio Sandroni, Tobias Cronberg
Part 4	ALS	ALS 714	SGAs Versus Tracheal Intubation	Among adults who are in cardiac arrest in any setting (P), does SGA insertion as first advanced airway (I), compared with insertion of a tracheal tube as first advanced airway (C), change survival with favorable neurologic/functional outcome at discharge, 30 days, 60 days, 180 days, and/or 1 year; survival only at discharge, 30 days, 60 days, 180 days, and/or 1 year; ROSC; CPR parameters; development of aspiration pneumonia (O)?	Jerry Nolan, Charles Deakin
Part 4	ALS	ALS 723	ECPR Versus Manual or Mechanical CPR	Among adults who are in cardiac arrest in any setting (P), does the use of ECPR techniques (including extracorporeal membrane oxygenation or cardiopulmonary bypass) (I), compared with manual CPR or mechanical CPR (C), change survival with favorable neurologic/functional outcome at discharge, 30 days, 60 days, 180 days, and/or 1 year; survival only at discharge, 30 days, 60 days, 180 days, and/or 1 year; ROSC (O)?	Mayuki Aibiki, Tzong-Luen Wang
Part 4	ALS	ALS 778	SDE Versus HDE	In adult patients in cardiac arrest in any setting (P), does HDE (at least 0.2 mg/kg or 5 mg bolus dose) (I), compared with SDE (1 mg bolus dose) (C), change survival to 180 days with good neurologic outcome, survival to 180 days, survival to hospital discharge with good neurologic outcome, survival to hospital discharge, ROSC (O)?	Laurie Morrison, Clifton Callaway, Steve Lin
Part 4	ALS	ALS 782	Mechanical CPR Devices	Among adults who are in cardiac arrest in any setting (P), do automated mechanical chest compression devices (I), compared with standard manual chest compressions (C), change survival with favorable neurologic/functional outcome at discharge, 30 days, 60 days, 180 days, and/or 1 year; survival only at discharge, 30 days, 60 days, 180 days, and/or 1 year; ROSC (O)?	Steven Brooks, Laurie Morrison
Part 4	ALS	ALS 783	Basic Versus Advanced Airway	Among adults who are in cardiac arrest in any setting (P), does insertion of an advanced airway (tracheal tube or SGA) (I), compared with basic airway (bag-mask device with or without oropharyngeal airway) (C), change survival with favorable neurologic/functional outcome at discharge, 30 days, 60 days, 180 days, and/or 1 year; survival only at discharge, 30 days, 60 days, 180 days, and/or 1 year; ROSC; CPR parameters; development of aspiration pneumonia (O)?	Jerry Nolan, Jan-Thorsten Graesner

(Continued)



CoSTR Part 4: PICO Appendix, *Continued*

Part	Task Force	PICO ID	Short Title	PICO Question	Evidence Reviewers
Part 4	ALS	<a href="#">ALS 784</a>	Timing of Administration of Epinephrine	Among adults who are in cardiac arrest in any setting (P), does early epinephrine delivery by IV or IO route (eg, less than 10 minutes after the beginning of resuscitation) (I), compared with delayed timing of epinephrine delivery (eg, more than 10 minutes after the beginning of resuscitation) (C), change survival with favorable neurologic/functional outcome at discharge, 30 days, 60 days, 180 days, and/or 1 year; survival only at discharge, 30 days, 60 days, 180 days, and/or 1 year; ROSC (O)?	Tonia Nicholson, Michael Donnino
Part 4	ALS	<a href="#">ALS 788</a>	Epinephrine Versus Placebo	Among adults who are in cardiac arrest in any setting (P), does the use of epinephrine (I), compared with placebo or not using epinephrine (C), change survival with favorable neurologic/functional outcome at discharge, 30 days, 60 days, 180 days, and/or 1 year; survival only at discharge, 30 days, 60 days, 180 days, and/or 1 year; ROSC (O)?	Laurie Morrison, Clifton Callaway, Steve Lin
Part 4	ALS	<a href="#">ALS 789</a>	Epinephrine Versus Vasopressin in Combination With Epinephrine	Among adults who are in cardiac arrest in any setting (P), does use of both vasopressin and epinephrine (I), compared with using epinephrine alone (C), change survival with favorable neurologic/functional outcome at discharge, 30 days, 60 days, 180 days, and/or 1 year; survival only at discharge, 30 days, 60 days, 180 days, and/or 1 year; ROSC (O)?	Clifton Callaway, Laurie Morrison, Steve Lin
Part 4	ALS	<a href="#">ALS 790</a>	Targeted Temperature Management	Among patients with ROSC after cardiac arrest in any setting (P), does inducing mild hypothermia (target temperature 32°C–34°C) (I), compared with normothermia (C), change survival with favorable neurologic/functional outcome at discharge, 30 days, 60 days, 180 days, and/or 1 year; survival only at discharge, 30 days, 60 days, 180 days, and/or 1 year (O)?	Joshua Reynolds, Katherine Berg
Part 4	ALS	<a href="#">ALS 791</a>	Duration of TTM	In patients with ROSC after cardiac arrest in any setting (P), does induction and maintenance of hypothermia for any duration other than 24 hours (I), compared with induction and maintenance of hypothermia for a duration of 24 hours (C), change survival with favorable neurologic/functional outcome at discharge, 30 days, 60 days, 180 days, and/or 1 year; survival only at discharge, 30 days, 60 days, 180 days, and/or 1 year (O)?	Theodoros Xanthos, Lars Wiuff Andersen
Part 4	ALS	<a href="#">ALS 802</a>	Timing of Induced Hypothermia	Among patients with return of pulses after cardiac arrest in any setting (P), does induction of hypothermia before some time point (eg, 1 hour after ROSC or before hospital arrival) (I), compared with induction of hypothermia after that time point (C), change survival with favorable neurologic/functional outcome at discharge, 30 days, 60 days, 180 days, and/or 1 year; survival only at discharge, 30 days, 60 days, 180 days, and/or 1 year (O)?	Theodoros Xanthos, Michael Cocchi
Part 4	ALS	<a href="#">ALS 808</a>	Ventilation rate during continuous chest compression	Among adults with cardiac arrest with a secure airway receiving chest compressions (in any setting, and with standard tidal volume) (P), does a ventilation rate of 10 breaths/min (I), compared with any other ventilation rate (C), change survival with favorable neurologic/functional outcome at discharge, 30 days, 60 days, 180 days, and/or 1 year; survival only at discharge, 30 days, 60 days, 180 days, and/or 1 year; ROSC (O)?	Koen Monsieurs, Jasmeet Soar, Gino Vissers
Part 4	ALS	<a href="#">ALS 834</a>	Lipid Therapy for Cardiac Arrest	In adult patients with cardiac arrest due to suspected drug toxicity (eg, local anesthetics, tricyclic antidepressants, others) (P), does administration of IV lipid (I), compared with no IV lipid (C), change survival with favorable neurologic/functional outcome at discharge, 30 days, 60 days, 180 days, and/or 1 year; survival only at discharge, 30 days, 60 days, 180 days, and/or 1 year; ROSC (O)?	Eric Lavonas, Mohammed Alhelail

(Continued)

CoSTR Part 4: PICO Appendix, *Continued*

Part	Task Force	PICO ID	Short Title	PICO Question	Evidence Reviewers
Part 4	ALS	ALS 868	Seizure Treatment	Among adults with ROSC after cardiac arrest in any setting (P), does effective seizure treatment (I), compared with no seizure control (C), change survival with favorable neurologic/functional outcome at discharge, 30 days, 60 days, 180 days, and/or 1 year; survival only at discharge, 30 days, 60 days, 180 days, and/or 1 year (O)?	Romergrzyko Geocadin, William Stacey
Part 4	ALS	ALS 879	Prevention of Fever After Cardiac Arrest	Among adults with ROSC after cardiac arrest in any setting (P), does prevention of fever to maintain strict normothermia (I), compared with no fever control (C), change survival with favorable neurologic/functional outcome at discharge, 30 days, 60 days, 180 days, and/or 1 year; survival only at discharge, 30 days, 60 days, 180 days, and/or 1 year (O)?	Katherine Berg, Lars Wiuff Andersen
Part 4	ALS	ALS 889	Oxygen dose during CPR	In adults with cardiac arrest in any setting (P), does administering a maximal oxygen concentration (eg, 100% by face mask or closed circuit) (I), compared with no supplementary oxygen (eg, 21%) or a reduced oxygen concentration (eg, 40%–50%) (C), change survival with favorable neurologic/functional outcome at discharge, 30 days, 60 days, 180 days, and/or 1 year; survival only at discharge, 30 days, 60 days, 180 days, and/or 1 year; ROSC (O)?	Anthony Lagina, Jasmeet Soar

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KEY WORDS: arrhythmia ■ cardiac arrest ■ emergency department ■ postresuscitation care ■ resuscitation



## Part 4: Advanced Life Support: 2015 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science With Treatment Recommendations

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